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Research Report

Seasonal Variations in Vitamin D Levels and the Incident Dementia Among Older Adults Aged ≥60 Years in the UK Biobank[1]

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Abstract.
Background: Limited knowledge exists regarding the association between dementia incidence and vitamin D insufficiency/deficiency across seasons.
Objective: This study aimed to evaluate the impact of seasonal serum vitamin D (25(OH)D) levels on dementia and its subtypes, considering potential modifiers.
Methods: We analyzed 193,003 individuals aged 60–73 at baseline (2006–2010) from the UK Biobank cohort, with follow-up until 2018. 25(OH)D were measured at baseline, and incident dementia cases were identified through hospital records, death certificates, and self-reports.
Results: Out of 1,874 documented all-cause dementia cases, the median follow-up duration was 8.9 years. Linear and nonlinear associations between 25(OH)D and dementia incidence across seasons were observed. In multivariable-adjusted analysis, 25(OH)D deficiency was associated with a 1.5-fold (95% CIs: 1.2–2.0), 2.2-fold (1.5–3.0), 2.0-fold (1.5–2.7), and 1.7-fold (1.3–2.3) increased incidence of all-cause dementia in spring, summer, autumn, and winter, respectively. Adjusting for seasonal variations, 25(OH)D insufficiency and deficiency were associated with a 1.3-fold (1.1–1.4) and 1.8-fold (1.6–2.2) increased dementia incidence, respectively. This association remained significant across subgroups, including baseline age, gender, and education levels. Furthermore, 25(OH)D deficiency was associated with a 1.4-fold (1.1–1.8) and 1.5-fold (1.1–2.0) higher incidence of Alzheimer's disease and vascular dementia, respectively. These associations remained significant across all subgroups.
Conclusions: 25(OH)D deficiency is associated with an increased incidence of dementia and its subtypes throughout the year.

Keywords: Alzheimer's disease, dementia, moderation analysis, season, vitamin D

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INTRODUCTION

Dementia is a neurocognitive disorder that is associated with a significant functional deficit in language, behavior, and cognition [1, 2]. Globally, this disorder presents a formidable challenge, affecting an estimated 55 million individuals and adding nearly 10 million new cases annually [3]. In 2019, dementia was attributed to 12.5% of all deaths in England and Wales [4]. Financially, the worldwide cost of dementia surged from $818 billion in 2015 to approximately $1.3 trillion by 2019 [3]. These figures underscore the substantial burden that dementia imposes on global healthcare systems. Importantly, cognitive decline may commence years prior to the manifestation of clinical symptoms [5], offering a potential window for preventive interventions. Given the absence of effective treatments to halt the progression of dementia, identifying key modifiable risk factors remains a critical imperative.

Recently, as there is no established treatment to halt the progression of dementia, understanding modifiable factors like dietary intake becomes crucial for both prevention and insight into its pathogenesis. There has been an increasing number of studies investigating the potential role of vitamin D in the development of dementia however, the findings have been inconsistent so far [6–9]. A 30-year prospective cohort study of 10,186 Danish people found a relationship between low serum vitamin D levels and an elevated incidence of Alzheimer's disease (AD), yet not the development of vascular dementia [10]. Data from the Three-City Bordeaux cohort of 916 French adults aged ≥65 demonstrated that vitamin D at baseline was associated with an increased risk of incident dementia over 12 years [11]. Conversely, the Rotterdam Study of 6,087 adults aged ≥55 years demonstrated no significant association between the incidence of dementia and serum vitamin D deficiency [12]. Amid strong evidence for seasonal fluctuations in vitamin D exposure, multivariable models were adjusted for the season of serum collection in only a handful of studies [10–12]. Given the association of vitamin D levels with recognized dementia risk factors, including stroke, hypertension, cardiovascular disease, obesity, diabetes, and depression, which are key contributors to the development of dementia [7, 13–18], it is of great importance to investigate the interaction of vitamin D and dementia risk factors with the incidence of dementia.

Using the UK Biobank, we sought to identify cut-off points for vitamin D insufficiency and deficiency across seasons that were associated with incident dementia. We also aimed to examine whether the association between vitamin D insufficiency and deficiency and incident dementia differed across subgroups of important dementia risk factors and whether the association was mediated by newly developed chronic conditions.

METHODS

Study population

This study utilized the UKB cohort study data, which included >500,000 United Kingdom (UK) population ranging in age from 40 to 73 years old at baseline. Participants were recruited from the UK during the period spanning from 2006 to 2010 [19]. The design and population details have been explained elsewhere [19]. A total of 502,505 subjects, whose ages ranged from 40 to 73 years, were recruited at the baseline. Individuals with aged ≥60 years were screened for analysis due to the higher prevalence of dementia within this specific age group. This UKB Study was ethically approved. During the recruitment phase, all individuals provided informed consent via electronic signatures. The current investigation was carried out under the UKB resource application number 62443.

