

## **Vitamin D status, cognitive decline and incident dementia: The Canadian Study of Health and Aging**

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## Abstract

**Objective:** Vitamin D could prevent cognitive decline because of its neuroprotective, anti-inflammatory and antioxidant properties. This study aimed to evaluate the associations of plasma 25-hydroxyvitamin D (25(OH)D) concentrations with global cognitive function and incident dementia, including Alzheimer's disease (AD). **Methods:** The Canadian Study of Health and Aging is a 10-year cohort study of a representative sample of individuals aged 65 or older. A total of 661 subjects initially without dementia with frozen blood samples and follow-up data were included. Global cognitive function was measured using the validated Modified Mini-Mental State (3MS) examination. A consensus diagnosis of all-cause dementia and AD was made between the physician and the neuropsychologist according to published criteria. Cognitive declines for a 5-year increase in age at specific 25(OH)D concentrations were obtained using linear mixed models with repeated measures. Hazard ratios of incident dementia and AD were obtained using semi-parametric proportional hazards models with age as time scale. **Results:** Over a mean follow-up of 5.4 years, 141 subjects developed dementia of which, 100 were AD. Overall, no significant association was found between 25(OH)D and cognitive decline, dementia or AD. Higher 25(OH)D concentrations were associated with an increased risk of dementia and AD in women, but not in men. **Conclusions:** This study does not support a protective effect of vitamin D status on cognitive function. Further research is needed to clarify the relation by sex.

**Key words:** 25-hydroxyvitamin D, Cognitive impairment, Alzheimer disease, Prospective study

## **Introduction**

Fifty million people worldwide were living with dementia in 2018 and according to projections, this number will rise to an estimated 152 million by 2050.(Alzheimer's Disease International 2018) Mild cognitive impairment (MCI) can affect up to 23% of older people, nearly three-fold the proportion of individuals with dementia.(Luck et al. 2010) It has been estimated that 46% of people with MCI will develop dementia within three years.(Tschanz et al. 2006) Considering the social and economic burden of cognitive decline, identification of preventive factors is greatly needed.

Vitamin D could maintain cognitive function because of its neuroprotective, anti-inflammatory and antioxidant properties.(Aspell et al. 2018; Littlejohns et al. 2016) However, prospective studies on the role of 25-hydroxyvitamin D (25(OH)D), the main biomarker of vitamin D status, in cognitive function have shown inconsistent results. Protective and no association were equally reported. (Overman et al. 2017; Llewellyn et al. 2010; Slinin et al. 2012; Kuzma et al. 2016; Toffanello et al. 2014; Wilson et al. 2014; Feart et al. 2017; Bartali et al. 2014; Licher et al. 2017; Knekt et al. 2014; Littlejohns et al. 2014) Pooled estimates from two meta-analyses found weak protective effects on dementia(Jayedi et al. 2018; Sommer et al. 2017) and Alzheimer's disease (AD).(Jayedi et al. 2018) Furthermore, sex differences in this association have not been studied extensively. This difference is relevant as the prevalence of dementia and AD is higher among women,(Prince et al. 2015) and that they usually show lower concentrations of 25(OH)D.(Greene-Finestone et al. 2011)

This study will fill this gap in the literature by contributing to the body of prospectively collected data on blood 25(OH)D concentrations and the risk of cognitive decline, all-cause dementia and AD among older individuals, and by evaluating the potential effect modification of risk associated with sex.

## **Method**

### ***Study population***

The Canadian Study of Health and Aging (CSHA) is a longitudinal study of dementia conducted in a representative sample of people aged 65 years or older. More details about CSHA are provided elsewhere.(Lindsay et al. 2004) In brief, 18 research centers participated at the baseline examination in 1991-1992 (CSHA-1) and two follow-ups in 1996-1997 (CSHA-2) and 2001-2002 (CSHA-3). Subjects were randomly selected from the Enumeration Composite in the province of Ontario and from Medicare lists in the other provinces.(Lindsay et al. 2004) Institutionalized subjects were selected from random samples of institutions. The ethics review committees in each research center and the coordinating center approved each phase.

At baseline, 10,263 men and women were recruited of which 97% were Caucasian and 9,008 were living in the community, and 1,255 in institutions. Community-dwelling subjects were screened for dementia with the 100-point Modified Mini-Mental State (3MS) examination.(Teng and Chui 1987) All subjects with a 3MS score <78 and a random sample of those who scored >77 were invited to an extensive, standardized, clinical examination conducted by a nurse, a physician and a psychometrist (if 3MS score >49). Institutionalized subjects were automatically invited to the clinical examination. A similar diagnostic process was used at each phase. In total, 2,914

subjects in CSHA-1, 2,305 in CSHA-2 and 1,386 in CSHA-3 were clinically examined.(Lindsay et al. 2004)

Nine of the 18 centers in CSHA-1 and all centers in CSHA-2 participated in a sub-study which requested non-fasting blood samples for future research. In CSHA-1, all subjects with dementia and an equal number of subjects without dementia randomly chosen were invited to provide blood. In CSHA-2, all clinically assessed subjects were invited to provide blood. In total, 422 subjects in CSHA-1 and 1,312 in CSHA-2 provided blood. After exclusion of 499 subjects with dementia, 1,235 subjects without dementia were eligible for the present study. Frozen blood samples were still available for 661 of them, and served for plasma 25(OH)D concentration measurement (Figure 1).

