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No Clear Support for a Role for Vitamin D in Parkinson's Disease: A Mendelian Randomization Study

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Abstract

Background—Observational studies have found that relative to healthy controls, patients with Parkinson's disease have lower circulating concentrations of 25-hydroxyvitamin D, a clinical biomarker of vitamin D status. However, the causality of this association is uncertain. We undertook a Mendelian randomization study to investigate whether genetically decreased 25-hydroxyvitamin D concentrations are associated with PD to minimize confounding and prevent bias because of reverse causation.

Methods—As instrumental variables for the Mendelian randomization analysis, we used 4 single-nucleotide polymorphisms that affect 25-hydroxyvitamin D concentrations (rs2282679 in *GC*, rs12785878 near *DHCR7*, rs10741657 near *CYP2R1*, and rs6013897 near *CYP24A1*). Summary effect size estimates of the 4 single-nucleotide polymorphisms on PD were obtained from the International Parkinson's Disease Genomics Consortium (including 5333 PD cases and 12,019 controls). The estimates of the 4 single-nucleotide polymorphisms were combined using an inverse-variance weighted meta-analysis.

Results—Of the 4 single-nucleotide polymorphisms associated with 25-hydroxyvitamin D concentrations, one (rs6013897 in *CYP24A1*) was associated with PD (odds ratio per 25-hydroxyvitamin D-decreasing allele, 1.09; 95% confidence interval, 1.02–1.16; $P = 0.008$), whereas no association was observed with the other 3 single-nucleotide polymorphisms ($P > 0.23$). The odds ratio of PD per genetically predicted 10% lower 25-hydroxyvitamin D concentration, based on the 4 single-nucleotide polymorphisms, was 0.98 (95% confidence interval, 0.93–1.04; $P = 0.56$).

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Conclusions—This Mendelian randomization study provides no clear support that lowered 25-hydroxyvitamin D concentration is causally associated with risk of PD.

Keywords

Mendelian randomization; Parkinson's disease; vitamin D

Parkinson's disease (PD) is the second most common form of neurodegeneration among the elderly population. PD is clinically characterized by tremors, rigidity, slowness of movement, and postural imbalance. The disease is likely a result of combinations of genetic and environmental factors.[1–4] Among environmental factors, evidence indicates that vitamin D may be implicated in the development of PD.[5] Vitamin D is a steroid hormone with pivotal roles in a variety of organs, including the brain.[6,7] It is obtained from the diet and can be made in the skin from sunshine exposure. Systematic reviews and a meta-analyses of observational studies have found that patients with PD have significantly lower circulating concentrations of 25-hydroxyvitamin D (25OHD), a clinically relevant and stable biomarker of vitamin D status, compared with healthy controls.[8,9] Moreover, vitamin D supplementation and working outdoors have been observed to be inversely associated with PD.[10] It remains unclear, however, whether the observational associations are causal or related to confounding or reverse causation bias. The onset of PD may result in reduced outdoor activity and dietary changes, which consequently could lead to reduced circulating 25OHD concentrations because of reverse causation.

Genetic studies have provided the opportunity to assess the genetic determinates of blood 25OHD concentrations. A genome-wide association study (GWAS) identified 4 genetic variants (single-nucleotide polymorphisms [SNPs]) that affect 25OHD concentration,[11] and a recent meta-analysis of 21 cohort studies provided estimates of the percentage change in 25OHD concentration per effect allele for the four 25OHD-associated genetic variants.[12]

Mendelian randomization is an approach that uses genetic variants associated with the phenotype (eg, 25OHD concentration) as proxies for the phenotype to determine the causal association between the phenotype and disease risk. This method minimizes some of the crucial limitations of observational studies, such as confounding because genetic variants are randomly allocated during inception. Reverse causation bias is precluded because genotypes are not affected by disease. We therefore implemented a Mendelian randomization approach to evaluate the hypothesis that genetically lowered 25OHD concentration is associated with PD.

Methods

Genetic Variants and Data Sources

This Mendelian randomization was performed using summary-level data from GWASs on 25OHD concentration and PD. As instrumental variables, we selected all SNPs associated with 25OHD concentration at genome-wide statistical significance ($P < 5 \times 10^{-8}$) in a GWAS on vitamin D (the Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits [SUNLIGHT]), which included 33,996 individuals of European

