RESEARCH ARTICLE

Nonsteroidal Anti-Inflammatory Use and *LRRK2* Parkinson's Disease Penetrance

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ABSTRACT: Background: The penetrance of leucine rich repeat kinase 2 (*LRRK2*) mutations is incomplete and may be influenced by environmental and/or other genetic factors. Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to reduce inflammation and may lower Parkinson's disease (PD) risk, but their role in *LRRK2*-associated PD is unknown.

Objectives: The objective of this study is to evaluate the association of regular NSAID use and *LRRK2*-associated PD.

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Methods: Symptomatic ("LRRK2-PD") and asymptomatic ("LRRK2-non-PD") participants with *LRRK2* G2019S, R1441X, or I2020T variants (definitely pathogenic variant carriers) or G2385R or R1628P variants (risk variant carriers) from 2 international cohorts provided information on regular ibuprofen and/or aspirin use (≥2 pills/week for ≥6 months) prior to the index date (diagnosis date for PD, interview date for non-PD). Multivariate logistic regression was used to evaluate the relationship between regular NSAID use and PD for any NSAID, separately for ibuprofen and aspirin in all carriers and separately in pathogenic and risk variant groups.
Results: A total of 259 LRRK2-PD and 318 LRRK2-non-PD participants were enrolled. Regular NSAID use was associated with reduced odds of PD in the overall cohort (odds ratio [OR], 0.34; 95% confidence interval [CI], 0.21–0.57) and in both pathogenic and risk variant carriers ($OR_{Pathogenic}$, 0.38; 95% CI, 0.21–0.67 and $OR_{RiskVariant}$, 0.19; 95% CI, 0.04–0.99). Similar associations were observed for ibuprofen and aspirin separately ($OR_{Ibuprofen}$, 0.19; 95% CI, 0.07–0.50 and $OR_{Aspirin}$, 0.51; 95% CI, 0.28–0.91).
Conclusions: Regular NSAID use may be associated with reduced penetrance in *LRRK2*-associated PD. The LRRK2 protein is involved in inflammatory pathways and appears to be modulated by regular anti-inflammatory use. Longitudinal observational and interventional studies of NSAID exposure and LRRK2-PD are needed to confirm this association. © 2020 International Parkinson and Movement Disorder Society

Parkinson's disease (PD) represents the second most common neurodegenerative illness after Alzheimer's disease and is characterized clinically by bradykinesia, rest tremor, rigidity, and postural instability as well as a variety of nonmotor features.[1,2] The pathogenesis of PD is unknown, although both genetic and environmental factors are known to play a role.[3,4] The most common Mendelian genetic form of PD is caused by pathogenic variants in the leucine rich repeat kinase 2 (*LRRK2)* gene, which phenotypically closely resembles idiopathic PD.[5,6] Pathogenic variants in this gene are inherited in an autosomal dominant fashion with reduced age-dependent lifetime penetrance. Although still debated and highly variable across different populations, penetrance is estimated at approximately 30% by age 80.[7-9] The factors responsible for the decreased penetrance of these mutations are largely unknown. Several other variants in *LRRK2* have also been associated with modestly increased risk of PD (odds ratio [OR],1.5–3) and are predominantly found in Asian populations.[10]

Inflammation has long been thought to have a role in the pathogenesis of PD at multiple levels in both sporadic and familial diseases.[11] Neuroinflammatory responses may perpetuate degenerative neuronal injury, ultimately leading to PD. In large epidemiological studies, nonsteroidal anti-inflammatory medication (NSAIDs) use, including both ibuprofen and aspirin, has been associated with lower PD risk,[12-14] although this has not been universally observed.[15-18] Because the LRRK2 protein is expressed in most immune cells, including microglia, and may influence inflammatory pathways,[19-21] we investigated whether regular NSAID use affected the risk of PD in 2 well-characterized international *LRRK2* cohorts.

Methods

Participants

This study used phenotypic and environmental data collected from members of 2 large international cohorts of *LRRK2* pathogenic or risk variant carriers: the Parkinson's Disease Genetic and Environmental Modifiers (PD-GEM, 26 sites) and the Michael J. Fox Foundation LRRK2 Cohort Consortium (MJFF-LCC cross-sectional cohort, 14 sites). For both cohorts, demographic information, PD diagnosis and age of diagnosis, clinical features, response to therapy, and family history of PD are available. Case report forms and standard operating procedures for the MJFF-LCC cohorts can be found at https://www.michaeljfox.org/data-sets. A description of the study cohorts and determination of *LRRK2* status in the PD-GEM cohorts are described in Marras and colleagues.[22] Information regarding the relatedness of participants belonging to the cohorts was available for approximately 30% of participants. Participants with *LRRK2* G2019S, R1441X, and I2020T mutations were defined as "pathogenic variant carriers,"[23-25] and those with G2385R or R1628P were defined as as "risk variant carriers."[26] Those participants meeting the criteria for PD were defined as symptomatic (LRRK2-PD) and those without PD as asymptomatic (LRRK2-non-PD). The breakdown of participant totals, LRRK2-PD and LRRK2-non-PD, age at exam, variant group, cohort, and region of origin are listed in Supplementary Table 1. Only cohort sites that provided information on NSAID use were included for this analysis.

