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Depression in Parkinson’s Disease

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Depression in Parkinson's Disease

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in Epidemiology

by

Shu-Haur Hsieh

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ABSTRACT OF THE THESIS

Depression in Parkinson's Disease

by

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Master of Science in Epidemiology

University of California, Los Angeles, 2020

Professor Beate R. Ritz, Chair

Depression and anxiety are common mood disorders associated with Parkinson's disease (PD). Among environmental factors, organophosphate (OPs) pesticide exposures have been previously linked to depression as well as to PD. Here we not only re-examine the relationship between depression and anxiety prior to PD onset, but for the first time are also considering whether OPs pesticide exposure modifies this association. From 2001 to 2015, we recruited 832 PD patients diagnosed early in the disease and 817 unaffected population controls from three counties in central California. We collected information about depression and anxiety diagnoses and psychotropic medication use prior to PD onset, and also generated ambient residential and/or the workplace address measures of OP pesticide exposures based on a geographic information system derived

agricultural pesticide exposure report system. Employing logistic regression models, we analyzed the association between depression/anxiety and PD adjusting for sex, age at diagnosis/interview, race, smoking, and education. Risk of PD was increased among those diagnosed with depression/anxiety and medication use prior to PD diagnosis ($OR_{depression\ \&\ anxiety\ \&\ medication\ use}$ = 1.73, 95% CI = 1.37-2.18), and the estimated effect sizes increased with depression/anxiety diagnoses being closer to the time of PD diagnosis, especially in males. While not formally statistically significant, OP exposures seemed to modify the size of the effect estimate for a depression/anxiety diagnosis and PD and the joint effects of depression/anxiety and OP pesticide exposures together were very large in males ($OR_{Frequent\ exposure\ +\ Received\ depression\ and/or\ anxiety\ diagnosis}$ = 5.00, 95%CI = 2.54-9.87).

These results further support the notion that depression and anxiety might be early symptoms in the prodromal phase of PD and that in males OP exposures may contribute to mood disorders prior to PD onset.

The thesis of Shu-Haur Hsieh is approved.

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2020

Table of Contents

List of Tables

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the U.S. and worldwide, and it is a complex disease with multiple causes (1). Previous research reported that the prevalence of depression and anxiety in PD patients is higher than in the general population (2, 3). For depression, the prevalence in PD patients varies from 2.7% to 90%, (weighted mean 35%) (4), and for anxiety from 24.5% to 46.7% (weighted mean 31%) (5) compared with a prevalence of depression of 7.1%, and of anxiety of 19.1% among U.S. adults (6, 7). It has been proposed that deficits in the monoaminergic systems and changes in levels of inflammatory and neurotrophic molecules might contribute to these mood disorders in PD patients (8).

Depression and anxiety may develop reactively as a response to the diagnosis of PD and fears about future disability or as a result of adverse life events (9, 10). However, here we are interested in identifying risk factors for depression in PD that is not reactive. Thus, we are only investigating depression and anxiety that occurred prior to a PD diagnosis. Previous studies stated that the loss of neurons in the dorsal raphe nuclei (DRN) that secrete serotonin and dysfunction of catecholamine (norepinephrine and dopamine) synthesized in locus coeruleus (LC) might be related to prodromal depression in PD (11). The LC and DRN are affected at Braak Stage 2, while the substantia nigra is affected only at Stage 3. It can explain the occurrence of depression before motor symptoms and diagnosis (12).

Amongst environmental toxicants, organophosphate pesticides (OPs) have also been found to increase PD. OPs affect the nervous system is through inhibition of the acetylcholinesterase, an enzyme that hydrolyzes acetylcholine to cease cholinergic transmission, and this is a system also affected in PD (13, 14). In addition to inhibiting acetylcholinesterase, OPs may also contribute to PD risk because of their ability to enhance oxidative stress by increasing the production of reactive

oxygen species (15, 16). Inhibition of the acetylcholinesterase by OPs may cause depression because the inhibition of the acetylcholinesterase affects the balance of acetylcholine and dopamine (17). Chronic exposure to OPs may underlie psychological disorder through stimulating glutamatergic, dopaminergic, and serotonergic synaptic transmission by inhibition of the acetylcholinesterase (11). OPs may also regulate muscarinic Acetylcholine (ACh) receptor (18, 19), and the upregulation and supersensitivity of the muscarinic ACh receptor is associate with depression (20). OPs may increase neurotransmitter serotonin (5-HT) release, down-regulating 5-HT_{1A} autoreceptor that increases the risk of mood disorder (21). Furthermore, the genetic susceptibility of paraoxonase (PON1) may also play a role in the relationship between OPs and depression (17). Slow PON1 metabolizing may lower the inactivate of OPs through hydrolysis and is associated with the development of depression (22, 23).

