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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.

References

1. Palacios N, Gao X, McCullough ML, et al. Caffeine and risk of Parkinson's disease in a large cohort of men and women. Mov Disord 2012;27(10):1276–1282.
2. Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52(3):276–284.
3. Froestl W, Muhs A, Pfeifer A. Cognitive enhancers (nootropics). Part 1: drugs interacting with receptors. Update 2014. J Alzheimer's Dis 2014;41(4):961–1019.
4. Rivera-Oliver M, Diaz-Rios M. Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases: a review. Life Sci 2014;101(1–2):1–9.
5. Svenningsson P, Hall H, Sedvall G, Fredholm BB. Distribution of adenosine receptors in the postmortem human brain: an extended autoradiographic study. Synapse 1997;27(4):322–335.
6. Mori A. International review of neurobiology. Adenosine receptors in neurology and psychiatry.Preface. Int Rev Neurobiol 2014;119: xv–xvi.
7. Pinna A, Serra M, Morelli M, Simola N. Role of adenosine A2A receptors in motor control: relevance to Parkinson's disease and dyskinesia. J Neural Transm 2018;
8. Kase H, Aoyama S, Ichimura M, et al. Progress in pursuit of therapeutic A2A antagonists: the adenosine A2A receptor selective antagonist KW6002: research and development toward a novel nondopaminergic therapy for Parkinson's disease. Neurology 2003; 61(11 Suppl 6):S97–S100.
9. Mizuno Y, Kondo T. Japanese Istradefylline study G. adenosine A2A receptor antagonist istradefylline reduces daily OFF time in Parkinson's disease. Mov Disord 2013;28(8):1138–1141.
10. Chen JF, Cunha RA. The belated US FDA approval of the adenosine A2A receptor antagonist istradefylline for treatment of Parkinson's disease. Purinergic Signal 2020;16(2):167–174.
11. Ishibashi K, Miura Y, Wagatsuma K, Toyohara J, Ishiwata K, Ishii K. Occupancy of adenosine A2A receptors by istradefylline in patients with Parkinson's disease using (11)C-preladenant PET. Neuropharmacology 2018;143:106–112.
12. Ishibashi K, Miura Y, Wagatsuma K, Toyohara J, Ishiwata K, Ishii K. Adenosine A2A receptor occupancy by long-term Istradefylline Administration in Parkinson's disease. Mov Disord 2021;36(1):268–269.
13. Nehlig A. Interindividual differences in caffeine metabolism and factors driving caffeine consumption. Pharmacol Rev 2018;70(2): 384–411.
14. Lammertsma AA, Hume SP. Simplified reference tissue model for PET receptor studies. Neuroimage 1996;4(3 Pt 1):153–158.
15. Wu Y, Carson RE. Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging. J Cereb Blood Flow Metab 2002;22(12):1440–1452.
16. Kapur S, Zipursky RB, Jones C, et al. The D2 receptor occupancy profile of loxapine determined using PET. Neuropsychopharmacology 1996;15(6):562–566.
17. Remington G, Mamo D, Labelle A, et al. A PET study evaluating dopamine D2 receptor occupancy for long-acting injectable risperidone. Am J Psychiatry 2006;163(3):396–401.
18. Ishikawa M, Ishiwata K, Ishii K, et al. High occupancy of sigma-1 receptors in the human brain after single oral administration of fluvoxamine: a positron emission tomography study using [11C] SA4503. Biol Psychiatry 2007;62(8):878–883.
19. Zhou X, Boellaard R, Ishiwata K, et al. In vivo evaluation of (11)C-Preladenant for PET imaging of adenosine A2A receptors in the conscious monkey. J Nucl Med 2017;58(5):762–767.
20. Nieber K. The impact of coffee on health. Planta Med 2017;83(16): 1256–1263.
21. Postuma RB, Anang J, Pelletier A, et al. Caffeine as symptomatic treatment for Parkinson disease (cafe-PD): a randomized trial. Neurology 2017;89(17):1795–1803.