Definition of PD

PD status was defined in accordance with standard diagnostic criteria for PD (UK Brain Bank, National Institutes of Health)[1] using available investigator assessments and clinical information.

Environmental Exposure Data

In both study cohorts, environmental exposures were assessed by using the NSAID module of the Parkinson's Disease Risk Factor Questionnaire, a validated set of questionnaires developed to provide a standard tool for

general use in epidemiologic studies of PD risk factor questionnaire (RFQ-U) case report forms (CRFs), version 1.0 Epidemiology Working Group of the Collaborative Centers for PD Environmental Research, https://commondataelements.ninds.nih.gov/report-viewer/23354/Risk%20Factor%20Questionnaire%20(RFQ)%20-%20Physical%20Activity%20and%20Sleep). The Parkinson's Disease Risk Factor Questionnaire assesses lifelong exposures including amount, duration, and time of use in freestanding questionnaires, each covering a specific domain, such as smoking, caffeine, and alcohol consumption. For this specific analysis, the history of regular NSAID use was determined using the following questions:

1. Have you ever *regularly* taken ibuprofen-based nonaspirin medications, that is, at least 2 pills per week for 6 months or longer? These include ibuprofen, Advil, Motrin, Nuprin, and others.
2. Have you ever *regularly* taken aspirin, that is, at least 2 pills per week for 6 months or longer?
3. Have you ever *regularly* taken *other* anti-inflammatory medications for pain, inflammation, or swelling, that is, at least 2 pills per week for 6 months or longer? [Please do NOT include use of Tylenol or acetaminophen, or narcotic pain relievers such as Vicodin, codeine, or Demerol.]

—*IF YES*: (a) At what age (or in what year) did you start regularly taking *X*; (b) At what age (or in what year) did you stop regularly taking *X*; (c) On average, about how many pills per week did you take?

Regular use of any NSAID prior to the index date was defined as ≥2 pills/week for ≥6 months. Smoking status, also evaluated with the Parkinson's Disease Risk Factor Questionnaire, was included in all the models as ever (≥1 cigarette per day for ≥6 months) versus never smoker.

Statistical Analysis

All statistical data analysis was performed using SPSS version 21 (IBM SPSS Statistics, Armonk, NY). Means and standard deviations are presented for normally distributed continuous variables. Two-sample *t* tests or nonparametric equivalent and chi-square tests were

TABLE 1. Subject characteristics

Characteristics	Total N	LRRK2-PD N (%)	LRRK2-PD % Male	LRRK2-non-PD N (%)	LRRK2-non-PD % Male
Subject totals[a]	577	259	51.0	318	38.7
Age, mean (SD, range)[b]	577	66.2 (11.5, 26–94)		60.9 (14.9, 18–89)	
Age groups					
<50	142	71 (50)	53.5	71 (50.0)	40.8
50–59	148	90 (60.8)	41.1	58 (39.2)	39.7
60–69	154	69 (44.8)	50.7	85 (55.2)	36.5
70–79	105	27 (25.7)	40.7	78 (74.3)	37.2
>79	28	2 (7.1)	50.0	26 (92.9)	42.3
Gene group[c]					
Pathogenic variants age, mean (SD, range)[b]	401	66.3 (11.7, 26–94)		52.0 (14.1, 19–87)	
Pathogenic variants					
Overall	401	232 (57.9)	49.1	169 (42.1)	41.4
G2019S	315	189 (60.0)	49.7	126 (40.0)	40.5
R1441	80	37 (46.3)	48.6	42 (53.8)	44.2
I2020T	7	7 (100.0)	42.9	0 (0)	0.0
Risk variants age, mean (SD, range)[b]	176	65.1 (9.7, 45–81)		70.9 (7.6, 52–89)	
Risk variants					
Overall	176***	27 (15.3)	63.0	149 (84.7)	35.6
G2385R	114	24 (21.1)	66.7	90 (78.9)	38.9
R1628P	64	5 (7.8)	40.0	59 (92.2)	30.5
Region					
Africa[d]	11	11 (100.0)	27.3	0 (0.0)	0.0
Asia[e]	181	32 (17.7)	59.4	149 (82.3)	35.6
Australia	10	8 (80.0)	62.5	2 (20.0)	0.0
Europe[f]	273	167 (61.2)	50.9	106 (38.8)	45.3
North America[g]	102	41 (40.2)	46.3	61 (59.8)	36.1

