dementia in women with cerebrovascular disease

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ABSTRACT

Objective: To determine whether calcium supplementation is associated with the development of dementia in women after a 5-year follow-up.

Methods: This was a longitudinal population-based study. The sample was derived from the Prospective Population Study of Women and H70 Birth Cohort Study in Gothenburg, Sweden, and included 700 dementia-free women aged 70–92 years. At baseline in 2000–2001, and at follow-up in 2005–2006, the women underwent comprehensive neuropsychiatric and somatic examinations. A CT scan was performed in 447 participants at baseline. Information on the use and dosage of calcium supplements was collected. Dementia was diagnosed according to DSM-III-R criteria.

Results: Women treated with calcium supplements (n = 98) were at a higher risk of developing dementia (odds ratio [OR] 2.10, 95% confidence interval [CI] 1.01–4.37, $p = 0.046$) and the subtype stroke-related dementia (vascular dementia and mixed dementia) (OR 4.40, 95% CI 1.54–12.61, $p = 0.006$) than women not given supplementation (n = 602). In stratified analyses, calcium supplementation was associated with the development of dementia in groups with a history of stroke (OR 6.77, 95% CI 1.36–33.75, $p = 0.020$) or presence of white matter lesions (OR 2.99, 95% CI 1.28–6.96, $p = 0.011$), but not in groups without these conditions.

Conclusions: Calcium supplementation may increase the risk of developing dementia in elderly women with cerebrovascular disease. Because our sample was relatively small and the study was observational, these findings need to be confirmed. ***Neurology*® 2016;87:1674–1680**

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; **DSM-III-R** = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; **ICD** = *International Classification of Diseases*; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **VaD** = vascular dementia; **WHI CaD** = Women's Health Initiative Calcium/Vitamin D supplementation study; **WML** = white matter lesion.

Dementia[1] and osteoporosis are leading causes of disability in the elderly. Because calcium deficiency contributes to osteoporosis, daily dietary calcium intake of 1,000–1,200 mg is recommended.[2] Such a large calcium intake through diet alone can be difficult; therefore, calcium supplements are widely used.[2] However, recently, the safety of calcium supplements has been questioned.[3] Dietary calcium in the recommended range seems to be safe or might even be protective against vascular events,[4] while the literature on calcium supplementation is inconclusive.[5] Some trials have reported an association between calcium supplementation and increased risk for vascular events,[6] while others have reported no association.[7,8] A permanent increase in calcium levels increases vascular risk.[9] Vascular risk factors are related to vascular dementia (VaD) and Alzheimer disease (AD).[10,11] Thus, if calcium supplement intake increases the risk for vascular events, it might increase the risk for dementia. Calcium supplementation might have direct toxic effects on vulnerable neurons, because the increased calcium levels may amplify ischemic cell death and worsen the outcome after cerebrovascular events.[12] The relation

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between calcium supplement and dementia may be especially strong in persons with vasculopathies such as stroke or ischemic white matter lesions (WMLs). Therefore, we hypothesized that calcium supplementation is associated with an increased risk of dementia and this association is accentuated in individuals already compromised by ischemic cerebrovascular disease, such as those with a history of stroke or ischemic WMLs. This hypothesis was tested using a population sample of elderly women initially free from dementia with a 5-year follow-up.

METHODS

Sample. The baseline sample was derived from the 2000–2003 examinations of the Prospective Population Study of Women and the H70 Study in Gothenburg, Sweden.[13]

Samples were obtained from the Swedish Population Registry, based on birth date, and included persons living in private households and residential care.[13]

The baseline sample has been described previously.[13,14] The study included women born on certain dates in 1908, 1914, 1918, 1922, and 1930 and living in Sweden on September 1, 2000.[14] Among the 1,200 women selected, 49 died before examination, 12 could not speak Swedish, and 21 had emigrated from Sweden, leaving an effective sample of 1,018.[13,14] Among these, 789 participated in a neuropsychiatric examination (response rate, 77.5%).[13,14] At baseline, 89 women had dementia and were excluded, leaving an effective sample size of 700 women for this study (4 born in 1908, 27 in 1914, 137 in 1918, 193 in 1922, and 339 in 1930).[14] Differences between participants and nonparticipants have been described previously.[13]

A follow-up examination was performed in 2005–2006. Of the 700 women examined at baseline, 64 died before follow-up, and 531 participated in the follow-up examination (response rate, 83.5%; 275 women born in 1930 and 256 born in 1908, 1914, 1918, or 1922).

