CLINICAL INVESTIGATION

Low Vitamin D Levels and Risk of Incident Delirium in 351,000 Older UK Biobank Participants

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BACKGROUND/OBJECTIVES: Delirium is common in older adults, especially following hospitalization. Because low vitamin D levels may be associated with increased delirium risk, we aimed to determine the prognostic value of blood vitamin D levels, extending our previous genetic analyses of this relationship.

DESIGN: Prospective cohort analysis.

SETTING: Community-based cohort study of adults from 22 cities across the United Kingdom (the UK Biobank).

PARTICIPANTS: Adults aged 60 and older by the end of follow-up in the linked hospital inpatient admissions data, up to 14 years after baseline (n = 351,320).

MEASUREMENTS: At baseline, serum vitamin D (25-OH-D) levels were measured. We used time-to-event models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between vitamin D deficiency and incident hospital-diagnosed delirium, adjusted for age, sex, assessment month, assessment center, and ethnicity. We performed Mendelian randomization genetic analysis in European participants to further investigate vitamin D and delirium risk.

RESULTS: A total of 3,634 (1.03%) participants had at least one incident hospital-diagnosed delirium episode. Vitamin D deficiency (<25 nmol/L) predicted a large incidence in delirium (HR = 2.49; 95% CI = 2.24–2.76; $P = 3*10^{-68}$, compared with >50 nmol/L). Increased risk was not limited to the deficient group: insufficient levels (25–50 nmol/L) were also at increased risk (HR = 1.38; 95% CI = 1.28–1.49; $P = 4*10^{-18}$). The association was independent of calcium levels, hospital-diagnosed fractures, dementia, and other relevant cofactors. In genetic analysis, participants carrying more vitamin D–increasing variants had a reduced likelihood of incident delirium diagnosis (HR = .80 per standard deviation increase in genetically instrumented vitamin D: .73–.87; $P = 2*10^{-7}$).

CONCLUSION: Progressively lower vitamin D levels predicted increased risks of incident hospital-diagnosed delirium, and genetic evidence supports a shared causal pathway. Because low vitamin D levels are simple to detect and inexpensive and safe to correct, an intervention trial to confirm these results is urgently needed. **J Am Geriatr Soc 00:1-8, 2020.**

Keywords: delirium; vitamin D; risk factor; biomarker; genetic

Delirium is an acute fluctuating change in cognition associated with inattention, disorganized thinking, or altered level of consciousness, and it is common among hospitalized older adults.[1] It is potentially preventable and often underrecognized in clinical practice,[2] affecting 23% of acute hospital admissions in adults,[3] with considerable economic and societal costs.[4] Diagnosis rates in the community are much lower (1%–2%).[5] Causes of delirium are multifactorial involving both underlying or predisposing (e.g., dementia, advanced age) and precipitating factors, often acute events (e.g., hospitalization, surgery, anesthesia, infection), with inflammation, polypharmacy, constipation, catheterization, environment, pain, and stroke also implicated.[6]

There is increasing interest in the role of vitamin D in delirium and dementia, with a meta-analysis demonstrating a correlation between low vitamin D and reduced

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cognition.[7] Nevertheless, most of the studies included were observational, and this effect was not replicated in interventional studies with supplementation of vitamin D.[7] A further systematic review indicated a potential link between low levels of vitamin D and the development of dementia.[8] In our previous genetics study using Mendelian randomization methods, we found evidence for a causal link between lower vitamin D levels and higher risks of incident episodes of delirium in hospital inpatient records in the United Kingdom (UK) Biobank. However, serum vitamin D levels were not available at the time.[9] Here we build on this work by combining serum vitamin D levels, genetic information, and four additional years of hospital inpatient follow-up to further investigate this relationship.

In this study we aimed to estimate the association between serum vitamin D levels and risk of incident hospital-diagnosed delirium in a large community volunteer sample. Although delirium is underdiagnosed in the hospital setting,[2] previous work showed that delirium diagnoses made in the hospital setting are accurate with a high level of specificity.[10] We also aimed to extend our previous genetic analysis[9] with the increased numbers of incident delirium cases now available in the UK Biobank (n = 3,634 up from 544 in our previous work).

METHODS

The UK Biobank recruited 503,325 community-based volunteers aged 40 to 70 between 2006 and 2010 from across the United Kingdom.[11] Data collected at the baseline assessment included extensive questionnaires on demographic, health, and lifestyle information. Anthropometric measures were also taken, in addition to blood samples for future biochemical and genetic analysis. Ethical approval for the UK Biobank study was obtained from the North West Multi-Centre Research Ethics Committee.

