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Permalink

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Journal

International Journal of Epidemiology, 42(5)

ISSN

0300-5771

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Publication Date

2013-10-01

DOI

10.1093/ije/dyt170

Peer reviewed

Household organophosphorus pesticide use and Parkinson's disease

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Accepted 24 July 2013

Background Household pesticide use is widespread in the USA. Since the 1970s, organophosphorus chemicals (OPs) have been common active ingredients in these products. Parkinson's disease (PD) has been linked to pesticide exposures but little is known about the contributions of chronic exposures to household pesticides. Here we investigate whether long-term use of household pesticides, especially those containing OPs, increases the odds of PD.

Methods In a population-based case-control study, we assessed frequency of household pesticide use for 357 cases and 807 controls, relying on the California Department of Pesticide Regulation product label database to identify ingredients in reported household pesticide products and the Pesticide Action Network pesticide database of chemical ingredients. Using logistic regression we estimated the effects of household pesticide use.

Results Frequent use of any household pesticide increased the odds of PD by 47% [odds ratio (OR) = 1.47, (95% confidence interval (CI): 1.13, 1.92)]; frequent use of products containing OPs increased the odds of PD more strongly by 71% [OR = 1.71, (95% CI: 1.21, 2.41)] and frequent organothiophosphate use almost doubled the odds of PD. Sensitivity analyses showed that estimated effects were independent of other pesticide exposures (ambient and occupational) and the largest odds ratios were estimated for frequent OP users who were carriers of the 192QQ paraoxonase genetic variant related to slower detoxification of OPs.

Conclusions We provide evidence that household use of OP pesticides is associated with an increased risk of developing PD.

Keywords Environmental exposures, household pesticide use, organophosphorus pesticides, paraoxonase, Parkinson's disease, United States, California

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized clinically by both motor and non-motor symptoms and pathologically by loss of

dopaminergic neurons in the midbrain and presence of Lewy bodies. Pesticides in general have been associated with an increased risk for developing PD¹ but most human studies focused on occupational

exposures.^{2,3} Household pesticide use in the USA continues to be very common, with use prevalence as high as 80–90% of households.^{4–6} This is of concern since persistence of pesticides inside homes can lead to prolonged exposures of household members.^{7–9} Until recently, many pesticide products permitted for household use contained organophosphorus (OP) chemicals; e.g. the OP insecticides chlorpyrifos and diazinon were widely used in household applications prior to the United States Environmental Protection Agency phase-out from products permitted for household use in 2001 and 2004, respectively.^{10,11} Organophosphorus pesticides as a class and individual OPs such as chlorpyrifos and parathion have been associated with PD in a handful of studies.^{12–16}

Here we explore whether exposures to pesticides from household use, especially those containing OPs, impact the odds of developing PD. In addition, we also assess whether our results are consistent with genetic susceptibility expected among carriers of the 192QQ and 55MM variants in the gene encoding the xenobiotic enzyme paraoxonase (PON1) known to detoxify several common OPs.¹⁷

Methods

The UCLA Institutional Review Board approved the study, and all participants provided written informed consent.

Subject recruitment and enrolment

This case-control study enrolled incident idiopathic PD patients from 2001 to 2007 and population-based controls between 2001 and 2011 from three mostly rural agricultural counties (Kern, Tulare and Fresno) in central California. Subject recruitment^{18,19} and case criteria^{20,21} have been described elsewhere.

We identified 1167 PD patients through local neurologists, medical groups and public service announcements; 397 had received a PD diagnosis >3 years prior to recruitment, 134 lived outside the area, 51 did not have a PD diagnosis and 22 were too ill to participate. Of all eligible cases ($N=563$), 90 could not be examined, i.e. declined, moved, became too ill or died before we examined them. Our movement disorder neurologists examined 473 eligible patients and excluded 107, because they did not meet required criteria for idiopathic PD.²² Six subjects withdrew prior to interview.