### ***Measures***

#### ***Plasma 25-hydroxyvitamin D***

Vitamin D status was evaluated with plasma 25(OH)D, the main biomarker of vitamin D status. (G. Jones 2012) The half-life of 25(OH)D is about 14 days; 25(OH)D is a useful indicator to characterize the usual vitamin D status.(K. S. Jones et al. 2014) Blood samples were stored at the National Microbiology Laboratory, Winnipeg, Canada. Total plasma 25(OH)D was measured with a competitive assay using electrochemiluminescence on an Elecsys 2010 system (Roche Diagnostics, Laval, Canada), which was standardized by the National Institute of Standards and Technology.(Phinney 2008) Coefficients of variation were 11.0%, 4.3% and 8.3% at 12.0, 50.5 and 79.0 nmol/l, respectively.

### *Global cognitive function and dementia assessments*

Global cognitive function was measured with the validated 3MS.(Teng and Chui 1987) For all subjects who attended the clinical examination, preliminary diagnoses were made independently by a physician and a neuropsychologist, who subsequently reached a consensus diagnosis in a case conference. In CSHA-1, Diagnostic and Statistical Manual of Mental Disorders, 3<sup>rd</sup> edition, revised criteria (DSM-III-R) were used for all-cause dementia, and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria were used for AD. In CSHA-2 and CSHA-3, Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition criteria were used for all-cause dementia and AD. The diagnosis of cognitive impairment, no dementia (CIND) was made according to the DSM-III-R and the International Classification of Diseases, 10<sup>th</sup> revision criteria. CIND encompasses different sub-types of cognitive impairment including neurological disorder or those of vascular or psychiatric origin.(Graham et al. 1997)

### *Covariates*

Sociodemographic, lifestyle and medical history variables were obtained in subjects without dementia using a self-administered risk factor questionnaire at baseline or data from clinical examinations. These variables included age (continuous, years), education (continuous, years), sex, body mass index (BMI) (weight (kg) /height squared (m<sup>2</sup>), continuous), smoking status (ever been smoking regularly (almost every day) or not), alcohol intake (ever been drinking regularly (at least once a week) or not), history of stroke or myocardial infarction, and diabetes.

Hypertension was defined as a blood pressure >160 mm Hg systolic or >95 mm Hg diastolic, or a physician's diagnostic, or the use of medication for hypertension. The presence of allele e4 on the

apolipoprotein E gene (ApoE4 (yes/no)) was based on a modified method of Zivelin *et al.*(McLeod et al. 1998)

### ***Statistical analyses***

The distribution of 25(OH)D was log-transformed because it was right skewed. The 3MS scores and plasma 25(OH)D concentrations were used as continuous variables. To determine the effect of 25(OH)D on the change of the 3MS in time, an interaction term was introduced between 25(OH)D and age at each phase in a linear mixed model with repeated measures. For a better understanding of the trend in cognitive decline over time according to 25(OH)D in continuous, results are presented for 3 specific concentrations corresponding to the median points of each tertile group of the distribution (i.e. 23.4, 42.4 and 69.4 nmol/l). A differential effect of age and 25(OH)D by sex was investigated by introducing a triple interaction following the hierarchical principle. Model 1 was fit with a minimal adjusted set including age, sex, education, phase and 25(OH)D concentration by age interaction. Potential confounders including ApoE4, BMI, institutionalization, alcohol intake and smoking status were added in Model 2. Other potential confounders or intermediates including depression, hypertension, diabetes and history of stroke or myocardial infarction were further entered in Model 3.

Hazard ratios (HR) for all-cause dementia and AD according to the log-transformed 25(OH)D concentration in continuous were calculated using a semi-parametric proportional hazards models with delayed entry and age as the time scale. To facilitate interpretation of the results, the log-transformed 25(OH)D unit was set at 0.41, which corresponds to a 50% increase in 25(OH)D. Since the date of onset dementia was not known, time-to-event on the age scale was interval-



censored between the examination before diagnosis and the examination at the diagnosis.

Assuming that dementia could not be developed in a short period of time, subjects who remained cognitively normal, died, or were lost to follow-up, were right censored at 6 months after the last examination. Interaction terms between 25(OH)D and sex were included in the models where HRs were presented separately for men and women. The same sequence of adjustment as in the global cognitive function analysis was fit with the addition of CIND in Models 2 and 3, while the interaction with age could not be included as age was already entered as the time scale. Seasonal trends in 25(OH)D were examined graphically and modeled using generalized additive models. Aside from a slight linear trend in time, there was no evidence of fluctuations in our sample and therefore, seasons were no longer considered in the models. Furthermore, adjustment for physical activity gave similar results. In this old cohort, the institutionalization status could be viewed as a better proxy of sun exposure than physical activity.

Among the 661 subjects with 25(OH)D data, 40% had at least one missing data on one of the covariates. Data were complete for 25(OH)D, age, sex, education and phase which are the covariates included in Model 1, but 32 and 36 events of dementia in models 2 and 3 respectively, were lost in the adjustment because of missing data. Multiple imputation employing chained equations was therefore performed. As recommended, the number of imputed dataset was equal to the percentage of incomplete cases (40%).(White et al. 2011) Binary and categorical variables were imputed using logistic regressions, whereas continuous variables were imputed using predictive mean matching based on linear regressions.

Sensitivity analyses comprised: 1) multiple imputation on the 1,235 eligible subjects; 2) adjustment for the current intake of vitamin D supplements (either vitamin D or multivitamin); 3) restriction to subjects with no CIND at baseline for the cognitive decline analysis; and 4) with 25(OH)D in three categories (<25nmol/l; 25-49nmol/l and  $\geq$ 50nmol/l) for comparison with other studies on dementia.(Jayedi et al. 2018) An *a posteriori* sensitivity analysis stratifying by age was done.

