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NON-STEROIDAL ANTI-INFLAMMATORY USE AND LRRK2 PARKINSON'S DISEASE PENETRANCE

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CONFLICTS OF INTEREST

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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. Non-steroidal 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—To evaluate the association of regular NSAID use and *LRRK2* associated PD.

Methods—Symptomatic ("LRRK2-PD") and asymptomatic ("LRRK2-nonPD") participants with *LRRK2* G2019S, R1441X or I2020T variants ("definitely pathogenic variant carriers"), or G2385R or R1628P variants ("risk variant carriers") from two international cohorts provided information on regular ibuprofen and/or aspirin use (≥2 pills/week for ≥6 months) prior to 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—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 (OR=0.34, 95%CI 0.21–0.57), and in both pathogenic and risk variant carriers ($OR_{Pathogenic}$=0.38, 95%CI 0.21–0.67; $OR_{RiskVariant}$=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, $OR_{Aspirin}$=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.

INTRODUCTION

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 non-motor 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 disease[11]. Neuroinflammatory responses may perpetuate degenerative neuronal injury, ultimately leading to PD. In large epidemiological studies, non-steroidal 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]. Since 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 risk of PD in two well-characterized international *LRRK2* cohorts.

METHODS

Participants

This study utilized phenotypic and environmental data collected from members of two 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 (MJFF) 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 MJFF-LCC can be found at https://www.michaeljfox.org/data-sets. Description of study cohorts and determination of *LRRK2* status in PD-GEM are described in Marras et al[22]. Information regarding 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 as "Risk Variant Carriers"[26]. Those participants meeting criteria for PD were defined as symptomatic ("LRRK2-PD") and those without PD as asymptomatic ("LRRK2-nonPD"). The breakdown of participant totals, LRRK2-PD and LRRK2-nonPD, 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, NIH)[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 (PD-RFQ), a validated set of questionnaires developed to provide a standard tool for general use in epidemiologic studies of PD (RFQ-U 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 PD-RFQ assesses life-long 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, *history of regular NSAID use* was determined using the following questions:

1. Have you ever *regularly* taken ibuprofen-based non-aspirin medications, that is, at least two 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 two 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 two pills per week for 6 months or longer? [Please do NOT include use of Tylenol or acetaminophen, or narcotic pain relievers such as Vicodin or 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 index date was defined as ≥2 pills/week for ≥6 months. Smoking status, also evaluated with the PD-RFQ, was included in all the models as ever (≥one cigarette per day for ≥6 months) vs. never smoker.

Statistical Analysis

All statistical data analysis was performed using SPSS v21 (IBM SPSS Statistics, Armonk, NY). Mean and standard deviation are presented for normally distributed continuous variables. Two-sample t-tests or non-parametric equivalent and Chi-square tests were 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 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 dataset 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, in order to evaluate whether the effect of smoking would be greater in one genetic subpopulation than in another. To control for potential reverse causality (i.e., early undiagnosed disease causing increased usage of NSAIDs), exposure-lagging analysis was performed at 5 and 10 years prior to index date[27].

RESULTS

Of the 577 participants enrolled, 259 (44.9%) were LRRK2-PD and 318 (55.1%) were LRRK2-nonPD. Demographic and clinical characteristics are summarized in Table 1. Participants with PD were older than those without PD (mean 66.2 years, standard deviation, SD, 11.5 vs. 60.9 years, (SD 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-nonPD. 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, rates of regular NSAID use were higher among LRRK2-nonPD 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, rates of NSAID use were higher in LRRK2-nonPD in all 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%CI: 0.21–0.57, Table 4). Both aspirin and ibuprofen were independently associated with 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 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 confidence intervals 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 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)

Results of a 5-year lagged model (Table 4) were very similar to the primary analysis ($OR_{Any\ NSAID}$=0.48, 95%CI: 0.27–0.85). In the 10-year lag, confidence intervals were very 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

