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Organophosphate pesticides and *PON1* L55M in Parkinson's disease progression

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ABSTRACT

Background: Parkinson's disease (PD) has motor and non-motor features that contribute to its phenotype and functional decline. Organophosphate (OP) pesticides and *PON1* L55M, which influences OP metabolism, have been implicated in multiple mechanisms related to neuronal cell death and may influence PD symptom progression.

Objective: To investigate whether ambient agricultural OP exposure and *PON1* L55M influence the rate of motor, cognitive, and mood-related symptom progression in PD.

Methods: We followed a longitudinal cohort of 246 incident PD patients on average over 5 years (7.5 years after diagnosis), repeatedly measuring symptom progression with the Mini-Mental State Exam (MMSE), Unified Parkinson's Disease Rating Scale (UPDRS), and Geriatric Depressive Scale (GDS). OP exposures were generated with a geographic information system (GIS) based exposure assessment tool. We employed repeated-measures regression to assess associations between OP exposure and/or *PON1* L55M genotype and progression.

Results: High OP exposures were associated with faster progression of motor (UPDRS $\beta = 0.24$, 95% CI = -0.01 , 0.49) and cognitive scores (MMSE $\beta = -0.06$, 95% CI = -0.11 , -0.01). *PON1* 55MM was associated with faster progression of motor (UPDRS $\beta = 0.28$, 95% CI = 0.08 , 0.48) and depressive symptoms (GDS $\beta = 0.07$; 95% CI = 0.01 , 0.13). We also found the *PON1* L55M variant to interact with OP exposures in influencing MMSE cognitive scores ($\beta = -1.26$, 95% CI = -2.43 , -0.09).

Conclusion: Our study provides preliminary support for the involvement of OP pesticides and *PON1* in PD-related motor, cognitive, or depressive symptom progression. Future studies are needed to replicate findings and examine whether elderly populations generally are similarly impacted by pesticides or *PON1* 55M genotypes.

1. Introduction

Parkinson's disease (PD), a progressive neurodegenerative disorder with selective degeneration of dopaminergic neurons and the related motor symptoms, has many important non-motor features that contribute to its phenotype and functional decline. Cognitive impairment and neuropsychiatric symptoms are among the most prominent (Post et al., 2007). Dementia in PD patients is estimated to be as much as 2–6-fold more common than in unaffected individuals; up to 75% of PD patients who live > 10 years after diagnosis are expected to develop dementia, while depression affects up to half of all PD patients (Aarsland and Kurz, 2010). Over the course of disease, the severity and/

or frequency of motor and non-motor symptoms increase and health related quality of life becomes a major concern for patients and caregivers (Santos-García and de la Fuente-Fernández, 2013). Yet, very little is known about factors contributing to the course and progression of these disease features.

Pesticide exposures have consistently been associated with the development of PD (Freire and Koifman, 2012), but to date no epidemiologic studies have investigated the influence of pesticides on PD symptom progression. Pesticide exposures can induce oxidative stress and mitochondrial dysfunction and impair the ubiquitin-proteasome system, mechanisms that have been related to neuronal cell death in PD (Rhodes et al., 2013; Terry, 2012). For these same reasons, it is possible

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that these exposures may also contribute to faster symptom progression. Organophosphate (OP) insecticides are among the most commonly used pesticides agriculturally. The National Health and Nutrition Examination Survey (NHANES), 1999–2000, found that > 50% of participants in this national population sample had measurable levels of OP pesticide metabolites in their urine (NHANES, 2011). OPs have long been investigated in relation to PD susceptibility both due to neurotoxic action and their ability to induce oxidative stress among other mechanisms (Bagchi et al., 1995; Lukaszewicz-Hussain, 2010; Terry, 2012).

Additionally, OPs have been associated with other PD related non-motor symptoms. In general populations, OP pesticides have been reported as contributing to cognitive impairment, inducing deficits in signal detection, information processing, attention, and memory among others, and been linked to depression and suicide (Jaga and Dharmani, 2007; London et al., 2005; Terry, 2012; Zaganas et al., 2013). Animal studies have provided some support for these observations, finding that chronic, low level OP exposure (1) is associated with sensorimotor gating, spatial learning, recognition memory, cognitive flexibility and sustained attention (Terry, 2012), and (2) influences serotonin levels, possibly explaining how OP exposures may influence mood (Aldridge et al., 2005; London et al., 2005; Slotkin and Seidler, 2008).