We previously published a study that established an increased risk of PD with the prior occurrence of depression/anxiety in the first UCLA Parkinson's Environment and Genes (PEG) study (2000-2010) (24). Since this publication, we doubled the PS case number in PEG, allowing us to, for the first time, efficiently examine effect measure modification by gender and OP pesticide exposures.

2. Method

This study is part of the PEG study, a population-based case-control study conducted in Fresno, Tulare, and Kern counties in California. All subjects have provided informed consent, and all procedures described in this study have been approved by the University of California, Los Angeles (UCLA), Institutional Review Board for human subjects.

2.1 Study Population

In this study, cases were recruited if they were current residents in one of three counties (Fresno, Tulare, or Kern) who had lived in California for five years or more, not too ill to participate, examined and diagnosed by a UCLA PEG study movement disorder specialists, and been diagnosed with PD within the past five years. Our diagnostic criteria for diagnosing clinically probable or possible PD have previously published (24, 25). The first wave of PD patients (diagnosed within three years of enrolment) were recruited from 2001 to 2007 through local neurology medical groups, medical centers, and the Veterans Affairs hospital. The second wave of PD cases (diagnosed within five years of enrolment) was recruited from 2011 to 2015 with the help of the California PD registry (CAPDR). For 1,167 initially (2001-2007) invited patients, 604 were not eligible. From among 563 eligible, 90 were lost between screening and a mandatory clinic visiting, and 94 cases were excluded after the UCLA Movement disorder specialist established that they did not meet published criteria for idiopathic PD (26), leaving 379 cases. After excluding cases who provided incomplete information or were found not to have idiopathic PD at a follow-up visit, 360 cases remained for study. From among 2,714 cases who were initially contacted from 2011 to 2015, 1,980 were not eligible. From the remaining 734 cases, 85 cases refused to participate, 47 cases did follow an invitation for a physical examination by UCLA movement disorder specialists at a local clinic, and 119 cases were excluded after examination as they were classified as Parkinsonism or not having idiopathic PD. After excluding the cases that provided incomplete information for analyses, 472 cases remained for analyses. Thus, from the two waves of recruitment, we have assembled 832 PD cases for analyses.

Population controls in the first PEG study were recruited from 2001 to 2007 by mail or phone for a screening that established that they did not have PD; they also lived in one of the three counties and in California for at last five years or more, and were 35+ years of age. A total of 1,212

potential population controls were eligibility screened, and 755 were eligible after excluding those who were too young, terminally ill, or lived mostly outside the study area. We enrolled 521 controls, and 389 controls provided information that was needed for analyses. The second wave of population controls was recruited as part of the Center for Gene-Environment Research in Parkinson's Disease (CGEP) study. We randomly selected residential parcels from the tax-collector record and visited five homes around the index parcel in-person to recruit eligible controls. After excluding controls who were ineligible and provided incomplete information, 428 controls were enrolled. Thus, a total of 817 population controls are available for the analyses.

2.2 Data Collection

Study participants at baseline provided information about diagnoses of depression and anxiety including their age at first diagnosis as well as psychotropic medication use for depression and/or anxiety; specifically type (name), amount (pills per day/week), duration (weeks or months), and age at first and last use of each medication were reported. Interviewers were blinded to the subject's PD status as this information together with demographic and lifestyle characteristics were collected by telephone.

2.3 Organophosphate Exposure Assessment

Ambient Pesticide Exposures

Ambient residential pesticide exposure and ambient workplace pesticide exposure were estimated with a geographic information system (GIS) – based computer model. This model combined data from California state-mandated pesticide exposure reports (CA PUR) (27) that include information on agricultural pesticide applications and the date, location, amount applied, with land-use surveys from California's Department of Water Resources (28) and geocoded lifetime residential and occupational address histories of participants. Pounds of chemical per acre

per year within a 500m radius surrounding each address were estimated. We then calculate yearly average exposures for each chemical from 1974 to the date that is ten years before the date of PD diagnosis for cases or ten years before the date of interview for controls by summing years specific averages divided by the total number of years in the relevant period. Simple imputation was used if the geocoded location information for a participant in any given year was missing. Based on the information from CDPR and the pesticide action network (PAN) pesticide database, data from the PUR system showed that members of the study population were potentially exposed to some 40 chemicals classified as OPs (29). We dichotomized into "frequent" versus "occasional" exposures based on the OPs poundage per acres being at or above versus below the median in exposed control.