[a]Test of gender distribution between PD and non-PD, $\chi^2 = 8.579$, $P = 0.03$.
[b]Age at enrollment; test of age difference, $P < 0.05$.
[c]As a result of overlapping mutations, the total count of variant carriers exceeds the total count of gene group.
[d]All from Algeria.
[e]China, n = 175; Japan, n = 4; Singapore, n = 2.
[f]Spain, n = 162; France, n = 30; Germany, n = 20; Italy, n = 23; Norway, n = 22; Portugal, n = 16.
[g]United States, n = 76; Canada, n = 26.
LRRK2, leucine rich repeat kinase; PD, Parkinson's disease; SD, standard deviation.

used in unadjusted analyses. The relationship between NSAID use and PD was determined using logistic regression. Models were calculated for any regular NSAID use and separately for ibuprofen or aspirin use. We considered use of NSAIDs prior to the diagnosis date in LRRK2-PD and prior to the interview date in non-PD (index date). Analyses were performed for all genotypes combined and separately for pathogenic and risk variant groups. All logistic models were adjusted for index age (as a continuous variable), gender, and smoking history. Both race/ethnicity and region of origin in our data set were highly correlated with specific *LRRK2* variants, and adjusting for race/ethnicity and/or region of origin did not significantly alter the results of the models. For those models that included all genotypes combined, we adjusted for gene group (pathogenic or risk variant carriers) and included a product term for the interaction between smoking and gene group to evaluate whether the effect of smoking would be greater in 1 genetic subpopulation than in another. To control for potential reverse causality (ie, early undiagnosed disease causing increased usage of NSAIDs), exposure-lagging analysis was performed at 5 and 10 years prior to the index date.[27]

Results

Of the 577 participants enrolled, 259 (44.9%) were LRRK2-PD and 318 (55.1%) were LRRK2-non-PD. Demographic and clinical characteristics are summarized in Table 1. Participants with PD were older than those without PD (mean 66.2 years; standard deviation, 11.5 vs. 60.9 years [standard deviation, 14.9]; $P < 0.001$) and more likely to be men (51% vs. 38.7%; $P = 0.003$). More than half of the participants carried the common G2019S pathogenic variant, including 189 (76.5%) LRRK2-PD and 126 (39.6%) LRRK2-non-PD. The specific region of origin of all carriers is listed in Supplementary Table 1. Approximately 70% were derived from the MJFF-LCC cohort and 30% from PD-GEM, and as expected, all risk variant carriers were from Asian sites (Supplementary Table 1). Among those with PD, age at onset did not differ between pathogenic and risk variant carriers, and clinical features at time of exam were comparable with the exception of presence of disease asymmetry and having a positive response to levodopa therapy, both of which were more common among pathogenic variant carriers (95.5% vs. 81.5% and 95.4% vs. 90.9%, respectively; $P = 0.001$ for both; Supplementary Table 2).

In the overall sample, the rates of regular NSAID use were higher among LRRK2-non-PD than in LRRK2-PD (31.8% vs. 10.9%), including for both ibuprofen (7.3% vs. 2.4%) and aspirin (24.2% vs. 8.2%; Table 2). A similar pattern was observed when pathogenic and risk variants were analyzed separately and when men were studied individually. Among women, the rates of NSAID use were higher in LRRK2-non-PD in all