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

Cloé Domenighetti, MSc,[1]
Pierre-Emmanuel Sugier, PhD,[1]
Ashwin Ashok Kumar Sreelatha, MSc, MTech,[2]
Claudia Schulte, MSc,[3,4] Sandeep Grover, PhD,[2]
Océane Mohamed, MSc,[1] Berta Portugal, MSc,[1]
Patrick May, PhD,[5] Dheeraj R. Bobbili, PhD,[5]
Milena Radivojkov-Blagojevic, MSc,[6] Peter Lichtner, PhD,[6]
Andrew B. Singleton, PhD,[7,8] Dena G. Hernandez, PhD,[7]
Connor Edsall, MSc,[7] George D. Mellick, PhD,[9]
Alexander Zimprich, MD,[10] Walter Pirker, MD,[11]
Ekaterina Rogaeva, PhD,[12] Anthony E. Lang, MD,[12,13,14,15]
Sulev Koks, MD, PhD,[16,17] Pille Taba, MD, PhD, FEAN,[18,19]
Suzanne Lesage, PhD,[20] Alexis Brice, MD,[20]
Jean-Christophe Corvol, MD, PhD,[20,21]
Marie-Christine Chartier-Harlin, PhD,[22]
Eugénie Mutez, MD,[22] Kathrin Brockmann, MD,[3,4]
Angela B. Deutschländer, MD,[23,24,25]
Georges M. Hadjigeorgiou, MD,[26,27]
Efthimos Dardiotis, MD,[26] Leonidas Stefanis, MD, PhD,[28,29]
Athina Maria Simitsi, MD, PhD,[28]
Enza Maria Valente, MD, PhD,[30,31]
Simona Petrucci, MD, PhD,[32,33] Stefano Duga, PhD,[34,35]
Letizia Straniero, PhD,[34] Anna Zecchinelli, MD,[36]
Gianni Pezzoli, MD,[37] Laura Brighina, MD, PhD,[38,39]
Carlo Ferrarese, MD, PhD,[38,39] Grazia Annesi, PhD,[40]
Andrea Quattrone, MD,[41] Monica Gagliardi, PhD,[42]
Hirotaka Matsuo, MD, PhD,[43] Yusuke Kawamura, MD,[43]
Nobutaka Hattori, MD, PhD,[44] Kenya Nishioka, MD, PhD,[44]
Sun Ju Chung, MD, PhD,[45] Yun Joong Kim, MD, PhD,[46]

*__Correspondence to:__ Dr. Alexis Elbaz, INSERM U1018 CESP, Hôpital Paul Brousse, Bâtiment 15/16, 16 Avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France; E-mail: alexis.elbaz@inserm.fr

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Pierre Kolber, MD,[47]
Bart P.C. van de Warrenburg, MD, PhD,[48]
Bastiaan R. Bloem, MD, PhD,[48] Jan Aasly, MD,[49]
Mathias Toft, MD, PhD,[50] Lasse Pihlstrøm, MD, PhD,[50]
Leonor Correia Guedes, MD, PhD,[51,52]
Joaquim J. Ferreira, MD, PhD,[51,53]
Soraya Bardien, PhD,[54] Jonathan Carr, PhD,[55]
Eduardo Tolosa, MD, PhD,[56,57] Mario Ezquerra, PhD,[58]
Pau Pastor, MD, PhD,[59,60] Monica Diez-Fairen, MSc,[59,60]
Karin Wirdefeldt, MD, PhD,[61,62] Nancy L. Pedersen, PhD,[62]
Caroline Ran, PhD,[63] Andrea C. Belin, PhD,[63]
Andreas Puschmann, MD, PhD,[64] Clara Hellberg, MD,[64]
Carl E. Clarke, MD,[65] Karen E. Morrison, MD,[66]
Manuela Tan, PhD,[67] Dimitri Krainc, MD, PhD,[68]
Lena F. Burbulla, PhD,[68,69,70,71] Matt J. Farrer, PhD,[72]
Rejko Krüger, MD,[5,47,73,74] Thomas Gasser, MD,[3,4]
Manu Sharma, PhD,[2] Alexis Elbaz, MD, PhD,[1*]
and the Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease (Courage-PD) Consortium