Initially, we recruited controls from the population using Medicare lists (in 2001) but, after the instatement of the Health Insurance Portability and Accountability Act (HIPAA), we solely used residential tax assessor records from the tri-county area. Two sampling strategies were implemented to maximize control enrolment success: first, we randomly selected residential parcels and enrolled via mail and phone, and second, we randomly selected clusters of

neighbouring households and enrolled participants during in-person visits at their doorstep. Control sampling strategies have been described in detail elsewhere.^{18,23}

Of 1212 potential controls contacted through the first recruitment strategy, 457 were ineligible (409 were <35 years of age, 44 were too ill to participate and 4 did not reside in target counties). Furthermore, 409 eligible controls declined, became too ill or moved after screening and prior to interview, leaving 346 controls recruited via phone and mail. In addition, an early mailing, for which the number of eligible subjects who declined remains unknown, produced 62 controls with home pesticide use information from interviews. We screened 4756 individuals for eligibility at their doorstep, finding 3515 to be ineligible (88% due to age criteria) and leaving 1241 eligible controls, of whom 634 declined participation and 607 controls enrolled. However, 183 subjects agreed to an abbreviated questionnaire without household pesticide information and were excluded.

Of all cases and controls enrolled, in total 357 cases and 807 controls provided information necessary for analyses of household pesticide use. For 278 cases and 397 controls of Caucasian race, we have both *PON1* genotype and household pesticide use information to assess modifications of OP pesticide effects on PD due to differences in OP metabolism from known functional variants.

Exposure assessment

Trained staff collected information on demographic characteristics, smoking history and lifetime household pesticide use. Participants self-reported personal use of pesticide products during four age periods: young adult (16–<25 years), adult (25–<45 years), middle age (45–<65 years), and senior (≥ 65 years) in three micro-environments, i.e. inside the home, outdoors on lawns and in yards, or during gardening activities. Subjects were asked to recall names of products and the pesticide targets (e.g. cockroaches, spiders, ants, termites, bees/hornets/wasps, flies, weed control, plant disease); some recalled specific chemicals (e.g. malathion, diazinon). We also elicited information about formulation of products (e.g. liquid, granules, bait, powder) and frequency of use, i.e. none or rare (once a year or less), occasional (2–11 times a year) or regular use (once a month or more; note: nobody reported more than once a week average use). We prompted interviewees who recalled a portion of the product name with similarly sounding products with the same target and formulation. All interviews for cases and controls enrolled through our first sampling strategy were conducted from 2001 through 2007 and from 2009 through 2011 for controls enrolled through our second strategy. Throughout, we employed the same primary interviewers and supervisors.

We supplemented our interview data with information about ingredients of reported home and garden use pesticide products from the California Department of Pesticide Regulation (CDPR) product label database.²⁴ Over 70% of products in this database have registration dates from the year 1970 and later. We compared dates of active registration listed in the CDPR database with dates of reported pesticide use to identify products for sale in California in those years. We also cross-referenced targets (e.g. ants, weeds) and formulation (e.g. liquid, granules) reported with targets, types (e.g. herbicide, insecticide, fungicide) and formulations listed in the CDPR database to identify products possibly used if product names were recalled incompletely. The active ingredient contributing the largest percentage to a product's composition was identified as the main ingredient. For some pesticides used before 1970, information on product composition was not available through CDPR; instead we identified the most likely main active ingredient with the same brand name (e.g. Black Flag) and target (e.g. ants). For some products, chemical composition varied over time, thus we considered the subject exposed to all possible main active ingredients. In addition, we also assigned chemical classes for each main active ingredient using the Pesticide Action Network (PAN) pesticide database.²⁵

The organophosphorus pesticides we identified in reported products included glyphosate, chlorpyrifos, bensulide, dichlorvos, diazinon, malathion, tetrachlorvinphos, oxydemeton-methyl, parathion, demeton, glufosinate-ammonium, disulfoton and methidathion.

