Vitamin D: marker, cause or consequence of depression? An exploration using genomics

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ABSTRACT

Background: Observational studies suggest an association between circulating vitamin D and depression. Trials testing the effect of vitamin D supplementation on depression reported inconclusive findings. It remains unknown whether the vitamin D-depression association stems from shared etiology or from a direct causal relationship. We explored the nature of the association between 25-hydroxyvitamin D (25-OH-D) and major depressive disorder (MDD) exploiting data and statistical tools from genomics.

Methods: Results from the two largest GWAS on 25-OH-D (79,366 samples) and major depressive disorder (MDD; 135,458 cases and 344,901 controls) were applied to individual-level data (>2,000 subjects with measures of genotype, circulating 25-OH-D and DSM-IV lifetime MDD) and summary-level data analyses.

A genetic association between 25-OH-D and MDD was tested by polygenic risk scores (PRS) and by estimating genetic correlation between traits. Two-sample Mendelian Randomization (2SMR) analyses tested the potential bidirectional causality between 25-OH-D and depression.

Results: In individual-level data, the 25-OH-D PRS was associated (p=1.4e-20) with 25-OH-D level, but not with lifetime MDD. Conversely, the MDD PRS was associated with MDD (p=2.3e-5), but not with 25-OH-D. In summary-level data analyses, the rg between the traits was low and not significant (-0.06, p=0.11). 2SMR analyses provided no evidence of a significant causal role of 25-OH-D for MD and vice versa.

Conclusions: The use of genomics tools indicated that shared etiology or direct causality between vitamin D concentrations and depression is unlikely: vitamin D may represent a marker rather than a cause, or consequence, of depression.

INTRODUCTION

Meta-analyses of large observational studies provided evidence of cross-sectional and longitudinal associations between circulating vitamin D and depression.[1] In >2,300 psychiatrically well-characterized participants from the Netherlands Study of Depression and Anxiety (NESDA), we previously showed[2] that concentrations of 25-hydroxyvitamin D (25-OH-D, the body reserve of vitamin D) were lower in patients with remitted and current depressive disorders as compared to healthy controls. Furthermore, in patients with current depression low 25-OH-D was associated with symptoms severity and chronicity of depressive disorders after 2 years. It is not trivial to disentangle whether this observational correlation stems from shared underlying aetiological roots or a direct causal relationship between vitamin D and depression. Alternatively, as highlighted by Ioannidis,[3] observational associations emerging in nutritional epidemiology may be the product of unresolved confounding. Nevertheless, several hypotheses based on preclinical data emerged about the potential impact of vitamin D on brain structure (vitamin D receptor is expressed in prefrontal cortex, amygdala and hippocampus) and pathophysiological processes relevant for mood.[4] Meta-analyses[5–7] pooling results from trials testing the effect of vitamin D supplementation on depression reported substantially inconclusive findings.

To move forward it is crucial to obtain a clearer knowledge of the exact nature of the vitamin D-depression relationship. Do both traits emerge from a common genetic liability? Does vitamin D truly exert a potential causal effect on depression, or is the effect in the reverse direction?

Genetic research has made enormous progress over the last years, and now provide unique opportunities to investigate shared risk and causality between traits applying new statistical tools and results from genome-wide association studies (GWAS).[8] In the latest GWAS[9] on 25-OH-D serum concentrations, the estimate of genetic correlation with depressive symptoms

was not-significant, indicating lack of shared genetic risk. Nevertheless this result may have been affected by the different genetic architectures of depression (highly polygenic with many genetic variants with small effects) and 25-OH-D (few genetic loci with relatively larger effect sizes), or by the use of data for depression from GWAS[10] relatively underpowered as compared to those currently available.

In the present study, we leveraged on results from the two largest GWAS on 25-OH-D (SUNLIGHT consortium: 79,366 samples)[9] and MDD (Psychiatric Genomics Consortium (PGC): 135,458 cases and 344,901 controls)[11]. We estimated the degree of genetic overlap between the two traits using both individual-level data (in NESDA[2]) and summary-level data analyses. Using summary data, Mendelian randomization analyses exploring the potential bidirectional causality between 25-OH-D and depression were also performed.