The UK Biobank Study's ethical approval had been granted by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee. All participants provided informed consent through electronic signature at recruitment.

Vitamin D

Serum 25-hydroxyvitamin D (25(OH)D), a proxy for vitamin D status, was used as the indicator of vitamin D levels and measured using a chemiluminescence immunoassay (DiaSorin Liaison XL, DiaSorin Ltd., UK) between 2006 and 2010. The assay for 25OHD had an analytical sensitivity (lower detection limit) of 10 nmol/L representing the lowest measurable analyte level that can be distinguished from zero. Quality control was conducted by the UK Biobank central team. The average coefficients of variation of 25OHD derived from internal quality control samples ranged from 5.0% to 6.1%. External quality assurance results showed that 100% of participated distributions ($n = 108$) were acceptable (assurance scheme registration: RIQAS Immunoassay Specialty 1).

Ascertainment of incident dementia

All-cause dementia cases in the UK Biobank Study were ascertained using hospital inpatient records, death registers, and self-reported data. Data on admissions and diagnoses were used to identify dementia cases with a primary/secondary diagnosis using the international classification diseases (ICD) coding system (detailed in Supplementary Table 1). Additional cases were defined as underlying/contributory cause of death being dementia through linkage to death register data. Dementia was also defined by reporting a diagnosis of dementia during follow-up. The earliest recorded date regardless of sources was used as the onset date of dementia. Person-years were calculated from the date of baseline assessment to the date of onset dementia, date of death, or the end of follow-up (1 March 2018 for England and Wales and 1 March 2017 for Scotland), whichever came first.

Covariates

Age (years), sex (females, males), ethnicity (Whites, non-whites), education (0–5 years, 6–12 years,≥13 years), and income (<18,000£, 18,000–30,999£, 31,000–51,999£, 52,000–100,000£,> 100,000£) were self-reported. Sleep duration was assessed with the survey item "About how many hours sleep do you get in every 24 h?". Questions about walking, moderate physical activity, and vigorous physical activity, which were similar to those used in the short form of the International Physical Activity Questionnaire [20], were used to estimate excess metabolic equivalent (MET)-hours/week of physical activity during work and leisure time. A healthy diet score was computed based on seven commonly eaten food groups following recommendations on dietary priorities for cardiometabolic health [21] with a higher score representing a healthier diet. A higher healthy diet score has been shown to be associated with a lower risk of dementia [22].

Systemic conditions at baseline were based on self-reported data or interviews. Participants were asked whether they had ever been told by a doctor that they had certain common medical conditions, including heart attack, angina, stroke, hypertension, and diabetes. Depression was recorded during the interview with a research nurse. Newly developed systemic conditions during follow-up (before the onset of dementia) were identified using hospital inpatient records and self-reported data (Supplementary Table 1). Body mass index (BMI) was computed based on the weight in kilograms divided by height in meters, and obesity was defined as BMI $\geq 30\,kg/m^2$ [23].

Statistical analysis

Data of baseline characteristics were expressed as frequency (percentage) and means ± standard deviations (SDs). To examine the seasonal effect on the 25(OH)D, the regression splines method was used to smooth the relationship between 25(OH)D and the day of the year when the serum was collected (0–365). Hazard ratio curves for 25(OH)D with incident dementia were fitted using the Cox regression model with penalized spline smoothing adjusted for age, gender, and the day of the year when serum was collected [24]. This analysis was conducted for summer, autumn, winter, and spring separately. Both linear and non-linear relationships were tested and cubic regression splines with four knots were examined. The cut-off points for the two knots with lower 25(OH)D levels adjusted for age, gender, and the day of the year when the serum was collected were used to define insufficiency and deficiency for each season.

Cox proportional hazard regression models were used to examine the association of 25(OH)D insufficiency and deficiency with incident dementia. The following models were tested: 1) age and gender; 2) model 1 plus the day of the year when serum was collected, ethnicity, education, income, diet score, vitamin D supplement, smoking, alcohol consumption, sleep, physical activity, BMI, cholesterol, glycosylated hemoglobin, cystatin C, depression, hypertension, diabetes, heart disease, and chronic kidney disease at baseline. We then analyzed the association of 25(OH)D insufficiency and deficiency with incident dementia stratified by important factors such as age, gender, education, physical activity, diet score, smoking, depression, hypertension, diabetes, heart disease, and chronic kidney disease.

The potential mediation effects of newly developed systemic conditions during follow-up (before onset dementia) on the association between lower levels of 25(OH)D (insufficiency and deficiency combined) and incident dementia were estimated using Cox proportional hazards regression models [25].

We also examined the association between quintiles of 25(OH)D by month when serum was collected and incident dementia. The association of 25(OH)D insufficiency (25–49.9 nmol/L) and deficiency (≥50 nmol/L) defined by non-season specific cut-off points with incident dementia was then analyzed.