[1]*UVSQ, Univ. Paris-Sud, Inserm, Team "Exposome, Heredity, Cancer and Health," CESP, Université Paris-Saclay, Villejuif, France* [2]*Centre for Genetic Epidemiology, Institute for Clinical Epidemiology and Applied Biometry, University of Tubingen, Tubingen, Germany* [3]*Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tubingen, Tubingen, Germany* [4]*German Center for Neurodegenerative Diseases (DZNE), Tubingen, Germany* [5]*Translational Neuroscience, Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Esch-Belval, Luxembourg* [6]*Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany* [7]*Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda, Maryland, USA* [8]*Center For Alzheimer's and Related Dementias, NIA, NIH, Bethesda, Maryland, USA* [9]*Griffith Institute for Drug Discovery, Griffith University, Nathan, Queensland, Australia* [10]*Department of Neurology, Medical University of Vienna, Wien, Austria* [11]*Department of Neurology, Wilhelminenspital, Wien, Austria* [12]*Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada* [13]*Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, Ontario, Canada* [14]*Division of Neurology, University of Toronto, Toronto, Ontario, Canada* [15]*Krembil Brain Institute, Toronto, Ontario, Canada* [16]*Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Murdoch, Australia* [17]*Perron Institute for Neurological and Translational Science, Nedlands, Western Australia, Australia* [18]*Department of Neurology and Neurosurgery, University of Tartu, Tartu, Estonia* [19]*Neurology Clinic, Tartu University Hospital, Tartu, Estonia* [20]*Department of Neurologie, Sorbonne Université, Institut du Cerveau—Paris Brain Institute—ICM, INSERM, CNRS, Assistance Publique Hôpitaux de Paris,*

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Paris, France [21]*Department of Neurology, CIC Neurosciences, Assistance Publique Hôpitaux de Paris, Paris, France* [22]*University Lille, Inserm, CHU Lille, UMR-S 1172—LilNCog—Centre de Recherche Lille Neurosciences & Cognition, Lille, France* [23]*Department of Neurology, Ludwig Maximilians University of Munich, München, Germany* [24]*Department of Neurology, Max Planck Institute of Psychiatry, Munich, Germany* [25]*Department of Neurology and Department of Clinical Genomics, Mayo Clinic Florida, Jacksonville, Florida, USA* [26]*Department of Neurology, Laboratory of Neurogenetics, University of Thessaly, University Hospital of Larissa, Larissa, Greece* [27]*Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus* [28]*First Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece* [29]*Center of Clinical Research, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece* [30]*Department of Molecular Medicine, University of Pavia, Pavia, Italy* [31]*Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Mondino Foundation, Pavia, Italy* [32]*UOC Medical Genetics and Advanced Cell Diagnostics, S. Andrea University Hospital, Rome, Italy* [33]*Department of Clinical and Molecular Medicine, University of Rome, Rome, Italy* [34]*Department of Biomedical Sciences, Humanitas University, Milan, Italy* [35]*Humanitas Clinical and Research Center, IRCCS, Milan, Italy* [36]*Parkinson Institute, Azienda Socio Sanitaria Territoriale (ASST) Gaetano Pini/CTO, Milan, Italy* [37]*Parkinson Institute, Fontazione Grigioni, Milan, Italy* [38]*Department of Neurology, San Gerardo Hospital, Monza, Italy* [39]*Department of Medicine and Surgery and Milan Center for Neuroscience, University of Milano Bicocca, Milan, Italy* [40]*Institute for Biomedical Research and Innovation, National Research Council, Cosenza, Italy* [41]*Institute of Neurology, Magna Graecia University, Catanzaro, Italy* [42]*Institute of Molecular Bioimaging and Physiology National Research Council, Catanzaro, Italy* [43]*Department of Integrative Physiology and Bio-Nano Medicine, National Defense Medical College, Saitama, Japan* [44]*Department of Neurology, Juntendo University School of Medicine, Tokyo, Japan* [45]*Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea* [46]*Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea* [47]*Neurology, Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg* [48]*Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Nijmegen, The Netherlands* [49]*Department of Neurology, St Olav's Hospital and Norwegian University of Science and Technology, Trondheim, Norway* [50]*Department of Neurology, Oslo University Hospital, Oslo, Norway* [51]*Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal* [52]*Department of Neurosciences and Mental Health, Neurology, Hospital de Santa Maria, Centro Hospitalar Universitario Lisboa Norte (CHULN), Lisbon, Portugal* [53]*Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal* [54]*Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa* [55]*Division of Neurology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa* [56]*Parkinson's Disease and Movement Disorders Unit, Neurology Service, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain* [57]*Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED: CB06/05/0018-ISCIII), Barcelona, Spain* [58]*Lab of Parkinson Disease and Other Neurodegenerative*