Genotyping methods

Using whole blood or saliva samples from participants, genotyping for *PONI* L55M (rs854560) was conducted at the UCLA Genotyping and Sequencing Core Facility via pyrosequencing,¹⁵ and for Q192R (rs662) with the Fluidigm BioMark HD system (Fluidigm Corporation, South San Francisco, CA) at the University of Washington. Genotyping call rates for *PONI* L55M and *PONI* Q192R were 100% and 93%, respectively, and we did not detect departure from Hardy-Weinberg equilibrium in controls. We considered *PONI* 55MM and *PONI* 192QQ as 'risk' genotypes, because results for human serum analyses of *PONI* diazoxonase activity suggested median metabolic activity in carriers of these homozygous variants is lowest.²⁷

Statistical methods

We included only household pesticide products that subjects reported having personally used in their home, in yards and on lawns, or for gardening. We present results for progressively more specific pesticide usage beginning with (i) any use of household pesticides, then for types/classes of main active ingredients including (ii) any organophosphorus pesticide, (iii) subclasses of organophosphate (e.g. dichlorvos,

tetrachlorvinphos) and organothiophosphates (e.g. chlorpyrifos, diazinon, malathion, oxydemeton-methyl, parathion, demeton, disulfoton, methidathion) and finally (iv) the most commonly used insecticides, diazinon and chlorpyrifos.

We also excluded exposures reported for the past 10 years prior to the index age to account for the extended preclinical state of PD.²⁶ We calculated a weighted average frequency of pesticide use, first multiplying the midpoint of the reported pesticide use frequency category (i.e. for rare use: 0.5 times/year, occasional use: 6.5 times/year, regular use: 32 times/year) by years in each age period except for 10 years prior to index date, and summing across the periods before dividing by the total number of years between age 16 years and the index age minus 10. We also calculated weighted averages without lagging, and, using the same method, calculated weighted averages for exposures at younger ages only (16–<45 years). Similarly, we calculated weighted averages for each of the four age periods of exposure. We dichotomized household pesticide use into 'frequent use' as an average frequency at or above the median of the exposure distribution in exposed controls and 'never use/rare use' for an average frequency below the median. We also examine indoor and outdoor (i.e. yards, lawns, gardening) use separately. Subjects who reported use but did not specify a product name were excluded in analyses of organophosphorus use, but included as 'exposed' for any type of household pesticide use.

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) in unconditional logistic regression analysis adjusting for age (continuous) at index date (i.e. year of diagnosis for cases and year of interview for controls), sex, race (White/non-White), smoking (ever/never), education (<12 years, 12 years and >12 years), and family history of PD in first-degree relatives (yes/no). We assessed effects for any pesticide use as well as for each organophosphorus pesticide group. As reference group for all comparisons we used 'never use/rare use' of any household pesticides, thereby excluding those who used other types/classes of pesticides from the comparison when considering specific sub-categories of pesticides.

In sensitivity analyses, we excluded 62 controls from an unknown base of eligible subjects and stratified by gender. Additionally, we adjusted for ambient pesticide exposures at residences and workplaces based on a geographic information system (GIS) model we developed using the California Pesticide Use Reporting system during 1974–99,^{18,19} by weighting annual pounds of pesticide applied by proportion of acreage treated within a 500-metre buffer around addresses and summing exposures over the 26-year period. We created indicator variables, one for residential and one for workplace exposures, for ever having greater than median exposure (in exposed controls) for four types of pesticides [organochlorines

(OC), organophosphorus, dithiocarbamates (DTC) and paraquat (PQ)]. We also adjusted for a job exposure matrix (JEM) derived life-time cumulative occupational pesticide measure (none, low, medium, high) based on work history and detailed job tasks information.²³ Finally, we assessed modification of the effect estimate for PD from home pesticide use by *PONI* 192QQ genotype, and also the combined *PONI* diplotype (55MM, 192QQ), to identify low metabolizers.²⁷ We used SAS Version 9.2 to conduct all analyses.

Results

Our study participants were mostly older than 60 years of age; cases were more likely to be male, less educated than controls and more often never smokers (Table 1).

Frequent household pesticide use increased the odds of developing PD by 47% (95% CI: 1.13, 1.92). However, for organophosphorus and organothiophosphate classes of chemicals, associations were larger (70–100% increase), and both common active ingredients chlorpyrifos and diazinon contributed to the increase (Table 2). Point estimates for unlagged exposures were slightly attenuated (Supplementary Table 1, available as Supplementary Data at *IJE* online) and for OP exposure at younger ages (16–<45) slightly increased. Susceptibility window analyses in the four age periods yielded smaller estimates in the older ages (Supplementary Table 2, available as Supplementary Data at *IJE* online).