Many OP pesticides are activated to a toxic analog (oxon) by cytochrome P450 (Costa et al., 2003), and the oxon is subsequently detoxified by the paraoxonase activity of the PON1 hydrolyzing enzyme (Costa and Furlong, 2007). Activity of PON1 is influenced by common single nucleotide polymorphisms (SNPs) in the *PON1* gene, including *PON1* L55M (rs854560). *PON1* L55M has been shown to directly influence PON1 levels and activity (Brophy et al., 2001; Garin et al., 1997; Mackness et al., 1993). We have previously reported statistical interactions between this variant and OP exposures related to PD risk (Lee et al., 2013), and there is evidence for a role of PON1 in Alzheimer's and vascular dementia, potentially through its anti-atherosclerotic function (Wehr et al., 2009; Zhuh et al., 2015). PON1 is an arylesterase, responsible for metabolism of aromatic esters (Cervellati et al., 2014). Both paraoxonase and arylesterase activities of the protein are responsible for the anti-inflammatory and antioxidant activities of high density lipoprotein (HDL) and PON1 has been shown to prevent LDL oxidation in-vitro (Cervellati et al., 2014).

Here, we will investigate whether long-term low level estimated ambient agricultural OP exposure assessed with a geographic information system (GIS) that employed pesticide use reports and land use information, and *PON1* L55M genetic variation act together to influence the rate of motor, cognitive, and mood symptom progression in PD. We will rely on a prospectively followed population-based cohort of Parkinson's patients from three highly agricultural Central California counties, followed on average for more than seven years into their disease course.

2. Methods

All procedures described were approved by the University of California at Los Angeles (UCLA) Human Subjects Committee and informed consent was obtained from all participants.

2.1. Study population

This longitudinal cohort includes 246 PD patients recruited as part of the Parkinson's Environment and Gene (PEG) population-based case-control study in Central California. More detail on recruitment methods (Costello et al., 2009; Gatto et al., 2010) and case definition criteria (Kang et al., 2005) for the case-control study and the longitudinal cohort (Ritz et al., 2012) have been published previously. Briefly, 373 incident, idiopathic PD patients, diagnosed within 3 years of recruitment, compose the base population for this longitudinal cohort. All patients were seen by movement disorder specialists (JB, YB) at least

once at baseline, many on multiple occasions, and confirmed as having probable idiopathic PD based on published criteria (Hughes et al., 1992). At the first follow-up after baseline (on average 3.5 years after baseline), 108 patients were lost to follow-up (64 were deceased, 6 too ill, 17 withdrew, and 21 could not be re-contacted). We successfully re-examined 265 patients during follow-up, and 13 of these participants were re-classified as not having idiopathic PD upon examination. Of the remaining 252 PD patients, 246 provided the data necessary for this investigation. Of these patients, 65 (26%) participated in 2 exams (3.6 years of mean follow-up, 5.9 years into disease), 174 (71%) in 3 exams (5.7 years of mean follow-up, 7.6 years into disease), and 7 (3%) participants in 4 exams (6.3 years of mean follow-up, 8.0 years into disease).

2.2. Assessment of PD progression

Trained interviewers collected detailed information on demographic and risk factors and for each participant UCLA movement disorder specialists conducted physical examinations at baseline and during each follow-up to assess progression. Specifically, motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) part III, which assesses speech, facial expression, tremor, rigidity, hand, arm, and leg movements, posture, gait, postural stability, and bradykinesia. If possible, patients were examined off PD medications (82% of the baseline exams and 80% of follow-up exams). For patients who we could only examine on medication, we estimated an off-score by adding the difference of the whole study population's mean off- and mean on- scores at the time of exam to the patient's on-score (Ritz et al., 2012). Cognitive function was assessed at each exam with the Mini-Mental State Exam (MMSE), a widely used 30-point instrument that tests for orientation, attention, memory, language, and visual-spatial skills. For 3 patients at baseline and 6 during the first follow-up exam, we had to substitute the in-person MMSE with a 26-point telephone version of the MMSE and applied validated weights to make these scores comparable as recommended (Newkirk et al., 2004). Finally, we used the Short Form Geriatric Depression Scale (GDS) to measure depression symptoms with 15 questions it has been widely used and validated in older populations (Burke et al., 2015). We previously validated the GDS in our PD population, finding high sensitivity and positive predictive value compared with the Structured Clinical Interview for DSM Disorders (SCID) and Patient Health Questionnaire (PHQ-9) instruments (Thompson et al., 2011).