2.4 Statistical Analysis

Logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for depression and anxiety and PD as the ratio of odds for PD among those with pre-existing depression or anxiety versus those without these psychiatric diagnoses or treatments for the disorders. We also adjusted the ORs to address potential confounding by gender, age at diagnosis/interview (< 55 years, 55 to 65 years, > 65 years), race (Caucasian, Latino, other), pack-years of smoking (0, 0+ to 9, 10 to 39, 40+), and years of formal education (< 12 years, 12 years, 13 to 16 years, > 16 years).

We used two outcome measures: depression/anxiety diagnosis only and depression/anxiety diagnosis plus treatment. We also ensured that the age of depression and/or anxiety diagnosis and/or medication use was prior to the index date (for cases PD diagnosis, for controls time of interview). We then excluded the cases and controls whose depression and/or anxiety diagnosis and/or medication use had occurred more than 2, 5, 10, and 20 years before the index age in order to analyze depression and/or anxiety that had first occurred within the past 2, 5, 10, and 20 years.

We also stratified all analyses by gender.

Finally, we investigated whether 1) gender modifies the association between depression/anxiety and PD and 2) OPs modify the association of depression and PD (by gender), using stratified analyses and introducing product terms into logistic models to assess multiplicative interactions. All analyses in this study were conducted in SAS version 9.4.

3. Result

Study participants were predominantly Caucasian (76.6% in cases vs. 69.3% in controls) and did not have a family history of PD (83.9% in cases vs. 92.0% in controls). Cases completed less years of education (> 12 years: 60.7% of cases vs. 64.5% of controls), smoked less per year (cases 9.4 packs per year vs. controls 12.3 packs per year). Cases were slightly older than controls (67.7 years in cases vs. 65.9 years in controls), more frequently male (63.1% of cases vs. 46.3% of controls), more likely to have received a depression and/or anxiety diagnosis and use depression and/or anxiety medications (44.1% cases vs. 30.0% controls) (Table 1).

The odds of being diagnosed with depression and/or anxiety before the index date was higher in PD cases (OR = 1.61, 95% CI = 1.28-2.04), especially those also reporting to have been treated (OR = 1.73, 95% CI = 1.37-2.18). Males with PD had higher odds of a depression/anxiety diagnosis (OR = 2.12, 95% CI = 1.50-3.00) whether or not treated and the closer the diagnosis of depression and/or anxiety was made to a PD diagnosis, the stronger the effect estimates became. Females with PD had only a slightly higher odds of having been diagnosed with depression/anxiety in general (OR = 1.23, 95% CI = 0.88-1.73), but for those medicated the effect size was stronger (OR = 1.41, 95% CI = 1.01-1.96), and again associations were much stronger when the age of a depression/anxiety diagnosis was close in time to a PD diagnosis (Table 2).

We formally investigated effect measure modification by sex for a depression/anxiety diagnosis and PD, and we saw some evidence as the p-value for interaction was 0.016 (Table 3).

Finally, we also assessed effect measure modification with ambient OPs exposures, both at the residence and/or the workplace to investigate whether OP exposure modified the relationship between depression/anxiety and in males and females' PD (Table 4). None of the interaction test p-values were not formally statistically significant; however, the ORs we estimated for the joint effects were higher than the sum of the main effects for a depression/anxiety diagnosis and OP pesticide exposures alone minus the effects for the reference group. In males, the joint effect of ambient workplace OPs exposure and depression and/or anxiety was especially high ($OR_{\text{Frequent exposure + Received depression and/or anxiety diagnosis}} = 5.00$, 95%CI = 2.54-9.87).

Table 1

Demographic characteristic and risk factor distribution of California Central valley Parkinson's study subjects.