Examinations were conducted at a geriatric outpatient clinic in Gothenburg. Home visits were offered to participants who refused examinations at the hospital and to participants who had moved to other areas within Sweden.

Assessments. ***Neuropsychiatric baseline and follow-up examinations.*** These assessments were conducted by experienced psychiatric research nurses.[13] We used the same methodology as the one employed in a previous study.[13] The semi-structured examinations included ratings of psychiatric symptoms and signs and mental functioning tests, including assessments of memory, aphasia, apraxia, executive functioning, personality changes, and the Mini-Mental State Examination (MMSE), as described previously.[1,13]

Participants also underwent somatic examinations, including medical history, blood pressure, and serum total and high-density lipoprotein cholesterol level measurements.[13] Presence of diabetes mellitus and cigarette smoking status were ascertained.[13] In addition, *APOE* genotyping was performed.[13]

Drug utilization was recorded according to the Anatomical Therapeutic Chemical classification system.[13] Information on regular drug use, including calcium supplements, was collected from multidose drug-dispensing lists.[13] Participants were asked to show the interviewer the drugs they used.[13] A participant was classified as a user if drug use was documented by either source.[13] Information on duration of drug use or dosage regimen was unavailable, but the average recommended daily dose of calcium supplements in Sweden is 1,000 mg.

Education was categorized as mandatory (6 years in participants born in 1908–1922, 7 years in participants born in 1930) or more than mandatory.[13]

Close informant interviews. Interviews were performed by psychiatric research nurses at both examinations.[13] The interviews were semi-structured and included questions about changes in behavior and cognitive function (e.g., memory, intellectual ability, language, and executive function), personality changes, psychiatric symptoms, activities of daily living, and in case of dementia, onset age, and disease course, as described previously.[1,13]

An experienced neurologist, blinded to all clinical data, evaluated all brain CT scans, as described previously.[15] The Gothenburg scale was used to rate WMLs.[15,16] WMLs were defined as diffusely distributed periventricular or subcortical areas of decreased attenuation below that expected for normal white matter.[15,16] Interobserver agreement for WMLs between the rater and a neuroradiologist was fair ($\kappa = 0.30$).[15] Of the 700 women, 447 consented to undergo a CT scan (63.9%) of the brain. The sample has been described in detail previously.[15]

Dementia diagnoses. Dementia was diagnosed according to the DSM-III-R criteria[17] by geriatric psychiatrists at consensus meetings using a symptom algorithm with data from the psychiatric examination and the key informant interview.[1,11] Each symptom was considered when it attained a level that caused significant difficulties in everyday life.[1,11] A final diagnosis was made from the combined information.[1,11]

AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.[18,19] The criteria for VaD were similar to the criteria proposed by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherce et l'Enseignement en Neurosciences.[20] VaD was diagnosed when there was a temporal relationship (within 1 year) between a history of acute focal neurologic symptoms and signs (hemiparesis or motor aphasia) and the first symptoms of dementia.[19,20] A diagnosis of mixed dementia was made when both AD and cerebrovascular disease contributed to dementia. VaD and mixed dementia were combined as stroke-related dementia.[19,20]

Dementias due to other causes (e.g., alcoholic dementia, normal-pressure hydrocephalus, and vitamin B_{12} deficiency) were diagnosed as described previously.[1,21]

For those lost to follow-up in 2005 (deceased and refusals), dementia diagnoses were made from the data in the Swedish Hospital Discharge Registry (using ICD diagnoses from 1980 onwards). In the whole dementia sample, 9 participants were diagnosed based on only the registry data (2 participants with calcium supplementation, 7 without calcium supplementation). In Sweden, almost all inhabitants are included in public health services and have equal chances of being in the hospital discharge register.