In further analysis, we examined association of 25(OH)D insufficiency (25–49.9 nmol/L) and deficiency (≥50 nmol/L) with incident dementia subtypes, including AD and vascular dementia.

Data analyses were conducted using SAS 9.4 for Windows (SAS Institute Inc.) and all p values were two-sided with statistical significance set at <0.05.

RESULTS

Population selection and baseline characteristics

Baseline data were collected among 502,505 participants. After excluding individuals with missing data on 25(OH)D ($n = 54{,}155$), with age younger than 60 years ($n = 255{,}213$), or with prevalent demen-

Table 1
Baseline characteristics of participants according to 25(OH)D status

	Women ($n = 98{,}984$)	Men ($n = 94{,}019$)	p
Age (y)	64.0 ± 2.9	64.3 ± 2.9	<0.0001
Ethnicity			0.0974
Whites	95,757 (96.7)	90,823 (96.6)	
Non-whites	3227 (3.3)	3196 (3.4)	
Education			<0.0001
0–5 y	23,060 (23.3)	27,084 (28.8)	
6–12 y	47,036 (47.5)	41,293 (43.9)	
≥13 y	27,471 (27.8)	24,263 (25.8)	
Missing	1,417 (1.4)	1,379 (1.5)	
Household income (£)			<0.0001
<18,000	29,050 (29.3)	24,182 (25.7)	
18,000–30,999	25,130 (25.4)	25,934 (27.6)	
31,000–51,999	13,885 (14.0)	18,851 (20.1)	
52,000–100,000	5,844 (5.9)	10,100 (10.7)	
>100,000	1,333 (1.3)	2,467 (2.6)	
Unknown	8,367 (8.5)	2,373 (2.5)	
Not answered	1,537 (15.5)	10,112 (10.8)	
Physical activity (MET-min/week)	2,700 ± 2,200	2,800 ± 2,600	<0.0001
Diet score	4.3 ± 1.3	3.6 ± 1.4	<0.0001
Vitamin D supplementation	3,080 (3.1)	1,931 (2.1)	<0.0001
25(OH)D (nmol/L)			
Spring	45.6 ± 20.2	45.3 ± 19.5	0.0712
Summer	56.8 ± 19.1	60.4 ± 20.0	<0.0001
Autumn	53.9 ± 19.8	56.1 ± 20.4	<0.0001
Winter	44.2 ± 19.8	42.9 ± 19.0	<0.0001
Combined	50.4 ± 20.4	51.4 ± 21.0	<0.0001
Sleep duration (h)	7.2 ± 1.2	7.3 ± 1.1	<0.0001
Alcohol consumption			<0.0001
Never	6,746 (6.8)	2,407 (2.6)	
Previous	4,018 (4.1)	3,333 (3.5)	
Current	88,011 (88.9)	88,085 (93.7)	
Missing	209 (0.2)	194 (0.2)	
Smoking			<0.0001
Never	56,414 (57.0)	39,070 (41.6)	
Former	35,442 (35.8)	45,169 (48.0)	
Current	6,562 (6.6)	9,192 (9.8)	
Missing	566 (0.6)	588 (0.6)	
BMI (kg/m^2)	27.4 ± 4.9	27.86 ± 4.0	<0.0001
Cholesterol (mmol/L)	5.9 ± 1.0	5.26 ± 1.1	<0.0001
Glycosylated hemoglobin (mmol/mol)	37.1 ± 5.9	37.5 ± 7.5	<0.0001
Cystatin C (mg/L)	0.9 ± 0.2	1.0 ± 0.2	<0.0001
Diabetes	4,236 (4.3)	7,713 (8.2)	<0.0001
Stroke	1,775 (1.8)	2,845 (3.0)	<0.0001
Heart disease	4,318 (4.4)	10,765 (11.4)	<0.0001
Hypertension	33,629 (34.0)	37,192 (39.6)	<0.0001
Depression	5,518 (5.6)	3,339 (3.6)	<0.0001
Kidney failure	52 (0.1)	63 (0.1)	0.19
Kidney stone	505 (0.5)	1312 (1.4)	0.0449

Data are mean (standard deviation), or N (%). BMI, body mass index; MET, metabolic equivalent. *T-test was used to test the difference of continuous variables across subgroups of 25(OH)D status and Chi-square for categorical variables.

tia ($n = 134$), 193,003 adults (51.3% females) aged 60–73 years (mean ± SD: 64.2 ± 2.9) were included in the final analysis. Women were more likely to have low income and education, lower levels of physical activity and higher diet quality than men. Men had higher BMI, cystatin C, and glycosylated hemoglobin than women. Men had a higher prevalence of diabetes, stroke, heart disease, and depression than women (all p-values<0.05, Table 1).

Incidence of dementia

Over 1,721,817 person-years of follow-up (median [interquartile range] length of follow-up: 8.9 [8.3–9.5] years), 1874 cases of incident all-cause dementia were documented.