2.3. Organophosphate exposure assessment

We estimated ambient exposure to OP pesticides based on residential or occupational proximity to pesticide application, primarily from commercial agricultural applications. We used a geographic information system (GIS) based computer model which links California state mandated pesticide use reports (CA-PUR) for all commercial pesticide application since 1974, which contain information on date, location, type and amount of pesticide applied (provided within 1-sq. mile grids) (CDPR, 2013), with land use surveys, providing the location of specific crops and used to assess a more precise location of application within the 1-sq. mile CA-PUR grid (CDWR, 2013), and geocoded lifetime address histories for each of our participants (both residential and occupational addresses). For each pesticide reported to the CA-PUR, we calculated the pounds applied per year within a 500-m buffer of each residential and occupational address of our participants since 1974.

A total of 36 pesticides are considered OPs in the pesticide action network (PAN) pesticide database (Kegley et al., 2014) and contributed to our OP exposure measure; for a more detailed description see (Paul et al., 2015). Briefly, for each pesticide, we summed the pounds of pesticide applied per year and per acre within the 500-m buffer of each address within the study-period (1974-baseline interview), and then

Table 1
Baseline demographic characteristics and health indicators by ambient OP exposure and PON1 metabolizing status.

Characteristic Mean $\pm$ SD or n (%)	Cohort (n = 246)	OP exposure		PON1 metabolizing status	
		None/Low (n = 197)	High (n = 49)	Fast/Average (n = 204)	Slower (n = 39)
Demographics					
Age at interview	68.9 $\pm$ 9.8	68.8 $\pm$ 10.1	69.1 $\pm$ 8.2	68.7 $\pm$ 9.5	69.5 $\pm$ 11.4
Age at diagnosis	67.0 $\pm$ 9.9	67.0 $\pm$ 10.3	67.0 $\pm$ 8.1	66.8 $\pm$ 9.6	67.7 $\pm$ 11.5
PD duration (years)					
Prior to baseline	2.0 $\pm$ 1.5	2.0 $\pm$ 1.4	2.2 $\pm$ 2.0	2.1 $\pm$ 1.6	1.9 $\pm$ 1.4
Last follow-up	7.5 $\pm$ 2.6	7.1 $\pm$ 2.7	7.1 $\pm$ 3.3	7.0 $\pm$ 2.7	7.5 $\pm$ 3.0
Follow-up (years)	5.2 $\pm$ 2.1	5.2 $\pm$ 2.1	5.2 $\pm$ 2.4	5.0 $\pm$ 2.1	5.8 $\pm$ 2.3
PD family history	38 (15%)	32 (16%)	6 (12%)	30 (15%)	8 (21%)
European ancestry	197 (81%)	161 (82%)	36 (73%)	161 (79%)	34 (87%)
Male	140 (57%)	104 (53%)	36 (73%)*	116 (57%)	22 (56%)
Ever smoker	111 (45%)	92 (47%)	19 (39%)	95 (47%)	14 (36%)
Years of school	13.7 $\pm$ 4.4	13.9 $\pm$ 4.3	12.9 $\pm$ 4.8	13.8 $\pm$ 4.4	13.3 $\pm$ 3.6
Baseline health indicators					
MMSE	28.1 $\pm$ 2.3	28.3 $\pm$ 2.1	27.5 $\pm$ 2.7*	28.2 $\pm$ 2.4	27.8 $\pm$ 1.8
GDS	3.2 $\pm$ 3.3	3.2 $\pm$ 3.3	3.2 $\pm$ 3.3	3.3 $\pm$ 3.4	2.6 $\pm$ 2.4
UPDRS III	19.6 $\pm$ 9.6	19.3 $\pm$ 9.2	21.0 $\pm$ 10.8	19.6 $\pm$ 9.3	19.0 $\pm$ 10.6
Exposures of interest					
High OP exposure	49 (20%)	–	–	40 (20%)	9 (23%)
Slow PON1 metabolizer ^a	39 (16%)	30 (15%)	9 (18%)	–	–

^a Based on PON1 rs854560 (Lee et al., 2013; O'Leary et al., 2005).