Assessment of cardiovascular risk. As described previously, a 10-year cardiovascular risk score based on the primary care formula from the Framingham Heart Study was calculated.[13]

Assessment of osteoporosis-associated fractures. To assess the confounding effect of indication for treatment, we assessed fractures related to osteoporosis (hip, wrist, vertebrae compression, and upper arm fractures).[22,23] Information on fractures was obtained from self-report and the Hospital Discharge Registry.

Statistical methods. Fisher exact test was used to test differences in proportions. A 2-tailed level of significance was employed ($p < 0.05$). Differences in age and cardiovascular risk scores at baseline were examined using the Mann-Whitney *U* test. Multivariate logistic regressions were used to investigate the relationship between calcium

use at baseline and development of dementia during the 5-year follow-up. The overall effect of calcium supplements on dementia, in general, was examined first. Thereafter, we divided dementia into the following subtypes: AD, mixed dementia, and VaD.

In addition, we examined the relationship between calcium supplementation and development of dementia, and stratified the sample by history of stroke and presence of WMLs at baseline. In the regression models, we controlled for baseline age, education, total vascular risk, and presence of *APOE* ε4. Using separate regression models, we controlled for possible confounders, such as estrogens, cortisone, and vitamin D. SPSS for Windows (v. 17, SPSS Inc., Chicago, IL) was implemented in all statistical tests.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Ethics Committee for Medical Research at the University of Gothenburg. All participants provided informed consent before participating in the study.[13]

RESULTS Table 1 shows the baseline characteristics in 2000 for participants treated (n = 98) and those not treated (n = 602) with calcium supplementation. There were no differences between the groups in the baseline characteristics of age, MMSE scores, and education. History of stroke at baseline (n = 54) or follow-up (n = 54) was noted in 108 individuals. Five participants had a stroke after dementia was diagnosed. There was no association between calcium supplementation and stroke at baseline ($p = 0.68$) or new stroke during follow-up ($p = 0.54$). Of those who received calcium supplements at baseline (n = 98), 77 (77.6%) received follow-up in 2005. At follow-up, 50 women (64.9%) were still using calcium supplementation. Among the 447 participants for whom CT scan was performed, 316 (70.7%) had WMLs. There was no association between calcium supplementation and WMLs at baseline ($p = 0.779$).

Relationship between calcium supplementation and type of dementia. Fifty-nine women developed dementia between 2000 and 2005. Table 2 shows the different types of dementia among women who took calcium supplements at baseline and those who did not.

Table 3 shows the association between calcium supplementation and dementia at follow-up. Women treated with calcium supplements had a higher risk of developing dementia (odds ratio [OR] 2.10, 95% confidence interval [CI] 1.01–4.37, $p = 0.046$) and the subtype dementia with stroke (VaD or mixed AD/VaD) (OR 4.4, 95% CI 1.54–12.61, $p = 0.006$) than the women who did not take calcium supplementation.

Development of dementia in women with and without a history of stroke. We stratified the sample into women with (n = 108) and without (n = 592) a history of stroke (table 4). In the group with history of stroke, calcium supplementation was associated with development of dementia (OR 6.77, 95% CI 1.36–33.75, $p = 0.020$), but there was no relationship between calcium supplementation and development of dementia in the group without a history of stroke (OR 1.49, 95% CI 0.61–3.63, $p = 0.381$; table 4).

Development of dementia in those with and those without WMLs. We stratified the CT sample into women with (n = 316) and without (n = 131) WMLs (table 5). In the group with WMLs, calcium supplementation was associated with development of dementia (OR 2.99, 95% CI 1.28–6.96, $p = 0.011$), whereas in the group without WMLs, none of the women who used calcium supplements developed dementia ($p = 0.351$).

