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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Dairy Intake and Parkinson's Disease: A Mendelian Randomization Study

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ABSTRACT: Background: Previous prospective studies highlighted dairy intake as a risk factor for Parkinson's disease (PD), particularly in men. It is unclear whether this association is causal or explained by reverse causation or confounding.

Objective: The aim is to examine the association between genetically predicted dairy intake and PD using two-sample Mendelian randomization (MR).

Methods: We genotyped a well-established instrumental variable for dairy intake located in the lactase gene (rs4988235) within the Courage-PD consortium (23 studies; 9823 patients and 8376 controls of European ancestry).

Results: Based on a dominant model, there was an association between genetic predisposition toward higher dairy intake and PD (odds ratio [OR] per one serving per day = 1.70, 95% confidence interval = 1.12–2.60, $P = 0.013$) that was restricted to men (OR = 2.50 [1.37–4.56], $P = 0.003$; P -difference with women = 0.029).

Conclusions: Using MR, our findings provide further support for a causal relationship between dairy intake and higher PD risk, not biased by confounding or reverse causation. Further studies are needed to elucidate the underlying mechanisms. © 2022 International Parkinson and Movement Disorder Society

Key Words: dairy intake; Parkinson's disease; Mendelian randomization

Previous studies highlighted dairy intake as a risk factor of Parkinson's disease (PD). A meta-analysis of prospective studies reported a 40% increased PD risk in participants with the highest intake.¹ It is unclear whether the association is causal or explained by confounding or reverse causation, given the long prodromal phase of PD.²

Mendelian randomization (MR) uses genetic variants associated with exposures as instrumental variables (IVs) to estimate causal relationships between exposures and outcomes. MR analyses are less likely to be biased by confounding or reverse causation than observational studies if a set of assumptions are met.³ The association between a single-nucleotide polymorphism (SNP), located upstream of the lactase gene (LCT-13190, rs4988235-C/T), and lactase persistence (ie, the ability to digest lactose) is well established, and rs4988235 has been used as an IV for dairy intake in many studies.^{4,8}

We examined whether the dairy intake–PD association is causal by performing a two-sample MR analysis.

Patients and Methods

Two-Sample MR

Effect size estimates and standard errors (SEs) for SNP-exposure and SNP-outcome associations from independent samples are used to estimate the causal exposure–outcome association. To be valid IVs, SNPs (1) should be associated with the exposure, (2) should not be directly associated with the outcome except through the exposure, and (3) should not be associated with unmeasured confounders of the exposure–outcome association (no horizontal pleiotropy).³

rs4988235–Dairy Association

We used rs4988235 as the IV for dairy intake. TT/TC genotypes are associated with lactase persistence and the ability to digest lactose and CC with nonpersistence. In the largest Mendelian Randomization of Dairy Consumption Working Group study (N = 184,802), TC + TT genotypes were associated with 0.20 (SE = 0.029, $P = 3.15 \times 10^{-12}$) more dairy servings per day than the CC genotype.⁴ The F-statistic⁹ is 3291.6, and the proportion of the exposure variance explained (R^2)¹⁰ is 1.75%, in agreement with previous estimates.¹¹

The association between rs4988235 and dairy consumption has been replicated in several populations of European ancestry. This provides a biological basis for using this variant in MR studies in European populations to increase the plausibility of the assumptions required for causal inference.⁶

rs4988235–PD Association

We used rs4988235 genotypes (NeuroChip) from 26 sites included in Courage-PD (Supplementary

Methods in Appendix S1). Within each study, the frequency of rs4988235-TC + TT genotypes was compared in patients and controls of European ancestry using logistic regression, adjusted for sex and the first four principal components. For our main analyses, we excluded studies with ≤ 5 patients or controls with the TC + TT or CC genotypes. We meta-analyzed log-odds ratios (OR) and SEs using a fixed or random (if $I^2 > 25\%$) effects model.