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descent from 15 cohorts.[11] The 4 SNPs were uncorrelated and were located in or close to the following genes: *GC* (rs2282679), *DHCR7* (rs12785878), *CYP2R1* (rs10741657), and *CYP24A1* (rs6013897). These genes encode enzymes and carrier proteins involved in vitamin D synthesis or metabolism. Effect-size estimates (β coefficients and standard errors) for the 25OHD-asssociated SNPs were not available in the SUNLIGHT GWAS. However, summary effect-size estimates for the four 25OHD-associated SNPs were reported in a study from the collaboration investigating vitamin D and the risk of cardiovascular disease and related traits (D-CarDia).[12] D-CarDia includes 21 cohorts, totaling 42,024 individuals of European ancestry from the United States, Canada, the United Kingdom, Sweden, Finland, and Germany.[12] A linear regression model was fitted for each SNP, with natural log-transformed 25OHD as the dependent variable and adjusted for age, sex, geographical site, and/or principal components from the population stratification analysis as well as month of blood sample collection and laboratory batch, where relevant.[12] The β coefficients were obtained from the linear regression model with natural log-transformed 25OHD concentration. The percentage difference in 25OHD concentration per effect allele was obtained from (exp[β] − 1) × 100. The analyses were conducted separately for each cohort, and results were summarized using meta-analysis.[12] We extracted the summarized results for each of the 4 SNPs.

Summary effect-size estimates of the four 25OHD-related SNPs on PD were acquired from the International Parkinson's Disease Genomics Consortium (IPDGC).[4] The 5 PD GWAS data sets included in the IPDGC were from the United States, the United Kingdom, Germany, and France and consisted of 5333 PD cases and 12,019 controls, with genotyped and imputed data on 7,689,524 SNPs.[4] Because our Mendelian analysis is based on summary statistics acquired from previously published GWASs, we have not sought additional ethical approval.

Statistical Analysis

An instrumental variable (IV) was constructed for each 25OHD-associated SNP by dividing the effect-size estimate (ln[OR]) for the SNP-PD association (acquired from the IPDGC meta-analysis) by the effect-size estimate (exp[β] − 1) × 100) for the SNP–25OHD association (acquired from the meta-analysis of 21 cohorts in D-CarDia); see Supplemental Figure 1. The 4 IV estimates were summarized using an inverse-variance weighted meta-analysis,[13] and heterogeneity among the IV estimates was quantified using the I^2 statistic. All results are presented as the odds ratio of PD per 10% decrease in 25OHD concentration. All tests were 2-sided and considered statistically significant at P 003C; 0.05. The analyses were conducted in Stata, version 14.1 (StataCorp, College Station, TX).

Assessment of Pleiotropy

The weighted median and MR-Egger regression methods[14,15] were used to assess and account for pleiotropy (ie, where a genetic variant affects more than 1 phenotypic characteristic). Furthermore, a publicly available GWAS database[16] was searched for associations of the 25OHD-associated SNPs with other phenotypes.

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Power Calculation

We estimated the statistical power for the Mendelian randomization analysis at a 2-sided α of 0.05 using the online tool mRnd (http://cnsgenomics.com/shiny/mRnd/).[17]

Results

Of the four 25OHD-associated SNPs, the SNP in the *GC* locus was most strongly associated with 25OHD concentration, with an 8.45% change in 25OHD concentration per effect allele (Table 1). One of the SNPs (rs6013897 in the *CYP24A1* locus) was associated with PD (OR per 25OHD-decreasing allele, 1.09; 95% CI, 1.02–1.16; $P = 0.008$), whereas no association was observed with the other 3 SNPs ($P > 0.23$; Table 1). The OR of PD per genetically predicted 10% lower 25OHD concentration conferred by the four 25OHD-lowering alleles was 0.98 (95% CI, 0.93–1.04; $P = 0.56$), with heterogeneity among the IV estimates (I^2 = 63.1%); see Supplemental Figure 2. A sensitivity analysis using the weighted median method yielded similar results (OR, 0.97; 95% CI, 0.92–1.03). In MR-Egger regression analysis, there was no clear evidence of pleiotropy (MR-Egger intercept, −0.064; $P = 0.23$) or a causal effect ($P = 0.23$). Our power calculation showed that we had about 80% power to detect an OR of 1.25 or higher.

None of the 25OHD-associated genetic variants were associated with other phenotypes at genome-wide significance ($P < 5 \times 10^{-8}$), but they had associations at nominal significance ($P < 0.05$) with several phenotypes, for example, years of education, glomerular filtration rate (a measure of kidney function), various anthropometric measures, blood pressure, and cholesterol and serum urate concentrations (Supplemental Table 1).

Discussion

This is the first Mendelian randomization study investigating the potential role of vitamin D in the development of PD. Our results showed no association between genetically predicted lower vitamin D concentration and PD. The OR for the association was close to null. Thus, our study decreases the probability that 25OHD levels have a clinically relevant impact on the risk of PD.