* *P*-value < 0.05.

divided by the number of years in the time period to create a yearly average. Both residential and occupational addresses were included, and participants could have been exposed at both locations, one, or neither. We then dichotomized this yearly average. As the toxicity per poundage of each chemical is not necessarily similar across all OPs, we dichotomized the yearly average pounds of chemical applied to each of the 36 chemicals according to the chemical-specific median pounds per acre among the exposed, and then counted the number of OP chemicals each participant was estimated to be exposed to. Given the uncertainty in this exposure method (including assuming participant was at the recorded location during the relevant time period, wind patterns, etc.), we then used this count to characterize those participants most likely to be highly exposed (top quartile of count) or low/moderately exposed, as our primary exposure assessment.

2.4. PON1 L55M genotyping

Participants provided blood or saliva samples for genetic analyses, which were stored and processed at the UCLA Biologic Specimen Core Facility. PON1 L55M (rs854560) genotyping was conducted at the UCLA Genotyping and Sequencing Core Facility using pyrosequencing, which achieved a 100% call rate. For PON1 L55M, a significant decrease in mean PON1 enzyme activity from LL > LM > MM genotypes has been observed in human serum (O'Leary et al., 2005). Thus, 55MM genotype (TT, homozygous variant) was used to designate “slower” PON1 metabolizing. We also present sensitivity analysis treating the genotype in an additive manner, where LM corresponds to a predicted risk and MM corresponds to twice this risk. We previously reported a positive interaction between the SNP and OP exposures for PD in our study (Lee et al., 2013; Manthripragada et al., 2010).

2.5. Statistical methods

To evaluate differences in baseline demographics and symptom characteristics between OP exposure groups and PON1 metabolizing status we used either chi-square or student's two-tailed *t*-tests. We used repeated-measures regression analyses (Proc MIXED; SAS 9.4, SAS Institute, Cary, NC) to investigate between-subject and within-subject (time-dependent/progression) associations between OP exposure and PON1 and progression scores (MMSE, UPDRS, GDS) over follow-up.

The residuals from our final outcome models did not deviate significantly from normality (Shapiro-Wilk test *P*-value: UPDRS = 0.983; MMSE = 0.902; GDS = 0.906), thus we did not transform the outcome scores.

Including interaction terms between exposures and age (in years, centered at the mean age at time of baseline exam (68.9 years) as the time structure) allows us to estimate the change in score for the three different outcome scores according to exposure over time. The regression coefficient (β) for the interaction terms with age represent the difference in annual change in outcome score (UPDRS, MMSE, or GDS), for example the yearly difference in score between OP exposed and unexposed subjects. For model selection, we started with the full model including OP exposure, PON1 status, age, and possible interaction terms; after step-wise removing terms based on change in estimates with at least one outcome, we included the following terms of interest: OP exposure, PON1, age, OP * age, PON1 * age, and OP * PON1. Allowing the OP * PON1 interaction to vary with time was not predictive of any of the outcomes; the models including and excluding this term were not statistically different (likelihood ratio test $P \geq 0.2897$), and the models excluding OP * PON1 * age had a lower AICC (better fit), thus we did not include the term. Similarly, we excluded the quadratic time term (age * age) as the models without the term had a lower AICC (better fit). In each model we also adjusted for age of diagnosis, sex, European ancestry (yes/no), years of education; we again allowed each potential confounder to vary with time, and included those predictive of at least one outcome, which were age * age of diagnosis and age * years of education. A multiple test correction was not implemented, as the exposures under analysis were selected based on previous research reports that supported associations with PD. We also present sensitivity analysis treating the genotype in an additive manner, such that each copy of the variant allele (T) increases the risk by the same amount. We used SAS 9.4 (SAS Institute Inc., Cary, NC) for all analysis.

3. Results

Both demographic characteristics and baseline health indicators were similar by OP exposure and PON1 metabolizing status, although those most highly OP exposed were more likely to be male and have lower baseline MMSE scores (Table 1). Patients enrolled at baseline

Table 2

Repeated measures linear model results for three separate models, predicting change in 1) Mini-Mental State Exam, 2) Unified Parkinson's Disease Rating Scale, and 3) Geriatric Depression Scale.