We compared the rs4988235-PD association in Courage-PD and in data from the International Parkinson Disease Genomics Consortium (iPDGC), overall¹² and by sex.¹³

Reverse MR Analysis

We examined whether genetic liability toward PD is associated with dairy intake through a reverse MR analysis where PD genetic susceptibility was the exposure and dairy intake the outcome. We used 38 top SNPs associated with PD in an iPDGC GWAS as IVs¹⁴ and excluded 1 palindromic SNP. We extracted summary statistics for these SNPs from the UK Biobank GWAS for milk intake ($N = 64,943$; ukb-b-2966).¹⁵ For PD, we did not use the largest and most recent iPDGC GWAS, because it included UK Biobank participants¹² and overlap of SNP-exposure and SNP-outcome associations leads to bias. ORs are scaled to 1-unit increase in log odds of liability to PD.¹⁶

Statistical Methods

We used the *TwoSampleMR*,¹⁷ *phenoscanner*,^{18,19} and *ieugwasr*¹⁵ R packages (R Foundation for Statistical Computing, Vienna, Austria), Stata (StataCorpLP, College Station, TX, USA), and SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Two-sided P -values ≤ 0.05 were considered statistically significant.

The MR estimate (Wald ratio) for the dairy products-PD association was computed as the exponentiated ratio of the rs4988235-PD association to the rs4988235-exposure association.³ Sensitivity analyses are described in Supplementary Methods in Appendix S1.

For reverse MR analyses, we used the random-effects inverse-variance-weighted method for multiple genetic instruments. Heterogeneity between IVs was tested using the Cochran's Q -statistic. In sensitivity analyses, we used other MR approaches less sensitive to pleiotropic effects (MR-Egger, weighted median method and mode-based methods, MR-PRESSO [Mendelian Randomization Pleiotropy RESidual Sum and Outlier]).³

Standard Protocol Approvals, Registrations, and Patient Consents

Individual studies received approval from institutional review boards from their countries. Informed

consent was obtained from participants or from a caregiver, legal guardian, or other proxy.

Data Availability

All the results can be reproduced using the Supplementary Material in Appendix S1.

Results

MR Analysis of the Relation between Dairy Intake and PD

Data were available for 10,198 patients and 8686 controls. After three sites with ≤ 5 patients or controls carrying the CC or TC + TT genotypes were excluded, analyses were based on 9823 patients and 8376 controls (Table S1 in Appendix S1).

The distribution of rs4988235 is presented in Table S2 in Appendix S1. rs4988235-T frequency was highest in Scandinavian countries and lowest in Italy. Figure 1 (overall) and Figures S1–S3 (stratified analyses) show forest plots of the rs4988235-PD association by site. Overall, rs4988235-TC + TT genotypes were more frequent in PD patients than controls (OR = 1.11, 95% confidence interval [CI] = 1.02–1.21, $P = 0.013$; $I^2 = 24.5\%$, P -heterogeneity = 0.14; Table 1). This association was present in men (OR = 1.20, 95% CI = 1.07–1.35, $P = 0.003$; $I^2 = 0.0\%$, P -heterogeneity = 0.72) but not in women. In men, the association was similar in countries with rs4988235-T

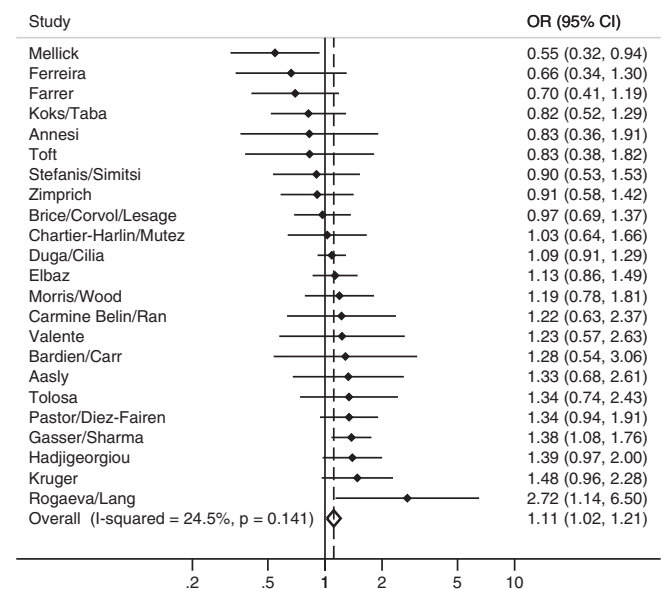


FIG. 1. Forest plot of the association between rs4988235 and PD under a dominant model. Abbreviations: OR, odds ratio; CI, confidence interval. ORs were pooled using a fixed-effect meta-analysis. Associations between rs4988235 and PD under a dominant model (TC + TT vs. CC genotypes) are presented in each study from the Courage-PD consortium.