METHODS

All methods reported hereby are extensively described in eMaterials. Individual-level data analyses were based on up to 2,376 NESDA participants with measures of genotype, circulating 25-OH-D and DSM-IV lifetime diagnoses of MDD (1,750 cases). Polygenic risk scores (PRS) for 25-OH-D and MDD were built based on GWAS summary statistics from, respectively, SUNLIGHT consortium (79,366 samples)[9] and PGC (135,458 cases and 344,901 controls).[11] The PRS for increased 25-OH-D included the six independent genome-wide significant SNPs, jointly explaining an appreciable proportion (38%) of SNP-heritability in the discovery GWAS.[9] PRS for MDD was built based on the full polygenic signal from the PGC GWAS using LDpred method.[12] Same- and cross-trait associations of PRS with 25-OH-D concentrations and lifetime MDD diagnosis were estimated using regression models adjusted for sex and 10 ancestry-informative genetic principal components. The proportion of variance explained by GPRS was additionally estimated. In additional analyses focusing on MDD cases, the association between the two PRS and symptom severity measured by Inventory of Depressive Symptoms ($IDS\text{-}SR_{30}$)[13] was also estimated adjusting for sex and principal components.

Finally, summary-level data analyses were run using results from the GWAS of the two traits. Firstly, LD-score regression[14] was applied to GWAS summary statistics to estimate genome-wide genetic correlation between 25-OH-D and MD. Then, the six genome-wide significant SNPs for increased 25-OH-D were used as instrument in two-sample MR (2SMR)[15] testing the potential causal role of vitamin D on MDD using inverse-variance weighted fixed effects-meta-analysis (sensitivity analyses included median- and mode-mode base estimators). Opposite MR analyses testing the causal role of depression for 25-OH-D levels were additionally run using 37 independent genome-wide significant SNPs selected form the discovery GWAS[11] as instrument for MDD.

RESULTS

In analyses based on NESDA data, each SD increase in 25-OH-D levels was associated with lower odds of lifetime MDD (sex-adjusted OR=0.77,95%CIs=0.70-0.87, *p*=5.8e-6). The PRS for increased 25-OH-D was strongly associated (per SD increase: β=5.28, *p*=1.4e-20; full results in Table 1) with 25-OH-D level, explaining 3.5% of trait variance (figure 1). No association was found with MDD; furthermore, when focusing on 1,750 MDD cases, PRS for 25-OH-D was not associated (β =-0.17, 95%CIs=-0.80-0.46, *p*=0.60) with symptoms severity measured with IDS-SR_{30}. In contrast, the PRS for MDD was associated with MDD (per SD increase: OR=1.27, *p*=2.3e-5, explaining 1.7% of MDD liability variance, but not with 25-OH-D levels. Within cases, MDD PRS was associated with symptoms severity (β =1.29, 95%CIs=0.66-1.93, *p*=6.5e-5).

These results were complemented with summary-level data analyses. The estimate of genome-wide genetic correlation between 25-OH-D levels and MD was not significantly different from 0 (rg=-0.06,se= 0.04,*p*=0.11). Table 2 report the main results from 2SMR analyses; the genetic instrument for 25-OH-D was not causally related to MDD risk (OR=0.96, *p*=0.50). Similarly, no significant evidence of a causal role of MDD on 25-OH-D levels was found (β =-0.02, *p*=0.60).