Serum Vitamin D

Serum 25-hydroxyvitamin D (25[OH]D, a proxy for vitamin D levels) measurement (in nanomole per liter) was performed by the immunoassay analyzer DiaSorin Liaison XL, with data on 448,376 participants at baseline passing the quality control procedures applied by the UK Biobank central team[12] (see the UK Biobank report for sensitivity, interassay variability, and other information[13]).

We performed exploratory analysis on the following potential vitamin D covariates: age, sex, self-reported ethnicity (split into six groups: White, Asian, Black, Other, Mixed, or Missing), assessment month (season), and assessment center (see Supplementary Methods S1 for details). We adjusted for these covariates in all analyses.

Participants were split into three groups of vitamin D levels according to the UK National Institute for Health and Care Excellence (NICE) guidelines for the management of vitamin D deficiency or insufficiency in adults[14]: deficient for vitamin D if serum 25[OH]D levels are less than 25 nmol/L; insufficient vitamin D if serum 25(OH)D levels are in the range of 25 to 50 nmol/L; and vitamin D levels sufficient if serum 25(OH)D levels are above 50 nmol/L.

Delirium Diagnosis

Follow-up disease ascertainment from hospital admissions records was available up to 14 years after assessment (ending March 2020: data from Wales or Scotland were censored to February 29, 2016, and October 31, 2016, respectively). A total of 270,299 of the 351,320 participants (76.9%) included in this analysis had at least one hospital admission after the baseline assessment. Diagnosis of delirium was ascertained using International Diagnosis of Diseases, Tenth Revision (ICD-10) code F05 (see Supplementary Table S1 for all ICD-10 codes used in this analysis). Due to the rarity of delirium diagnoses before age 60[5] (of the 3,634 participants with a hospital diagnosis of delirium, only 44 occurred before the age of 60), and that delirium in younger groups may have different etiology, participants were excluded if they did not reach age 60 by the date of censoring. Participants with a previous delirium diagnosis at baseline (n = 45) were excluded. In the primary analysis, no other exclusions were made. See Supplementary Methods S1 for details on sensitivity analyses such as the effect of exclusions (e.g., bone fractures).

Analysis of Vitamin D Association with Incident Delirium

A total of 351,320 participants aged 60 and older at any time during follow-up had sufficient data for analysis of vitamin D and risk of incident delirium. Stata v.15.1 was used for analysis. Cox proportional hazards regression models estimated the association between vitamin D and incident delirium, with adjustment for age, sex, assessment center, assessment month, and self-reported ethnicity (see Supplementary Methods for details). Visual inspection of Kaplan-Meier plots and application of the Stata function estat phtest detail to estimate Schoenfeld residuals were used to test for violations of the proportional hazards assumption.

To model the nonlinear effect of vitamin D (nmol/L) on rate of incident delirium diagnosis from Cox proportional hazards regression models, we used the natural polynomial smoothing spline function in R (v.4.0.2) package pspline (v.1.0–18) and package survival (v.3.1–12). We used default options for the smoothing parameters (modifying these did not meaningfully affect the results).

Genetic Data

Genotyping and quality control were performed centrally by the UK Biobank team.[15] In brief, directly genotyped genetic variants (n = 805,426) are available in 488,377 UK Biobank participants, from two almost identical platforms sharing more than 95% of variants: the Affymetrix Axiom UKB array (in 438,427 participants) and the Affymetrix UKBiLEVE array (in 49,950 participants). Genotype imputation was successful in 487,442 participants and increased the number of genetic variants to approximately 96 million.[15]

Mendelian Randomization Analysis

Mendelian randomization (MR) analyses are used to determine whether an association between a risk factor (e.g., vitamin D) and an outcome (e.g., delirium) may share

a causal pathway. If individuals carrying more vitamin D–increasing genetic variants have greater risk of delirium, this supports the hypothesis of a shared causal pathway. We previously applied these methods to an earlier version of the UK Biobank data[9] and here extend the analysis using the longer follow-up now available (n = 3,405 delirium cases, up from 544 in our previous work). Briefly, known genetic variants associated with circulating 25[OH]D concentration were extracted from a large meta-analysis by Jiang et al.[16] that was independent of the UK Biobank cohort. R (v.4.0.2) packages MendelianRandomization (v.0.4.2) and RadialMR (v.0.4)[17] were used. See Supplementary Methods S1 for details.

RESULTS

We analyzed 351,320 UK Biobank participants who reached age 60 before the end of the follow-up period and had complete data (end March 2020; see Methods for details and Supplementary Figure S1 for cohort flowchart). There were 3,634 (1.0%) participants with an incident delirium diagnosis in the hospital admissions data (Table 1).

We observed significant variation in vitamin D associated with season (highest average levels recorded in August, lowest in February: Supplementary Table S2 and Supplementary Figure S2), assessment center (highest average levels recorded in Cardiff, lowest in Glasgow; Supplementary Table S3), and self-reported ethnicity (highest average levels in participants reporting White ethnicity, lowest in those reporting any Asian ethnicity; Supplementary Tables S4 and S5).