TABLE 1 Genetic association between rs4988235 and PD and causal effect of genetically predicted dairy product intake on PD, overall and by sex, age, and PD duration

Characteristics	N Studies	N Patients	N Controls	Genetic association				MR estimate per one-serving per day			
				OR (95% CI)		P-value	I ² (%)	P-het.	OR (95% CI)		P-diff.
				TC + TT vs. CC					TC + TT vs. CC	P-value	
All participants	23	9823	8376	1.11 (1.02–1.21)	0.013	24.5	0.14	1.70 (1.12–2.60)	0.013	–	
Men	21	5701	3770	1.20 (1.07–1.35)	0.003	0.0	0.72	2.50 (1.37–4.56)	0.003	–	
Women	20	3586	4180	1.01 (0.89–1.14)	0.91	18.0	0.23	1.04 (0.56–1.92)	0.91	0.029	
Age ≤67 years	15	3205	3495	1.05 (0.89–1.25)	0.55	26.7	0.16	1.30 (0.55–3.04)	0.55	–	
Age >67 years	15	3186	2710	1.14 (0.94–1.38)	0.19	38.8	0.062	1.90 (0.73–4.96)	0.19	0.56	
PD duration ≤7 years	20	4293	7148	1.10 (1.00–1.22)	0.060	0.0	0.48	1.62 (0.98–2.69)	0.060	–	
PD duration >7 years	20	3630	7542	1.16 (0.98–1.38)	0.089	40.4	0.032	2.08 (0.89–4.86)	0.089	0.13	

Only studies with >5 patients and controls with the CC and TC + TT genotypes were included. Overall, we excluded three sites; in stratified analyses, we excluded additional sites (Table S2 in Appendix S1).

For genetic associations, ORs and their 95% CI were computed using fixed (if I² ≤ 25%) or random (if I² > 25%) effects meta-analysis.

Abbreviations: PD, Parkinson's disease; MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; P-het., P-value for heterogeneity; P-diff., P-value for the difference between subgroups.

frequency below (OR = 1.19, 95% CI = 1.03–1.38, $P = 0.019$) or above (OR = 1.22, 95% CI = 0.99–1.51, $P = 0.061$) the median (50.6%). Associations by median age or disease duration were similar. No individual study explained the association in leave-one-out meta-analysis (not shown).

Table 1 presents the MR estimates. Higher genetically predicted dairy intake was associated with higher PD risk (OR_{1 serving/day} = 1.70, 95% CI = 1.12–2.60, $P = 0.013$). The association was present in men (OR = 2.50, 95% CI = 1.37–4.56, $P = 0.003$) but not in women (P -difference = 0.029). In men, MR estimates were similar (P -difference = 0.89) in countries with rs4988235-T frequency below (OR = 2.39, 95% CI = 1.15–4.97, $P = 0.019$) or above (OR = 2.73, 95% CI = 0.95–7.85, $P = 0.061$) the median. Associations by median age (P -difference = 0.56) or disease duration (P -difference = 0.13) were similar.

Analyses that included sites with ≤5 patients or controls with the TC + TT or CC genotypes yielded similar results (Table S3 in Appendix S1).

We replicated the rs4988235–PD association in iPDGC (OR per T allele = 1.12, 95% CI = 1.08–1.17, $P = 7.41 \times 10^{-9}$; Table S4 in Appendix S1) and checked that our findings remained after exclusion of 2692 patients and 1668 controls from four sites overlapping with iPDGC (MR estimate in men = 2.08, 95% CI = 1.07–4.04, $P = 0.032$). In iPDGC, contrary to our findings, the association was present in women (OR = 1.08, 95%

CI = 1.03–1.12, $P = 0.00072$) and men (OR = 1.10, 95% CI = 1.06–1.14, $P = 2.65 \times 10^{-7}$).

rs4988235 is ~1,144,000 base-pairs away from rs57891859, a known PD-associated SNP.¹² However, both SNPs are not in LD ($r^2 = 0.005$),²⁰ and the rs4988235–PD association remained after adjustment for rs57891859 (OR = 1.10, 95% CI = 1.01–1.20, $P = 0.02$).