25(OH)D by seasons

The proportion of blood sampling for spring, summer, autumn, and winter was 28.9%, 26.9%, 24.1%, and 20.1%, respectively. There was significant variation across seasons with the mean 25(OH)D for spring, summer, autumn, and winter as 45.4 nmol/L, 58.6 nmol/L, 54.9 nmol/L, and 43.5 nmol/L, respectively. Similar trends were found in women and men but higher 25(OH)D in summer and autumn and lower 25(OH)D in winter and early spring was observed in men than women (Fig. 1).

Hazard ratio curves for 25(OH)D with incident dementia across seasons

The risk of incident dementia increased with decreasing 25(OH)D adjusted for age, gender, and the day of the year when serum was collected (Fig. 2), and similar trends were observed for all seasons (Supplementary Figure 1). The cut-off points for 25(OH)D insufficiency and deficiency were 35.2 nmol/L and 17.8 nmol/L, respectively, for spring, and 50.4 nmol/L and 28.0 nmol/L for summer, 46.2 nmol/L and 24.0 nmol/L for autumn, and 33.4 nmol/L and 16.9 nmol/L for winter. Both linear and non-linear relationships between 25(OH)D and incident dementia were observed for spring, summer, and autumn (all p-values<0.05). Linear ($p = 0.0002$) but not non-linear relationship ($p = 0.13$) was found for winter. The prevalence of 25(OH)D insufficiency and deficiency was 29.9% and 5.0%, respectively.

As shown in Supplementary Table 2, individuals with 25(OH)D deficiency were more likely to be females, have low income and education, and be non-whites. 25(OH)D deficiency was associated with higher BMI, cystatin C, and glycosylated hemoglobin, and lower physical activity and diet score. 25(OH)D deficiency was also associated with a higher prevalence of diabetes, obesity, stroke, heart disease, and depression at baseline.

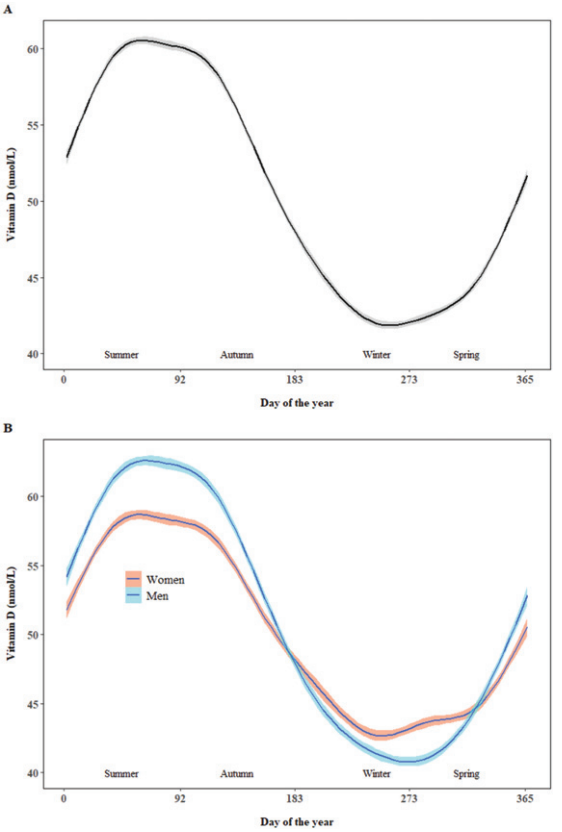

Fig. 1. Nonparametric smoothing plot with 95% confidence interval of fitted 25(OH)D against day of year. The day of year began from the first date of summer (1 June in United Kingdom).

25(OH)D insufficiency and deficiency and incident dementia

There was a lower probability of survival free of dementia during follow-up in individuals with vitamin insufficiency or deficiency (Fig. 3). 25(OH)D insufficiency (HR (95% CI): 1.5 (1.3–1.8)) and deficiency (1.6 (1.1–2.3)) tested in spring were both associated with an increased risk of incident dementia (Table 2). The multivariable-adjusted HR (95% CI) for incident dementia associated with 25(OH)D insufficiency and deficiency was 1.3 (1.1–1.5) and 1.9 (1.4–2.6) for summer, respectively. The corresponding numbers for autumn were 1.1 (0.9–1.4)

