Intake of dairy foods and risk of Parkinson disease

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ABSTRACT

Objective: To prospectively examine the association between commonly consumed dairy products and the risk of Parkinson disease (PD) in women and men.

Methods: Analyses were based on data from 2 large prospective cohort studies, the Nurses' Health Study (n = 80,736) and the Health Professionals Follow-up Study (n = 48,610), with a total of 26 and 24 years of follow-up, respectively. Both US-based studies were conducted via mailed biennial questionnaires. Dietary intake was assessed with food frequency questionnaires administered repeatedly over the follow-up period. Incident cases of PD (n = 1,036) were identified via questionnaires and subsequently confirmed by reviewing medical records. We also conducted a meta-analysis to combine our study with 3 previously published prospective studies on total milk intake and PD risk and 1 study on total dairy intake and PD risk.

Results: While total dairy intake was not significantly associated with PD risk in our cohorts, intake of low-fat dairy foods was associated with PD risk. The pooled, multivariable-adjusted hazard ratio (HR) comparing people who consumed at least 3 servings of low-fat dairy per day to those who consumed none was 1.34 (95% confidence interval [CI] 1.01–1.79, p trend = 0.04). This association appeared to be driven by an increased risk of PD associated with skim and low-fat milk (HR 1.39, 95% CI 1.12–1.73, p trend <0.01). Results were similar in women and men (p for heterogeneity >0.05). In the meta-analysis, the pooled relative risk comparing extreme categories of total milk intake was 1.56 (95% CI 1.30–1.88), and the association between total dairy and PD became significant (HR 1.27, 95% CI 1.04–1.55).

Conclusions: Frequent consumption of dairy products appears to be associated with a modest increased risk of PD in women and men. *Neurology*® 2017;89:46–52

GLOSSARY

CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; NHS = Nurses' Health Study; PD = Parkinson disease.

Evidence from previous prospective studies suggests that intake of dairy products may be associated with an increased risk of Parkinson disease (PD).^{1–5} Dairy products are widely consumed and thus could constitute an important modifiable risk factor for this disease. However, it remains unclear whether certain dairy foods or nutrients contained in dairy products are driving this association and whether associations are present among women and men or only among men. Previous results from the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)¹ suggested an association between dairy intake and increased PD risk among men. Here, we present data from the NHS and HPFS cohorts from up to an additional 12 years of follow-up with a total of 1,036 incident cases of PD to further investigate potential associations between dairy foods and nutrients derived from dairy products and the risk of PD.

METHODS Study population. The NHS cohort began in 1976 when 121,700 female registered nurses 30 to 55 years of age responded to a mailed questionnaire, answering questions about their medical histories and health-related behaviors. Similarly, the HPFS was established when 51,529 male health professionals 40 to 75 years of age responded to a similar questionnaire. Members of both

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Supplemental data
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Table 1 Age-adjusted characteristics of the study population at baseline by category of dairy intake