TABLE 2. Regular NSAID use by age, gene group, and region

	Any NSAID		Ibuprofen		Aspirin	
Characteristics	LRRK2-PD	LRRK2-non-PD	LRRK2-PD	LRRK2-non-PD	LRRK2-PD	LRRK2-non-PD
Overall, n (%)	28 (10.9)	101 (31.8)	6 (2.37)	23 (7.26)	21 (8.20)	77 (24.21)
Age						
<50	3 (4.2)	9 (12.7)	0 (0.0)	8 (11.27)	2 (2.9)	3 (4.23)
50-59	6 (6.7)	14 (24.1)	1 (1.12)	6 (10.34)	5 (5.6)	7 (12.07)
60-69	14 (20.3)	32 (37.6)	4 (5.97)	4 (4.71)	10 (14.7)	25 (29.41)
70-79	5 (18.5)	35 (44.9)	1 (4.0)	3 (3.85)	4 (14.8)	32 (41.03)
>79	0 (0.0)	11 (42.3)	0 (0.0)	2 (8.0)	0 (0.0)	10 (38.46)
Gene group						
Pathogenic variants carriers						
All	26 (11.2)	38 (22.5)	6 (2.7)	20 (11.9)	19 (8.3)	15 (8.9)
G2019S	24 (12.7)	31 (24.6)	6 (3.3)	18 (14.4)	17 (9.1)	12 (9.5)
R1441	2 (5.4)	7 (16.3)	0 (0.0)	2 (4.7)	2 (5.6)	3 (7.0)
I2020T	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Risk variant carriers						
All	2 (7.1)	63 (42.3)	0 (0.0)	3 (2.0)	2 (7.1)	62 (41.6)
G2385R	2 (8.3)	33 (36.7)	0 (0.0)	1 (1.1)	2 (8.3)	33 (36.7)
R1628P	0 (0.0)	30 (50.8)	0 (0.0)	2 (3.4)	0 (0.0)	29 (49.2)
Region						
Asia	2 (6.3)	63 (42.3)	0 (0.0)	3 (2.0)	2 (6.3)	62 (41.6)
Australia	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Europe	10 (6.0)	18 (17.0)	1 (0.6)	11 (10.5)	9 (5.4)	4 (3.8)
North America	15 (36.6)	20 (32.8)	5 (12.8)	9 (14.8)	9 (22.5)	11 (18.0)

NSAID, nonsteroidal anti-inflammatory drugs; LRRK2, leucine rich repeat kinase; PD, Parkinson's disease.

groups with the exception of aspirin use in pathogenic variant carriers, which was higher among those with PD, although the sample size was small in this subgroup (Table 3).

In the adjusted logistic regression models, regular NSAID use was associated with lower risk for PD ($OR_{any\ NSAID}$, 0.34; 95% confidence interval [CI], 0.21–0.57; Table 4). Both aspirin and ibuprofen were independently associated with a lower risk of PD ($OR_{Ibuprofen}$, 0.19; 95% CI, 0.07–0.50; OR_{ASA}, 0.51; 95% CI, 0.28–0.91), and similar findings were seen in both pathogenic and risk variant carriers when analyzed

TABLE 3. NSAID use by age, genetic mutation, and gender

	Any NSAID		Ibuprofen		Aspirin	
	LRRK2-PD	LRRK2-non-PD	LRRK2-PD	LRRK2-non-PD	LRRK2-PD	LRRK2-non-PD
Analysis restricted to men						
Overall, n (%)	12 (9.5)	35 (28.5)	1 (0.8)	7 (5.7)	11 (8.53)	29 (23.6)
Gene group						
Pathogenic variants carriers						
All	11 (9.6)	17 (24.3)	1 (0.9)	6 (8.7)	10 (8.9)	11 (15.7)
G2019S	10 (10.6)	12 (23.5)	1 (1.1)	5 (10.0)	9 (9.8)	8 (15.7)
R1441X	1 (5.6)	5 (26.3)	0 (0.0)	1 (5.3)	1 (5.6)	3 (15.8)
I2020T	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Risk variant carriers						
All	1 (5.9)	18 (34.0)	0 (0.0)	1 (1.9)	1 (5.9)	18 (34.0)
G2385R	1 (6.3)	10 (28.6)	0 (0.0)	0 (0.0)	1 (6.3)	10 (28.6)
R1628P	0 (0.0)	8 (44.4)	0 (0.0)	1 (5.6)	0 (0.0)	8 (44.4)
Analysis restricted to women						
Overall (n, %)	16 (12.4)	66 (33.8)	5 (4.07)	16 (8.2)	10 (7.87)	48 (24.6)
Gene group						
Pathogenic variants carriers						
All	15 (12.7)	21 (21.2)	5 (4.4)	14 (14.1)	9 (7.7)	4 (4.0)
G2019S	14 (14.7)	19 (25.3)	5 (5.6)	13 (17.3)	8 (8.4)	4 (5.3)
R1441X	1 (5.3)	2 (8.3)	0 (0.0)	1 (4.2)	1 (5.6)	0 (0.0)
I2020T	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Risk variant carriers						
All	1 (9.1)	45 (46.9)	0 (0.0)	2 (2.1)	1 (9.0)	44 (45.8)
G2385R	1 (12.5)	23 (41.8)	0 (0.0)	1 (1.8)	1 (12.5)	23 (41.8)
R1628P	0 (0.0)	22 (53.7)	0 (0.0)	1 (2.4)	0 (0.0)	21 (51.2)

NSAID, nonsteroidal anti-inflammatory drugs; LRRK2, leucine rich repeat kinase; PD, Parkinson's disease.