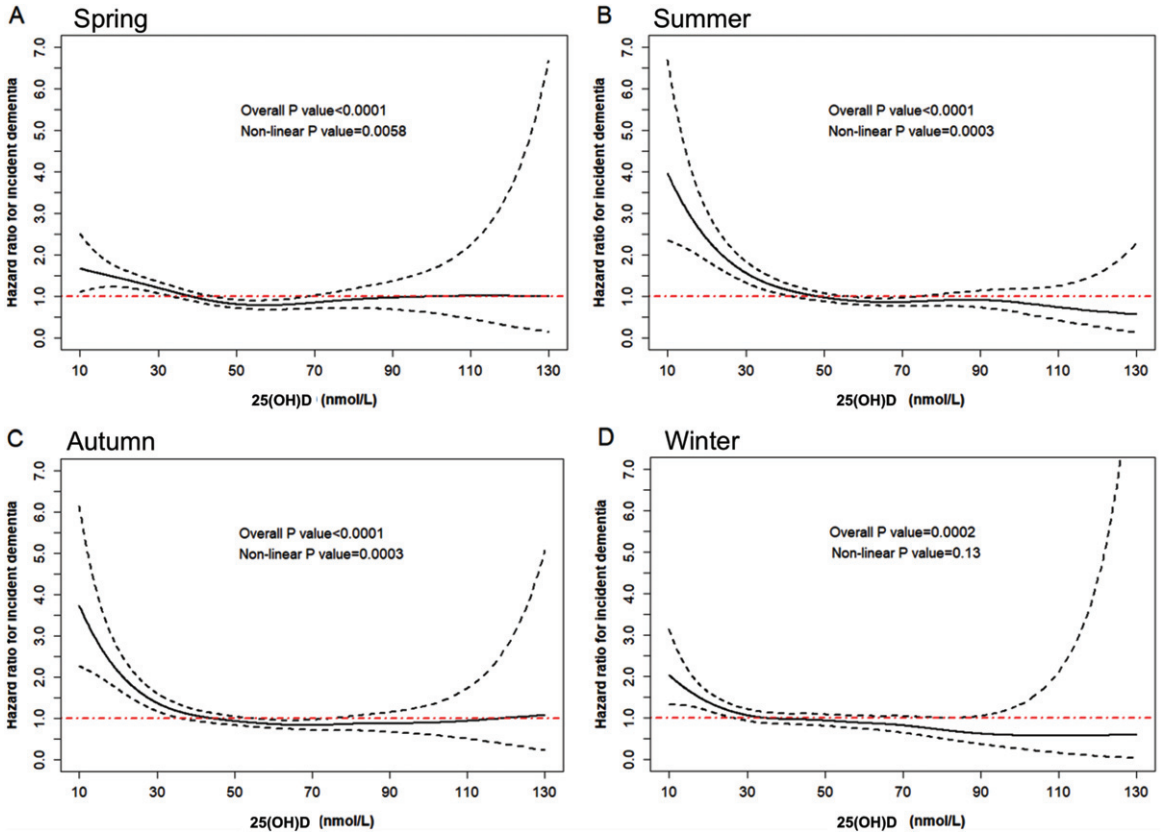

Fig. 2. Hazard ratio curves for 25(OH)D with incident dementia. The curves were fitted using the Cox regression model with penalized spline smoothing adjusted for age, gender, and the day of the year when serum was collected. The solid black line represents the estimated hazard ratio for incident dementia, the dashed black line represents the 95% CI (Confidence Interval), and the red line represents when the hazard ratio is 1. Panels A, B, C, and D represent the curve for spring, summer, autumn, and winter, respectively. Both linear and non-linear relationships were tested and cubic regression splines with four knots were examined.

and 2.1 (1.5–2.9), respectively. 25(OH)D insufficiency tested in winter was associated with an increased risk of incident dementia before (HR (95% CI): 1.3 (1.0–1.6)) but not after adjustment for all covariates (1.2 (0.9–1.5)). 25(OH)D deficiency tested in winter was independently associated with an increased risk of incident dementia (1.7 (1.1–2.5)). The multivariable-adjusted HR (95% CI) for incident dementia associated with 25(OH)D insufficiency and deficiency with seasons combined was 1.3 (1.1–1.4 and 1.84 (1.6–2.2), respectively. Similar results were observed when 25(OH)D insufficiency and deficiency were defined using non-season-specific cut-off points (Supplementary Table 3).

Vitamin D deficiency tested in spring (HR (95% CI): 1.4 (1.1–1.8)), summer (2.0 (1.4–2.9)) or autumn (1.8 (1.3–2.4)) but not winter (1.1 (0.8–1.4)) was associated with an increased risk of AD. The multivariable-adjusted HR (95% CI) for incident AD associated with vitamin D deficiency with sea-

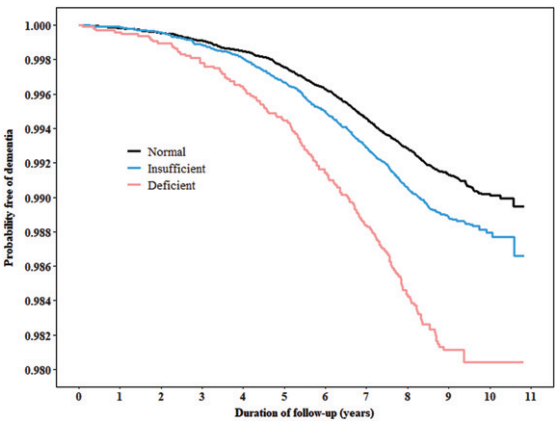

Fig. 3. Kaplan-Meier curves for rates of all-cause dementia by 25(OH)D status. The cut-off points for 25(OH)D insufficiency and deficiency were 35.2 nmol/L and 17.8 nmol/L, respectively, for spring, 50.4 nmol/L and 28.0 nmol/L for summer, 46.2 nmol/L and 24.0 nmol/L for autumn, and 33.4 nmol/L and 16.9 nmol/L for winter. The cut-off points were estimated based on the knots generated in Fig. 2.