	Case (n=832) n (%) / Mean (SD)	Control (n=817) n (%) / Mean (SD)
Age	67.74 (10.59)	65.92 (11.71)
Sex		
Female	307 (36.9%)	439 (53.7%)
Male	525 (63.1%)	378 (46.3%)
1st Degree Relative with PD	134 (16.1%)	65 (8.0%) (missing=13)
Race		
White	637 (76.6%)	566 (69.3%)
Black	5 (0.6%)	26 (3.2%)
Latino	138 (16.6%)	155 (19.00%)
Asian	22 (2.6%)	25 (3.1%)
Native American	29 (3.5%)	43 (5.3%)
Missing	1 (0.1%)	2 (0.2%)
Education		
< 12 years	140 (16.84%)	119 (14.6%)
= 12 years	187 (22.5%)	171 (20.9%)
> 12 years	505 (60.7%)	527 (64.5%)

Table 1 (Continued)

Demographic characteristic and risk factor distribution of California Central valley Parkinson's study subjects.

	Case (n=832) n (%) / Mean (SD)	Control (n=817) n (%) / Mean (SD)
Education (continued)		
< 12 years	140 (16.8%)	119 (14.6%)
= 12 years	187 (22.5%)	171 (20.9%)
13 to 16 years	319 (38.3%)	333 (40.8%)
>16 years	186 (22.4%)	194 (23.8%)
Cigarette (pack-year)	9.43 (19.55)	12.28 (20.12)
0	457 (54.9%)	397 (48.6%)
0+ to 9	169 (20.3%)	144 (17.6%)
10 to 39	143 (17.2%)	185 (22.6%)
40+	63 (7.6%)	91 (11.1%)
Depression and/or anxiety diagnosis		
Never received	514 (61.8%)	598 (73.2%)
Ever received	318 (38.2%)	219 (26.8%)
Depression and/or anxiety diagnosis diagnosed within 10 years prior to index date [a b]		
Never received	514 (81.2%)	598 (86.3%)
Ever received	119 (18.8%)	95 (13.7%)
Never received depression and anxiety diagnosis	514 (61.8%)	598 (73.2%)
Received anxiety diagnosis and never received depression diagnosis	67 (8.1%)	33 (4.0%)
Received depression diagnosis and never received anxiety diagnosis	108 (13.00%)	88 (10.8%)
Received depression and anxiety diagnosis	143 (17.2%)	98 (12.0%)

Table 1 (Continued)

Demographic characteristic and risk factor distribution of California Central valley Parkinson's study subjects.

	Case (n=832) n (%) / Mean (SD)	Control (n=817) n (%) / Mean (SD)
Never received depression and anxiety diagnosis within 10 years prior to index date [b]	514 (81.2%)	598 (86.3%)
Received anxiety and never received depression diagnosis within 10 years prior to index date [b]	22 (3.5%)	13 (1.9%)
Received depression and never received anxiety diagnosis within 10 years prior to index date [b]	47 (7.4%)	38 (5.5%)
Received depression and anxiety diagnosis within 10 years prior to index date [b]	50 (7.9%)	44 (6.4%)
Diagnosis + no medication use	63 (19.8%)	41 (18.7%)
Diagnosis + medication use	255 (80.2%)	178 (81.3%)
Depression and/or anxiety diagnosis and/or medical use		
Never diagnosis and/or medication use	465 (55.9%)	572 (70.0%)
Ever diagnosis and/or medication use	367 (44.1%)	245 (30.0%)
Depression and/or anxiety diagnosis and/or medication use within 10 years prior to index age [c]		
Never diagnosis and/or medication use	465 (77.8%)	572 (84.5%)
Ever diagnosis and/or medication use	133 (22.2%)	105 (15.5%)

[a] Index date: age at PD diagnosis for cases; age at interview for controls.

[b] 633 cases and 693 controls diagnosed as depression and/or anxiety within 10 years prior to index date

[c] 598 cases and 677 controls diagnosed as depression and/or anxiety and/or medication use within 10 years prior to index date

Table 2

Association between psychiatric disorders diagnosed and/or medication history before Parkinson's disease and Parkinson's disease diagnosis.