## **Results**

Compared with non-deficient subjects, those with 25(OH)D concentrations <50nmol/l were, on average, older, more likely to be women, had a lower 3MS and a higher BMI (Table 1). They were also more likely to be institutionalized, less likely to ever been smoking or drinking alcohol, and to be taking vitamin D or multivitamin supplements. They also showed a higher prevalence of diabetes, depression and CIND.

### *Cognitive decline*

Overall, 3MS scores showed mean declines ranging from 1.95 to 2.20 points (all p-values <0.01) for each 5-year increase in age, regardless of specific 25(OH)D concentrations and models (Table 2). These declines were not significantly associated with 25(OH)D concentrations. Declines were more pronounced among women than men (p-values for 25(OH)D by sex interactions <0.03 for all models). Results were similar with multiple imputations among eligible subjects, with additional adjustment for vitamin D supplementation, and when restricted to subjects with no CIND at baseline (Online Ressource, Tables S1-S3).

### *Dementia and Alzheimer's disease*

Over a mean follow-up of 5.4 years, 141 subjects developed all-cause dementia, including 100 incident cases of AD. No significant association was found between 25(OH)D and dementia or AD in models 1 and 2. A significantly increased risk with higher concentration of 25(OH)D was observed for AD only in Model 3 (Table 3). An interaction was found between 25(OH)D and sex for AD ( $p=0.0173$ ), but not for all-cause dementia ( $p=0.1261$ ). Among men, no significant association was observed between 25(OH)D concentration and dementia or AD, but estimates showed protective HRs. In contrast, among women, a 50% increase of 25(OH)D concentration was marginally significantly associated with a higher risk of dementia in models 2 and 3 (HRs of 1.16 and 1.17, respectively), and AD in all models (HRs of 1.25, 1.28, 1.31, respectively). Similar results were observed when 25(OH)D was treated in categories (Online Resource. Table S4). HRs were also similar in the sensitivity analyses with multiple imputations among all eligible subjects, and with additional adjustment for vitamin D supplementation (Online Resource Tables S5-S6).

### **Discussion**

Our study suggests that vitamin D status is not associated with global cognitive function or its decline. Moreover, there is no association between plasma 25(OH)D concentrations and the incidence of all-cause dementia or AD, except for women, where higher 25(OH)D concentrations seemed to increase the incidence of dementia and AD.

Prospective studies on vitamin D status and global cognitive function have shown conflicting results. Among the 15 studies retrieved from the literature, 7 found no association between

25(OH)D and cognitive performance.(Kilpatrick et al. 2018; Olsson et al. 2017; Graf et al. 2014; van Schoor et al. 2016; Slinin et al. 2010; Breitling et al. 2012; Perna et al. 2014) In contrast, 7 studies found a positive association between low 25(OH)D and cognitive decline,(Llewellyn et al. 2010; Slinin et al. 2012; Kuzma et al. 2016; Toffanello et al. 2014) or lower cognitive score,(Wilson et al. 2014; Feart et al. 2017; Bartali et al. 2014) compared to higher concentrations. Finally, one study among subjects aged  $\geq 85$  years found a positive association with both low and high 25(OH)D concentrations and cognitive decline when compared to the middle category.(Granic et al. 2015)

Prospective studies on 25(OH)D and the risk of dementia and AD also showed conflicting results. Five(Olsson et al. 2017; Karakis et al. 2016; Graf et al. 2014; Afzal et al. 2014; Schneider et al. 2014) out of 9 retrieved studies found no association between low 25(OH)D and the risk of dementia or AD, while the other 4(Licher et al. 2017; Feart et al. 2017; Knekt et al. 2014; Littlejohns et al. 2014) found a positive association. However, pooled estimates from two recent systematic reviews and meta-analyses, including respectively seven and five of these studies, reported significant associations of deficient 25(OH)D status ( $< 25\text{nmol/l}$ ) with the risk of dementia,(Jayedi et al. 2018; Sommer et al. 2017) and a marginally significant association with the risk of AD,(Jayedi et al. 2018) compared to 25(OH)D concentrations  $\geq 50\text{nmol/l}$ .

Methodological issues could explain some of the discrepancies noted between studies in the literature. Regarding the characteristics of the populations, our population included older subjects at baseline, with a mean age of 81 years compared to other studies where mean ages ranged from 56 to 78 years.(Licher et al. 2017; Feart et al. 2017; Knekt et al. 2014; Littlejohns et al. 2014;

Olsson et al. 2017; Karakis et al. 2016; Afzal et al. 2014; Schneider et al. 2014; Wilson et al. 2014; Bartali et al. 2014; Llewellyn et al. 2010; Slinin et al. 2012; Kuzma et al. 2016; Toffanello et al. 2014; Kilpatrick et al. 2018; van Schoor et al. 2016; Slinin et al. 2010; Breitling et al. 2012; Perna et al. 2014) Two studies were conducted among older people than ours.(Graf et al. 2014; Granic et al. 2015) Like us, no association between low vitamin D status ( $25(\text{OH})\text{D} < 25\text{nmol/l}$ ) and the development of dementia compared to subjects with high status ( $25(\text{OH})\text{D} \geq 75\text{nmol/l}$ ) was found in one of these studies.(Graf et al. 2014) A U-shaped association between three categories of  $25(\text{OH})\text{D}$  concentrations made from season-standardized quartiles of the study population was observed in the other study.(Granic et al. 2015) Both low and high categories of  $25(\text{OH})\text{D}$  concentrations showed higher odds of cognitive decline compared to subjects in the middle category. This study was the only one that reported a counterintuitive association as we found in women. Among previous studies on global cognitive function, the length of follow-ups varied from 2 to 12 years, and from 2 to 21 years among studies on dementia. The vast majority of the studies considered several important potential confounders including age, sex, education, season, lifestyle habits and co-morbidities including depression. Only three studies adjusted for ApoE4(Feart et al. 2017; Graf et al. 2014; Licher et al. 2017) and only one used multiple imputation to address missing data as we did.(Licher et al. 2017)