Table 2
The risk for incident dementia associated with 25(OH)D by seasons

	25(OH)D			
	Normal	Insufficient	Deficient	*p*-trend
Spring				
Range (nmol/L)	10.0–17.8	17.9–35.2	≥35.3	
Events	281	186	33	
Person-years	319,338	146,930	24,354	
Incidence	0.9	1.3	1.4	
HR (95% CI), Model 1	1.0	1.5 (1.2–1.8)	1.6 (1.1–2.3)	<0.0001
HR (95% CI), Model 2	1.0	1.5 (1.3–1.8)	1.6 (1.1–2.3)	<0.0001
Summer				
Range (nmol/L)	10.0–28.0	28.1–50.4	≥50.5	
Events	314	179	55	
Person-years	302,662	137,969	22,775	
Incidence	1.0	1.3	2.41	
HR (95% CI), Model 1	1.0	1.3 (1.1–1.6)	2.5 (1.9–3.3)	<0.0001
HR (95% CI), Model 2	1.0	1.3 (1.1–1.5)	1.9 (1.4–2.6)	<0.0001
Autumn				
Range (nmol/L)	10.0–24.0	24.1–46.2	≥46.3	
Events	263	140	52	
Person-years	272,827	125,247	20,621	
Incidence	1.0	1.1	2.5	
HR (95% CI), Model 1	1.0	1.2 (1.0–1.5)	2.7 (2.0–3.7)	<0.0001
HR (95% CI), Model 2	1.0	1.1 (0.9–1.4)	2.1 (1.5–2.9)	<0.0001
Winter				
Range (nmol/L)	10.0–16.9	17.0–33.4	≥33.5	
Events	217	122	32	
Person-years	227,625	10,4421	17,049	
Incidence	1.0	1.2	1.9	
HR (95% CI), Model 1	1.0	1.3 (1.0–1.6)	2.1 (1.4–3.0)	0.0002
HR (95% CI), Model 2	1.0	1.2 (0.9–1.5)	1.7 (1.1–2.5)	0.0246
Combined				
Events	1,075	627	172	
Person-years	1,122,451	514,566	84,800	
Incidence	1.0	1.2	2.0	
HR (95% CI), Model 1	1.0	1.3 (1.2–1.5)	2.2 (1.9–2.6)	<0.0001
HR (95% CI), Model 2	1.0	1.3 (1.1–1.4)	1.8 (1.6–2.2)	<0.0001

Incidence of dementia represents number of cases per 1000 person-years. Hazard ratio (95% CI) for incident dementia associated with 25(OH)D status was estimated using Cox proportional regression models. Model 1 was adjusted for age and gender; Model 2 was adjusted for model 1 plus the day of the year when serum was collected, ethnicity, education, income, diet score, 25(OH)D supplement, smoking, alcohol consumption, sleep, physical activity, BMI, cholesterol, glycosylated hemoglobin, cystatin C, depression, hypertension, diabetes, heart disease, and chronic kidney disease at baseline.

sons combined was 1.4 (1.2–1.6) (Supplementary Table 4). Vitamin D deficiency tested in summer, autumn, or winter but not spring was associated with an increased risk of vascular dementia. In the multivariable analysis, vitamin D deficiency with seasons combined was associated with an increased risk of vascular dementia (HR (95% CI): 1.3 (1.1–1.6), Supplementary Table 5).

Moderation analysis

The association between low levels of 25(OH)D (insufficiency/deficiency) and incident dementia was stronger in individuals with lower education (HR (95% CI) for 0–5 years: 1.6 (1.4–1.9), 6–12 years: 1.2 (1.0–1.4),≥13 years: 1.3 (1.0–1.6); *p*-value for interaction =0.0442). No significant interaction for other factors was observed (Fig. 4).

Mediation analysis

Percentage of the total effect of the association between low levels of 25(OH)D (insufficiency/deficiency) and incident dementia explained by stroke, depression, diabetes, and heart disease identified during follow-up was 5.9%, 4.7%, 3.8%, and 2.3%, respectively. These conditions together explained 12.9% of the association (Supplementary Figure 2).