Table 1 Baseline characteristics of the study population[a] by daily calcium supplement use

	Calcium use		
	No	Yes	*p* Value[b]
All (% of sample)	602 (86)	98 (14)	
Age, y, mean (SD)	75.2 (5.5)	75.9 (5.6)	$U = 27{,}493$, $p = 0.243$
MMSE score, mean (SD)	27.7 (1.8)	27.9 (1.8)	$U = 27{,}802$, $p = 0.389$
Education beyond mandatory, n (%)	195 (32.4)	41 (41.8)	$p = 0.136$
Stroke up to 2000, n (%)	48 (8.0)	6 (6.1)	$p = 0.683$
Stroke after baseline, n (%)	45 (7.5)	9 (9.2)	$p = 0.541$
Mean (SD) stroke age, y	75.6 (12.5)	80.6 (7.1)	$U = 542$, $p = 0.165$
CT scan 2000, n (%)	375 (62)	72 (73)	$p = 0.041$
WML, n (%)	266 (70.9)	50 (69.4)	$p = 0.779$
Mean age of those with WML (SD), y	75.3 (5.5)	76.8 (5.5)	$U = 5{,}664$, $p = 0.074$
APOE ε4, n (%)[c]	152 (27.7)	19 (21.1)	$p = 0.202$

Abbreviations: MMSE = Mini-Mental State Examination; WML = white matter lesions.
[a] Excluding participants with a dementia diagnosis at baseline 2000–2001.
[b] Mann-Whitney *U* tests where stated; otherwise, Fisher exacts tests.
[c] Sixty-one cases had no information on the presence of the *APOE* ε4 allele.

Table 2 Dementia development at follow-up by calcium supplement use excluding participants with dementia at baseline

	Calcium use, n (%)	
Dementia type	No, 602 (86)	Yes, 98 (14)
AD	29 (4.8)	4 (4.1)
VaD/AD	14 (2.4)	8 (8.2)
VaD	10 (1.7)	3 (3.1)
Mixed (AD/vascular)	4 (0.7)	5 (5.1)
Other causes	2 (0.3)	2 (2)
All dementia cases	45 (7.5)	14 (14.3)

Abbreviations: AD = Alzheimer disease; VaD = vascular dementia.

Osteoporosis-associated fractures and treatment with cortisone, estrogen, and calcium supplementation with or without vitamin D. The frequency of fractures was 40.8% (n = 40) in the group that received calcium supplements and 20.8% (n = 125) in the group that did not ($p < 0.001$). The main results remained unchanged in women with history of stroke and presence of WMLs when osteoporotic fractures and treatment with cortisone, estrogens, and vitamin D (only 14 of 98 individuals took calcium supplements without vitamin D) were included in the regression models (data not shown).

DISCUSSION We found a relationship between calcium supplementation and increased risk for dementia in elderly women in this 5-year follow-up study. This association was mainly confined to individuals with cerebrovascular disease (history of stroke or presence of WMLs) at baseline.

Stroke and WMLs increase the risk for dementia.[24,25] Herein, we add to this finding by showing that calcium supplementation further increases this risk. There may be several explanations for our results. Both WMLs and stroke are markers of generalized cerebrovascular disease with different types of vessel pathology, share common risk factors, and often co-occur. Histopathologically, WMLs are related to diffuse ischemic incomplete infarcts, presumably caused by hypoperfusion and ischemia,[26] and stroke is related to ischemic infarcts, often surrounded by a penumbra of incomplete infarction. The mechanism of calcium supplements in the pathogenesis of dementia could be the steep increase in serum calcium levels caused by the supplements.[27] Neurons located in areas of hypoperfusion might be especially vulnerable to the excitatory and excitotoxic effects of the calcium-level peaks caused by the supplementation. Calcium plays a central role in the mechanisms of cell death. In necrosis, the transmembrane influx of calcium ions activates proteases that are responsible for degrading critical proteins and disrupting membrane function.[28] Studies in in vitro models have shown that some surviving neurons undergo apoptosis several hours after the membrane potential is restored. Blocking calcium influx via NMDA receptors prevents both necrosis and apoptosis. This indicates the crucial role of calcium influx and intracellular calcium overload in the genesis of apoptosis and necrosis.[29]