Adjustment for ambient pesticide exposures at residences or workplaces attenuated estimates for household OP pesticide use minimally [OR=1.59 (95% CI: 1.12, 2.25)]; similarly adjustment for life-time occupational pesticide exposures using our JEM estimates made no difference [OR=1.69 (95% CI: 1.19, 2.40)] (Table 3).

Separating indoor and outdoor household pesticide use resulted in similar size 50–70% increases in the odds ratio, but more participants reported use of organophosphorus pesticides outdoors on lawns, yards or in gardens (25.9% of cases and 17.4% of controls outdoors vs 3.0% and 1.8% indoors). Odds ratio estimates for use of any household pesticide were not different for men and women.

The influence of *PONI* 192QQ genotype (Table 4) was assessed in Caucasians only. As expected, we observed no increase in the OR with any *PONI* genotype in never/rare users of household pesticides, and a small 41% increase for subjects reporting frequent use of any pesticide who carried 192RR and QR genotypes; but we observed much larger ORs (2.62–3.71) in frequent users of OPs who carried the 192QQ genotype compared with never/rare users who were carriers of 192RR and QR genotypes. Carriers of the *PONI* diplotype, 55MM-192QQ, had an almost 6-fold increase in the odds of PD, though this estimate was

Table 1 Characteristics of study population

Characteristic	Cases (N = 357) n (%)	Controls (N = 807) n (%)
Sex (male)	205 (57.4)	371 (46.0)
Age ^a		
Mean ± SD	68.3 ± 10.2	66.2 ± 11.6
Range	34–88	35–99
≤60 years	75 (21.0)	254 (31.5)
>60 years	282 (79.0)	553 (68.5)
Cigarette smoking		
Never	187 (52.4)	389 (48.2)
Former	150 (42.0)	328 (40.6)
Current	20 (5.6)	90 (11.2)
Race		
White	287 (80.4)	564 (69.9)
Non-White	70 (19.6)	242 (30.0)
Unspecified		1 (0.1)
Education		
0–<12 years	66 (18.5)	116 (14.4)
12 years	96 (26.9)	166 (20.6)
>12 years	195 (54.6)	525 (65.0)
First-degree relative with PD ^b		
No	305 (85.4)	742 (91.9)
Yes	52 (14.6)	65 (8.1)

^aThis is the age at diagnosis for cases and age at interview for controls.

^bWe assumed that 26 controls who did not report family history of PD did not have first-degree relatives with PD.

based on small numbers [OR=5.75 (95% CI: 1.41, 23.40)].

Our estimates for household pesticide use and joint analyses of household pesticide use and *PONI* 192 genotype were similar after excluding the 62 controls recruited in early mailings.

Discussion

Our population-based case-control study of PD conducted in California's Central Valley suggests that household pesticide use increases the odds of developing PD especially for products that contain OPs as active ingredients independent of occupational and ambient exposures. Moreover, our results are corroborated by our finding that carriers of the *PONI* 192QQ variant or the 55MM-192QQ diplotype using household pesticides are at higher risk than non-carriers who are rarely or un-exposed.

Few previous studies have analysed personal household pesticide use in relation to PD risk. In contrast to our results, a case-control study in Washington State did not find an association of PD with personal use of

Table 2 Parkinson's disease associations with average household pesticide use frequency from age 16 years until 10 years prior to index age in the Central Valley of California

Pesticide use	Cases <i>n</i> (%)	Controls <i>n</i> (%)	Crude OR	Adjusted OR ^a (95% CI)
Any household pesticide usage				
Never use/rare use	196 (54.9)	504 (62.5)	1.00	1.00
Frequent use ^b	161 (45.1)	303 (37.5)	1.37	1.47 (1.13, 1.92)
Any organophosphorus (OP) pesticide use^c				
Never use/rare use	196 (70.3)	504 (80.6)	1.00	1.00
Frequent use ^b	83 (29.7)	121 (19.4)	1.76	1.71 (1.21, 2.41)
Chemical classes within OP pesticides				
Organophosphate				
Never use/rare use	196 (75.1)	504 (84.1)	1.00	1.00
Frequent use ^b	65 (24.9)	95 (15.9)	1.76	1.72 (1.18, 2.51)
Organothiophosphate				
Never use/rare use	196 (85.2)	504 (92.3)	1.00	1.00
Frequent use ^b	34 (14.8)	42 (7.7)	2.08	1.95 (1.17, 3.23)
Individual organothiophosphate pesticides				
Chlorpyrifos				
Never use/rare use	196 (95.6)	504 (98.2)	1.00	1.00
Frequent use ^b	9 (4.4)	9 (1.8)	2.57	2.73 (1.03, 7.24)
Diazinon				
Never use/rare use	196 (90.3)	504 (94.0)	1.00	1.00
Frequent use ^b	21 (9.7)	32 (6.0)	1.69	1.58 (0.87, 2.88)

^aAdjusted for age (continuous), sex, smoking, race, PD family history and education.