TABLE 4. Logistic regression models

	Overall Model OR (95% CI)	5-Year LagModel OR (95% CI)	10-Year LagModel OR (95% CI)	Model for Men* OR (95% CI)	Model for Women* OR (95% CI)
Overall[a]					
Any NSAID	0.34 (0.21–0.57)	0.48 (0.27–0.85)	0.90 (0.47–1.74)	0.28 (0.13–0.61)	0.42 (0.21–0.82)
Ibuprofen	0.19 (0.07–0.50)	0.25 (0.08–0.72)	0.52 (0.16–1.71)	0.06 (0.01–0.50)	0.27 (0.09–0.78)
Aspirin	0.51 (0.28–0.91)	0.72 (0.37–1.43)	1.57 (0.69–3.56)	0.41 (0.18–0.93)	0.77 (0.32–1.85)
Pathogenic variant carriers[a]					
Any NSAID	0.38 (0.21–0.67)	0.51 (0.27–0.98)	1.05 (0.49–2.28)	0.27 (0.11–0.65)	0.48 (0.23–1.03)
Ibuprofen	0.19 (0.07–0.50)	0.23 (0.08–0.69)	0.49 (0.14–1.66)	0.07 (0.01–0.66)	0.25 (0.08–0.74)
Aspirin	0.79 (0.38–1.67)	1.11 (0.46–2.69)	5.14 (1.11–23.82)	0.45 (0.17–1.20)	1.86 (0.54–6.42)
Risk variant carriers[a]					
Any NSAID	0.19 (0.04–0.99)	0.17 (0.02–1.66)	0.50 (0.04–5.85)	0.09 (0.01–1.07)	0.26 (0.03–2.75)
Ibuprofen	0.00	0.00	0.00	0.00	0.00
Aspirin	0.20 (0.04–1.00)	0.18 (0.02–1.70)	0.53 (0.04–6.26)	0.09 (0.01–1.07)	0.27 (0.03–2.84)

*Model adjusted for index age and smoking
[a]Model adjusted for index age, gender, smoking. and gene group.
OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs.

TABLE 5. Logistic regression models by age group

	Age Group<50* OR (95% CI)	Age Group50-69* OR (95% CI)	Age Group>69* OR (95% CI)	Age Group≤ 64* OR (95% CI)	Age Group≥65* OR (95% CI)
Any NSAID	0.37 (0.09–1.48)	0.42 (0.22–0.81)	0.38 (0.00–0.31)	0.36 (0.19–0.67)	0.28 (0.10–0.76)
Ibuprofen	0	0.26 (0.08–0.86)	0.11 (0.00–1.87)	0.21 (0.7–0.60)	0.15 (0.01–1.68)
Aspirin	0.90 (0.14–5.95)	0.70 (0.33–1.52)	0.09 (0.01–0.60)	0.56 (0.26–1.22)	0.47 (0.16–1.38)

*Model adjusted for gender and smoking.
OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs.

separately. In gender-specific models adjusted for smoking and gene group (pathogenic or risk carrier), overall NSAID use was associated with lower PD risk; however, when broken down by NSAID type, the CIs for the results for aspirin in women were wide and no longer statistically significant. In analyses stratified by age groups (<50, 50–69, >69 and ≤ 64, ≥65), overall NSAID use was associated with lower PD risk in all age groups, but when studied separately by NSAID, the results were only significant for ibuprofen in the younger group, likely reflecting increased uncertainty from a small sample size (Table 5). The analysis was repeated separately in each cohort, and the results were similar for each (MJFF-LCC $OR_{any\ NSAID}$, 0.26; 95% CI, 0.13–0.52; PD-GEM $OR_{any\ NSAID}$, 0.44; 95% CI, 0.19–1.02; Mantel-Haenszel test of homogeneity *P* value = 0.59)

The results of a 5-year lagged model (Table 4) were similar to the primary analysis ($OR_{Any\ NSAID}$, 0.48; 95% CI, 0.27–0.85). In the 10-year lag, CIs were wide and no longer significant, with the exception of aspirin, which suggested an increased risk (10-year lag OR_{ASA}, 5.14; 95% CI, 1.11–23.82). However, the much smaller sample size in this subgroup precludes confident interpretations.