DISCUSSION

We examined the nature of the association between vitamin D and depression using data and statistical tools from genomics. Evidence of a common genetic base between the two traits, emerging from shared etiology or through a direct causal mechanism, that could potentially explain their phenotypic association was not found. Even in data from the NESDA cohort, showing a strong phenotypic association between 25-OH-D and MDD,[2] the underlying polygenic risk for each trait was not associated with the phenotype of the other trait, indicating the lack of genetic overlap. In line with these findings, different MR analyses provided no evidence of a causal effect of 25-OH-D levels on major depression risk, despite the use of a strong instrument for 25-OH-D (explaining ~4% of variance) and input data drawn from large GWAS studies. Also, a reverse causal association from MDD to 25-OH-D was not detected. Based on the present findings, unresolved confounding[3] should be considered at this stage the most likely explanation for the association reported by observational studies. The relationship between blood concentrations of 25-OH-D levels may be indeed affected by several factors such health-related lifestyle, habits relates to sun exposure, physical activity, diet and comorbidity. The present findings represent a cautionary tale for further research testing the potential therapeutic effect of vitamin D supplementation on depression, as the expectations of a direct causal effect of vitamin D on mood should be substantially reconsidered.

Nevertheless, hypovitaminosis D in depression remains an important issue. As we previously demonstrated[2] one third of patients with established psychiatric diagnoses had 25-OH-D levels considered insufficient and risk for musco-skeletal complications. Normalization of vitamin D in depressed patients may therefore be important to prevent related complications and disability which may, in turn, indirectly impact on depression itself in particular during late-life. Nevertheless, applying genomics tools we found that that shared etiology or direct

causality between vitamin D concentrations and depression are unlikely: vitamin D may represent a health marker rather than a cause, or consequence, of depression.

Table 1. Same- and cross-trait associations of polygenic risk scores with circulating 25-hydroxyvitamin D and Major Depressive Disorder in >2,000 participants from NESDA.

	25-OH-D			MDD		
	N=2,376	mean = 64.6 *(28.0) nmol/L*		1,771 cases + 370 controls		
PRS	β	**95%CIs**	***p***	**OR**	**95%CIs**	***p***
25(OH)D	5.28	4.18 - 6.39	1.4E-20	0.93	8.29 - 1.04	0.20
MDD	-0.57	-1.70 - 0.55	0.32	1.27	1.14 - 1.43	2.3E-05

Results from linear (outcome: 25-OH-D) and binary logistic (outcome: MDD) regression analyses adjusted for sex and ten ancestry-informative genetic principal components.
Unit of measure 25(OH)D: nmol/l (multiply by 0.4 to obtain ng/ml).

Table 2. Two-samples Mendelian Randomization analyses based on GWAS summary statistics estimating causal effects between circulating 25-hydroxyvitamin D and Major Depressive Disorder

			Inverse Variance Weighted			Weighted Median			Weighted Mode		
Exposure	**Outcome**	**N SNPs**	**β/OR**	**95%CIs**	***p***	**β/OR**	**95%CIs**	***p***	**β/OR**	**95%CIs**	***p***
25-OH-D	**MD**	**6**[a]	0.96	0.90 - 1.10	0.50	0.98	0.89 - 1.12	0.68	0.98	0.88 - 1.09	0.71
MD	**25(OH)D**	**37**	-0.02	-0.04 - 0.01	0.25	-0.002	-0.04 - 0.03	0.90	0.01	-0.05 - 0.08	0.65

Unit of measures: 25-OH-D, 1 unit increase in (log)concentrations; MDD, 1 log-unit increase in risk.
SNP effects heterogeneity assessment:

- 25-OH-D causal for MDD, Cochran's Q p=0.87; MDD causal for 25-OH-D, Cochran's Q p=0.18
- leave-one-out SNP IVW analyses (eFigure1b and eFigure2b) indicated that the estimates were substantially not influenced by individual SNPs

[a] eTable2 shows the estimated power for each of the 6 vitamin D-associated SNP to be found significantly (α=0.05) associated with MDD in PGC GWAS assuming a true causal link between 25-OH-D and MDD. None of the 6 SNPs, for which adequate statistical power was established, was found to be associated with MDD, additionally confirming that that the phenotypic link between Vitamin-D and MDD is not attributable to a causal effect of Vitamin-D on MDD liability.