	Cases without depression and/or anxiety	Cases with depression and/or anxiety	Controls without depression and/or anxiety	Controls with depression and/or anxiety	Cases/controls	
	n	n (%)	n	n (%)	OR[a]	95%CI
All cases						
Diagnosis model	514		598			
Depression and/or anxiety within 2 years prior to index date [b]		44 (7.9%)		25 (4.0 %)	2.41	(1.41, 4.09)
Depression and/or anxiety within 5 years prior to index date		83 (13.9%)		54 (8.3%)	2.14	(1.46, 3.14)
Depression and/or anxiety within 10 years prior to index date		119 (18.8%)		95 (13.7%)	1.72	(1.26, 2.36)
Depression and/or anxiety within 20 years prior to index date		164 (24.2%)		145 (19.5%)	1.57	(1.20, 2.05)
Depression and/or anxiety any time prior to index date		238 (31.7%)		211 (26.1%)	1.61	(1.28, 2.04)
Diagnosis + Medication Model	465		572			
Depression and/or anxiety within 2 years prior to index date		50 (9.7%)		30 (5.0%)	2.32	(1.42, 3.80)
Depression and/or anxiety within 5 years prior to index date		93 (16.7%)		62 (9.8%)	2.19	(1.52, 3.15)
Depression and/or anxiety within 10 years prior to index date		133 (22.2%)		105 (15.5%)	1.88	(1.39, 2.55)
Depression and/or anxiety within 20 years prior to index date		186 (28.6%)		164 (22.3%)	1.69	(1.30, 2.19)
Depression and/or anxiety any time prior to index date		266 (36.4%)		237 (29.3%)	1.73	(1.37, 2.18)

Table 2 (Continued)

Association between psychiatric disorders diagnosed and/or medication history before Parkinson's disease and Parkinson's disease diagnosis.

	Cases without depression and/or anxiety	Cases with depression and/or anxiety	Controls without depression and/or anxiety	Controls with depression and/or anxiety	Cases/controls	
	n	n (%)	n	n (%)	OR[a]	95%CI
Sex						
Male only						
Diagnosis model	339		311			
Depression and/or anxiety within 2 years prior to index date		30 (8.1%)		11 (3.4%)	2.98	(1.42, 6.26)
Depression and/or anxiety within 5 years prior to index date		53 (13.5%)		20 (6.0%)	2.92	(1.65, 5.18)
Depression and/or anxiety within 10 years prior to index date		80 (19.1%)		33 (9.6%)	2.52	(1.60, 3.97)
Depression and/or anxiety within 20 years prior to index date		106 (23.8%)		47 (13.1%)	2.27	(1.53, 3.35)
Depression and/or anxiety any time prior to index date		137 (28.8%)		62 (16.6%)	2.12	(1.50, 3.00)
Diagnosis + Medication Model	313		302			
Depression and/or anxiety within 2 years prior to index date		34 (9.8%)		15 (4.7%)	2.54	(1.32, 4.88)
Depression and/or anxiety within 5 years prior to index date		56 (15.2%)		25 (7.7%)	2.49	(1.47, 4.21)
Depression and/or anxiety within 10 years prior to index date		84 (21.2%)		36 (10.7%)	2.53	(1.63, 3.93)
Depression and/or anxiety within 20 years prior to index date		116 (27.0%)		51 (14.5%)	2.38	(1.63, 3.48)
Depression and/or anxiety any time prior to index date		148 (32.1%)		71 (19.0%)	2.11	(1.52, 2.94)

Table 2 (Continued)

Association between psychiatric disorders diagnosed and/or medication history before Parkinson's disease and Parkinson's disease diagnosis.

	Cases without depression and/or anxiety	Cases with depression and/or anxiety	Controls without depression and/or anxiety	Controls with depression and/or anxiety	Cases/controls	
	n	n (%)	n	n (%)	OR[a]	95%CI
Female only						
Diagnosis model	175		287			
Depression and/or anxiety within 2 years prior to index date		14 (7.4%)		14 (4.7%)	1.76	(0.78, 3.97)
Depression and/or anxiety within 5 years prior to index date		30 (14.6%)		34 (10.6%)	1.50	(0.85, 2.63)
Depression and/or anxiety within 10 years prior to index date		39 (18.2%)		62 (17.8%)	1.13	(0.70, 1.82)
Depression and/or anxiety within 20 years prior to index date		58 (24.9%)		98 (25.5%)	1.02	(0.68, 1.53)
Depression and/or anxiety any time prior to index date		101 (36.6%)		149 (34.2%)	1.23	(0.88, 1.73)
Diagnosis + Medication Model	152		270			
Depression and/or anxiety within 2 years prior to index date		16 (9.5%)		15 (5.3%)	2.07	(0.95, 4.52)
Depression and/or anxiety within 5 years prior to index date		37 (19.6%)		37 (12.1%)	1.85	(1.08, 3.16)
Depression and/or anxiety within 10 years prior to index date		49 (24.4%)		69 (20.4%)	1.37	(0.87, 2.14)
Depression and/or anxiety within 20 years prior to index date		70 (31.5%)		113 (29.5%)	1.14	(0.77, 1.68)
Depression and/or anxiety any time prior to index date		118 (43.7%)		166 (38.1%)	1.41	(1.01, 1.96)

[a] ORs are adjusted for sex, age, race, pack-years of smoking, and education.