It has been hypothesized that calcium supplements affect the vessels, and thus, may potentiate changes in the vessel walls in individuals with vascular disease, thereby leading to ischemia and hypoperfusion. Atherosclerosis is a long-term process with different stages, and calcium deposits become more common in the advanced stages. The large- and medium-sized vessels of individuals with stroke become compromised, which may make them more vulnerable to the effect of calcium supplementation. WMLs are related to small vessel disease, i.e., arteriolosclerosis, hyalinosis, and lumen narrowing of the small penetrating arteries and arterioles in the white matter.[30] The steep increase in serum calcium levels after calcium supplementation might lead to increased coagulability, lipohyalinosis, or altered vascular flow and might be mediated through calcium receptors or changes in calcium-dependent hormone levels.[27] Another explanation may be that calcium supplementation stimulates vascular calcification by abnormal extraosseous deposition in atherosclerotic plaques.[31]

Dietary calcium might be protective against vascular disease.[4,32] The difference between dietary calcium and calcium intake by supplements could be explained by variations in corresponding changes in serum calcium concentration. Dietary intake does not increase the serum calcium levels to the same extent as supplements.[27]

Table 3 Use of calcium supplements and risk for different types of dementia in women followed up for 5 years

	Any dementia		Vascular or mixed dementia		Alzheimer disease	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Calcium use at baseline	2.1 (1.01–4.37)	0.046	4.4 (1.54–12.61)	0.006	0.66 (0.19–2.25)	0.503

Abbreviations: CI = confidence interval; OR = odds ratio.
Logistic regression models included age at baseline, education beyond mandatory, total vascular risk, and presence of the *APOE* ε4 allele.

Table 4 Use of calcium supplements and risk for development of any type of dementia in women followed up for 5 years and stratified by history of stroke

	No history of stroke (n = 592)	
	OR (95% CI)[a]	*p* Value
Calcium use at baseline[b] (dementia/total); no (n = 33/n = 509); yes (n = 18/n = 83)	1.49 (0.61–3.63)	0.381
	History of stroke up to 2005 (n = 108)	
	OR (95% CI)[a]	***p* Value**
Calcium use at baseline[c] (dementia/total); no (n = 12/93); yes (n = 6/15)	6.77 (1.36–33.75)	0.020

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Logistic regression models included age at baseline, education beyond mandatory, total vascular risk, and presence of the *APOE* ε4 allele.
[b] Calcium use at baseline in 2000 for 700 women. In parentheses, the total number is given and the number of women who developed dementia.
[c] Calcium use at baseline in 2000 for 700 women. In parentheses, the total number is given and the number of women who developed dementia.

In addition, dietary calcium intake involves simultaneous intake of all other components of calcium-containing foods and much lower dosages of calcium than calcium supplements.

The relationship between calcium supplements and risk of dementia and cardiovascular events was examined in the Women's Health Initiative Calcium/Vitamin D supplementation study (WHI CaD).[6,8,33] In this large 7-year randomized controlled trial, the assignment of participants to calcium and vitamin D supplement groups was not related to the development of incident cognitive impairment or dementia,[33] myocardial infarction, or stroke.[8] However, in WHI CaD, about half of the women were taking personal (non-study-protocol) calcium, vitamin D, or both. A comprehensive reanalysis,[6] only including women who did not take personal calcium and vitamin D supplements, showed that calcium supplementation increased the risk of myocardial infarction or stroke.[6] There was no such reanalysis for dementia or cognitive decline. In our study, calcium supplementation was not related to stroke during the follow-up or to WMLs at baseline, although cerebrovascular disease and dementia are closely related. As discussed previously, calcium supplements may only be hazardous to already compromised neurons. A previous study demonstrated that use of calcium-containing dietary supplements was associated with greater brain lesion volume on MRI.[34]