Several previous Mendelian randomization studies have assessed the association between genetically predicted 25OHD and other diseases, including other neurodegenerative diseases and brain disorders. Using the same genetic instrument as in the present study, those studies have provided evidence that decreased 25OHD concentration is associated with increased risk of Alzheimer's disease,[18] multiple sclerosis,[19,20] and hypertension[21] but not associated with schizophrenia[22] or coronary artery disease.[23]

Our findings corroborate the results from a recent prospective study of 12,762 US adults, (including 67 incident PD cases identified during 19 years of follow-up), which showed no association between 25OHD concentration and PD risk, regardless of how serum 25OHD was modeled.[24] However, another prospective study of 3173 Finnish adults (including 50 PD cases diagnosed over a 29-year follow-up period) found that serum 25OHD concentration was significantly inversely associated with risk of PD.[25] Several case-control studies have

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found that PD patients have lower circulating 25OHD concentrations compared with healthy controls.[8,9] The observational associations are possibly explained by reverse causation bias or confounding from diet, obesity, or lifestyle factors (eg, physical activity, which is associated with both sunlight exposure and risk of PD[2]. Furthermore, low vitamin D status may be just a general marker of poor health.[26]

Although Mendelian randomization studies prevent bias because of reverse causation and minimize bias because of confounding, results from these studies could be biased by pleiotropy. Our sensitivity analyses showed no clear evidence of pleiotropic effects. However, because we used only 4 SNPs, the MR-Egger approach lacks statistical power. We also searched a GWAS database to investigate whether the 25OHD-associated genetic variants are associated with other phenotypes. It is interesting to note that the 25OHD-decreasing A allele of rs6013897 in the *CYP24A1* locus, which was associated with higher odds of PD, is associated with lower serum urate (uric acid). Urate is a potent antioxidant that appears to protect against dopaminergic neuron degeneration and has been inversely associated with risk of PD in prospective studies[2] and in a Mendelian randomization study.[27] Hence, the observed association between the pleiotropic *CYP24A1* locus and PD in this study may be mediated by lower serum urate concentrations.

A shortcoming of this Mendelian randomization study is that we were unable to examine a potential nonlinear association between 25OHD concentration and PD risk. We therefore could not assess whether vitamin D deficiency affects the risk of PD. Our study population only included individuals of European ancestry with 25OHD concentrations in the middle of the distribution. Our null results may also have been influenced by canalization, in which physiologic buffering may have diminished the effect of genetically lowered vitamin D levels. Although we have not observed this phenomenon in both a Mendelian randomization study of Alzheimer's disease[18] and multiple sclerosis,[19] we cannot exclude that this may have influenced our results for PD. Another limitation is that the four 25OHD-associated SNPs explain a relatively small proportion of the variation in 25OHD concentrations (3.6% in a large study of individuals of European descent[28]. This limited the statistical power to detect a weak association between genetically predicted 25OHD concentration and PD.

In conclusion, this Mendelian randomization study provides no evidence that circulating 25OHD concentration plays a major role in the development of PD in individuals of European ancestry. However, this study could not rule out a small effect of 25OHD on PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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TABLE 1

Characteristics of the 25OHD-associated single-nucleotide polymorphisms used as instrumental variables

						Vitamin D results		Parkinson's disease results[a]	
SNP	**Locus**	**Chr**	**Effect allele[b]**	**Allele frequency[c]**	**Pathway**	**Effect on 25OHD (% change)[d]**	***P* for association with 25OHD[e]**	**OR (95% CI) of PD per effect allele[b]**	***P* for association with PD**
rs2282679	*GC*	4	G	0.28	Metabolism	−8.45	1.9×10^{-109}	0.97 (0.91–1.02)	0.233
rs12785878	*DHCR7*	11	G	0.25	Synthesis	−3.70	2.1×10^{-27}	1.00 (0.94–1.06)	0.977
rs10741657	*CYP2R1*	11	G	0.61	Synthesis	−3.12	3.3×10^{-20}	1.00 (0.95–1.05)	0.943
rs6013897	*CYP24A1*	20	A	0.19	Metabolism	−1.85	6.0×10^{-10}	1.09 (1.02–1.16)	0.008

25OHD, 25-hydroxyvitamin D; Chr, chromosome; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

[a] Summary-level data, including ln(ORs), standard errors, and *P* values, per effect allele for Parkinson's disease were acquired from the IPDGC.

[b] 25OHD-decreasing allele.

[c] Allele frequency in the IPDGC.

[d] The effect size estimates represent the percentage change in 25OHD concentration per effect allele (25OHD-decreasing allele) and were obtained from a meta-analysis of 21 European ancestry cohort studies included in the D-CarDia collaboration.

[e] *P* for the association between the single-nucleotide polymorphism and 25OHD concentration in the SUNLIGHT consortium.

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