Two hypotheses could partly explain the association between  $25(\text{OH})\text{D}$  concentrations and AD among women. First, a selection survival bias might have occurred which in our case, could partly explain the spurious risk effect observed with the increase of vitamin D concentrations, most notably in women. Subjects had to survive without dementia until the entry into the study. Subjects with low vitamin D status, who did not die or develop dementia before the beginning of

the study, might show some characteristics that prevent the development of the disease. This type of bias is frequent in studies of the determinants of dementia and, according to a simulation study, tends to show a deleterious effect where no real effect is present.(Mayeda et al. 2016) This may be especially true among the older subjects. In our study, women were older than men, and more likely to be institutionalized. In a sensitivity analysis stratified by age (<80, ≥80 years), the risk for dementia and AD among women were higher in the older age group (HRs: 1.36 (95% CI 1.13-1.65) and 1.31 (95% CI 1.07-1.60) respectively), than in the younger age group (0.89 (95% CI 0.70-1.13) and 1.07 (95% CI 0.71-1.61)).

Second, our association could be confounded by vitamin D supplementation. In a study,(Granic et al. 2015) the positive association of high 25(OH)D with cognitive impairment was non-significant when analysis was restricted to non-users of vitamin D supplements. People who take vitamin D supplements may have presented a vitamin D deficiency long before beginning to take the supplement, and older women are usually prescribed vitamin D supplements for the prevention of osteoporosis.(Greene-Finestone et al. 2011) Vitamin D supplementation seems to be an important determinant of 25(OH)D concentrations among older women, but of less importance among men.(Greene-Finestone et al. 2011) In our study, few subjects reported taking vitamin D supplements, but the information may be biased because subjects may have forgotten to mention over-the-counter, natural products. However, adjustment for vitamin D supplementation gave similar results.

Finally, it is plausible that high 25(OH)D concentrations have an adverse effect with aging. In a large-scale longitudinal study, a reverse J-shaped association between 25(OH)D concentrations

and mortality was found.(Durup et al. 2012) Lower mortality risks were found at 25(OH)D concentrations of 50-60 nmol/l. Compared to 50 nmol/l, there was a 1.5 and 2-fold increased risk of mortality in the high and low concentration groups, respectively. On the other hand, our results on cognitive decline did not support the findings observed in women when AD was the outcome.

### *Strengths and limitations*

This analysis has strengths. The population-based study sample included both community-dwelling and institutionalized subjects, and dementia and AD were diagnosed according to a rigorous clinical process using published criteria.

There are a number of limitations. First, a selection bias may have occurred. Subjects with a 25(OH)D measurement and subjects who participated in the sub-study with blood sampling were younger and had better cognitive performance than those without 25(OH)D measurement or without blood sampling. Thus, subjects included in our analysis could be less at risk of dementia and could have higher 25(OH)D concentrations than those not included. However, sensitivity analysis with multiple imputations among all eligible subjects showed similar results. Second, reverse causation is possible. Poorer cognitive function could influence the quality of diet and thus, 25(OH)D concentrations at baseline, but the exclusion of CIND subjects at baseline yielded similar results. Third, vitamin D status was only assessed once and could not be representative of vitamin D status over the course of the follow-up. Thus, non differential misclassification could have occurred in the measure of vitamin D which would generally lead to an underestimation of the true effect. However, it was demonstrated that vitamin D status was relatively stable over a

five-year period(Hofmann et al. 2010) and a 14-year period.(Jorde et al. 2010). Finally, the possibility of residual confounding remains.

### **Conclusion and Relevance**

Overall, this study does not support the protective effect of vitamin D status on cognitive decline or dementia. A significant positive association with incident dementia and AD was found among women that seems more pronounced in the very old. This result must be taken with caution considering the possibility of a survival bias in this old cohort. Moreover, these results were not replicated in the analysis on cognitive decline. The role of vitamin D in maintaining cognitive function and preventing dementia is still supported by a plausible biological mechanism.(Aspell et al. 2018) Despite the non-conclusive results of this study, further research is needed to clarify this relation, in particular in women.



**Table 1. Baseline characteristics of the study sample by plasma vitamin D status (n=661)**

Characteristics	Non-deficient	Deficient/Insufficient	Whole sample <sup>a</sup>
	(25(OH)D $\geq$ 50 nmol/l) <sup>a</sup>	(25(OH)D <50 nmol/l) <sup>a</sup>	
	(n= 236)	(n= 425)	(n=661)
Age (y)	80.4 $\pm$ 5.9	81.3 $\pm$ 6.5	81.0 $\pm$ 6.3
Sex			
Men	114 (48.3)	153 (36.0)	267 (40.4)
Women	122 (51.7)	272 (64.0)	394 (59.6)
Education (y)	9.9 $\pm$ 4.3	9.7 $\pm$ 3.9	9.7 $\pm$ 4.0
3MS score	83.1 $\pm$ 11.1	81.9 $\pm$ 12.1	82.3 $\pm$ 11.8
CIND (yes)	79 (33.5)	165 (38.8)	244 (36.9)
BMI (kg/m <sup>2</sup> )	25.0 $\pm$ 4.3	25.8 $\pm$ 5.2	25.5 $\pm$ 4.9
Carrier of ApoE4 (yes)	46 (19.5)	87 (20.5)	133 (20.1)
Institutionalized (yes)	26 (11.0)	73 (17.2)	99 (15.0)
Alcohol drinking (yes)	95 (44.6)	121 (32.0)	216 (36.6)
Smoking (yes)	113 (52.3)	168 (44.4)	281 (47.3)