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Movement Disorders, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain [59]*Fundació per la Recerca Biomèdica i Social Mútua Terrassa, Barcelona, Spain* [60]*Movement Disorders Unit, Department of Neurology, Hospital Universitari Mutua de Terrassa, Barcelona, Spain* [61]*Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden* [62]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden* [63]*Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden* [64]*Department of Clinical Sciences Lund, Neurology, Lund University, Skåne University Hospital, Lund, Sweden* [65]*University of Birmingham and Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom* [66]*Faculty of Medicine, Health and Life Sciences, Queens University, Belfast, United Kingdom* [67]*Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom* [68]*Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA* [69]*Metabolic Biochemistry, Biomedical Center (BMC), Faculty of Medicine, Ludwig-Maximilians-Universität München, Munich, Germany* [70]*Munich Cluster for Systems Neurology (SyNergy), Munich, Germany* [71]*German Center for Neurodegenerative Diseases (DZNE), Munich, Germany* [72]*Department of Neurology, McKnight Brain Institute, University of Florida, Gainesville, Florida, USA* [73]*Parkinson's Research Clinic, Centre Hospitalier de Luxembourg, Strassen, Luxembourg* [74]*Transversal Translational Medicine, Luxembourg Institute of Health (LIH), Strassen, Luxembourg*

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 Diary 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-statistic[9] 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), overall[12] 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 IVs[14] 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 participants[12] 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

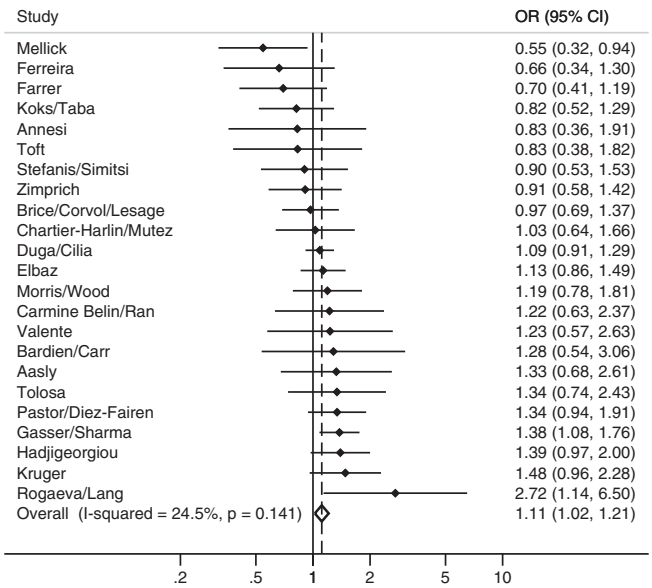

FIG. 1. Forest plot of the association between rs4988235 and PD under a dominant model. Abbreviations: OR, odds ratio; CI, confidence interval. ORs were pooled using a fixed-effect meta-analysis. Associations between rs4988235 and PD under a dominant model (TC + TT vs. CC genotypes) are presented in 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 OR (95% CI) TC + TT vs. CC	*P*-value	I^2 (%)	*P*-het.	MR estimate per one-serving per day OR (95% CI) TC + TT vs. CC	*P*-value	P-diff.
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 $I^2 \leq 25\%$) or random (if $I^2 > 25\%$) 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 levels[5] 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