Vitamin D Deficiency Is Associated with Increased Risk of Incident Delirium

We estimated the effect of serum vitamin D (nmol/L) on rates of incident delirium diagnosis in Cox proportional hazards regression models adjusted for age, sex, assessment center, assessment month, and self-reported ethnicity, first using a smoothing spline parameter to model continuous and nonlinear effects: decreasing vitamin D was significantly associated with risk of incident delirium (spline $P = 1.8*10^{-32}$), with risk progressively increasing below approximately 75 nmol/L (Figure 1A).

Participants with deficient vitamin D levels (<25 nmol/L) at the baseline assessment were at increased risk for incident delirium (hazard ratio [HR] = 2.49; 95% confidence interval [CI] = 2.25–2.76; $P = 3*10^{-68}$) compared with those with sufficient levels (≥50 nmol/L) in Cox proportional hazards regression models adjusted for age, sex, assessment center, assessment month, and self-reported ethnicity (Figure 1B). Participants with insufficient levels were also at increased risk (HR = 1.38; 95% CI = 1.28–1.49; $P = 4*10^{-18}$).

In sex-stratified analysis, the effect of vitamin D deficiency on risk of incident delirium was similar in men compared with women (n = 164,288 men; HR = 2.51; 95% CI = 2.19–2.88; $P = 3*10^{-39}$; n = 187,032 women; HR = 2.50; 95% CI = 2.14–2.92; $P = 7*10^{-31}$), and there was no significant interaction ($P > .05$).

We repeated the analysis only in the 335,517 participants (96%) who self-reported as White because individuals of other ethnic groups are known to have lower vitamin D levels while retaining the same level of bioavailable vitamin D.[20] The association between vitamin D deficiency and incident delirium was very similar to the overall estimate (HR = 2.58; 95% CI = 2.32–2.87; $P = 7*10^{-70}$), and there was no significant interaction ($P > .05$). Due to low numbers of non-White participants (Table 1), analysis of other ethnic groups was underpowered.

Table 1. Summary Statistics of 351,320 UK Biobank Participants Eligible for Primary Analysis

	Mean (SD)	Min, Max
Age at baseline, y	60.39 (5.76)	47.06, 73.89
Age at end of follow-up or death, y	70.95 (5.71)	60.00, 86.28
Vitamin D at baseline, nmol/L	49.45 (20.93)	10, 335
Time to first delirium episode, y (n = 3,634)	8.63 (2.25)	.11, 12.84
Time to death, y (n = 23,584)	7.22 (3.07)	.01, 13.06
	N	%[a]
Sex, women	187,032	53.24
Vitamin D, categories		
Sufficient (>50 nmol/L)	162,514	46.26
Insufficient (25–50 nmol/L)	145,890	41.53
Deficient (<25 nmol/L)	42,916	12.22
Self-reported ethnicity[b]		
White	335,517	95.5
Asian	6,135	1.8
Black	4,121	1.2
Other	2,486	.7
Mixed	1,469	.4
Prefer not to answer/Do not know/Missing	1,592	.5
Highest education level attained[b]		
None	70,843	20.4
CSEs/GCSEs/O-levels	56,432	16.3
A-levels/NVQ/HND/HNC	59,282	17.1
Professional qualification (e.g., nursing, teaching)	53,392	15.4
College or university degree	107,108	30.9
Smoking status		
Never	185,203	53.0
Former	131,260	37.6
Current	33,053	9.5
Died during follow-up	23,584	6.7
Delirium during follow-up	3,634	1.0
Any recorded hospital admission during follow-up	270,299	76.9
Genetically European, with vitamin D genetics	326,558	93.0

[a]Percentage of total participants without missing data for that phenotype.
[b]Combined groups; see Supplementary Information for more detailed subgroups.

Sensitivity Analyses

In sensitivity analyses using Fine and Gray competing risks regression, accounting for mortality as the competing risk (23,584 of 351,320 participants died during follow-up), the results remained consistent (deficient sub HR = 2.33; 95%

