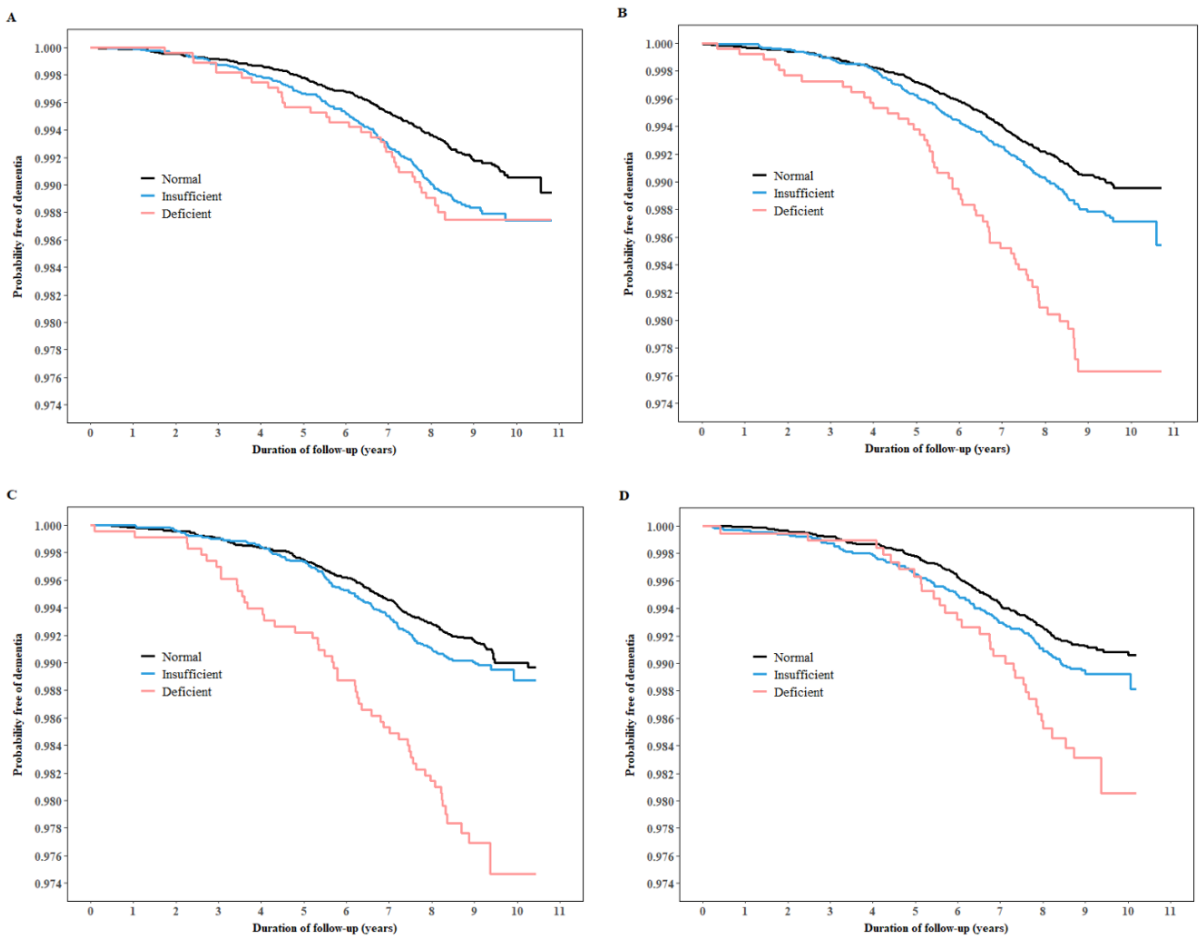
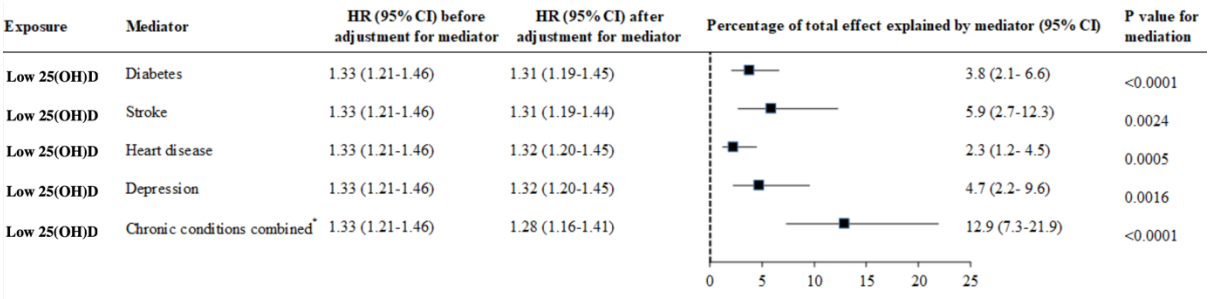
Supplementary Material