Characteristic	Outcome 1: MMSE			Outcome 2: UPDRS			Outcome 3: GDS		
	β coefficient	95% CI	P value	β coefficient	95% CI	P value	β coefficient	95% CI	P value
Age	−0.27	(−0.39, −0.15)	< 0.0001	1.28	(0.71, 1.85)	< 0.0001	0.13	(−0.05, 0.31)	0.146
High OP exposure * age	−0.06	(−0.11, −0.01)	0.037	0.24	(−0.01, 0.49)	0.057	0.03	(−0.05, 0.11)	0.419
Slower PON1 metabolizer * age	0.005	(−0.04, 0.05)	0.836	0.28	(0.08, 0.48)	0.007	0.07	(0.01, 0.13)	0.034
High OP exposure	−0.09	(−0.61, 0.43)	0.730	−0.73	(−3.12, 1.66)	0.551	0.10	(−0.64, 0.84)	0.798
Slower PON1 metabolizer	−0.38	(−0.95, 0.19)	0.190	0.23	(−2.36, 2.82)	0.864	−0.36	(−1.17, 0.45)	0.380
High OP exposure * slower PON1 metabolizer	−1.26	(−2.43, −0.09)	0.036	0.57	(−4.75, 5.89)	0.833	−0.33	(−2.00, 1.34)	0.695

Abbreviations: MMSE = Mini-Mental State Exam; UPDRS = Unified Parkinson's Disease Rating Scale; GDS = Geriatric Depression Scale.

Models also controlled for age at PD diagnosis, age * age at PD diagnosis, sex, European ancestry, years of schooling, and age * years of schooling.

who were too ill or died before a second exam was conducted were significantly older, had less years of education, worse baseline exam scores (MMSE, UPDRS, GDS), and a lower proportion of PON1 slower metabolizers than patients we re-enrolled for at least one follow-up exam; however, they were similar in terms of PD duration, sex, smoking status, European ancestry, and OP exposure status (Supplemental Table 1). Participants not ill or deceased but lost to follow-up for other reasons were not statistically different from enrolled patients in terms of demographic factors, baseline exam scores, OP exposure, or PON1 status.

Using repeated measures linear regression models and controlling for age at diagnosis (and interaction with time), sex, European ancestry, and years of schooling (and interaction with time), we found that the highly OP exposed group of patients were associated with significantly faster annual decline in MMSE (high OP exposure * age β = −0.06, 95% CI = −0.11, −0.01; Table 2). Slower PON1 metabolizer status was associated with a lower MMSE score, though non-significantly (slower PON1 β = −0.38, 95% CI = −0.95, 0.19; Table 2), and we estimated a statistical interaction between OP exposure and PON1, indicating slower metabolism and OP exposure together may contributed to lower MMSE scores (PON1 * OP β = −1.26, 95% CI = −2.43, −0.09; Table 2).

For the UPDRS-III, higher scores represent worse motor symptoms. Again, high OP exposure was associated with faster motor decline, (high OP exposure * age β = 0.24, 95% CI = −0.01, 0.49; Table 2), although the 95% confidence interval does include the null value. Additionally, slower PON1 metabolizing status was associated with faster progression of motor symptoms scores (slower PON1 * age β = 0.28, 95% CI = 0.08, 0.48; Table 2); we did not see evidence for a statistical interaction between PON1 metabolizing status and OP exposure and UPDRS; see Table 2. OP exposure was not associated with changes in GDS measured depressive symptom scores in our population (Table 2); however, slower PON1 metabolizers were associated with a faster increase in GDS score (slower PON1 * age β = 0.07; 95% CI = 0.01, 0.13; Table 2). When we treated PON1 metabolizing status in an additive manner, we estimated very similar associations, see Supplemental Table 2.

4. Discussion

The rate and patterns of PD symptoms during disease progression are highly variable. Considerable motor and non-motor symptoms may accumulate over time and contribute strongly to disability and diminished quality of life (Global Parkinson's Disease Survey Steering Committee, 2002; Poewe and Mahlknecht, 2009); though, some patients are spared major disabilities until later in disease progression. Although there is a notable knowledge gap regarding factors that contribute to or modify this heterogeneity of phenotype and severity, there are few longitudinal population-based PD cohorts, and investigators are just beginning to examine what may have an influence.

Here, for the first time, we present evidence that long-term organophosphate pesticide exposure and/or PON1 L55M slow metabolizer status are associated with PD symptom progression in three major domains – motor, cognitive, and mood-related symptom decline.