^bSubjects with an average frequency of use per year during ages 16–<10 years prior to index age that was at or above the median in exposed controls were assigned to the 'Frequent Use' category. For all comparisons, those in the 'Never Use/Rare Use' category had an average frequency of use per year during ages 16–<10 years prior to index age that was below the median for any household pesticide.

^cSubjects may be counted in multiple sub-categories of organophosphorus pesticide usage.

any household pesticide product (including those containing OPs).¹³ A French case-control study found a 40% increase in the OR for PD for gardening related pesticide exposures but 95% CIs included the null (95% CI: 0.90, 2.30).²⁸ A recent PD meta-analysis reported a summary risk ratio of 1.18 (95% CI: 0.86, 1.63) for household pesticide use relying on three studies—including the two we referenced above.¹ Our study is unique, since we used information on main active ingredients from CDPR to augment detailed questionnaire data. CDPR registers all pesticide products, including those meant for household use, before they can be sold in California.

Organophosphorus pesticides are still used in large amounts agriculturally.^{29,30} Chlorpyrifos is permitted for use in ant and roach bait in homes,³¹ and other organophosphorus pesticides with similar mechanisms of toxicity, such as bensulide, are also still permitted as ingredients in household pesticide products.³² Thus, it is important to consider contributions of household organophosphorus pesticide use in PD studies since decades of past use exposed a large proportion of the US population. Although in general

OP elimination from the body is fast, for more lipophilic agents, such as chlorpyrifos and diazinon, some proportion stored in body fat may be more gradually released into circulation and eliminated.^{33,34} Pesticides may also persist for longer periods in carpet dust.⁷ A recent study in the Salinas Valley of California suggests that household pesticide use may contribute a considerable proportion to pesticide exposures from indoor dust even in agricultural areas, with the finding that concentrations of chlorpyrifos and diazinon in household dust samples were 40–80% lower in 2006 than in 2000–02 when both pesticides were ingredients of household pesticide products.³⁵ We recently reported that behaviours such as ventilation and cleaning of pesticide treated areas that would minimize pesticide exposures after in-home treatment and use of personal protective equipment during applications are uncommon.⁴ Animal studies indicated that OPs, such as chlorpyrifos, may affect dopaminergic neurotransmission,^{36,37} and chronic low exposure to some OPs may result in mitochondrial dysfunction and apoptosis of neurons.³⁸ Moreover, it has been suggested that

Table 3 Parkinson's disease associations with average household pesticide use frequency from age 16 years until 10 years prior to index age; additional adjustment for other sources of pesticide exposure