Results of this study suggest that regular use of NSAID medication may lower 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 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 (MPTP)[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 IL-1b, IL-6 and TNFα, 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 PD subjects[33], and genetic variants affecting expression of certain cytokines have been linked to increased risk for neurodegenerative disorders, including PD[34]. Endogenous alpha-synuclein is involved in normal immune function[35], and pathogenic alpha-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 non-aspirin NSAID use including ibuprofen may decrease risk for PD[12–17]. However, the findings from such studies are heterogeneous and not universal, since 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 non-aspirin NSAID use on 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 two more recent meta-analyses, one supported the association of non-aspirin NSAID on PD risk (pooled 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]. While 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 sub-groups 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 up-regulation 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 range from 0.90–0.95[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 non-exposed[7–9]), although the heterogeneity of 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, since 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. More recently, specific peripheral immune profiles were able to discriminate between three different clinical severity phenotypes in LRRK2-PD, suggesting that certain pro-inflammatory 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 while largely unknown, concrete evidence of this interaction is starting to arise[46, 47]. While 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 very few genetic or environmental factors have been associated with LRRK2-PD disease expression. Using data from a GWAS replication genotyping in a large case-control study with prospectively collected environmental information, Gao et al. examined the potential interaction between PD SNPs from several genes and HLA loci and smoking and caffeine intake[47]. 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]. While still unknown, the modulation of urate levels on LRRK2-PD could be related to neuroinflammation, since 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 due to insufficient data. Since 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 (that is, higher NSAID use among manifesting carriers).

Since 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 >7–8mg/dL) are entirely asymptomatic[55], and the incidence of gouty symptoms among the many hyperuricemic individuals with levels between 7–8mg/dL is very low[56]. Urate levels reported in unaffected LRRK2 individuals had means below 7mg/dL and many below 6mg/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, while there is some evidence for higher rates of stoicism, harm avoidance and less novelty seeking behavior among PD patients[57,58], there is little data to support that such personality traits would necessarily result in lessened analgesic intake, especially preceding a diagnosis of Parkinson’s disease. Results in lagged analyses additionally suggest that observed results were not due to differential use of NSAIDs by persons with early undiagnosed PD, since pain is commonly reported prior to PD motor symptom onset[59]. Also, as stated above, 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 and second-degree relatives of cases in many centers. Very limited information was available on 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, though the confidence intervals were wide (unrelated cohort $OR_{\text{Any NSAID}}$=0.11, 95%CI: 0.01–1.14).

Our study has significant strengths, including the large numbers of manifesting and non-manifesting *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 two 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, since 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 or not this relationship is causal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Subject characteristics

	Total	LRRK2_PD		LRRK2_nonPD	
	N	N (%)	% male	N (%)	% male
Subject totals *	577	259	51.0	318	38.7
Age (mean, SD, range) **	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 ***					
Pathogenic variants age **	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 **	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 *a*	11	11 (100.0)	27.3	0 (0.0)	0.0
Asia *b*	181	32 (17.7)	59.4	149 (82.3)	35.6
Australia	10	8 (80.0)	62.5	2 (20.0)	0.0
Europe[c]	273	167 (61.2)	50.9	106 (38.8)	45.3
North America *d*	102	41 (40.2)	46.3	61 (59.8)	36.1

*Test of gender distribution between PD and non-PD, chi square=8.579, p=0.03

**Age at enrollment; test of age difference, p<0.05

***Due to overlapping mutations the total count of variant carriers exceeds the total count of gene group

a: all from Algeria

b: China n=175, Japan n=4, Singapore n=2; b: Spain n=162, France n=30, Germany n=20, Italy n=23, Norway n=22, Portugal n=16

d: USA n=76, Canada=26.

Table 2.

Regular NSAID use by age, gene group and region

	Any NSAID		Ibuprofen		Aspirin	
	LRRK2-PD	**LRRK2-nonPD**	**LRRK2-PD**	**LRRK2-nonPD**	**LRRK2-PD**	**LRRK2-nonPD**
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)

Table 3.

NSAID use by age and genetic mutation, by gender.

	Any NSAID		Ibuprofen		Aspirin	
Analysis restricted to men						
	LRRK2-PD	LRRK2-nonPD	LRRK2-PD	LRRK2-nonPD	LRRK2-PD	LRRK2-nonPD
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						
	LRRK2-PD	LRRK2-nonPD	LRRK2-PD	LRRK2-nonPD	LRRK2-PD	LRRK2-nonPD
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)

Table 4.

Logistic Regression Models

	Overall Model OR (95%CI)	5y Lag Model OR (95%CI)	10y Lag Model OR (95%CI)	Model for Men** OR (95%CI)	Model for Women** OR (95%CI)
Overall *					
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 *					
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 *					
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, gender, smoking and gene group

** Model adjusted for index age and smoking

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Table 5.

Logistic Regression Models by Age Group

	Age Group <50* OR (95%CI)	Age Group 50–69* 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