	Total dairy intake		Low-fat dairy intake		High-fat dairy intake	
	<1 serving/day	≥3 servings/day	<1 serving/day	≥3 servings/day	<1 serving/day	≥3 servings/day
NHS, 1984-2010	n = 18,251	n = 16,200	n = 48,885	n = 3,436	n = 37,379	n = 10,187
Age, y ^a	50.5 (7.0)	51.2 (7.2)	50.6 (7.1)	52.6 (7.1)	51.3 (7.2)	50.5 (7.1)
Body mass index, kg/m ²	25.7 (4.9)	25.9 (5.0)	25.7 (4.9)	26.4 (5.2)	25.9 (4.9)	25.6 (5.1)
Current smoker, %	30	23	28	17	23	31
Past smoker, %	30	32	30	35	33	29
White, %	96	98	97	99	97	99
Activity, MET-h/wk ^b	12.7 (18.6)	15.2 (24.0)	13.2 (20.3)	18.6 (30.5)	14.4 (20.6)	13.4 (22.2)
Coffee, servings/d	1.8 (1.8)	1.8 (1.8)	1.9 (1.8)	1.6 (1.7)	1.6 (1.7)	2.2 (1.8)
Alcohol, g/d	7.9 (12.8)	6.1 (10.2)	7.6 (12.1)	4.6 (8.6)	6.3 (10.9)	7.8 (12.1)
Total energy intake, kcal/d	1,434 (448)	2,104 (515)	1,662 (522)	2,157 (503)	1,568 (468)	2,105 (542)
HPFS, 1986-2010	n = 12,176	n = 9,574	n = 28,979	n = 2,394	n = 26,608	n = 4,413
Age, y ^a	54.4 (9.5)	54.9 (10.0)	54.3 (9.7)	55.8 (10.0)	54.9 (9.8)	54.9 (9.9)
Body mass index, kg/m ²	25.4 (3.3)	25.6 (3.4)	25.5 (3.3)	25.6 (3.5)	25.4 (3.3)	25.6 (3.3)
Current smoker, %	11	11	11	7	9	17
Past smoker, %	46	39	45	37	45	39
White, %	93	98	95	98	95	97
Activity, MET-h/wk ^b	17.4 (24.6)	19.5 (27.3)	17.7 (24.9)	21.2 (27.7)	19.2 (26.2)	17.4 (24.0)
Coffee, servings/d	1.3 (1.6)	1.5 (1.7)	1.4 (1.6)	1.1 (1.6)	1.2 (1.5)	1.9 (1.8)
Alcohol, g/d	12.1 (16.5)	10.4 (15.1)	12.3 (16.2)	8.3 (13.5)	10.7 (14.9)	13.2 (17.5)
Total energy intake, kcal/d	1,669 (525)	2,414 (626)	1,884 (603)	2,522 (620)	1,815 (551)	2,477 (661)

Abbreviations: HPFS = Health Professionals Follow-up Study; MET = metabolic equivalent of task; NHS = Nurses' Health Study.

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

^aValue is not age-adjusted.

^bMETs from recreational and leisure-time activities.

cohorts have been sent follow-up questionnaires every 2 years to update information on health-related exposures and newly diagnosed diseases. For the present analysis, the baseline population was composed of the 81,757 nurses and 49,934 health professionals who completed baseline food frequency questionnaires on usual dietary intake. We excluded individuals who reported implausible total energy intake at baseline (<660 or >3,500 kcal/d for women and <800 or >4,200 kcal/d for men), had a previous diagnosis of PD, or had missing baseline dietary information. A total of 48,610 men and 80,736 women were thus included in the analysis.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Human Research committees at the Brigham and Women's Hospital and the Harvard School of Public Health.

Dietary assessment and other covariates. Usual diet was assessed through food frequency questionnaires. Participants were asked how often over the past year they consumed a commonly used portion of each food. Nine possible responses were provided, ranging from never to ≥6 times per day. Nutrient intakes were calculated by multiplying the frequency response by the nutrient content of the specified portion size based on data from the US Department of Agriculture and manufacturers. Participants were also asked about supplemental vitamin use. Diet was assessed in the NHS in 1984 (baseline), in 1986, and every 4 years thereafter and in HPFS in 1986 (baseline) and every 4 years thereafter. Intakes of foods and nutrients assessed in this way have been

validated previously against diet records among subsets of participants in both the NHS and HPFS cohorts.⁶⁻⁹ Correlations between intakes of dairy foods measured by the food frequency questionnaire and by diet records were 0.52 to 0.88 in HPFS⁹ and 0.57 to 0.94 in NHS.⁸ Data on other covariates of interest, including smoking, body mass index, physical activity, and coffee and alcohol intake, were also collected via self-report questionnaires for both cohorts.

Ascertainment of PD cases. Cases of PD were identified with biennial self-report questionnaires. Before 2003, when individuals indicated a diagnosis of PD, we contacted their treating neurologists or internists who were asked either to confirm the diagnosis or to send copies of the patients' medical records. Cases were confirmed if the physician considered the PD diagnosis definite or probable, the medical record included a final diagnosis of PD by a neurologist, or the medical record indicated the presence of at least 2 of the 3 cardinal signs of PD (resting tremor, rigidity, bradykinesia) in the absence of evidence for other diagnosis. Since 2003, the above procedure was used except that medical records were requested for all self-reported cases and were reviewed by a neurologist specializing in movement disorders. In the event that the determination of the movement disorders specialist differed from that of the neurologist, the decision of the movement disorder specialist was used. Our analyses included only confirmed cases.