In WHI CaD, the authors stated that the effect of vitamin D alone on cognition is difficult to determine.[33] In this study, we did not detect a modifying effect of vitamin D. Even if cross-sectional and prospective studies linked vitamin D deficiency to AD, VaD, and cognitive decline,[35] existing data are insufficient to conclude that vitamin D supplementation reduces the risk for any chronic diseases than osteoporosis.[36]

The strengths of this study include the population-based sample, the detailed examinations, the prospective design, and the large response rate at follow-up. However, the study has a few limitations. First, we had no information on dietary calcium, serum calcium, or calcium use (causal or persistent). However, about two-thirds of those followed up after 5 years were still on the supplements. An even higher proportion probably comprises persistent users. Inclusion of causal users may underestimate the effect of calcium supplements on the risk of dementia.

Second, it must be emphasized that this is an observational study. Therefore, we cannot infer causality from our analyses or exclude the possibility of confounding by indication, because persons using calcium supplements may be less healthy than other individuals. However, we found no differences between the groups for most health factors, except that women on supplementations were more likely to have had a fracture. Our results remained unchanged even when controlling for osteoporosis-associated fractures. In addition, from a fracture perspective, it may be

Table 5 Dementia cases and use of calcium supplements in women with and without CT scan and white matter lesions (WMLs) at baseline in 2000

	CT (n = 447), n					
	No WML[a]		WML[a]		No CT (n = 253), n	
	No stroke	Stroke	No stroke	Stroke	No stroke	Stroke
No dementia						
No dementia and calcium supplementation use	21	1	35	4	19	4
No dementia and no calcium supplementation use	94	7	202	43	180	31
Dementia						
Dementia and calcium supplementation use	0	0	7	4	1	2
Dementia and no calcium supplementation use	6	2	16	5	11	5

[a] WMLs according to the Gothenburg scale on CT of the brain.

problematic if these women did not take calcium supplementation.

Third, information from participants who have a fracture and can self-report information may differ from those whose information is only obtained from the registry.[37]

Fourth, the overall sample size, particularly of dementia cases, was small (only 14 of 98 who used calcium supplementation had dementia) and might have led to a low statistical power in some of the subgroups; for example, the number of individuals with pure VaD was too small for separate analyses, which required us to merge this group with that of mixed dementia. However, both these entities had a history of stroke and are expected to share the same vulnerability to calcium supplements.

Fifth, CT scans were not performed at follow-up. Thus, we were unable to assess the effect of calcium supplements on changes in WMLs or silent strokes.

Sixth, CT is less sensitive than MRI for detecting WMLs and is more influenced by bone-hardening artifacts.[38] However, CT is better for delineating clinically relevant WMLs[39] and is the most widely used imaging technique worldwide. In addition, there is scarce evidence to propose that MRI is better than CT in identifying cerebrovascular changes related to dementia.[40] Moreover, as CT is less sensitive to motion artefacts and requires a shorter examination time, it may be more appropriate for older adults. Although the visual rating of WMLs on CT is a rather coarse method, we have previously identified associations between WMLs and both dementia and depression.[38] In fact, the absence of perfect agreement probably attenuates the observed relationships.

Seventh, the same individual rated all scans, which may enhance the possibility for systematic error.

Finally, our study was conducted in women; therefore, we cannot generalize these results to men.

AUTHOR CONTRIBUTIONS

Jürgen Kern and Silke Kern analyzed and interpreted the data, conducted the literature search, and wrote the paper. Kaj Blennow, Henrik Zetterberg, Margda Waern, Xinxin Guo, and Anne Börjesson-Hanson contributed with the analysis and interpretation of the data and revised the article critically for important intellectual content. Ingmar Skoog and Svante Östling conceived and designed the study, refined the study methods, were involved in analysis and interpretation of the data, and revised the article critically for important intellectual content. The corresponding author attests that the authors had access to all the study data, take responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. All authors gave final approval of the version to be published. The corresponding author affirms that he has listed everyone who contributed significantly to the work.

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DISCLOSURE

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