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



Supplementary Figure 1. Kaplan-Meier curves for rates of all-cause dementia by 25(OH)D status for spring, summer, autumn, and winter. Panels A, B, C, and D represent the curve for spring, summer, autumn, and winter, respectively. 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.



Supplementary Figure 2. Mediation analysis of the association between low levels of 25(OH)D and incident dementia by newly developed systemic conditions. HR (95% CI) for incident dementia associated with low levels of 25(OH)D was estimated using Cox proportional regression models adjusted for age, gender, ethnicity, education, income, diet score, physical activity, BMI, cholesterol, glycosylated haemoglobin, cystatin C, hypertension, diabetes, depression, heart disease, and stroke at baseline. Central squares of each horizontal line represent the mean percentage of total effect mediated by newly developed conditions during follow-up (before the onset of dementia). The horizontal line indicates the range of the 95% CI and the vertical dash line indicates the percentage of 0.0. Low levels of 25(OH)D refer to 25(OH)D insufficiency and deficiency combined.

*The potential mediation effect of those systemic conditions as significant mediators combined was computed for the association between low levels of 25(OH)D and incident dementia.

Supplementary Table 1. Codes for international classification disease and self-reported fields for dementia

ICD-9	ICD-10	Self-reported fields
331.0, 290.4, 331.1, 290.2, 290.3, 291.2, 294.1, 331.2, 331.5	F00, F00.0, F00.1, F00.2, F00.9, G30, G30.0, G30.1, G30.8, G30.9, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, I67.3, F02.0, G31.0, A81.0, F02, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05.1, F10.6, G31.1, G31.8	1263

Supplementary Table 2. Baseline characteristics of participants according to 25(OH)D status