We found that high cumulative OP exposure, estimated from residential and occupational proximity to OP pesticide application, slow PON1 metabolizer status (55MM), and the interactions between these two factors were associated with faster cognitive decline, as measured by the MMSE, over follow-up. PON1 metabolizer status appeared to interact with OP exposure, such that slow PON1 metabolizer patients with high OP exposures exhibited lower MMSE scores. We did not associate PON1 alone with faster cognitive decline during follow-up. We observed similar results for the UPDRS-III, where the highly OP exposed patients showed a faster increase in UPDRS over time. Further, slower PON1 metabolizing status predicted faster motor function decline during follow-up. We did not estimate a statistical interaction between PON1 and OP exposure on motor score, which might suggest that OP exposure and PON1 influence motor progression independently or that we did not have enough sample size to estimate such an interaction. Although OP exposure does not appear to play a role in the depressive symptoms progression in our PD population, again, slow PON1 metabolizer status was associated with a faster rate of developing depressive symptoms, suggesting PON1 influences depression independent of OP metabolism.

Organophosphate pesticides are designed to inhibit acetylcholinesterase enzyme activity, resulting in an excess of cholinergic stimulation acutely affecting the motor and central nervous system of targeted insects (Terry, 2012). Additionally, cell toxicity may also result from the induction of mitochondrial dysfunction and oxidative stress, with some evidence that low-level chronic exposures may have lasting toxic effects (Kaur et al., 2007; Soltaninejad and Abdollahi, 2009; Terry, 2012; Zaganas et al., 2013). Our findings, that PD patients chronically exposed to OP pesticides at low ambient levels experience faster cognitive decline, are supported by a growing body of evidence that links long-term pesticide exposure to memory, learning, and attention deficits, as well as dementia and Alzheimer's disease (AD) among others (Hayden et al., 2010; Terry, 2012; Zaganas et al., 2013). A large cohort investigation (n = 3084, with 500 dementia cases and 344 AD cases) in Cache County, UT, which reported occupational pesticide exposure increased the risk of dementia (hazard ratio (HR) = 1.38, 95% CI = 1.09, 1.76) and AD (HR = 1.53, 95% CI = 1.05, 2.23) (Hayden et al., 2010). This study replicated a French study of 1507 elderly whose cognitive performance was worse among those occupationally exposed to pesticides (insecticides, herbicides, or fungicides); analysis in men showed a significant association between AD and occupational exposure (relative risk (RR) = 2.39, 95% CI = 1.02, 5.63) (Baldi et al., 2003). Two meta-analyses have reported low level OP exposures are associated with reduced cognitive function (Meyer-Baron et al., 2015; Ross et al., 2013). The Agricultural Health Study, a large study of licensed pesticide applicators in the US, found that long-term moderate

levels of OP exposure was cross-sectionally associated with an increased risk of experiencing neurologic symptoms, including cognitive dysfunction (Kamel et al., 2007). Although OP exposure has not been investigated relative to motor symptom decline, OP exposure has widely been associated with PD susceptibility (Alavanja et al., 2004; Wirdefeldt et al., 2011). It is possible that the same biologic pathways play a role for PD susceptibility and progression, namely oxidative stress and mitochondrial dysfunction (Bagchi et al., 1995; Terry, 2012).

PON1 is important for OP metabolism and specifically detoxification. The L55M SNP was associated with modifying the risk of developing PD after OP exposure in our study previously, where we estimated a significant statistical interaction (Lee et al., 2013; Manthripragada et al., 2010). Here, we newly followed these PD patients from soon after their diagnosis to document decline over the course of disease. We found that this same variant seems to modify OP exposure associations related to cognitive decline. Furthermore, the 55MM genotype, which results in lower PON1 activity, alone predicts higher UPDRS and GDS scores over follow-up. Beyond its function for OP metabolism, PON1, as a component of high density lipoproteins (HDL), acts in an anti-oxidant and anti-atherosclerotic fashion preventing low density lipoproteins (LDL) from being oxidized (Zhao et al., 2012). Which of these functions contribute to cognitive decline in PD or both remains unclear. Though multiple independent investigations associate PON1 with AD and vascular dementia, both by examining genomic variation and with enzyme activity (Alam et al., 2014). A recent meta-analysis of 69 studies associated L55M, as one of four polymorphisms apart from APOE, with vascular dementia (Zhub et al., 2015). Numerous studies observed serum PON1 activity was decreased in dementia or AD patients, and one reported that MMSE scores were dependent on PON1 activity (Bednarska-Makaruk et al., 2013; Dantoine et al., 2002; Erlich et al., 2006; Helbecque et al., 2004; Sato and Morishita, 2015; Wehr et al., 2009). Although this provides biological plausibility for PON1's contributions to cognitive decline in PD aside from OP metabolism, further investigation is required. Though it should be noted, based on current epidemiologic research, PON1 alone may not be related to PD development in the absence of OP exposure, PON1 L55M was not associated with PD based on PD susceptibility GWAS meta-analyses (Lill et al., 2012; Liu et al., 2012).