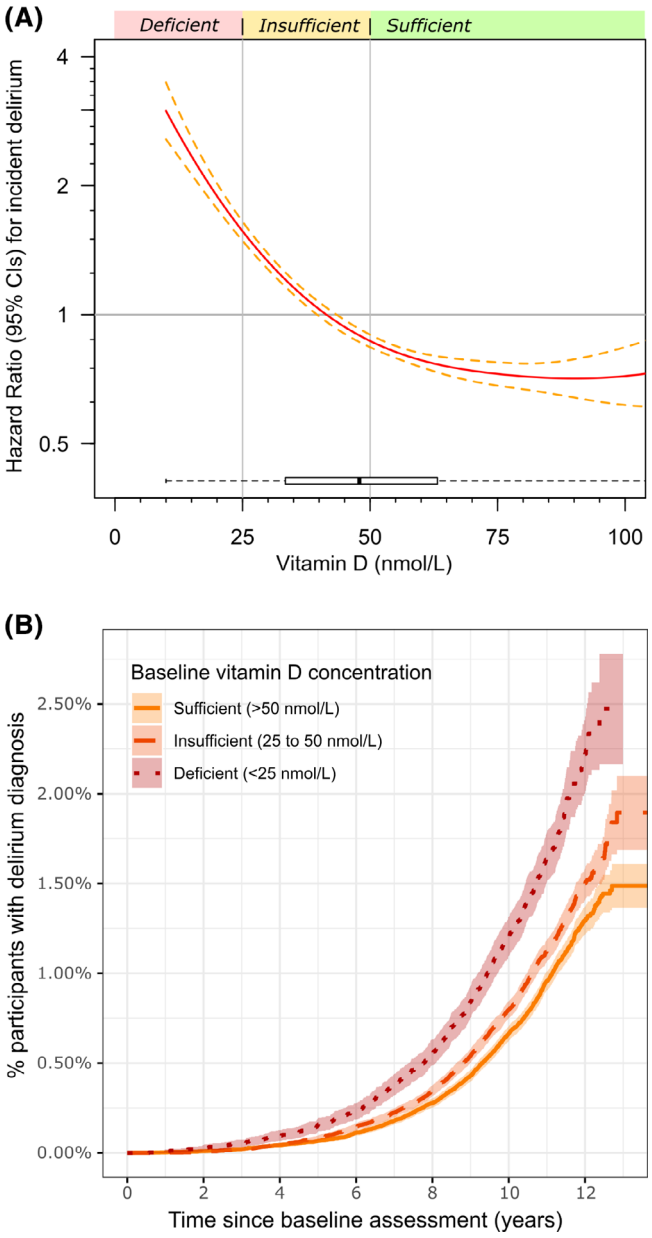

Figure 1. Serum vitamin D and rates of incident delirium diagnosis. (A) Analysis of serum vitamin D (nmol/L) at baseline and rates of incident delirium diagnosis using Cox proportional hazards regression models adjusted for age, sex, assessment center, assessment month, and self-reported ethnicity. A smoothing spline function was applied to determine the nonlinear effect of vitamin D on risk of incident delirium. The x-axis is limited to 100 nmol/L for clarity; see Supplementary Figure S3 for the unrestricted plot. (B) Unadjusted cumulative event plot showing the proportion of the participants with a diagnosis of delirium in the hospital in three groups, based on baseline vitamin D sufficiency. R package survminer (v.0.4.8) was used for plot B. CI, confidence interval.

CI = 2.10–2.58; $P = 3*10^{-56}$; insufficient sub HR = 1.36; 95% CI = 1.26–1.47; $P = 1*10^{-15}$).

The results were also consistent after multiple additional adjustments and exclusions were made (Table 2). First was an adjustment for baseline smoking status and educational attainment, a proxy for socioeconomic status (vitamin D deficiency HR = 2.38; 95% CI = 2.14–2.64; $P = 2*10–59$). Next was excluding 30,528 participants who reported taking vitamin D supplements at baseline (HR = 2.46; 95% CI = 2.21–2.74; $P = 2*10^{-59}$). Next, we additionally excluded 45,197 participants with hospital-diagnosed bone fractures, chronic kidney disease (CKD), dementia, liver disease (any), or Parkinson's disease (HR = 2.40; 95% CI = 2.00–2.89; $P = 6*10^{-21}$). Similar trends were seen for insufficient vitamin D levels (Table 2).

Vitamin D deficiency was associated with lower calcium levels (coefficient −.020 mmol/L: −.019 to −.021; $P = 4*10^{-281}$), but there was no linear association between calcium levels and incident delirium diagnosis (HR per mmol/L = .76; .52–1.10; $P = .14$). In nonlinear analysis, calcium levels below 2.27 mmol/L or greater than 2.57 mmol/L were associated with increased delirium risk using a smoothing spline in Cox proportional hazards regression models adjusted for age, sex, assessment center, assessment month, and self-reported ethnicity (spline $P = .03$; Supplementary Figure S4). The association between vitamin D and incident delirium remained consistent after inclusion of the calcium spline term in the model (vitamin D deficiency HR = 2.52; 95% CI = 2.24–2.83; $P = 2*10^{-54}$).