Statistical analysis. Participants contributed person-time from the age in months at the date of returning the baseline food

Table 2 Relative risk of PD by intake of individual dairy products

	Categories, servings/d				
Dairy category	<1	1-<2	2-<3	≥3	p Trend
Total dairy					
Women					
Cases, n	53	183	158	88	
Person-years	283,001	730,398	503,542	353,654	
Relative risk (95% CI)					
Age-adjusted	1.0	1.19 (0.87-1.61)	1.40 (1.03-1.92)	1.20 (0.85-1.69)	0.25
Multivariate ^a	1.0	1.13 (0.82-1.55)	1.27 (0.91-1.78)	1.06 (0.73-1.55)	0.81
Men					
Cases, n	100	214	134	106	
Person-years	202,474	370,658	199,337	165,352	
Relative risk (95% CI)					
Age-adjusted	1.0	1.09 (0.86-1.38)	1.20 (0.92-1.56)	1.15 (0.87-1.51)	0.26
Multivariate ^a	1.0	1.10 (0.86-1.41)	1.25 (0.95-1.66)	1.24 (0.91-1.68)	0.13
Pooled analysis					
Multivariate ^a	1.0	1.11 (0.92-1.35)	1.26 (1.02-1.56)	1.16 (0.92-1.48)	0.19
Low-fat dairy					
Women					
Cases, n	219	184	61	18	
Person-years	1,034,327	568,957	208,969	58,172	
Relative risk (95% CI)					
Age-adjusted	1.0	1.36 (1.11-1.65)	1.24 (0.93-1.65)	1.32 (0.81-2.14)	0.02
Multivariate ^a	1.0	1.30 (1.06-1.59)	1.15 (0.85-1.54)	1.20 (0.73-1.97)	0.13
Men					
Cases, n	264	180	67	42	
Person-years	512,523	266,065	111,033	46,154	
Relative risk (95% CI)					
Age-adjusted	1.0	1.19 (0.98-1.44)	1.01 (0.77-1.33)	1.48 (1.06-2.06)	0.07
Multivariate ^a	1.0	1.15 (0.94-1.40)	0.98 (0.74-1.30)	1.42 (1.00-2.02)	0.16
Pooled analysis					
Multivariate ^a	1.0	1.22 (1.06-1.40)	1.06 (0.86-1.29)	1.34 (1.01-1.79)	0.04
High-fat dairy					
Women					
Cases, n	283	144	32	23	
Person-years	985,292	563,851	184,842	136,556	
Relative risk (95% CI)					
Age-adjusted	1.0	1.01 (0.82-1.23)	0.74 (0.51-1.06)	0.84 (0.55-1.29)	0.18
Multivariate ^a	1.0	0.99 (0.80-1.22)	0.73 (0.50-1.06)	0.86 (0.55-1.33)	0.19
Men					
No. of cases	349	137	37	31	
Person-years	522,450	268,774	80,500	65,070	
Relative risk (95% CI)					
Age-adjusted	1.0	0.81 (0.66-0.99)	0.71 (0.50-1.00)	0.72 (0.53-1.05)	0.01
Multivariate ^a	1.0	0.83 (0.68-1.03)	0.75 (0.53-1.07)	0.79 (0.53-1.16)	0.07

Continued

Table 2 Continued

	Categories, servings/d				
Dairy category	<1	1-<2	2-<3	≥3	p Trend
Pooled analysis					
Multivariate ^a	1.0	0.91 (0.77-1.07)	0.74 (0.57-0.96)	0.82 (0.61-1.10)	0.03

Abbreviations: CI = confidence interval; PD = Parkinson disease.

Values were calculated using cumulative average intake levels.