Discussion

The results of this study suggest that the regular use of NSAID medication may lower the risk for PD among *LRRK2* variant carriers, including pathogenic and risk variants, and for both ibuprofen and aspirin. This finding supports a growing body of research evidence involving inflammatory pathways in PD pathogenesis and data from prior epidemiological studies supporting a potential role for NSAIDs in lowering the risk of sporadic PD.

Animal models as well as human epidemiological data support the importance of inflammatory mechanisms in PD at multiple levels. Activated microglia, inflammatory cytokines, and abnormalities in the complement system all appear to play significant roles.[28] Reactive microglia are observed in nigral pathology specimens in PD,[29] in humans and animals exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine,[29,30] and in other PD animal models.[29,31,32] Such activated microglia may underlie the oxidative stress thought to be largely responsible for dopaminergic cell loss in PD.[31] Increased levels of the inflammatory cytokines interleukin 1β, interleukin 6, and tumor necrosis factor α, known to sustain inflammation and immune responses, as well as the complement component C-reactive protein, have been found in basal ganglia and cerebrospinal fluid of subjects with PD,[33] and genetic variants affecting expression of certain cytokines have been linked to increased risk for neurodegenerative disorders, including PD.[34] Endogenous α-synuclein is involved in normal immune function,[35] and pathogenic α-synuclein directly induces both innate and adaptive immune responses in the central nervous system and in the periphery.[36] Pharmacologic immunosuppression and use of NSAIDs in rodent PD models also reduce neurodegeneration, highlighting aberrant neuroinflammation as a viable target for disease modification in PD.[37]

Epidemiological studies have shown that self-reported aspirin and nonaspirin NSAID use including ibuprofen may decrease the risk for PD.[12-17] However, the findings from such studies are heterogeneous and not universal because some studies did not find associations for aspirin,[14] or the protective effect of aspirin was only present in women,[13] or no association was found at all.[16] Several meta-analyses have evaluated these associations. A meta-analysis from 2010 suggested a protective effect for nonaspirin NSAID use on the risk for PD estimated at ∼15%,[12] although a Cochrane review in 2011 did not demonstrate sufficient evidence for the use of NSAIDs in PD prevention.[18] Among 2 more recent meta-analyses, 1 supported the association of non-aspirin NSAID on PD risk (pooled relative risk [RR] = 0.91; 95% CI, 0.84–0.99),[38] but could not demonstrate a dose response, and the other had a pooled RR in the same direction, but did not reach statistical significance (pooled RR = 0.95; 95% CI, 0.86–1.05).[39] Although it is likely that differences in methodology from the different studies underlie some of the heterogeneity in these results, pathophysiologic heterogeneity may also account for some of the variability. Studying genetically homogeneous subgroups such as *LRRK2* may provide additional insight.

The role of *LRRK2* in inflammation raises the possibility that inflammation may be even more important in

LRRK2-associated PD than in idiopathic PD.[21] Variants in the *LRRK2* gene have been associated with Crohn's disease and other chronic inflammatory conditions,[19,20] suggesting potentially common genetic, molecular, and cellular pathological pathways with PD. The LRRK2 protein is involved in inflammatory pathways and is highly expressed in monocytes, macrophages, and microglia.[40] Within monocytes, LRRK2 may have a role in their maturation.[41] Exposure to certain antigens results in LRRK2 upregulation and impaired autophagy in macrophages.[42] Lastly, the magnitude of the association between NSAID exposure and PD risk appears to be larger for LRRK2-PD. Pooled RR from meta-analyses of idiopathic PD ranged from 0.90 to 0.95,[12,38,39] and our observed OR of 0.34 would correspond to an RR of 0.42 (assuming a PD prevalence of 0.30 in nonexposed[7-9]), although the heterogeneity of the study designs and populations make this comparison difficult.

The physiologic pathways on which NSAIDs exert their potentially neuroprotective effects have not been definitively determined. NSAIDs inhibit cyclooxygenase enzymes and hence may protect against reactive oxidative species and glutamate induced toxicity.[43] In this specific genetic population, because the LRRK2 protein is known to be involved in inflammatory pathways[19,20,40,42] and impaired autophagy may result from LRRK2 protein upregulation, it is possible that modulation of this neuroinflammatory response by NSAIDs may modify the neurodegenerative effect of these mutations and variants. Recently, specific peripheral immune profiles were able to discriminate between 3 different clinical severity phenotypes in LRRK2-PD, suggesting that certain proinflammatory proteins could predict disease progression.[44] Peripheral inflammation has also been detected in asymptomatic G2019S carriers, and inflammatory markers can discriminate between idiopathic PD and LRRK2-PD.[45]