	25(OH)D			
	Normal	Insufficiency	Deficiency	p*
Age (y)	64.19 ± 2.84	64.09 ± 2.88	64.01 ± 2.89	<0.0001
Gender				<0.0001
Women	63,063 (50.2)	30,683 (53.1)	5,238 (54.9)	
Men	62,640 (49.8)	27,069 (46.9)	4,310 (45.1)	
Ethnicity				<0.0001
Whites	123,418 (98.2)	55,059 (95.3)	8,103 (84.9)	
Non-whites	2,285 (1.8)	2,693 (4.7)	1,445 (15.1)	
Education				<0.0001
0-5 y	33,711 (26.8)	15,270 (26.4)	2,753 (28.8)	
6-12 y	58,767 (46.8)	25,611 (44.3)	3,951 (41.4)	
≥13 y	31,471 (25.0)	16,046 (27.8)	2,627 (27.5)	
Missing	1,754 (1.4)	825 (1.4)	217 (2.3)	
Household income (£)				<0.0001
<18,000	32,709 (26.0)	17,059 (29.5)	3,464 (36.3)	
18,000-30,999	34,245 (27.2)	14,716 (25.5)	2,103 (22.0)	
31,000-51,999	22,074 (17.6)	9,358 (16.2)	1,304 (13.7)	
52,000-100,000	10,463 (8.3)	4,883 (8.5)	598 (6.3)	
>100,000	2,569 (2.0)	1,089 (1.9)	142 (1.5)	
Unknown	6,547 (5.2)	3,453 (6.0)	740 (7.8)	
Not answered	17,096 (13.6)	7,194 (12.5)	1,197 (12.5)	
Physical activity (MET-min/week)	2,900 ± 2500	2,500 ± 2200	2,200 ± 2,000	<0.0001
Diet score	4.1 ± 1.4	3.9 ± 1.4	3.7 ± 1.5	<0.0001
Vitamin D supplementation	4021 (3.2)	890 (1.5)	100 (1.0)	<0.0001
Sleep duration (h)	7.3 ± 1.1	7.2 ± 1.2	7.2 ± 1.3	<0.0001
Alcohol consumption				<0.0001
Never	4,808 (3.8)	3,337 (5.8)	1,008 (10.6)	
Previous	4,045 (3.2)	2,629 (4.6)	677 (7.1)	
Current	116,653 (92.8)	51,638 (89.4)	7,805 (81.7)	
Missing	197 (0.2)	148 (0.3)	58 (0.6)	
Smoking				<0.0001
Never	63,105 (50.2)	28,145 (48.7)	4,234 (44.3)	
Former	53,688 (42.7)	23,391 (40.5)	3,532 (37.0)	
Current	8,213 (6.5)	5,875 (10.2)	1,666 (17.4)	
Missing	697 (0.6)	341 (0.6)	116 (1.2)	
BMI (kg/m^2)	27.1 ± 4.1	28.4 ± 4.9	29.0 ± 5.7	<0.0001
Cholesterol (mmol/L)	5.6 ± 1.1	5.6 ± 1.1	5.5 ± 1.1	<0.0001
Glycosylated hemoglobin (mmol/mol)	36.8 ± 5.9	38.0 ± 7.7	39.5 ± 9.6	<0.0001
Cystatin C (mg/L)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.3	<0.0001
Diabetes	6,265 (5.0)	4,523 (7.8)	1161 (12.2)	<0.0001
Stroke	2,668 (2.1)	1,582 (2.7)	370 (3.9)	<0.0001
Heart disease	9,071 (7.2)	4,978 (8.6)	1,034 (10.8)	<0.0001
Hypertension	44,241 (35.2)	22,485 (38.9)	4,095 (42.9)	<0.0001
Depression	5,256 (4.2)	2,971 (5.1)	630 (6.6)	<0.0001
Kidney failure	75 (0.1)	28 (0.0)	12 (0.1)	0.32
Kidney stone	1,139 (0.9)	583 (1.0)	95 (1.0)	0.0449

Data are mean (standard deviation), or N (%). BMI, body mass index; MET, metabolic equivalent.

*ANOVA was used to test the difference of continuous variables across subgroups of 25(OH)D status and Chi-square for categorical variables.

Supplementary Table 3. Risk for dementia associated with 25(OH)D insufficiency and deficiency defined by non-season specific cut-off points

	25(OH)D			
	Normal (≥50 nmol/L)	Insufficient (25-49.9 nmol/L)	Deficient (<25 nmol/L)	p-trend
Spring				
Events	161	244	95	
Person-years	186,051	227,773	76,798	
Incidence	0.87	1.07	1.24	
HR (95% CI), Model 1	1.0	1.3 (1.0-1.5)	1.5 (1.2-1.9)	0.0061
HR (95% CI), Model 2	1.0	1.3 (1.1-1.6)	1.5 (1.2-2.0)	0.0058
Summer				
Events	319	185	44	
Person-years	306,102	142,325	14,979	
Incidence	1.04	1.30	2.94	
HR (95% CI), Model 1	1.0	1.3 (1.1-1.6)	3.0 (2.2-4.1)	<0.0001
HR (95% CI), Model 2	1.0	1.3 (1.0-1.5)	2.2 (1.5-3.0)	<0.0001
Autumn				
Events	228	171	56	
Person-years	242,346	152,306	24,043	
Incidence	0.94	1.12	2.33	
HR (95% CI), Model 1	1.0	1.2 (1.0-1.5)	2.6 (1.9-3.5)	<0.0001
HR (95% CI), Model 2	1.0	1.2 (1.0-1.5)	2.0 (1.5-2.7)	0.0001
Winter				
Events	100	175	96	
Person-years	119,781	166,649	62,665	
Incidence	0.83	1.05	1.53	
HR (95% CI), Model 1	1.0	1.3 (1.0-1.6)	1.9 (1.5-2.5)	<0.0001
HR (95% CI), Model 2	1.0	1.2 (1.0-1.6)	1.7 (1.3-2.3)	0.0017
Combined				
Events	808	775	291	
Person-years	854,279	689,053	178,485	
Incidence	0.95	1.12	1.63	
HR (95% CI), Model 1	1.0	1.2 (1.1-1.3)	1.8 (1.6-2.1)	<0.0001
HR (95% CI), Model 2	1.0	1.2 (1.1-1.3)	1.6 (1.4-1.9)	<0.0001

Incidence of dementia represents 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, 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.