^a Adjusted for age, pack-years of smoking, coffee intake, body mass index, physical activity, alcohol intake, and total energy intake.

frequency questionnaire until the age in months at the date of PD diagnosis, death, last completed questionnaire, or end of follow-up (June 2010 for NHS and January 2010 for HPFS), whichever occurred first. Analyses were stratified by age in months at the start of follow-up and calendar year of current questionnaire cycle. PD incidence was related to cumulative updated average intake from all available questionnaires up to the start of each 2-year follow-up period, categorized by cohort-specific quintile of intake¹⁰ for nutrient analyses and into 4-level variables for individual dairy foods. We adjusted for the number of missing food frequency questionnaires using indicator variables. In each analysis, the lowest intake category was used as the reference group. Age-adjusted and multivariate-adjusted hazard ratios (HRs) were estimated for each exposure with Cox proportional hazards models. Separate models were fit for each exposure of interest: total dairy; dairy protein; calcium from all sources, from foods, and from dairy sources; vitamin D from all sources, from foods, and from dairy sources; lactose; and individual dairy products, including skim or low-fat milk, whole milk, cream, cream cheese, cottage cheese, other cheese, ice cream, yogurt, sherbet or frozen yogurt, butter, and margarine. Nutrients were adjusted for total energy with the residual method so that they would be uncorrelated with total energy intake.¹¹ We also investigated high-fat dairy, including whole-fat milk, cream, ice cream, sour cream, butter, cream cheese, and other cheese, and low-fat dairy, including skim and low-fat milk, sherbet/frozen yogurt, yogurt, cottage cheese, and low-fat cheese. Primary multivariable models were adjusted for pack-years of smoking (never smoker, 1-<5, 5-<10, 10-<15, ≥15), coffee intake (none, <1, 1-3, 4-5, or ≥6 cups/d), body mass index (<21, 21-<25, 25-<30, 30-<35, or ≥35 kg/m²), physical activity (in quintiles), alcohol intake (none, 0.1-4.9, 5.0-9.9, 10.0-14.9, or ≥15 g/d for women and none, 0.1-9.9, 10.0-19.9, 20.0-29.9, or ≥30 g/d for men), and total energy intake (in quintiles). For tests of trend, the median value was assigned to each category and modeled as a continuous variable. The robustness of the results was tested by further adjustment for dietary patterns¹² and flavonoids intake.¹³ We conducted a lagged analysis excluding the first 4 years of follow-up in each cohort to address the possibility that participants could be experiencing PD symptoms at the time of questionnaire completion that would change their diet habits.

We also conducted a meta-analysis to combine our study with previously published prospective studies on milk and dairy intake and PD risk. We identified relevant studies through a PubMed search using key words (dairy or milk) and (Parkinson or Parkinson's disease) for all published studies in English by January 27, 2016. We identified 5 prospective studies of milk intake and PD risk¹⁻⁵ and 3 prospective studies of total dairy intake and PD risk^{1,3,5} (table e-1 at [Neurology.org](#)). However, because the previous HPFS/NHS study¹ overlaps the first 12 years of follow-up of the current study, it was not included in the meta-analysis. We

also excluded 1 study⁵ that reported effect estimates for a 1-SD increase in intake rather than comparing extreme intake categories. We used the *I*² statistic to assess heterogeneity across studies and used random-effects models to calculate the pooled relative risk. All statistical analyses were conducted with SAS (SAS Institute, Cary, NC) except the meta-analysis, which was conducted with Stata (version 11.2, StataCorp, College Station, TX).

RESULTS We identified 554 incident PD cases in men and 482 in women over the follow-up period. Selected baseline characteristics of cohort participants according to their dairy intake are shown in table 1. In the main analysis, the association between total dairy and PD risk was not significant (pooled multivariable-adjusted HR comparing those who eat at least 3 servings of dairy foods per day to those who eat <1 serving per day 1.16, 95% confidence interval [CI] 0.92-1.48, *p* trend = 0.19) (table 2). However, when looking specifically at low-fat dairy foods, we found an elevated risk of PD for individuals with high intake (pooled HR comparing extreme intake categories 1.34, 95% CI 1.01-1.79, *p* trend = 0.04). For high-fat dairy foods, the associations tended to be in the opposite direction. Although the HR comparing the highest category of intake to the lowest was not significant (HR 0.82, 95% CI 0.61-1.10), we found a significant linear trend for decreased risk associated with greater intake of high-fat dairy (*p* trend = 0.03). Results were similar when we categorized dairy intake by quintiles rather than in categories (figure 1). The elevated risk associated with low-fat dairy foods appeared to be driven by an association between PD and skim or low-fat milk (table e-2). After a 4-year lag analysis was conducted in which a total of 69 incident cases were excluded, the association between skim or low-fat milk and PD risk was similar (the HR comparing those who drink >1 serving per day to those who drink 1-3 servings per month or less increased from 1.39 [95% CI 1.12-1.73] in the main analysis to 1.41 [95% CI 1.13-1.75] in the lagged analysis, table e-3). Results were similar in men and women. In addition to skim and low-fat milk, intake of sherbet/frozen yogurt was associated with an increased risk of PD. In contrast, whole milk did not appear to be associated with PD