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Figure legend

Figure 1. Proportion of trait variance explained by polygenic risk scores for increased 25-hydroxyvitamin D and MDD in > 2,000 participants from NESDA.

See eMaterials section 2.3 for estimation of variance explained by PRS.

P-values from Table 1

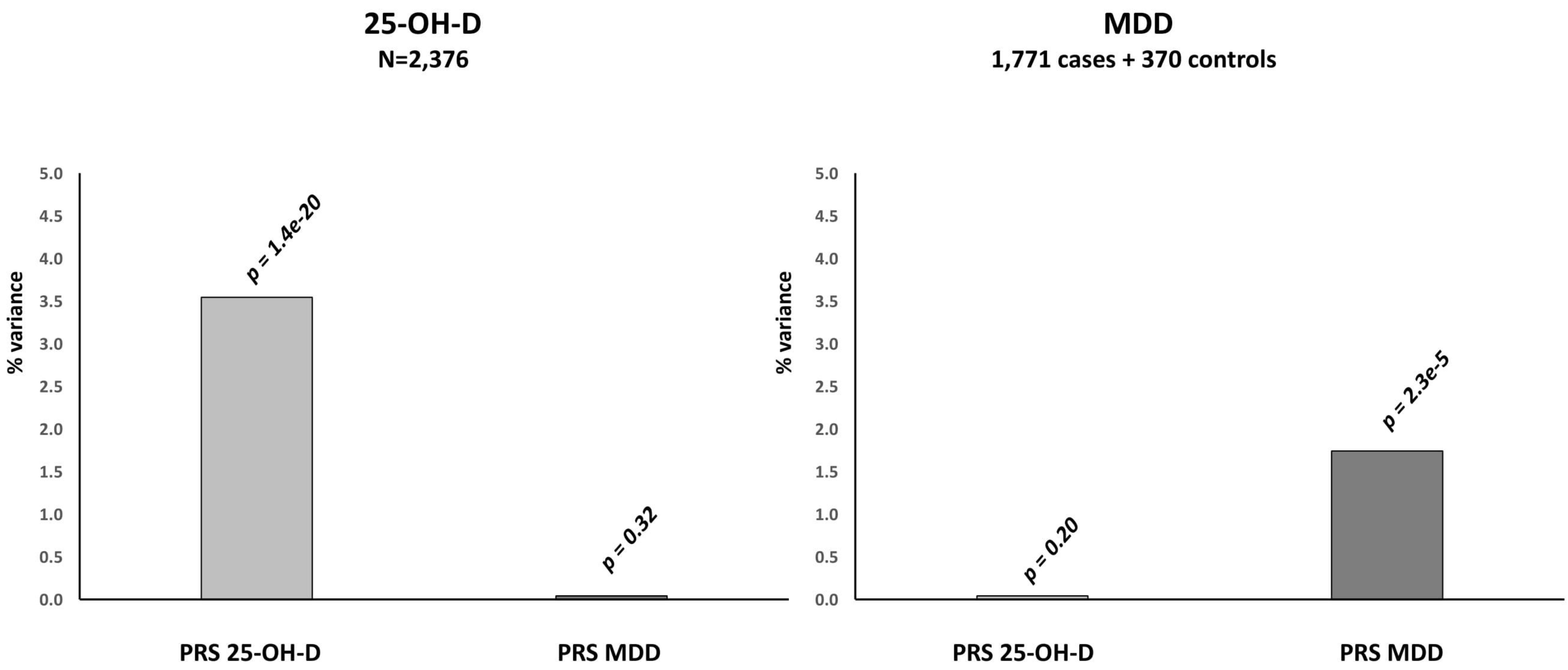
25-OH-D
N=2,376
MDD
1,771 cases + 370 controls
% variance
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
p = 1.4e-20
p = 0.32
p = 0.20
p = 2.3e-5
PRS 25-OH-D
PRS MDD
PRS 25-OH-D
PRS MDD

Figure 1