Additional COURAGE-PD investigators: Sophia N. Pchelina (Saint Petersburg, Russia), Thomas Brücke (Wien, Austria), Marie-Anne Loriot (Paris, France), Claire Mulot (Paris, France), Yves Koudou (Villejuif, France), Alain Destée (Lille, France), Georgia Xiromerisiou (Larissa, Greece), Christos Koros (Athens, Greece), Matina Maniati (Athens, Greece), Maria Bozi (Athens, Greece), Micol Avenali (Pavia, Italy), Margherita Canesi (Milan, Italy), Giorgio Sacilotto (Milan, Italy), Michela Zini (Milan, Italy), Roberto Cilia (Milan, Italy), Francesca Del Sorbo (Milan, Italy), Nicoletta Meucci (Milan, Italy), Rosanna Asselta (Milan, Italy), Radha Procopio (Catanzaro, Italy), Manabu Funayama (Tokyo, Japan), Aya Ikeda (Tokyo, Japan), Takashi Matsushima (Tokyo, Japan), Yuanzhe Li (Tokyo, Japan), Hiroyo Yoshino (Tokyo, Japan), Zied Landoulsi (Luxembourg, Luxembourg), Rubén Fernández-Santiago (Barcelona, Spain), Nicholas Wood (London, the United Kingdom), and Huw R. Morris (London, the United Kingdom). ■

Data Availability Statement

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

References

1. Jiang W, Ju C, Jiang H, Zhang D. Dairy foods intake and risk of Parkinson's disease: a dose-response meta-analysis of prospective cohort studies. Eur J Epidemiol 2014;29:613–619.
2. Elbaz A. Prodromal symptoms of Parkinson's disease: implications for epidemiological studies of disease etiology. Rev Neurol (Paris) 2016;172:503–511.
3. Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations. Wellcome Open Res 2019;4:186.
4. Mendelian Randomization of Dairy Consumption Working Group. Dairy consumption and body mass index among adults: Mendelian randomization analysis of 184802 individuals from 25 studies. Clin Chem 2018;64:183–191.
5. Mendelian Randomization of Dairy Consumption Working Group. Dairy intake and body composition and Cardiometabolic traits among adults: Mendelian randomization analysis of 182041 individuals from 18 studies. Clin Chem 2019;65:751–760.