Figure 1 Dairy intake and risk of PD

Associations of high-fat (A), low-fat (B), and total dairy (C) with risk of PD according to intake quintile with the use of cumulative average intake levels and adjusted for pack-years of smoking, physical activity, coffee intake, body mass index, alcohol intake, and total energy intake. PD = Parkinson disease.

risk (table e-2). We conducted further analyses including skim and low-fat milk and whole milk in the same model and found similar results. For skim and low-fat milk, the pooled HR comparing extreme categories was 1.39 (95% CI 1.10–1.74, p trend = 0.02).

We conducted further analyses of specific nutrients found in dairy products, including protein, calcium, vitamin D, and lactose. Neither total intakes nor intakes from dairy only were significantly associated with PD risk (table e-4). Results of lagged analyses (tables e-3 and e-5) were overall similar to those of the main analyses. We conducted further sensitivity analyses by restricting our case definition to definite PD, by analyzing only nonsmokers, and by censoring participants at age 85 because of the increasing difficulty of diagnosing PD at older ages. Again, results were similar to those of the main analyses. We also evaluated potential effect modification for the effect of low-fat dairy by running our analyses stratified by age (>65 vs <65 years old), smoking (ever vs never smokers), and coffee (drinkers vs nondrinkers). No significant interactions were observed (p interaction > 0.05 for all).

Finally, we pooled our results for milk intake with 3 previously published studies^{2–4} with a total of 1,725 PD cases and our total dairy results with 1 previously published study.³ The pooled relative risk for total milk intake was 1.56 (95% CI 1.30–1.88) (figure 2), and the pooled relative risk for total dairy intake was 1.27 (95% CI 1.04–1.55) (figure e-1).

DISCUSSION In this large prospective study, we found evidence for a modest association between PD risk and certain dairy products. Low-fat dairy products were associated with an increased risk of PD, and skim or low-fat milk and frozen yogurt appeared to contribute to this association.

The strengths of our study include the prospective design, which reduces the potential for reverse causation and recall bias that can affect retrospective studies of diet and disease. Both cohorts also had high follow-up rates and used validated dietary questionnaires, and exposure assessments were conducted repeatedly over the follow-up period. Our study is also the largest analysis of dairy and PD to date, with >1,000 incident PD cases.

Our study also has some weaknesses. Although previous validation studies suggest that our food frequency questionnaire captures intake levels in these cohorts reasonably well, some degree of misclassification of diet is inevitable. However, exposure misclassification is unlikely to explain the observed associations because we would expect this bias to attenuate associations toward the null owing to the prospective nature of our study. It is also possible that early symptoms of PD affected dietary behaviors or questionnaire responses; however, the results of our lag analysis suggest that any reverse causation was modest.

Our results largely agree with previous epidemiologic investigations of the association between dairy

Figure 2 Forest plot for milk intake and risk of PD

HRs are comparing highest and lowest intake category. For overall pooled estimate, $p < 0.00001$. CI = confidence interval; HR = hazard ratio; PD = Parkinson disease.

products and PD. This association in HPFS and NHS was first reported in 2002.¹ At that time, nearly 400 cases had been identified over 12 to 18 years of follow-up, and an association between PD risk and increased dairy intake was reported among men but not among women. An increased risk of PD associated with milk consumption was also observed in other cohorts, including the Cancer Prevention Study,³ the Honolulu Heart Program cohort,² and the Finnish Mobile Clinic Survey,⁴ although the last one reported an association only among women. Of note, only 45 male cases were included in the analysis, so low power could have affected the results. However, in the current cohort analysis and meta-analysis, we did not observe significant sex differences in the relationship between milk intake and PD risk. In addition, most of the milk consumed in the Finnish cohort was whole milk, whereas in our study population, skim and low-fat milk were more widely used, accounting for $\approx 90\%$ of total milk intake.