Vitamin supplement intake (yes)	62 (28.2)	77 (19.0)	139 (22.2)
Multivitamin (yes)	57 (25.9)	77 (19.0)	134 (21.4)
Vitamin D (yes)	7 (3.2)	2 (0.5)	9 (1.4)
Diabetes (yes)	22 (9.5)	82 (19.5)	104 (16.0)
History of stroke or myocardial infarction (yes)	77 (32.6)	146 (34.4)	223 (33.7)
Hypertension (yes)	84 (35.6)	152 (35.8)	236 (35.7)
Depression (yes)	13 (6.0)	39 (9.6)	52 (8.3)

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Note. 25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele e4 on the apolipoprotein-E gene; BMI, Body mass index; CIND, Cognitive impairment, no dementia; y, years. Missing values for: 3MS: n=5; alcohol drinking: n=70; BMI: n=40; depression: n=36; diabetes: n=10; smoking: n=67; multivitamin: n=36; vitamin D supplement: n=36.

<sup>a</sup> Mean  $\pm$  standard deviation or n (%).

**Table 2. Declines in 3MS scores for a 5-year increase in age at specific plasma 25(OH)D concentrations<sup>a</sup>**

	<b>Model 1<sup>b</sup></b>	<b>Model 2<sup>b</sup></b>	<b>Model 3<sup>b</sup></b>
	<b>Beta (95% CI)</b>	<b>Beta (95% CI)</b>	<b>Beta (95% CI)</b>
<b>25(OH)D</b>			
<b>Global</b>			
At 23.4 nmol/l	-2.20 (-2.94; -1.45)	-2.17 (-2.91; -1.42)	-2.19 (-2.94; -1.44)
At 42.4 nmol/l	-2.11 (-2.68; -1.53)	-2.05 (-2.63; -1.46)	-2.08 (-2.67; -1.49)
At 69.4 nmol/l	-2.03 (-2.80; -1.26)	-1.95 (-2.73; -1.17)	-1.98 (-2.76; -1.20)
<b>P-value for 25(OH)D</b>	0.7926	0.6879	0.6938
<b>P-value for 25(OH)D by age interaction</b>	0.7412	0.6682	0.6731
<b>Men</b>			
At 23.4 nmol/l	-1.52 (-2.61; -0.43)	-1.47 (-2.56; -0.38)	-1.48 (-2.57; -0.38)
At 42.4 nmol/l	-1.43 (-2.35; -0.51)	-1.35 (-2.27; -0.43)	-1.36 (-2.29; -0.44)
At 69.4 nmol/l	-1.35 (-2.35; -0.35)	-1.25 (-2.26; -0.25)	-1.26 (-2.27; -0.26)
<b>Women</b>			

At 23.4 nmol/l	-2.87 (-3.64; -2.11)	-2.86 (-3.64; -2.09)	-2.91 (-3.69; -2.13)
At 42.4 nmol/l	-2.78 (-3.48; -2.09)	-2.75 (-3.45; -2.04)	-2.79 (-3.51; -2.08)
At 69.4 nmol/l	-2.71 (-3.63; -1.79)	-2.65 (-3.58; -1.72)	-2.70 (-3.63; -1.76)

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Note. 25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele e4 on apolipoprotein-E gene; BMI, Body mass index; CI, confidence interval.

<sup>a</sup> These specific 25(OH)D concentrations correspond to the median points of each tertile group of the distribution of the study sample.

<sup>b</sup> Betas adjusted for age, education, sex and phase, with interaction term between 25(OH)D and age, and between sex and age in Model 1; additionally adjusted for ApoE4, BMI, alcohol drinking, smoking, institutionalization in Model 2; additionally adjusted for depression, hypertension, diabetes and history of stroke or myocardial infarction in Model 3.