[b] Index date: age at PD diagnosis for cases; age at interview for controls.

Table 3

Interaction, main, and joint effect estimates for receiving depression and anxiety diagnosis and sex in association with PD.

	Never received depression and anxiety diagnosis		Received depression and/or anxiety diagnosis		*p* for interaction
	Case/controls	Adj OR[a](95% CI)	Case/controls	Adj OR[a](95% CI)	
Sex					
Female	175/287	1.00 (reference)	101/149	1.22 (0.88, 1.69)	
Male	339/311	2.07 (1.60, 2.67)	137/62	4.53 (3.12, 6.56)	**0.016**[*]

Table 4

Interaction, main, and joint effect estimates for receiving depression and anxiety diagnosis and OPs exposure in association with PD stratified by sex.

	Never received depression and anxiety diagnosis		Received depression and/or anxiety diagnosis		p for interaction
OP Exposure Category	Case/controls	Adj OR[a](95% CI)	Case/controls	Adj OR[a](95% CI)	
Sex					
Male					
Ambient OP exposure					
Occasional use	183/197	1.00 (reference)	73/39	2.12 (1.35, 3.32)	
Frequent use	155/113	1.56 (1.12, 2.16)	64/23	3.34 (1.94, 5.75)	0.972
Ambient residential OP use					
Occasional use	218/218	1.00 (reference)	86/47	1.86 (1.23, 2.82)	
Frequent use	120/92	1.28 (0.91, 1.81)	51/15	3.76 (2.01, 7.07)	0.253
Ambient workplace OP use					
Occasional use	218/229	1.00 (reference)	84/50	1.85 (1.24, 2.79)	
Frequent use	120/81	1.57 (1.11, 2.23)	53/12	5.00 (2.54, 9.87)	0.196
Female					
Ambient OP exposure					
Occasional use	110/188	1.00 (reference)	60/91	1.24 (0.81, 1.89)	
Frequent use	65/99	1.26 (0.83, 1.91)	41/57	1.52 (0.91, 2.51)	0.945

Table 4 (Continued)

Interaction, main, and joint effect estimates for receiving depression and anxiety diagnosis and OPs exposure in association with PD stratified by sex.

	Never received depression and anxiety diagnosis		Received depression and/or anxiety diagnosis		p for interaction
OP Exposure Category	Case/controls	Adj OR[a](95% CI)	Case/controls	Adj OR[a](95% CI)	
Ambient residential OP use					
Occasional use	115/209	1.00 (reference)	63/96	1.32 (0.87, 2.01)	
Frequent use	60/78	1.58 (1.02, 2.44)	38/52	1.62 (0.96, 2.71)	0.468
Ambient workplace OP use					
Occasional use	130/222	1.00 (reference)	74/115	1.22 (0.83, 1.80)	
Frequent use	45/65	1.31 (0.82, 2.09)	27/33	1.66 (0.92, 3.00)	0.929

4. Discussion

We confirmed our previous findings that depression/anxiety - especially among those who were treated for these mood disorders - increased the risk of PD, most strongly in men. Furthermore, as we also saw before, estimate effect sizes tended to increase as a first depression/anxiety diagnosis was made more closely in time to the diagnosis of PD. This provides further supports for the hypothesis that depression and anxiety are early symptoms that occur in the prodromal phase of PD, consistent with previous studies (24, 30). For women with PD, the risk estimates were generally smaller and not always formally statistically significant, most likely due to a very high baseline rate of depression/anxiety we observed among female controls. As expected, requiring psychiatric treatment, however, increased the specificity of these diagnoses among women.

It is well-known that males have a higher risk of developing PD than females (31-33) while females are more often diagnosed with depression (34). Whether the later represents a bias among medical providers who might be more inclined to recognize and diagnose depression in women than men or gender-specific healthcare-seeking behaviors or true gender differences in such disorders in the communities we studied is unclear.