To explore the known reduced sun exposure in frail, less mobile individuals,[21] we performed an analysis adjusted for baseline frailty using the Frailty Index (FI) count of health deficits[19] as a continuous covariate (n = 232,087 with complete data); the estimate was modestly attenuated (HR = 2.16; 95% CI = 1.89–2.47; $P = 8*10^{-30}$) but not significantly different (FI to vitamin D interaction $P > .05$) (Table 2).

We performed a single analysis with adjustment for age, sex, assessment center, assessment month, self-reported ethnicity, smoking status, educational attainment, calcium levels, and FI, and excluded participants taking vitamin D supplements, with hospital-diagnosed CKD, bone fractures, dementia, liver disease, and Parkinson's disease. The association between vitamin D deficiency and incident delirium remained consistent, albeit slightly attenuated, in Cox proportional hazards regression models (n = 203,490 in analysis; HR = 2.33; 95% CI = 1.88–2.89; $P = 1*10^{-14}$; Table 2). Participants with insufficient vitamin D levels were also still at increased risk (HR = 1.31; 95% CI = 1.12–1.54; $P = 6*10^{-4}$).

Separately, we repeated the main analysis restricted to those participants hospitalized during the follow-up period (270,299 of 351,320 [76.9%]) and found that the association between vitamin D deficiency and incident delirium was similar to that in all participants (HR = 2.45; 95% CI = 2.21–2.72; $P = 8*10^{-66}$).

We also investigated whether the effect of vitamin D on delirium depended on the delirium diagnosis resulting from a surgical procedure (i.e., postoperative delirium only). Of 3,634 incident delirium cases, 1,473 (40.5%) were less than 72 hours after a recorded hospital operation. The effect of vitamin D deficiency on risk of incident delirium was consistent in an analysis restricted to only postoperative cases (HR = 2.60; 95% CI = 2.22–3.06; $P = 2*10^{-31}$) compared with an analysis restricted to those delirium diagnoses made where no surgical procedure was recorded (delirium diagnoses = 2,161; HR = 2.48; 95% CI = 2.17–2.82; $P = 2*10^{-42}$).

Table 2. Vitamin D Deficiency Is Associated with Increased Rates of Incident Delirium

Model	Vitamin D at baseline	N	N delirium	Person-years	HR (95% CI)	*P* value
Model 1[a]	Sufficient (>50 nmol/L)	162,514	1,484	1,728,790		
	Insufficient (25–50 nmol/L)	145,890	1,521	1,530,801	1.38 (1.28–1.49)	3.9*10–18
	Deficient (<25 nmol/L)	42,916	629	440,778	2.49 (2.24–2.76)	3.4*10–68
+ Adjusted for education and smoking status[b]		160,120	1,439	1,703,633		
	Insufficient (25–50 nmol/L)	143,609	1,472	1,507,279	1.37 (1.27–1.48)	1.3*10–16
	Deficient (<25 nmol/L)	42,012	618	431,646	2.38 (2.14–2.64)	1.5*10–59
+ Excluding vitamin D supplements		140,274	1,246	1,491,439		
	Insufficient (25–50 nmol/L)	134,247	1,374	1,408,789	1.40 (1.29–1.52)	6.2*10–17
	Deficient (<25 nmol/L)	40,692	598	418,019	2.46 (2.21–2.74)	2.1*10–59
+ Excluding comorbidities[c]		121,070	448	1,290,397		
	Insufficient (25–50 nmol/L)	115,022	473	1,209,590	1.32 (1.15–1.51)	4.1*10–5
	Deficient (<25 nmol/L)	33,924	211	349,874	2.40 (2.00–2.89)	6.0*10–21
+ Adjusted for calcium[b]		110,391	406	1,176,061		
	Insufficient (25–50 nmol/L)	105,366	447	1,107,064	1.37 (1.19–1.58)	8.9*10–6
	Deficient (<25 nmol/L)	31,194	197	321,497	2.45 (2.02–2.97)	2.6*10–20
+ Adjusted for Frailty Index[b]		92,593	327	987,394		
	Insufficient (25–50 nmol/L)	86,341	348	907,548	1.31 (1.12–1.54)	6.1*10–4
	Deficient (<25 nmol/L)	24,556	153	253,166	2.33 (1.88–2.89)	1.3*10–14

Abbreviations: CI, confidence intervals; HR, hazard ratio; N, sample size included in the model; N delirium, the number of incident delirium cases included in the model.

[a]Cox proportional hazards regression models adjusted for age, sex, assessment center, assessment month, and self-reported ethnicity.

[b]At baseline assessment, participants with missing data excluded.

[c]Ever diagnosed with bone fracture, chronic kidney disease, dementia, liver disease, or Parkinson's disease in the hospital admissions data to March 2020, prevalent or incident.