**Table 3. Hazard ratios (HR) for all-cause dementia and Alzheimer’s disease associated with 25(OH)D status (n=661)**

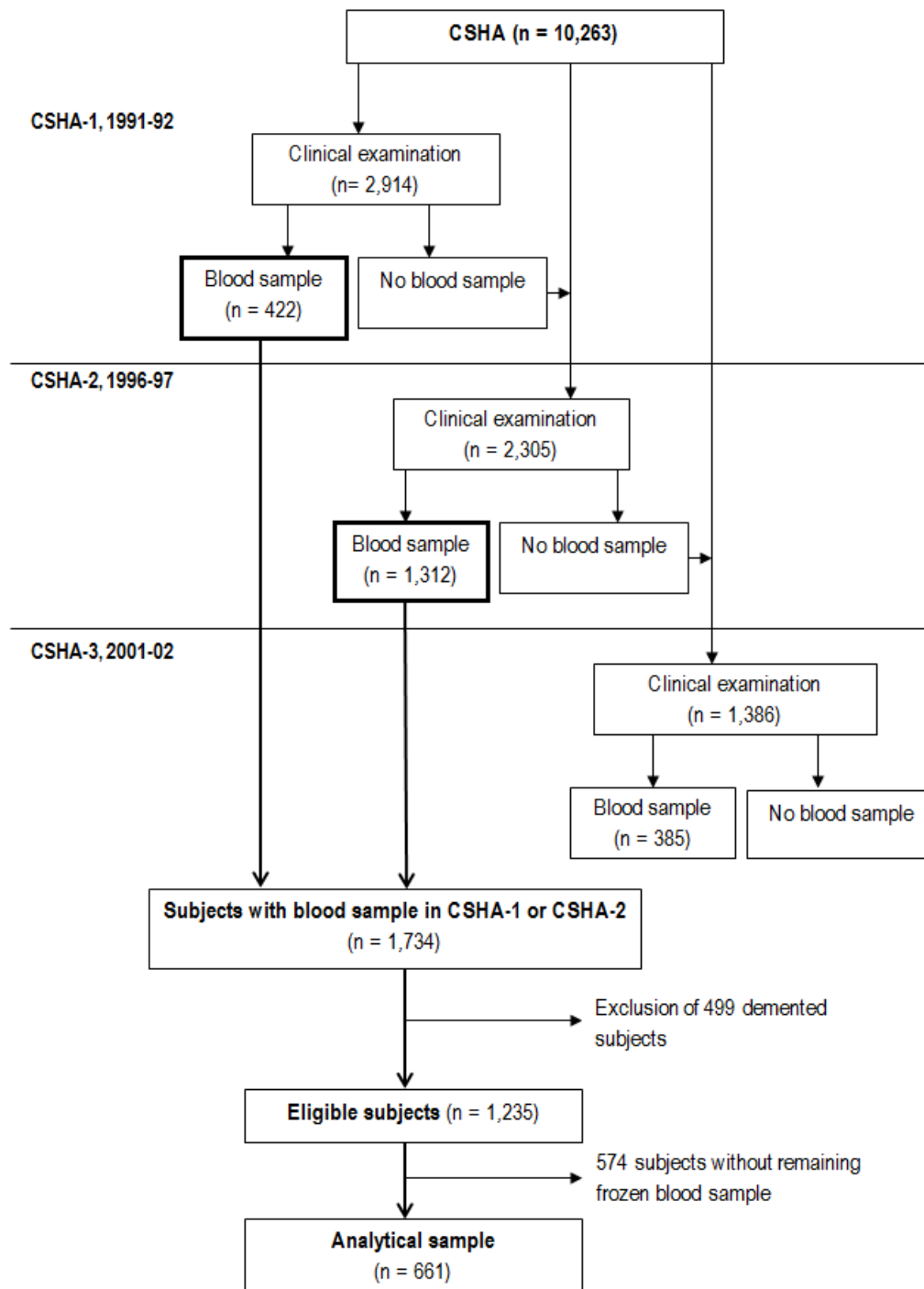
	Dementia		Alzheimer’s disease	
	Events (n, %)	HR (95% CI) <sup>a</sup>	Events (n, %)	HR (95% CI) <sup>a</sup>
<b>25(OH)D (per 50% increase)</b>				
<b>Global</b>	141 (21.3)		100 (15.1)	
Model 1		1.04 (0.92-1.17)		1.12 (0.97-1.30)
Model 2		1.09 (0.97-1.23)		1.15 (0.99-1.33)
Model 3		1.11 (0.98-1.26)		<b>1.18 (1.02-1.37)</b>
<b>Men</b>	47 (17.6)		34 (12.7)	
Model 1		0.92 (0.75-1.14)		0.87 (0.69-1.11)
Model 2		0.95 (0.77-1.18)		0.89 (0.70-1.14)
Model 3		0.98 (0.79-1.21)		0.93 (0.72-1.19)
<b>Women</b>	94 (23.9)		66 (16.8)	
Model 1		1.10 (0.95-1.27)		<b>1.25 (1.05-1.50)</b>
Model 2		<b>1.16 (1.01-1.35)</b>		<b>1.28 (1.08-1.53)</b>
Model 3		<b>1.17 (1.01-1.36)</b>		<b>1.31 (1.10-1.56)</b>

Note. 25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele e4 on apolipoprotein-E gene; BMI, Body mass index; CI, confidence interval; HR, hazard ratio; CIND, cognitive impairment, no dementia.

<sup>a</sup> HRs and 95% CIs adjusted for age (as time scale), sex, education and phase in Model 1; additionally adjusted for ApoE4, BMI, alcohol drinking, smoking, CIND and institutionalization in Model 2; additionally adjusted for depression, hypertension, diabetes and history of stroke and myocardial infarction in Model 3. An interaction term between 25(OH)D and sex was introduced in global models to obtain HRs separately for men and women.

VERSION ACCEPTED

**Fig. 1 Flowchart of the study sample from the Canadian Study of Health and Aging (CSHA)**



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## Supplementary material

### Vitamin D status, cognitive decline and incident dementia: The Canadian Study of Health and Aging

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**Table S1.** Declines in 3MS scores for a 5-year increase in age at specific plasma 25(OH)D concentrations<sup>a</sup>, with multiple imputation among 1,235 eligible subjects

	<b>Model 1<sup>b</sup></b> <b>Beta (95% CI)</b>	<b>Model 2<sup>b</sup></b> <b>Beta (95% CI)</b>	<b>Model 3<sup>b</sup></b> <b>Beta (95% CI)</b>
<b>25(OH)D</b>			
<b>Global</b>			
At 23.42 nmol/l	-2.45 (-3.13; -1.77)	-2.40 (-3.08; -1.71)	-2.42 (-3.11; -1.73)
At 42.35 nmol/l	-2.26 (-2.70; -1.81)	-2.20 (-2.66; -1.74)	-2.23 (-2.70; -1.77)
At 69.38 nmol/l	-2.10 (-2.79; -1.40)	-2.04 (-2.73; -1.34)	-2.07 (-2.77; -1.38)
<b>P-value for 25(OH)D</b>	0.5591	0.5397	0.5379
<b>P-value for 25(OH)D by age interaction</b>	0.5085	0.4978	0.5087

25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele e4 on apolipoprotein-E gene; BMI, Body mass index; CI, confidence interval.