Pesticide use	Cases n (%)	Controls n (%)	Crude OR	ORIGINAL MODEL Adjusted OR ^{a,b} (95% CI)	MODEL 1 Adjusted OR ^{a,c} (95% CI)	MODEL 2 Adjusted OR ^{a,d} (95% CI)
Any household pesticide usage						
Never use/rare use	196 (54.9)	504 (62.5)	1.00	1.00	1.00	1.00
Frequent use ^e	161 (45.1)	303 (37.5)	1.37	1.47 (1.13, 1.92)	1.41 (1.08, 1.84)	1.45 (1.11, 1.90)
Any organophosphorus (OP) pesticide use^f						
Never use/rare use	196 (70.3)	504 (80.6)	1.00	1.00	1.00	1.00
Frequent use ^e	83 (29.7)	121 (19.4)	1.76	1.71 (1.21, 2.41)	1.59 (1.12, 2.25)	1.69 (1.19, 2.40)
Chemical classes within OP pesticides						
Organophosphate						
Never use/rare use	196 (75.1)	504 (84.1)	1.00	1.00	1.00	1.00
Frequent use ^e	65 (24.9)	95 (15.9)	1.76	1.72 (1.18, 2.51)	1.57 (1.07, 2.30)	1.70 (1.16, 2.50)
Organothiophosphate						
Never use/rare use	196 (85.2)	504 (92.3)	1.00	1.00	1.00	1.00
Frequent use ^e	34 (14.8)	42 (7.7)	2.08	1.95 (1.17, 3.23)	1.95 (1.17, 3.25)	2.00 (1.18, 3.39)
Individual organothiophosphate pesticides						
Chlorpyrifos						
Never use/rare use	196 (95.6)	504 (98.2)	1.00	1.00	1.00	1.00
Frequent use ^e	9 (4.4)	9 (1.8)	2.57	2.73 (1.03, 7.24)	2.55 (0.96, 6.75)	2.81 (1.02, 7.71)
Diazinon						
Never use/rare use	196 (90.3)	504 (94.0)	1.00	1.00	1.00	1.00
Frequent use ^e	21 (9.7)	32 (6.0)	1.69	1.58 (0.87, 2.88)	1.61 (0.88, 2.95)	1.58 (0.86, 2.90)

^aAll models are adjusted for age (continuous), sex, smoking, race, education, and PD family history. Additional adjustments for other pesticide exposures are listed below.

^bORIGINAL MODEL: Unadjusted for other pesticide exposures.

^cMODEL 1: Additionally adjusted for ambient residential and ambient workplace exposures to pesticides (organophosphorus, organochlorine, dithiocarbamates and/or paraquat) from nearby agricultural applications.

^dMODEL 2: Additionally adjusted for a job exposure matrix (JEM) derived exposure to any pesticide.

^eSubjects with an average frequency of use per year during ages 16–<10 years prior to index age that was at or above the median in exposed controls were assigned to the 'Frequent Use' category. For all comparisons, those in the 'Never Use/Rare Use' category had an average frequency of use per year during ages 16–<10 years prior to index age that was below the median for any household pesticide.

^fSubjects may be counted in multiple sub-categories of organophosphorus pesticide usage.

Table 4 Combined effects of *PONI* Q192R and household pesticide usage from age 16 until 10 years prior to index age in association with Parkinson's disease, Caucasians only

Pesticide use	Never use/rare use				Frequent use ^a			
	Case <i>n</i>	Control <i>n</i>	Crude OR	Adjusted OR ^b (95% CI)	Case <i>n</i>	Control <i>n</i>	Crude OR	Adjusted OR ^b (95% CI)
Any household pesticide use								
<i>PONI</i> Q192R								
RR + RQ	74	133	1.00	1.00	62	84	1.33	1.41 (0.90, 2.21)
QQ	75	120	1.12	1.09 (0.72, 1.65)	67	60	2.01	1.96 (1.23, 3.11)
<i>OR for interaction</i>							1.35	1.27 (0.67, 2.42)
Any organophosphorus (OP) pesticide use^c								
<i>PONI</i> Q192R								
RR + RQ	74	133	1.00	1.00	28	48	1.05	1.03 (0.58, 1.82)
QQ	75	120	1.12	1.09 (0.72, 1.65)	37	24	2.77	2.62 (1.42, 4.83)
<i>OR for interaction</i>							2.35	2.34 (1.02, 5.35)
Chemical classes within OP pesticides								
Organophosphate use								
<i>PONI</i> Q192R								
RR + RQ	74	133	1.00	1.00	24	36	1.20	1.26 (0.68, 2.33)
QQ	75	120	1.12	1.09 (0.72, 1.66)	28	19	2.65	2.51 (1.28, 4.94)
<i>OR for interaction</i>							1.97	1.82 (0.74, 4.51)
Organothiophosphate use								
<i>PONI</i> Q192R								
RR + RQ	74	133	1.00	1.00	11	20	0.99	0.93 (0.41, 2.10)
QQ	75	120	1.12	1.09 (0.72, 1.66)	16	7	4.11	3.71 (1.42, 9.68)
<i>OR for interaction</i>							3.70	3.67 (1.05, 12.78)

^aSubjects with an average frequency of use per year during ages 16–<10 years prior to index age that was at or above the median in exposed controls were assigned to the 'Frequent Use' category. For all comparisons, those in the 'Never Use/Rare Use' category had an average frequency of use per year during ages 16–<10 years prior to index age that was below the median for any household pesticide.