One mechanism that has been proposed to explain the apparent association between certain dairy products and increased risk of PD is the antiuricemic effect of dairy proteins. A substantial body of evidence suggests that urate may be protective against PD.^{14–16} Milk proteins (casein and lactalbumin) and intact milk have been shown to reduce serum urate levels in healthy individuals,^{17,18} and consumption of low-fat, but not high-fat, dairy has been associated with a reduced risk of gout among participants in the HPFS.¹⁹ The lack of association with full-fat dairy products could be due to counteracting effect of saturated fats.²⁰ Total milk or yogurt consumption was

associated with lower serum urate levels in National Health and Nutrition Examination Survey (NHANES), but data for full-fat or low-fat dairy were not reported.²¹ According to the results from NHANES,²¹ consumption of >2 servings of dairy per day was associated with 0.19 mg/dL lower serum urate (95% CI -0.30 to -0.09), while >1 serving of milk per day was associated with 0.25 mg/dL lower serum urate (95% CI -0.40 to -0.09). While this might contribute to the observed association between milk and PD risk, this change in urate level may be too modest to completely explain our results. Another possible mechanism is possible contaminants found in dairy products such as pesticides. Recently, milk intake was found to be associated with lower neuronal density in the substantia nigra among nonsmokers in the Honolulu-Asia Aging Study.²² The same study also found an association between detectable heptachlor epoxide (which contaminated milk in Hawaii in the early 1980s) in the brain and milk intake among nonsmokers. However, in our study, we found similar associations between milk and PD among both smokers and nonsmokers, and the consistent finding of an increasing risk of PD with increasing milk intake across multiple studies seems more consistent with a general mechanism than specific contaminants.

Our results provide further evidence of an increased risk of PD associated with consumption of certain dairy products in men and women, in particular with skim and low-fat milk. Further research is needed to elucidate the mechanisms involved in this association.

AUTHOR CONTRIBUTIONS

Drafting/revising the manuscript (K.C.H., X.G., I.Y.K., M.W., M.G.W., M.A.S., A.A.), study concept/design (A.A., X.G., M.A.S.), analysis or interpretation of data (K.C.H., X.G., M.W., M.G.W., M.A.S., A.A.), statistical analysis (K.C.H.), acquisition of data (X.G., M.A.S., A.A.), study supervision (A.A.), and obtaining funding (A.A.).

STUDY FUNDING

This study was supported by NIH grants UM1 CA186107, UM1 CA167552, and R01 NS061858 and by Department of Defense grant W81XWH-14-0131.

DISCLOSURE

K. Hughes reports no disclosures relevant to the manuscript. X. Gao has served on committees of the Sleep Research Society, American Academy of Sleep Medicine, and Parkinson Study Group and received funding from the NIH/National Institute of Neurological Disorders and Stroke. He serves on the editorial boards of *Advances in Nutrition* and *Journal of Human Genetics*. I. Kim reports no disclosures relevant to the manuscript. M. Wang receives research support from the National Institute of Allergy and Infectious Diseases, National Institute of Environmental Health Sciences, National Cancer Institute, National Institute on Deafness and Other Communication Disorders, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Arthritis and Musculoskeletal and Skin Diseases, American Institute for Cancer Research, and the Breast Cancer Research Foundation. M. Weisskopf serves on the scientific advisory board for the Kaiser Permanente Research

Biobank and the National Institute of Environmental Health Sciences Gulf Long-term Follow-up Study. He has been funded by NIH grants R01ES 019188, R01ES024165, R21ES024700, R21ES019982, and R56NS082105. He has also received research support from the Muscular Dystrophy Association. He serves as an associate editor for *Environmental Health Perspectives* and the co-editor in chief of *Current Environmental Health Reports*. M. Schwarzschild was a consultant for Biotie Therapies. He serves on the Scientific Advisory Board of CBD Solutions. He is funded by NIH grants NS090259 and NS090246, Department of Defense grants W81XWH-11-1-0150 and W81XWH-14-1-0131, the Parkinson's Disease Foundation, Target ALS, and the Michael J. Fox Foundation for Parkinson's Research. A. Ascherio receives research grants from the NIH, the National Multiple Sclerosis Society, and the Department of Defense and served on a medical advisory board for Bayer HealthCare. Go to Neurology.org for full disclosures.

Received October 3, 2016. Accepted in final form February 27, 2017.

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