Vitamin D–Increasing Genetic Variants Are Associated with Vitamin D Levels

A genetic risk score (GRS) for the number of vitamin D–increasing variants each participant carried (weighted by the published effect on vitamin D levels by Jiang et al[16]) were computed in the 326,558 UK Biobank participants of European ancestry who met the inclusion criteria for analysis (see Methods). The GRS was strongly associated with serum vitamin D (nmol/L) in linear regression models adjusted for age at vitamin D assessment, sex, assessment center, assessment month, and ethnicity (coefficient per standard deviation [SD] of GRS = 3.37; 95% CI = 3.30–3.44; $P = 1*10^{-2,029}$). The proportion of the variation in vitamin D levels explained by the GRS was 1.2%.

Calcium serum levels (μmol/L) were increased in individuals with greater vitamin D GRS in linear regression models (coefficient per SD of GRS = 1.03; 95% CI = .68–1.37; $P = 8*10^{-9}$). However, this association lost significance when vitamin D was included as a covariate ($P = .3$), suggesting the effect of vitamin D GRS on calcium is via the effect on vitamin D.

Vitamin D–Increasing Genetic Variants Confirm Reduced Likelihood of Incident Delirium Diagnosis

In MR analysis we found consistent evidence that higher circulating vitamin D reduced the likelihood of incident hospital diagnosis of delirium: the primary analysis was of the MR-IVW penalized robust regression estimate (change in log(HR) for delirium per log(nmol/L) vitamin D = −.48; 95% CI = −.66 to −.30; $P = 2 \times 10^{-7}$) using the six vitamin D–associated variants from Jiang et al.[16] (Table 3; Figure 2A). The HR for delirium per SD genetically instrumented log(vitamin D) is .799 (.735–.869). Sensitivity analysis using Radial IVW (Figure 2B) or excluding the large-effect single nucleotide polymorphism rs3755967 showed consistent effect size (Table 3), albeit attenuated significance. We found no evidence for horizontal pleiotropy

Table 3. Mendelian Randomization Estimates for the Effect of Circulating Vitamin D on Delirium

Method[a]	Estimate[b]	95% CI	*P*
IVW	−.48	−.66 to −.30	2×10^{-7}
Weighted median	−.51	−1.02 to .00	.048
MR-Egger	−.41	−.73 to −.10	.010
MR-Egger (intercept)	.00	−.03 to .02	.755
Radial IVW	−.48	−.76 to −.20	.001
Radial MR-Egger	−.49	−1.01 to .04	.144
Radial MR-Egger (intercept)	.01	−.87 to .90	.977
IVW (excluding rs3755967)	−.41	−1.01 to .18	.173

[a]IVW, penalized robust inverse-variance weighted regression (assumes there is no unbalanced horizontal pleiotropy); MR-Egger (intercept), like IVW but the MR-Egger incept is not fixed, as deviation from the null is used to test for possible horizontal pleiotropy; MR-Egger, penalized robust Egger regression (assumes the genetic variants' effect is not correlated with any pleiotropic effect on the outcome); Radial IVW, Radial inverse-variance weighted regression using modified second-order weights (no significant outliers detected); Radial MR-Egger, intercept in unconstrained and assumes that pleiotropic effects are independent of the Radial weights; Weighted median, penalized weighted median estimate (assumes <50% of the weight in the analysis comes from invalid instruments).

[b]ln(HR) per ln(vitamin D). See Supplementary Table S6 for full details.