6. Hartwig FP, Davey SG. Lactase persistence and body mass index: the contribution of Mendelian randomization. Clin Chem 2018;64:4–6.
7. Hartwig FP, Horta BL, Smith GD, de Mola CL, Victora CG. Association of lactase persistence genotype with milk consumption, obesity and blood pressure: a Mendelian randomization study in the 1982 Pelotas (Brazil) birth cohort, with a systematic review and meta-analysis. Int J Epidemiol 2016;45(5):1573–1587.
8. Yang Q, Lin SL, Yeung SLA, et al. Genetically predicted milk consumption and bone health, ischemic heart disease and type 2 diabetes: a Mendelian randomization study. Eur J Clin Nutr 2017;71:1008–1012.
9. Burgess S, Thompson SG, Collaboration CCG. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol 2011;40:755–764.
10. Shim H, Chasman DI, Smith JD, et al. A multivariate genome-wide association analysis of 10 LDL subfractions, and their response to statin treatment, in 1868 Caucasians. PLoS One 2015;10:e0120758.
11. Bergholdt HKM, Larsen MK, Varbo A, Nordestgaard BG, Ellervik C. Lactase persistence, milk intake, hip fracture and bone mineral density: a study of 97 811 Danish individuals and a meta-analysis. J Intern Med 2018;284:254–269.
12. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol 2019;18:1091–1102.
13. Blauwendraat C, Iwaki H, Makarious MB, et al. Investigation of autosomal genetic sex differences in Parkinson's disease. Ann Neurol 2021;90:35–42.
14. Chang D, Nalls MA, Hallgrímsdóttir IB, et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. Nat Genet 2017;49:1511–1516.
15. Elsworth B, Lyon M, Alexander T, et al. The MRC IEU OpenGWAS data infrastructure. bioRxiv 2020;2020.2008. 2010:244293.
16. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. Eur J Epidemiol 2018;33:947–952.
17. Hemani G, Zheng J, Elsworth B, et al. The MR-base platform supports systematic causal inference across the human phenome. Elife 2018;7:e34408.
18. Staley JR, Blackshaw J, Kamat MA, et al. PhenoScanner: a database of human genotype-phenotype associations. Bioinformatics 2016;32:3207–3209.
19. Kamat MA, Blackshaw JA, Young R, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics 2019;35:4851–4853.
20. Machiela MJ, Chanock SJ. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. Bioinformatics 2015;31:3555–3557.
21. Zhang Z, Wang M, Yuan S, Larsson SC, Liu X. Genetically predicted milk intake and risk of neurodegenerative diseases. Nutrients 2021;13(8):2893.
22. Wang Y, Gao L, Lang W, et al. Serum calcium levels and Parkinson's disease: a Mendelian randomization study. Front Genet 2020;11:824.
23. Larsson SC, Singleton AB, Nalls MA, Richards JB. No clear support for a role for vitamin D in Parkinson's disease: a Mendelian randomization study. Mov Disord 2017;32:1249–1252.
24. Kia DA, Noyce AJ, White J, et al. Mendelian randomization study shows no causal relationship between circulating urate levels and Parkinson's disease. Ann Neurol 2018;84:191–199.
25. Olsson E, Byberg L, Höijer J, Kilander L, Larsson SC. Milk and fermented Milk intake and Parkinson's disease: cohort study. Nutrients 2020;12:2763.
26. Abbott RD, Ross GW, Petrovitch H, et al. Midlife milk consumption and substantia nigra neuron density at death. Neurology 2016;86:512–519.
27. Noyce AJ, Kia DA, Hemani G, et al. Estimating the causal influence of body mass index on risk of Parkinson disease: a Mendelian randomisation study. PLoS Med 2017;14:e1002314.
28. Heilbron K, Jensen MP, Bandres-Ciga S, et al. Unhealthy Behaviours and risk of Parkinson's disease: a Mendelian randomisation study. J Parkinsons Dis 2021;11(4):1981–1993.
29. Carter AR, Sanderson E, Hammerton G, et al. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. Eur J Epidemiol 2021;36:465–478.
30. Aslam H, Marx W, Rocks T, et al. The effects of dairy and dairy derivatives on the gut microbiota: a systematic literature review. Gut microbes 2020;12:1799533.
31. Hughes DA, Bacigalupe R, Wang J, et al. Genome-wide associations of human gut microbiome variation and implications for causal inference analyses. Nat Microbiol 2020;5:1079–1087.
32. Bergholdt HK, Nordestgaard BG, Varbo A, Ellervik C. Milk intake is not associated with ischaemic heart disease in observational or Mendelian randomization analyses in 98 529 Danish adults. Int J Epidemiol 2015;44:587–603.
33. Molsberry S, Bjornevik K, Hughes KC, Healy B, Schwarzschild M, Ascherio A. Diet pattern and prodromal features of Parkinson disease. Neurology 2020;95:e2095–e2108.
34. Yin W, Löf M, Pedersen NL, Sandin S, Fang F. Mediterranean dietary pattern at middle age and risk of Parkinson's disease: a Swedish cohort study. Mov Disord 2021;36:255–260.

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?

Nora Vanegas-Arroyave, MD,[1] Denise F. Chen, MD,[2] Peter M. Lauro, BA,[3] Gina Norato, ScM,[4] Codrin Lungu, MD,[5] and Mark Hallett, MD[6*]

*Correspondence to: Dr. Mark Hallett, Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Building 10, Room 7D37, 10 Center Dr MSC 1428, Bethesda, MD 20892-1428, USA; E-mail: hallettm@ninds.nih.gov

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