Mechanisms of motor symptom decline in PD are not well understood, and further research is needed to establish any role for PON1. Yet, several findings suggest a role of lipid and cholesterol metabolism in not only vascular dementia and AD, as discussed, but also PD pathogenesis (De Lau et al., 2006; Reiss et al., 2004). Multiple case-control and cohort studies have implicated lower levels of cholesterol with increased PD risk (De Lau et al., 2006; Huang et al., 2007; Simon et al., 2007), yet, again by what mechanism is unknown. Interestingly, in vitro studies show alpha-synuclein, a primary component of the aberrant protein aggregations in Lewy bodies of PD patients, is closely associated with cholesterol-enriched lipid rafts in the cell membranes, and alpha-synuclein oligomerization may be regulated by fatty acids (Welch and Yuan, 2003). Further, the concentration of coenzyme Q10, an electron acceptor in the mitochondrial respiratory chain and a powerful antioxidant, is highly dependent on cholesterol (Johansen et al., 1991; Kaikkonen et al., 1999). Given the importance of oxidative stress and mitochondrial dysfunction in PD pathogenesis, it is possible that cholesterol, and in turn PON1, is influencing motor symptom progression through coenzyme Q10 or alpha-synuclein oligomers. Finally, multiple studies associated lower PON1 activity with an increased risk of depression (Barim et al., 2009; Bortolasci et al., 2014; Rice et al., 2009), including a large cohort of British women in which slower PON1 metabolism as measured by the Q192R SNP was associated with increased depression risk (OR = 1.22, 95% CI = 1.05, 1.41) (Lawlor et al., 2007). This has also been attributed to the antioxidant and anti-inflammatory mechanisms of PON1.

As expected in a cohort of elderly subjects, we were unable to follow all PD patients enrolled at baseline. There was loss to follow-up due to

death and illness, these patients at baseline were older and had worse MMSE, UPDRS, and GDS exam scores, consequently selection bias is possible. However, loss to follow-up, either from mortality/illness or withdrawal, was not associated with OP exposure (see Supplemental Table 1). Thus, we expect non-differential loss to follow-up, that is loss which was associated with the outcome (MMSE, UPDRS, or GDS) but not OP exposure, which is expected to bias associations on the additive scale toward the null. Additionally, with our ambient pesticide exposure assessment, we estimated exposure from proximity to pesticide application, and did not measure pesticide exposure directly. The assessment model also does not account for meteorological factors that may influence pesticide drift and we had to assume that study participants were at their residential or occupational location during relevant periods; thus, exposure misclassification cannot be excluded. Lastly, although we do not have follow-up data for a non-PD population, and thus we cannot tell whether the longitudinal findings are specific to PD or whether the same type of symptom progression would be observed in a non PD affected population with similar risk factors to ours, this investigation still provides important potential insights into PD symptom and cognitive decline.

Our study is one of less than a handful of population-based prospective PD patient cohorts worldwide and the only one to date to collect environmental and occupational exposure data. All of our patients were seen in person and examined by UCLA movement disorder specialists (mainly JB, YB) to confirm diagnosis and assess progression; follow-up began early in disease course (within 3 years of diagnosis); and due to our population-based design, our results are more generalizable to PD populations than patient cohorts assembled at tertiary care centers. In terms of exposure assessment, the majority of epidemiologic studies to date rely on self-reported pesticide exposure, a method prone to recall error, as participants may forget or be unaware of pesticide use. Our pesticide exposure assessment relied on a GIS tool and pesticide use and land use records that do not rely on participant recall, and allows us to investigate specific pesticides or chemical classes of interest, like OPs, providing a good population and opportunity to investigate environmental exposures.

Although our findings need to be re-examined and replicated in future studies, this study provides support for the involvement of both OP pesticides and PON1 in PD motor and non-motor progression. Given the importance of symptom progression for patients' health related quality of life and for predicting mortality (Forsaa et al., 2010), addressing this knowledge gap and identifying modifiable predictors for rate or severity of symptoms during disease course is important for both patients and for developing preventive measures.

Conflict of interest

None

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.envint.2017.06.018>.

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