Subgroup	Cases/person-years		Incidence of dementia		Multivariable-adjusted hazard ratio (95% CI)	P-value for interaction
	Normal 25(OH)D	Low 25(OH)D	Normal 25(OH)D	Low 25(OH)D		
Age						0.49
<60 years	321/619196	248/341681	0.52	0.73	1.37 (1.15-1.62)	
≥60 years	754/503255	551/257685	1.50	2.14	1.35 (1.21-1.52)	
Gender						0.62
Females	447/563313	361/320453	0.79	1.13	1.32 (1.14-1.52)	
Males	628/559138	438/278913	1.12	1.57	1.38 (1.22-1.57)	
Ethinicity						0.0805
Whites	1042/1102876	743/563818	0.94	1.32	1.38 (1.25-1.52)	
Non-whites	33/19575	56/35548	1.69	1.58	1.01 (0.64-1.58)	
Education						0.0396
0-5 years	197/279779	154/165415	0.70	0.93	1.29 (1.04-1.61)	
6-12 years	474/524145	298/262879	0.90	1.13	1.18 (1.02-1.38)	
≥13 years	370/302883	314/161893	1.22	1.94	1.60 (1.37-1.87)	
Physical activity						0.67
0-600 MET-min/week	139/129189	140/102904	1.08	1.36	1.14 (0.90-1.45)	
601-2999 MET-min/week	656/672576	523/371143	0.98	1.41	1.42 (1.26-1.59)	
≥3000 MET-min/week	280/320686	136/125319	0.87	1.09	1.28 (1.04-1.58)	
Diet quality						0.93
Low	417/368767	362/230100	1.13	1.57	1.39 (1.20-1.60)	
High	658/753684	437/369266	0.87	1.18	1.34 (1.18-1.52)	
Smoking						0.84
Never	483/563323	343/287913	0.86	1.19	1.34 (1.17-1.55)	
Former	505/479384	336/239967	1.05	1.40	1.33 (1.15-1.53)	
Current	75/73554	112/67495	1.02	1.66	1.54 (1.14-2.08)	
Obesity						0.09
No	819/868496	499/390664	0.94	1.28	1.32 (1.18-1.48)	
Yes	206/234008	254/192755	0.88	1.32	1.48 (1.22-1.79)	
Diabetes						0.39
No	958/1066768	644/549016	0.90	1.17	1.33 (1.20-1.48)	
Yes	117/55683	155/50350	2.10	3.08	1.40 (1.09-1.79)	
Depression						0.63
No	995/1075485	732/567330	0.93	1.29	1.38 (1.25-1.52)	
Yes	80/46966	67/32036	1.7	2.09	1.17 (0.83-1.64)	
Hypertension						0.40
No	617/727317	434/362425	0.85	1.20	1.41 (1.24-1.60)	
Yes	458/395134	365/236941	1.16	1.54	1.29 (1.12-1.49)	
Heart disease						0.49
No	915/1041410	657/545663	0.88	1.20	1.38 (1.24-1.53)	
Yes	160/81041	142/53703	1.97	2.64	1.26 (0.99-1.60)	
Stroke						0.87
No	1010/1098650	735/581930	0.92	1.26	1.36 (1.24-1.51)	
Yes	65/23801	64/17436	2.73	3.67	1.17 (0.82-1.68)	

Fig. 4. Low levels of 25(OH)D and incident dementia stratified by important factors. Cox regression models were used to estimate the hazard ratio (95% CI) for incident dementia associated with low levels of vitamin D. Low levels of 25(OH)D refer to 25(OH)D insufficiency and deficiency combined.

Sensitivity analysis

Individuals in the first and secondary quintiles of month-specific 25(OH)D had a higher risk of incident dementia compared with those in the fifth quintile (HR (95% CI): 1.6 (1.4–1.8) for the first quintile, 1.2 (1.1–1.4) for the secondary quintile). Similar results were observed across seasons (Supplementary Table 6).

DISCUSSION

In this large population of older adults aged 60 years or over, there was significant variation in 25(OH)D between seasons. The cut-off points for 25(OH)D insufficiency and deficiency for summer and autumn were significantly higher than for spring and winter. 25(OH)D insufficiency and deficiency determined according to these cut-off points were both associated with an increased risk of incident dementia and this association was significant across seasons. Newly developed stroke, depression, diabetes, and heart disease mediated the association between low levels of 25(OH)D and incident dementia.

25(OH)D deficiency and insufficiency is a public health challenge globally [26]. Our research is consistent with previous studies demonstrating that there was significant seasonal variation in 25(OH)D [27]. The average 25(OH)D for summer was 15 nmol/L higher than that for winter in our study highlighting the importance of sunlight exposure as the major source of 25(OH)D for most adults [28]. Moreover, dietary intake is another determinant of 25(OH)D status. Previous study has found that the highest tertile of dietary 25(OH)D consumption is associated with a 27% dementia hazard reduction [29]. While meat is an important source of 25(OH)D but also is a risk factor for AD [30]. It is critical to obtain an adequate amount of 25(OH)D from selective dietary sources and sunlight exposure especially in winter and spring.