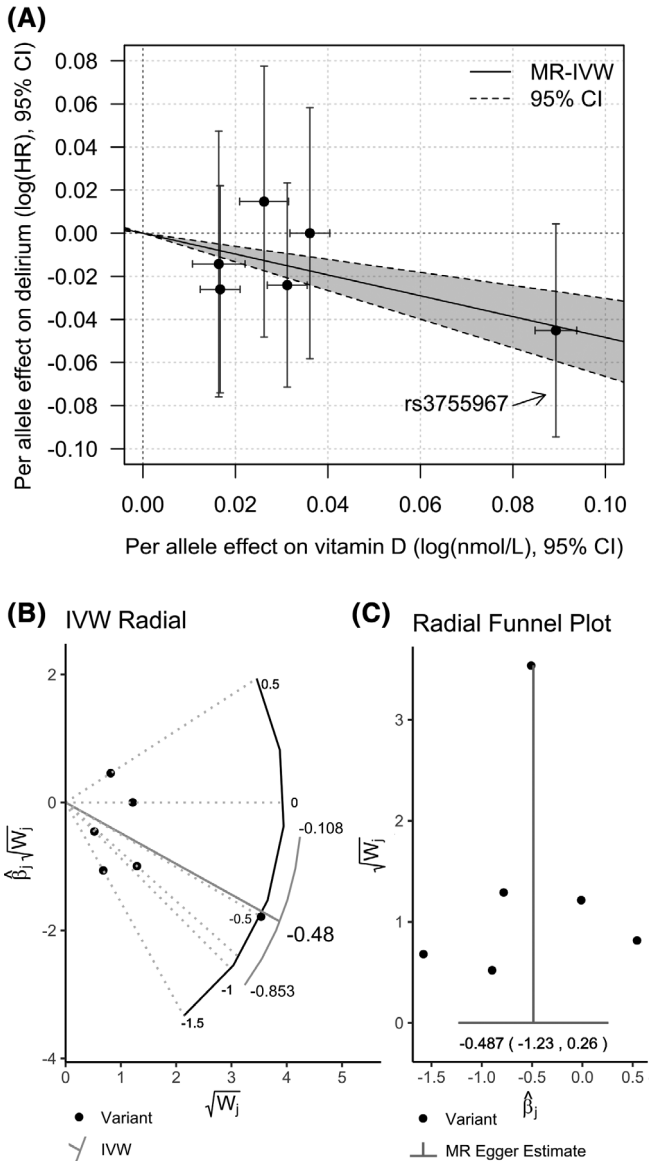

Figure 2. Vitamin D–increasing genetic variants associated with reduced likelihood of incident delirium diagnosis. (A) Six genetic variants are known to affect circulating 25(OH)D (vitamin D) levels (effect shown on the x-axis). We determined the association with risk of incident delirium for each genetic variant (shown on the y-axis). Mendelian randomization penalized robust inverse-weighted regression (MR-IVW) results (including 95% confidence intervals) show that genetic predisposition to higher serum vitamin D is associated with reduced likelihood of delirium diagnosis in the follow-up. (B) Radial IVW plot of results using modified second-order weights (no significant outliers were detected). (C) Radial MR-Egger funnel plot showing the regression intercept is not significantly different from the null (no evidence of pleiotropy).

with MR-Egger regression or Radial MR-Egger (intercept $P > .05$; Table 3 and Figure 2C). See Supplementary Table S6 for detailed results. In sensitivity analysis only analyzing the cases in the updated hospital admissions data since our previous publication[9] (n = 2,861 between February 2016 and March 2020), the association is consistent in effect but attenuated in significance compared with the analysis of diagnoses before February 2016 (n = 544; see Supplementary Table S7 and Supplementary Figure S5).

DISCUSSION

In this large prospective study of 351,320 community-based UK Biobank participants, aged 60 and older by the end of the 14 years of follow-up, vitamin D levels predicted increased risks of incident hospital-diagnosed delirium. Genetic evidence supports a shared causal pathway. The highest risk for delirium occurred in the vitamin D deficient group (<25 nmol/L) compared with those with sufficient levels (>50 nmol/L). Participants with vitamin D insufficiency (25–50 nmol/L) also had an increased risk of delirium at follow-up, with a smaller effect size, suggesting a dose-response relationship. Genetic results with a larger sample than we previously reported (n = 3,405, up from 544) continue to support a causal role overall, showing 20% reduction in delirium hazard per SD of genetically instrumented vitamin D (limitations discussed later). This research has important clinical relevance and consequences; although delirium is an acute diagnosis, it is known to increase the risk of dementia.[22] Whether this is a causative role or an unmasking of underlying cognitive vulnerability is unclear. However, prevention of delirium can potentially delay irreversible cognitive impairment.[23] Additionally, economic analyses in the United States have estimated that healthcare costs for patients with delirium are 2.5 times greater than for patients without delirium.[24]

This work is consistent with the results of a previous retrospective cross-sectional study revealing lower levels of vitamin D levels in patients with delirium in whom the levels were checked.[25] Low vitamin D levels were also more prevalent in patients with hip fractures and delirium (although the numbers included were small and prone to confounding).[26] A further retrospective cohort study of 4,508 participants showed higher levels of hospital-acquired delirium in those with lower vitamin D levels (checked before hospitalization). However, the number of delirium cases was only 4%, and they concluded that a future randomized controlled trial would need to be conducted.[27]

The association between vitamin D and delirium is plausible considering its hypothesized neuroprotective role in preventing oxidative damage to nervous tissue and influence on neuromediator synthesis.[28] Vitamin D is also thought to affect the inflammatory processes within the brain that increase vulnerability to injury.[29] Studies in rat models showed vitamin D has a protective effect on neurons from oxidative stress and the role of vitamin D in the growth and protection of neurones.[30] Vitamin D3 receptors were found not only in brain neurons but also in the spinal cord and in the peripheral nervous system.[31] In addition, vitamin D receptors were found in the hippocampus, an area of the brain affected by Alzheimer's disease and other neurodegenerative conditions.[32] Research also investigated the possible role of vitamin D in the reduction of β-amyloid in mouse models.[33] Vitamin D is also thought to impact systemic inflammation[34] that during aging impacts comorbidities, frailty, and other outcomes implicated in the pathogenesis of delirium.