According to PhenoScanner, rs4988235-T is positively associated with adiposity traits and inversely associated with low-density lipoprotein and total cholesterol (Table S4 in Appendix S1).

Reverse MR Analysis

Table S5 in Appendix S1 shows SNPs used for reverse MR analyses. There was no association between genetic liability toward PD and dairy intake (Table S6 in Appendix S1).

Discussion

Our findings suggest that higher genetically predicted dairy intake is associated with increased PD risk. A recent study that examined the relation between rs4988235 and several neurodegenerative diseases reported positive SNP–PD associations in iPDGC, in agreement with our findings, but did not perform a formal MR analysis and did not perform stratified analyses.²¹

In a meta-analysis of five prospective studies (USA, $n = 3$; Finland, $n = 1$; Greece, $n = 1$; 1083 PD

patients), the hazard ratio (HR) of PD for highest versus lowest dairy intake was 1.40 (95% CI = 1.20–1.63; $I^2 = 8.2\%$, P -heterogeneity = 0.37).¹ This association was present in men (HR = 1.66, 95% CI = 1.29–2.14) but not in women (HR = 1.15, 95% CI = 0.85–1.56). While our findings showed a similar sex difference, iPDGC data did not show a sex difference in the rs4988235–PD association.¹³ Therefore, additional studies are needed to examine this association in men and women and to understand the biological basis underlying a potential sex difference.

The mechanisms underlying the association between dairy intake and PD are unknown. Observational studies suggest that it is unlikely to be due to calcium or vitamin D, as only calcium and vitamin D from dairy products were positively associated with PD; in addition, MR studies do not support a causal association between calcium or vitamin D levels and PD.^{22,23} Others hypothesized that dairy intake increased PD risk by reducing uric acid,¹ but MR studies do not support a causal association between uric acid and PD.²⁴ Nevertheless, dairy intake could alter the absorption of other neuroprotective compounds.²⁵ The hypothesis that dairy products may be contaminated by pesticides was raised in the Honolulu-Asia Aging Study; milk intake was associated with *substantia nigra* neuron loss and heptachlor epoxide residues in brains of deceased participants without PD.²⁶ However, we found that the rs498823–PD association was similar across different parts of the world or by age; because pesticide use varies by location and time, contamination by pesticides is unlikely to fully explain the association. Previous studies showed that rs4988235 is associated with higher body mass index (BMI), and MR studies support a causal effect of dairy intake on BMI.^{4,7,8} Therefore, BMI could be a mediator of the dairy intake–PD association if BMI had an effect on PD (vertical pleiotropy). However, because MR studies suggest that higher BMI is associated with lower PD risk,^{27,28} the positive association between dairy intake and PD cannot be explained by the negative indirect effect of dairy intake on PD mediated by BMI, and there must be a positive direct effect.²⁹ Other mechanisms could involve changes in microbiota^{30,31} or lipid levels⁵ related to dairy consumption.

Our study has several strengths. We used data from a large international consortium in which PD patients were carefully assessed by movement disorders specialists and replicated the rs4988235–PD association in iPDGC. Associations were similar in stratified analyses (age, disease duration), thus suggesting that survival or incidence-prevalence biases are unlikely. The main limitation is that only one IV was available for dairy intake, which does not allow to use MR approaches that are robust to pleiotropy (eg, MR-Egger, MR-PRESSO). However, rs4988235 is a well-established genetic marker for dairy intake, with solid biological basis and functional evidence.⁴ In addition, a large study failed to

detect associations of rs4988235 with intake of fruit, vegetables, fish, fast food, and soda drinks, which suggests that the effect of rs4988235 on milk intake is disentangled from other dietary habits.³²

In conclusion, our findings suggest that dairy intake increases PD risk. Therefore, diets with limited milk intake (eg, Mediterranean diet) may be beneficial with respect to PD.^{33,34} Further studies are needed to understand the underlying mechanisms. ■

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APPENDIX

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Data Availability Statement

All the results from the paper can be reproduced using the Supplementary material.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Where Do Parkinson's Disease Patients Look While Walking?

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