PD is a complex disease believed to result from the combined effect of environmental and genetic determinants and although largely unknown, concrete evidence of this interaction is starting to arise.[46,47] Although gene–gene and gene–environment interactions are thought to underlie the incomplete and relatively low penetrance of *LRRK2* mutations and variants as well as its phenotypic heterogeneity, to date few genetic or environmental factors have been associated with LRRK2-PD disease expression. Using data from a genome-wide association study replication genotyping in a large case-control study with prospectively collected environmental information, Gao and colleagues[47] examined the potential interaction between PD single nucleotide polymorphisms (SNPs) from several genes and human leukocyte antigen loci and smoking and caffeine intake. They found a single significant interaction between a SNP near the *LRRK2* gene and combined smoking and caffeine intake; however, known *LRRK2* variants were not genotyped. In a recent case-control study from Israel, cigarette smoking and increase coffee and tea intake were associated with older age of onset of LRRK2-PD.[48] Lastly, unaffected *LRRK2* mutation carriers with higher urate levels have been found to have a reduced risk of developing PD,[49] adding to prior evidence suggesting a protective effect of urate in idiopathic PD.[50] Although still unknown, the modulation of urate levels on LRRK2-PD could be related to neuroinflammation because the urate-activated Nrf2 antioxidant pathway likely plays a role in LRRK2 pathogenesis.[51-53]

There are several limitations to this study. First, there are innate limitations of a case-control study design, including the potential for selection and recall bias. NSAID dosage information used in this analysis was obtained retrospectively via questionnaires, and the variables necessary to perform a reliable dose–response analysis could not be analyzed separately because of insufficient data. Because the questionnaires did not capture the indication for NSAID use, we cannot explore the possibility of confounding by indication. However, if an indication for NSAID use (such as chronic inflammatory conditions[19] or metabolic syndrome/cardiovascular risk factors[54] for aspirin) were also a cause of PD, one would expect the association with NSAIDs to be in the opposite direction (ie, higher NSAID use among manifesting carriers).

Because pain is a common indication for NSAID use, hyperuricemia is associated with gouty arthritis, and higher urate levels are associated with reduced PD risk, there is a question as to whether urate levels may be confounding the NSAID-PD association. However, the majority (>75%) of individuals with hyperuricemia (levels >7–8 mg/dL) are entirely asymptomatic,[55] and the incidence of gouty symptoms among the many hyperuricemic individuals with levels between 7 to 8 mg/dL is very low.[56] Urate levels reported in unaffected LRRK2 individuals had means below 7 mg/dL and many below 6 mg/dL. It would hence be unlikely that asymptomatic individuals within those urate levels would have higher rates of NSAID usage. Another potential confounder that could explain the findings would be related to stoicism as part of the "premorbid personality" described in PD leading to unwillingness to take NSAIDs for pain; however, although there is some evidence for higher rates of stoicism, harm avoidance, and less novelty seeking behavior among patients with PD,[57,58] there is little data to support that such personality traits would necessarily result in lessened analgesic intake, especially preceding a diagnosis of PD. The results in lagged analyses additionally suggest that the observed results were not the result of differential use of NSAIDs by persons with early undiagnosed PD because pain is commonly reported prior to PD motor

symptom onset.[59] Also, as stated previously, a reverse causation would be more likely in the opposite direction than the inverse relationship we observed. Another potential limitation is that case and control selection and recruitment methods differed between the centers, and not all centers recruited non-PD carrier controls (Supplementary Table 1). However, when the analysis was limited to each cohort separately, the results were similar for both cohorts even though the results limited to the smaller PD-GEM cohort were no longer statistically significant. Unaffected *LRRK2* variant carriers represent first-degree and second-degree relatives of cases in many centers. Very limited information was available on the relatedness of subjects from the cohorts, which precluded analytic adjustment. However, when limiting the analysis to those participants who were known to be unrelated (a subset of PD-GEM), this subcohort showed an association in the same direction as our main analysis, although the CIs were wide (unrelated cohort $OR_{Any\ NSAID}$, 0.11; 95% CI, 0.01–1.14).

Our study has significant strengths, including the large numbers of manifesting and nonmanifesting *LRRK2* carriers of both known pathogenic mutations and common risk variants from well-characterized international cohorts as well as the use of validated questionnaires on NSAIDs exposure.