<sup>a</sup> These specific 25(OH)D concentrations correspond to the median points of each tertile group of the distribution of the analytical sample.

<sup>b</sup> Betas adjusted for age, education, sex and phase, with interaction term between log of 25(OH)D and age and between sex and age in Model 1; additionally adjusted for ApoE4, BMI, alcohol intake, smoking, institutionalization in Model 2; additionally adjusted for depression, hypertension, diabetes and history of stroke or myocardial infarction in Model 3.

**Table S2.** Declines in 3MS scores for a 5-year increase in age at specific plasma 25(OH)D concentrations<sup>a</sup>, with additional adjustment for vitamin D supplement intake

	<b>Model 2b<sup>b</sup></b> <b>Beta (95% CI)</b>	<b>Model 3b<sup>b</sup></b> <b>Beta (95% CI)</b>
<b>25(OH)D</b>		
<b>Global</b>		
At 23.42 nmol/l	-2.16 (-2.91; -1.42)	-2.19 (-2.94; -1.44)
At 42.35 nmol/l	-2.05 (-2.64; -1.46)	-2.08 (-2.67; -1.49)
At 69.38 nmol/l	-1.95 (-2.73; -1.18)	-1.99 (-2.77; -1.20)
<b>P-value for 25(OH)D</b>	0.6930	0.7014
<b>P-value for 25(OH)D by age interaction</b>	0.6755	0.6837

25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele e4 on apolipoprotein-E gene; BMI, Body mass index; CI, confidence interval.

<sup>a</sup> These specific 25(OH)D concentrations correspond to the median points of each tertile group of the distribution.

<sup>b</sup> Betas adjusted for age, education, sex and phase, with interaction terms between log of 25(OH)D and age and between sex and age, ApoE4, BMI, alcohol drinking, smoking, institutionalization, and vitamin D supplement intake in Model 2b; additionally adjusted for depression, hypertension, diabetes and history of stroke or myocardial infarction in Model 3b.

**Table S3.** Declines in 3MS scores for a 5-year increase in age at specific plasma 25(OH)D concentrations<sup>a</sup>, restricted to subjects without CIND at baseline (n=417)

	<b>Model 1<sup>b</sup></b> <b>Beta (95% CI)</b>	<b>Model 2<sup>b</sup></b> <b>Beta (95% CI)</b>	<b>Model 3<sup>b</sup></b> <b>Beta (95% CI)</b>
<b>25(OH)D</b>			
<b>Global</b>			
At 23.42 nmol/l	-1.92 (-2.69; -1.15)	-1.87 (-2.65; -1.10)	-1.92 (-2.69; -1.14)
At 42.35 nmol/l	-1.78 (-2.34; -1.23)	-1.73 (-2.30; -1.17)	-1.76 (-2.33; -1.20)
At 69.38 nmol/l	-1.67 (-2.42; -0.93)	-1.62 (-2.38; -0.86)	-1.63 (-2.39; -0.87)
<b>P-value for 25(OH)D</b>	0.5927	0.5559	0.5183
<b>P-value for 25(OH)D by age interaction</b>	0.6483	0.6318	0.5885

25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele e4 on apolipoprotein-E gene; BMI, Body mass index; CI, confidence interval; CIND, cognitive impairment, no dementia.

<sup>a</sup> These 25(OH)D concentrations correspond to the median points of each tertile group of the distribution of the analytical sample.

<sup>b</sup> Betas adjusted for age, education, sex and phase, with interaction terms between log of 25(OH)D and age and between sex and age, BMI, alcohol drinking, smoking and institutionalization in Model 2; additionally adjusted for depression, hypertension, diabetes and history of stroke or myocardial infarction in Model 3.

**Table S4.** Hazard ratios (HR) for all-cause dementia and Alzheimer's disease associated with 25(OH)D in categories (n=661)

	Dementia		Alzheimer's disease	
	Events (n, %)	HR (95% CI) <sup>a</sup>	Events (n, %)	HR (95% CI) <sup>a</sup>
<b>Global</b>				
Model 1				
<25 nmol/l	27 (21.8)	Reference	17 (13.7)	Reference
25-49 nmol/l	59 (19.6)	0.94 (0.59-1.50)	42 (14.0)	1.16 (0.65-2.06)
≥50 nmol/l	55 (23.3)	1.23 (0.76-1.97)	41 (17.4)	1.62 (0.90-2.90)
Model 2				
<25 nmol/l		Reference		Reference
25-49 nmol/l		1.14 (0.71-1.83)		1.35 (0.75-2.43)
≥50 nmol/l		1.54 (0.94-2.52)		<b>1.83 (1.00-3.34)</b>
Model 3				
<25 nmol/l		Reference		Reference
25-49 nmol/l		1.20 (0.74-1.93)		1.43 (0.79-2.59)
≥50 nmol/l		<b>1.67 (1.01-2.75)</b>		<b>2.04 (1.10-3.77)</b>
<b>Men</b>				
Model 1				
<25 nmol/l	7 (20.0)	Reference	6 (17.1)	Reference
25-49 nmol/l	21 (17.8)	0.76 (0.32-1.79)	14 (11.9)	0.59 (0.23-1.55)
≥50 nmol/l	19 (16.7)	0.71 (0.30-1.69)	14 (12.3)	0.66 (0.37-1.06)
Model 2				
<25 nmol/l		Reference		Reference
25-49 nmol/l		0.94 (0.39-2.26)		0.65 (0.24-1.75)
≥50 nmol/l		0.83 (0.34-2.01)		0.67 (0.25-1.81)
Model 3				
<25 nmol/l		Reference		Reference
25-49 nmol/l		1.10 (0.45-2.68)		0.81 (0.29-2.23)
≥50 nmol/l		0.97 (0.39-2.41)		0.84 (0.31-2.33)