^bAdjusted for age (continuous), sex, smoking, and education. We did not adjust for family history of PD to avoid the issue of over-adjustment due to possible correlations of family history with *PONI* genotype.

^cSubjects may be counted in multiple sub-categories of organophosphorus pesticide usage.

neurotoxicity from OPs such as diazinon and chlorpyrifos may occur at levels lower than those eliciting acute toxicity.³⁹

Our analyses of organophosphorus pesticide use only account for main active ingredients and no other active or inert pesticide ingredients in products. Indeed, other active ingredients tend to change more frequently over time, making it more difficult to identify them accurately, and inert ingredients are not required to be reported. To limit exposure misclassification for OP pesticide usage, we excluded participants with frequent use who could not recall a specific product name or enough information to identify a product and active ingredient.

A particular strength of our study is the disease characterization largely limiting misclassification error, since cases were diagnosed by UCLA movement disorder specialists, and a majority of cases were

re-evaluated over time. However, as with all other case control studies we assessed exposures only retrospectively, possibly resulting in differential recall bias if cases ruminate about causes for disease and over-report or more accurately recall and report past household pesticide use than controls. Our exposure assessment for OP pesticides depended only partially on recall and in large part on information on active ingredients retrieved from the CDPR. We relied on this database to identify products and periods when they contained OP pesticides as main ingredients, information that participants would be unlikely to recall or differentially recall. In addition, no study participant would have been able to report use consistent with *PONI* genotype carrier status which was unknown to them. Similarly to our recent finding for ambient organophosphorus pesticide exposures,⁴⁰ we estimated the highest risk of PD in carriers of the

55MM-192QQ diplotype who were frequent users of household OPs. Given extensive evidence that the *PONI* Q192R single nucleotide polymorphism is functional^{41–45} and experimental data from human serum analyses that showed the Q allele influences *PONI* serum diazoxonase activity under close to physiological conditions,²⁷ finding the expected influence of slow OP metabolizer status on PD provides support that the associations are not solely attributable to recall bias. While a smaller proportion of eligible controls compared with cases participate in our study, this would only result in selection bias if household pesticide use was related to participation. However, it is less likely that selection bias would affect our results from joint analyses of home pesticide use and genotype, since subjects would not have been able to select themselves into our study based on *PONI* genotype and household pesticide use.

Although many epidemiologic studies have assessed associations between pesticides and PD, few have focused on household pesticide use or organophosphorus pesticides. Household pesticide use is highly prevalent in the USA, and organophosphorus pesticides are still used in household pesticide products. We enhanced our exposure assessment and limited recall bias by using the CDPR product label database to identify major active ingredients in products. Our findings for household pesticide use and PD were strongest in carriers of genetic variants associated with slow metabolism for OPs. This study contributes important evidence for an association between PD

and household pesticide use, specifically OP pesticide use.

Supplementary Data

Supplementary data is available at *IJE* online.

Funding

This work was supported by the National Institute of Environmental Health Sciences [ES10544, U54ES12078, 5P30 ES07048].

Acknowledgements

We are indebted to our study participants, neurologists in the Central Valley of California who assisted us with case ascertainment, our study movement disorder neurologists and Dr. Myles Cockburn who provided advice and assistance on generating our GIS exposure estimates. We gratefully thank the Checkoway, Farin and Zabetian laboratories at the University of Washington for genotyping our samples. We also thank Dr. Shannon L. Rhodes for advice and assistance with editing an early version of the manuscript as well as our field staff who conducted interviews and collected data for our study.

Conflict of interest: None declared.

KEY MESSAGES

- Results suggest that household pesticide use increases the odds of developing PD especially for products that contain OPs.
- This is further corroborated by our finding that carriers of the *PONI* variants for slow metabolism of OPs are at much higher risk when using household OP pesticides.
- We provide first evidence that even in agricultural areas with high levels of commercial pesticide applications, household pesticide use contributes to the increased odds of PD, even when adjusting for occupational and ambient pesticide exposures.

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