In summary, the results of this investigation in 2 large and well-characterized LRRK2 cohorts supports the hypothesis that both aspirin and ibuprofen may reduce the risk of PD manifestation. The optimal dose and duration of exposure and the exact mechanisms by which protection may be exerted are, however, unknown. Anti-inflammatory drugs may potentially be useful as disease-modifying treatments in *LRRK2*-PD, and the ability to identify an at-risk population makes interventions in this subgroup particularly feasible. Lastly, because studies of LRRK2 kinase inhibitors are already underway, the results of this study highlight the potential need to control for the use of concomitant anti-inflammatory medications. However, prospective observational and interventional studies are needed to establish definitively whether this relationship is causal. ■

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Appendix

The investigators in the LRRK2 Cohort Consortium contributed to the design and implementation of the LRRK2 Cohort Consortium and/or provided data and/or collected biospecimens but did not necessarily participate in the analysis or writing of this report. LRRK2 Cohort Consortium investigators include Beth Israel Medical Center, New York, NY: Rachel Saunders-Pullman, MD, MPH; Deborah Raymond, MSc; Andres Deik, MD; Matthew James Barrett, MD, MSc; Jose Cabassa, MD; Mark Groves, MD; Ann L. Hunt, DO; Naomi Lubarr, MD; Joan Miravite, NP; Christina Palmese, PhD; Rivka Sachdev, MD; Harini Sarva, MD; Lawrence Severt, MD, PhD; Vicki Shanker, MD; Matthew Carrington Swan, MD; Jeannie Soto-Valencia, BA; Brooke Johannes, MSc; Robert Ortega, MSc; Laurie Ozelius, PhD; Susan Bressman, MD. Columbia University Medical Center, New York, NY: Roy N. Alcalay, MD, MSc; Ming-X Tang, PhD; Helen Mejia Santana, MSc; Ernest Roos, MD; Martha Orbe-Reilly, MD; Stanley Fahn, MD; Lucien Cote, MD; Cheryl Waters, MD; Pietro Mazzoni, MD, PhD; Blair Ford, MD; Elan Louis, MD, MSc; Oren Levy, MD, PhD; Llency Rosado, MD; Diana Ruiz, BSc; Tsvyatko Dorovski, MSc, MBA; Lorraine Clark, PhD; Karen S Marder, MD, MPH. Hôpital de la Pitie-Salpetrière, Paris, France: Jean-Christophe Corvol, MD, PhD; Florence Cormier, MD; Anne-Marie Bonnet, MD; Marie-Laure Welter, MD, PhD; Valerie Mesnage, MD; Marie Vidailhet, MD; Emmanuel Roze, MD, PhD; Lucette Lacomblez, MD; David Grabli, MD, PhD. Hospital Donostia, San Sebastian, Spain: Jose Felix Mart i Masso, MD, PhD; Javier Ruiz Martinez, MD, PhD; Elisabet Mondragon Rezola, MD; Ainara Estanga Alustiza, BS; Ana Gorostidi Pagola, PhD. Hospital Clinic de Barcelona, Barcelona, Spain: Claustre Pont-Sunyer, MD; Dolores Vilas Rolan, MD; Ruben Fernandez-Santiago, PhD; Maria Quintana, BS; Manel Fernandez, BS; Laura Maragall, BA. National Institute of Neurology Tunis, Tunisia: Faycal Hentati, MD; Matthew Farrer, PhD; John Duda, MD; Matt Read, BS; Lefkos Middleton, MD, FRCP; Rachel Gibson, PhD; Joanne Trinh, BS; Samia Ben Sassi, MD; Mourad Zouari, MD; Rimamouri, PhD; Emna Farhat, MD; Fatma Nabli, MD. Norwegian University of Science of Technology, Trondheim, Norway: Jan Aasly, MD; Bjørg Johanne Warø, MD; Sigrid Andersen, PhD, MSc. PROGENI Study—Indiana University School of Medicine, Indianapolis, IN: John Bertoni, MD, PhD; Julie Carter, RN, MN, ANP; Lawrence Elmer, MD, PhD; Nestor Galvez Jimenez, MD; Wayne Martin, MD; Rajesh Pahwa, MD; Kelly Lyons, PhD; Stephen Reich, MD; Robert Rodnitzky, MD; Carmen Serrano Ramos, MD; Joanne Wojcieszek, MD. Tel Aviv Sourasky Medical Center, Tel Aviv, Israel: Anat Mirelman, PhD; Tanya Gurevich, MD; Anat Bar Shira, PhD; Mali Gana Weisz, PhD; Kira Yasinovsky; Maayan Zalis, DMD; Avner Thaler, MD; Avi Orr-Urtreger, MD, PhD; Nir Giladi, MD. Parkinson Institute, Sunnyvale, CA:

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Supporting Data

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