Supplementary Table 4. The risk for incident Alzheimer's disease associated with 25(OH)D by seasons

	25(OH)D			
	Normal (≥50 nmol/L)	Insufficient (25-49.9 nmol/L)	Deficient (<25 nmol/L)	p-trend
Spring				
Events	199	278	109	
Person-years	248,094	304,300	103,015	
Incidence	0.8	0.91	1.06	
HR (95% CI), Model 1	1.0	1.2 (1.0-1.4)	1.4 (1.1-1.7)	0.0420
HR (95% CI), Model 2	1.0	1.2 (1.0-1.4)	1.4 (1.1-1.8)	0.0370
Summer				
Events	342	199	37	
Person-years	405,174	188,662	19,920	
Incidence	0.84	1.05	1.86	
HR (95% CI), Model 1	1.0	1.3 (1.1-1.5)	2.3 (1.6-3.2)	<0.0001
HR (95% CI), Model 2	1.0	1.31 (1.1-1.6)	2.0 (1.4-2.9)	<0.0001
Autumn				
Events	283	215	55	
Person-years	320,929	202,327	32,135	
Incidence	0.88	1.06	1.71	
HR (95% CI), Model 1	1.0	1.2 (1.0-1.4)	1.9 (1.5-2.6)	<0.0001
HR (95% CI), Model 2	1.0	1.2 (1.0-1.5)	1.8 (1.3-2.4)	0.0005
Winter				
Events	151	206	87	
Person-years	159,023	222,118	83,875	
Incidence	0.95	0.93	1.04	
HR (95% CI), Model 1	1.0	1.0 (0.8-1.2)	1.1 (0.9-1.5)	0.55
HR (95% CI), Model 2	1.0	1.0 (0.8-1.2)	1.1 (0.8-1.4)	0.75
Combined				
Events	975	898	288	
Person-years	1,133,220	917,406	238,945	
Incidence	0.86	0.98	1.21	
HR (95% CI), Model 1	1.0	1.1 (1.1-1.3)	1.4 (1.3-1.6)	<0.0001
HR (95% CI), Model 2	1.0	1.2 (1.1-1.3)	1.4 (1.2-1.6)	<0.0001

Incidence of Alzheimer's disease represents cases per 1000 person-years. Hazard ratio (95% CI) for incident Alzheimer's disease 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, 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.

Supplementary Table 5. The risk for incident vascular dementia associated with 25(OH)D by seasons.

	25(OH)D			
	Normal (≥50 nmol/L)	Insufficient (25-49.9 nmol/L)	Deficient (<25 nmol/L)	p-trend
Spring				
Events	94	158	59	
Person-years	248,311	304,526	103,126	
Incidence	0.38	0.52	0.57	
HR (95% CI), Model 1	1.0	1.4 (1.1-1.8)	1.6 (1.1-2.2)	0.0097
HR (95% CI), Model 2	1.0	1.3 (1.0-1.7)	1.3 (0.9-1.9)	0.10
Summer				
Events	203	109	19	
Person-years	405,493	188,915	19,956	
Incidence	0.5	0.58	0.95	
HR (95% CI), Model 1	1.0	1.2 (1.0-1.5)	2.0 (1.3-3.3)	0.00664
HR (95% CI), Model 2	1.0	1.1 (0.8-1.3)	1.2 (0.7-2.0)	0.73203
Autumn				
Events	127	108	30	
Person-years	321,347	202,598	32,204	
Incidence	0.4	0.53	0.93	
HR (95% CI), Model 1	1.0	1.4 (1.1-1.8)	2.5(1.6-3.7)	<0.0001
HR (95% CI), Model 2	1.0	1.3 (1.0-1.7)	1.7 (1.1-2.6)	0.0331
Winter				
Events	61	116	60	
Person-years	159,308	222,404	83,930	
Incidence	0.38	0.52	0.71	
HR (95% CI), Model 1	1.0	1.4 (1.0-1.8)	1.9 (1.4-2.8)	0.0015
HR (95% CI), Model 2	1.0	1.3 (1.0-1.8)	1.5 (1.1-2.2)	0.0786
Combined				
Events	485	491	168	
Person-years	1,134,459	918,443	239,215	
Incidence	0.43	0.53	0.7	
HR (95% CI), Model 1	1.0	1.3 (1.1-1.5)	1.7 (1.4-2.1)	<0.0001
HR (95% CI), Model 2	1.0	1.2 (1.0-1.3)	1.3 (1.1-1.6)	0.0069