**Women**

## Model 1

<25 nmol/l	20 (22.5)	Reference	11 (12.4)	Reference
25-49 nmol/l	38 (20.8)	0.97 (0.56-1.69)	28 (15.3)	1.47 (0.72-2.97)
≥50 nmol/l	36 (29.5)	1.54 (0.88-2.69)	27 (22.1)	<b>2.35 (1.15-4.79)</b>

## Model 2

<25 nmol/l		Reference		Reference
25-49 nmol/l		1.16 (0.67-2.04)		1.72 (0.84-3.53)
≥50 nmol/l		<b>2.03 (1.14-3.60)</b>		<b>2.77 (1.34-5.74)</b>

## Model 3

<25 nmol/l		Reference		Reference
25-49 nmol/l		1.19 (0.68-2.08)		1.74 (0.84-3.60)
≥50 nmol/l		<b>2.15 (1.20-3.86)</b>		<b>3.01 (1.43-6.35)</b>

Note. 25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele e4 on apolipoprotein-E gene; BMI, Body mass index; CI, confidence interval; HR, hazard ratio; CIND, cognitive impairment, no dementia.

<sup>a</sup> HRs and 95% CIs adjusted for age (as time scale), sex, education and phase in Model 1; additionally adjusted for ApoE4, BMI, alcohol drinking, smoking, CIND and institutionalization in Model 2; additionally adjusted for depression, hypertension, diabetes and history of stroke and myocardial infarction in Model 3. An interaction term between 25(OH)D and sex was introduced in global models to obtain HRs separately for men and women.



**Table S5.** Hazard ratios (HR) for all-cause dementia and Alzheimer’s disease associated with plasma 25(OH)D concentration, with multiple imputation for 1,235 eligible subjects

	Dementia		Alzheimer’s disease	
	Events (n, %)	HR (95% CI) <sup>a</sup>	Events (n, %)	HR (95% CI) <sup>a</sup>
<b>25(OH)D (per 50% increase)</b>	160 (13.0)		112 (9.1)	
<b>Global</b>		1.04 (0.92-1.18)		1.12 (0.97-1.30)
Model 1		1.10 (0.97-1.25)		1.16 (0.99-1.34)
Model 2		1.11 (0.98-1.26)		<b>1.17 (1.01-1.37)</b>
Model 3				
<b>Men</b>	54 (10.2)		35 (6.6)	
Model 1		0.94 (0.76-1.16)		0.91 (0.71-1.15)
Model 2		0.97 (0.79-1.20)		0.92 (0.71-1.18)
Model 3		0.99 (0.80-1.23)		0.95 (0.73-1.23)
<b>Women</b>	106 (15.0)		77 (10.9)	
Model 1		1.10 (0.94-1.28)		<b>1.27 (1.07-1.51)</b>
Model 2		<b>1.16 (1.00-1.35)</b>		<b>1.27 (1.06-1.52)</b>
Model 3		<b>1.17 (1.00-1.36)</b>		<b>1.28 (1.06-1.54)</b>

25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele 4 on apolipoprotein-E gene; BMI, Body mass index; CI, confidence interval; HR, hazard ratio; CIND, cognitive impairment, no dementia.

<sup>a</sup> HRs and 95% CIs adjusted for age (as time scale), sex, education and phase in Model 1; additionally adjusted for ApoE4, BMI, alcohol drinking, smoking, CIND and institutionalization in Model 2; additionally adjusted for depression, hypertension, diabetes and history of stroke and myocardial infarction in Model 3. An interaction term between 25(OH)D and sex was introduced in global models to obtain HRs separately for men and women.

**Table S6.** Hazard ratios (HR) for all-cause dementia and Alzheimer’s disease associated with 25(OH)D concentration (n=661), with additional adjustment for vitamin D supplement intake

	<b>Dementia</b>		<b>Alzheimer’s disease</b>	
	<b>Events (n, %)</b>	<b>HR (95% CI)<sup>a</sup></b>	<b>Events (n, %)</b>	<b>HR (95% CI)<sup>a</sup></b>
<b>25(OH)D (per 50% increase)</b>				
<b>Global</b>	141 (21.3)		100 (15.1)	
Model 2b		1.09 (0.96-1.24)		1.16 (0.99-1.35)
Model 3b		1.10 (0.97-1.26)		<b>1.19 (1.01-1.39)</b>
<b>Men</b>	47 (17.6)		34 (12.7)	
Model 2b		0.95 (0.76-1.20)		0.90 (0.69-1.19)
Model 3b		0.98 (0.78-1.23)		0.94 (0.71-1.24)
<b>Women</b>	94 (23.9)		66 (16.8)	
Model 2b		1.15 (0.99-1.33)		<b>1.26 (1.05-1.51)</b>
Model 3b		1.15 (0.99-1.34)		<b>1.29 (1.08-1.56)</b>

25(OH)D, 25-hydroxyvitamin-D; 3MS, Modified Mini-Mental State examination; ApoE4, allele 4 on apolipoprotein-E gene; BMI, Body mass index; CI, confidence interval; HR, hazard ratio; CIND, cognitive impairment, no dementia.

<sup>a</sup> HRs and 95% CIs adjusted for age (as time scale), sex, education, phase, ApoE4, BMI, alcohol drinking, smoking, CIND, institutionalization and vitamin D supplement intake in Model 2b; additionally adjusted for depression, hypertension, diabetes and history of stroke and myocardial infarction in Model 3b. An interaction term between 25(OH)D and sex was introduced in global models to obtain HRs separately for men and women.