There are several potential mechanisms for the association between 25(OH)D deficiency and an increased risk of dementia. Age, gender, depression, hypertension, diabetes, heart disease, and chronic kidney disease may confound the association between 25(OH)D and incident dementia. All these covariates were adjusted for in our multivariable analysis suggesting the potential role of 25(OH)D on the development of dementia via other mechanisms. Evidence showed 25(OH)D and 25(OH)D receptors being related to mitochondrial gene transcription and energy metabolism in the human brain [31], and previous *vitro* and *in vivo* work has demonstrated that 25(OH)D has an important role in brain development and function [32]. 25(OH)D may be involved in the clearance of amyloid-β [33], and an optimal 25(OH)D level corresponds to lower tau protein levels in the cerebrospinal fluid, suggesting a reduced dementia risk [34]. In addition, 25(OH)D sufficiency was associated with reduced inflammation and oxidative stress [35, 36], which provides a rationale for the inverse association between 25(OH)D and dementia. Moreover, the deficiency is associated with increased dementia-related conditions' risks, including hypertension [37], diabetes [13, 17], cardiovascular disease and depression [14, 18]. further underscores the protective potential of 25(OH)D against the development of dementia.

Our study is in line with two previous prospective cohort studies demonstrating that 25(OH)D deficiency was associated with an increased risk of incident dementia [10, 11]. However, other prospective studies showed that 25(OH)D was not significantly associated with the incidence of dementia [7, 12, 38–40]. A meta-analysis involving these cohort studies demonstrated that 25(OH)D deficiency was associated with an increased risk of dementia (pooled relative risk (95% CI): 1.30 (1.1–1.5) [9]. The inconsistent findings may be due to the difference in population and mean age between cohorts in these studies. Although the season was adjusted for in some of these studies, misclassification of 25(OH)D deficiency cannot be solved as season-specific cut-off points were not used. Our study is the first to demonstrate that there was a significant non-linear relationship between 25(OH)D and incident dementia. We also estimated the cut-off points for 25(OH)D deficiency for each season with much lower levels in spring and winter than in summer and autumn. This suggests the definition of 25(OH)D insufficiency and deficiency should be season specific.

Our findings indicate that 25(OH)D deficiency is more strongly associated with an increased risk of dementia during spring and winter compared to autumn and summer. This pattern aligns with seasonal variations in sunlight exposure, which is a primary source of vitamin D. Notably, lower sunlight exposure in winter and spring correlates with reduced 25(OH)D levels, underscoring the importance of vitamin D supplementation during these seasons for dementia prevention.

As 25(OH)D deficiency is associated with an increased risk of hypertension, diabetes, cardio-

vascular disease, and depression [7, 13–16], these conditions may moderate or mediate the association between 25(OH)D deficiency and incident dementia. Our study showed that the association between 25(OH)D and incident dementia did not differ between individuals with and without these conditions. Our further analysis also demonstrated that stroke, depression, diabetes, and heart disease identified during follow-up were significant mediators for the association between 25(OH)D and incident dementia. These newly developed conditions together explained 12.9% of the total effect, but the association between 25(OH)D deficiency and incident dementia remained significant. However, no such study has been published so that more research is needed to warrant our findings.

To our knowledge, this is the first study to estimate the cut-off points for 25(OH)D insufficiency and deficiency for each season and their associations with the incidence of dementia. Our study also uniquely examined the potential mediation effects of newly developed well-known dementia risks on the association between 25(OH)D and incident dementia. The present study also has several limitations. Firstly, some cases of all-cause dementia might not be captured in the medical records or death registers. However, previous research has shown that there is a good agreement between dementia case ascertainment with primary care records [41]. Because of the observational design of our study, causal relationships cannot be established based on our findings. The predominant proportion of participants in our study were Caucasian, therefore the cut-off points for 25(OH)D insufficiency and deficiency may be unlikely to apply in other ethnic groups. Finally, our analysis was restricted to a subgroup of the UK Biobank cohort who were aged 60–73 years old. Thus, our findings may not be generalized to the whole population with a wide age range.

Conclusion

We found seasonal differences in cut-off points of 25(OH)D insufficiency and deficiency that were associated with an increased risk of incident dementia in older adults residing in the UK. Newly developed stroke, depression, diabetes, and heart disease mediated the association between 25(OH)D and incident dementia.

AUTHOR CONTRIBUTIONS

Jiahao Liu (Writing – original draft); Eddy Roccati, PhD (Data curation); Yutong Chen, BSc (Writing – review & editing); Zhuoting Zhu, MD, PhD (Project administration); Wei Wang, MD, PhD (Investigation); Mingguang He, MD, PhD (Funding acquisition; Resources); Xianwen Shang, MPH, PhD (Conceptualization; Formal analysis; Visualization; Writing – review & editing).

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

Restrictions apply to the availability of these data. Data was obtained from UK Biobank and are available https://www.ukbiobank.ac.uk with the permission of UK Biobank.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/ADR-230077.

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