We included only patients who had depression prior to PD diagnosis to exclude anyone with reactive depression that might not be due to changes in brain circuitry related to PD (10). Previously research indicated that PD patients are at least two times more likely to suffer from depression in the prodromal years before PD is diagnosed; this has been interpreted as indicative of a neurodegenerative process that causes mood disorders before motor symptoms appear (9). This process or the risk factors that contribute to it might be different than those that affect PD patients who do not develop depression prodromally. Also, depression has not been a common

feature in familial PD, and genetic factors do not seem to play any major role in the origin of depression in PD (9). Thus, here we explored whether environmental risk factors known to be associated with PD in general and possibly also with depression idependently in population studies also affect the risk of PD with depression more strongly. We here focused on OP exposures as they have been associated with depression among farmers (17). Also, neuroimaging studies that compared PD patients with depression and without depression found abnormal activity and inverse correlations between depression and brain volumes in the prefrontal and limbic regions in PD patients with but not without depression (35), and OP poisoning has been shown to result in neural loss in cholinergic areas of the brain such as the basal forebrain and the limbic system (36).

A recent review of imaging studies (35) concluded that depression in PD likely does not just result from a single brain region or neurotransmitter system but rather may involve the dysregulation of cortico-limbic networks in addition to the nigrostriatal pathway.

The PEG study cases and controls live and work in predominantly agricultural communities with a high prevalence of pesticide exposure and exposure including to OP pesticides. Previous studies have shown that OPs exposures might increase the risk of PD (37-40). OPs exposures are known to inhibit acetylcholinesterase, and especially among those in the population who constitutively have slow PON1 activity, the accumulation of toxic metabolites and free oxygen radicals can cause damage to the nervous system. That is elevated acetylcholine levels and resulting impairments of the dopamine and acetylcholine balance in the striatum may increase the risk of both neuropsychiatric and PD (17, 41). OPs exposure can also inhibit DRN, which secrets serotonin, and the inhibition of DRN is related to depression in PD patients (21, 42). Thus, we were interested in how OP exposures may affect both the onset of depression and anxiety during the prodromal stages of PD as well as of PD itself.

A study using Taiwan National Health Insurance (NHI) program investigated interactions between OPs or carbamate poisoning defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (ICD-9-CM code: 989.3) and comorbidities including depression, stroke, dementia, or psychosis with PD (37). They reported that the PD risk for those with comorbidities including depression was higher among individuals with a diagnosis of OPs or carbamate poisoning, even though the interaction was not formally statistically significant. We also found a higher joint effect of OPs exposure and depression/anxiety, suggesting that a depression/anxiety diagnosis prodromal to PD onset amongst those who are chronically OPs exposed increases the risk of developing PD more strongly than either factor alone, especially for males.

As our study enrolled a very large number of PD cases, it allowed us to examine effect measure modification relatively efficiently and to distinguish between male and female PD cases. Misclassification of PD diagnosis in PEG is limited because PD cases were recruited according to stringent diagnostic criteria and clinically evaluated by a UCLA movement disorder specialist often more than once during follow-up of the cases over many years. However, this study still has several limitations. First, selection bias may be an issue if depression history affects participation rates. Controls who have a depression and anxiety diagnosis may have been less willing to actively participate in this study, especially males. We also found that among our female controls, there was a very high lifetime prevalence of depression/anxiety of almost 35% similar to female PD cases. Because this information was obtained by self-report retrospectively, over- or underreporting may affect these estimates. Furthermore, some misclassification may be due to the timing of the depression/anxiety diagnoses, but studies have shown that self-reported age at onset of depression is fairly reliable (43, 44). We assess ambient pesticide exposure with the GIS method

using the CA-PUR record. Thus, recall bias may not be an issue because the assessment of ambient pesticide is record-based. However, we do not consider geographic features and wind patterns that may cause exposure misclassification.

For PD patients, the consequences of depression/anxiety in PD might be depressed mood, loss of interest and concentration, and anhedonia. The quality of life and cognitive domains for PD patients may also be negatively impacted by depression/anxiety (9, 45).

In summary, our results support an early depression/anxiety phenotype that emerges as an early symptom during the prodromal phase of PD, especially in males, and this phenotype seems to be more strongly related to toxicant exposures, in this case OP pesticide exposures. Whether this phenotype is also related to differences in progression rates and overall severity in males needs to be explored in future studies.

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