Incidence of vascular dementia represents cases per 1000 person-years. Hazard ratio (95% CI) for incident vascular 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, 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.

Supplementary Table 6. Risk for incident dementia associated with seasonal-specific 25(OH)D by seasons

	25(OH)D					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-trend
Spring						
Range (nmol/L)	10.0-27.4	27.5-37.8	37.9-48.6	48.7-62.0	≥62.1	
Events	86	86	87	113	128	
Person-years	98,418	98,500	97,560	97,994	98,150	
Incidence	0.87	0.87	0.89	1.15	1.30	
HR (95% CI), Model 1	1.0	1.0 (0.8-1.4)	1.0 (0.8-1.4)	1.4 (1.0-1.8)	1.6 (1.19-2.1)	0.0014
HR (95% CI), Model 2	1.0	1.02 (0.8-1.4)	1.1 (0.8-1.5)	1.4 (1.1-1.9)	1.6 (1.2-2.2)	0.0014
Summer						
Range (nmol/L)	10.0-42.0	42.1-53.0	53.1-62.5	62.6-74.1	≥74.2	
Events	103	90	91	109	155	
Person-years	92,657	93,650	92,174	92,176	92,750	
Incidence	1.11	0.96	0.99	1.18	1.67	
HR (95% CI), Model 1	1.0	0.9 (0.7-1.2)	0.93 (0.7-1.2)	1.12 (0.9-1.5)	1.6 (1.3-2.1)	<0.0001
HR (95% CI), Model 2	1.0	0.9 (0.7-1.2)	0.96 (0.7-1.3)	1.16 (0.9-1.5)	1.5 (1.1-1.9)	0.0026
Autumn						
Range (nmol/L)	10.0-37.3	37.4-48.8	48.9-59.2	59.3-71.3	≥71.4	
Events	83	66	90	86	130	
Person-years	84,039	84,025	84,290	82,814	83,528	
Incidence	0.99	0.79	1.07	1.04	1.56	
HR (95% CI), Model 1	1.0	0.8 (0.6-1.1)	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.7 (1.3-2.2)	<0.0001
HR (95% CI), Model 2	1.0	0.8 (0.6-1.1)	1.1 (0.8-1.5)	1.1 (0.8-1.5)	1.4 (1.1-1.9)	0.0076
Winter						
Range (nmol/L)	10.0-26.0	26.1-35.7	35.8-46.5	46.6-59.9	≥60.0	
Events	60	63	76	64	108	
Person-years	70,209	69,764	70,479	68,698	69,944	
Incidence	0.85	0.90	1.08	0.93	1.54	
HR (95% CI), Model 1	1.0	1.1 (0.7-1.5)	1.3 (0.9-1.8)	1.1 (0.8-1.5)	1.9 (1.4-2.6)	<0.0001
HR (95% CI), Model 2	1.0	1.1 (0.8-1.5)	1.3 (0.9-1.8)	1.1 (0.7-1.5)	1.7 (1.2-2.4)	0.0051
Combined						
Events	332	305	344	372	521	
Person-years	345,322	345,939	344,502	341,682	344,371	
Incidence	0.96	0.88	1.00	1.09	1.51	
HR (95% CI), Model 1	1.0	0.9 (0.8-1.1)	1.1 (0.9-1.2)	1.2 (1.0-1.4)	1.7 (1.5-1.9)	<0.0001
HR (95% CI), Model 2	1.0	1.0 (0.8-1.1)	1.1 (0.9-1.3)	1.2 (1.0-1.4)	1.5 (1.3-1.8)	<0.0001

Incidence of dementia represents 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, 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.