Previous MR studies with vitamin D showed an association between vitamin D–increasing alleles and Alzheimer's

disease.[35] However, this evidence was inconclusive or tentative in a MR systematic review.[36] Our previous article was, to the best of our knowledge, the first report of MR to estimate the relationship between vitamin D and delirium.[9]

The current article takes the previous work forward by combining serum vitamin D levels and genetic information to further investigate this relationship. The genetic variants associated with vitamin D are known to influence its synthesis and metabolism,[16] suggesting a direct relationship between vitamin D and delirium; our MR analysis results are consistent with lack of pleiotropic effects (i.e., via other pathways than vitamin D). The strength of the association between vitamin D genetic variants and incident delirium is attenuated when only using the "new" cases not included in our previous report.[9] Thus further work is required for full confirmation.

Supporting a causal role for vitamin D in mental health is a 2019 randomized clinical trial of vitamin D supplementation for 1 year in 200 older (aged ≥70 years) adults who experienced a fall in the previous year; there were significant improvements in mental health (the Mental Component Summary of the Short Form Health Survey 36-item patient health survey) in the groups achieving the highest vitamin D levels at 12 months[37] and strongest in those who were deficient at baseline.

In this analysis we used vitamin D levels above 50 nmol/L to define "sufficient" levels, in line with the relevant UK NICE guidelines.[14] However, in our nonlinear analysis of vitamin D levels with risk of delirium (Figure 1A), the lowest risk participants are those with levels of 75 nmol/L or higher, a target recommended by the U.S. Endocrine Society for treating and preventing vitamin D deficiency.[38] Our data suggest that 50 nmol/L may not be the optimum target for delirium prevention, although more data are needed.

This study has some limitations. The diagnosis of delirium for the purpose for this study was extracted from Hospital Episode Statistics data, and delirium is known to be underdiagnosed in hospital settings.[2] However, hospital diagnosis of delirium was shown to be more precise than in the community, with a higher level of specificity.[10] UK Biobank reflects a generally younger age group who were fit and able to attend assessment appointments and clinic visits. Although studying a younger population may limit generalizability to older adults, the mean age at end of follow-up was 71 years (range = 60–86), meaning our ability to capture more typical delirium cases seen in older hospitalized patients is improving. Remarkably, measured vitamin D levels are highly predictive of incident delirium up to 14 years before diagnosis, showing it is a good biomarker.

A related point to consider is that previous hypotheses suggested that the link between cognition and vitamin D deficiency may just be a marker of increased frailty associated with cognitive decline and less sun exposure.[21] We included adjustments for season and month of assessment, and test center as a measure to ameliorate the influence of variable sun exposure. Frail individuals are at increased risk of delirium,[18] yet the association between vitamin D deficiency and incident delirium was robust to adjustment for the baseline FI (of course, frailty status can change, but this observation means deficiency was not just a marker of baseline frailty). Vitamin D deficiency can be associated with other medical conditions that could increase the incidence of delirium. We found the association to be robust to exclusion of hospital-diagnosed bone fractures, CKD, and liver disease. Taken together, our results, including genetic analysis that is not susceptible to reverse causation and other traditional confounding factors, suggest that vitamin D deficiency could be playing a more central role in delirium susceptibility.

In conclusion, we demonstrated in this study that measured low vitamin D is associated with incident delirium, with genetic evidence supporting a causal role. Vitamin D deficiency is simple to rectify, at low cost and with minimal side effects. This study provides a rationale for further interventional trials assessing the relationship between vitamin D supplementation and cognition, with a focus on delirium prevention. Our results suggest that older adults should be routinely screened for vitamin D levels during general practitioner visits to help ensure they are at sufficient levels in the event that they require hospitalization where risk for delirium increases considerably.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: ICD-10 codes for clinical conditions from the hospital inpatient data.

Supplementary Table S2: Vitamin D levels associated with assessment month.

Supplementary Table S3: Vitamin D variation by assessment center.

Supplementary Table S4: UK Biobank ethnic group coding.

Supplementary Table S5: Collapsed groups and associations with vitamin D levels.

Supplementary Table S6: Expanded version of Table 3.

Supplementary Table S7: Mendelian randomization stratified by date of diagnosis.

Supplementary Figure S1: Cohort flowchart.

Supplementary Figure S2: Box plot of vitamin D by assessment month.

Supplementary Figure S3: Time-to-event model with smoothing spline function (vitamin D).

Supplementary Figure S4: Time-to-event model with smoothing spline function (calcium).

Supplementary Figure S5: Mendelian randomization stratified by date of diagnosis.