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Ambient Pyrethroid Pesticide Exposures in Adult Life and Depression in Older Residents of California's Central Valley

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Abstract: Pyrethroid pesticide exposures may be associated with the onset of depression in later life via disruption of dopaminergic, serotonergic, and neurological functioning. We sought to investigate the association between living near agricultural pyrethroid pesticide applications and depression measures in central California, using two waves (PEG 1&2, total N = 1,654) of a case control study of Parkinson's disease (PD). At enrollment, participants self-reported history of use of depression medications and dates of MD-diagnosed depression and anxiety. Participants also completed a Geriatric Depression Scale-Short Form upon enrollment. We used the California Pesticide Use Registry to assign estimated ambient pyrethroid pesticide exposures at participant's home addresses over the 5 years before the index date (date of outcome, or an age-matched year for participants without the outcome). We used logistic and linear regression to evaluate associations between living near any pyrethroid applications over the 5-year index period and measures of depression and anxiety. We also evaluated modification by study wave and PD status. We observed associations of pyrethroids with depression, depression medications, and anxiety (adjusted odds ratio [aOR] depression = 1.54, 95% confidence interval [CI] 1.14, 2.07; aOR depression medications = 1.68, 95% CI 1.25, 2.25; aOR anxiety = 1.60, 95% CI 1.17, 2.18). However, we observed no associations with mild/moderate depressive symptoms according to the GDS score at enrollment (aOR = 1.04, 95% CI 0.77, 1.42). We did not observe a consistent modification of the pyrethroid-depression associations by study wave and PD status. Ambient pyrethroid pesticide exposures may be associated with measures of depression in later life.

Keywords: Pesticides; Pyrethroids; Depression; Mental health; Agriculture

Introduction

In 2017, over 17 million adults in the United States (7.1%) had at least one major depressive episode, with 44% being treated with medication.[1] Depression in the elder population additionally has consequences for other health outcomes, including increased risk for suicide and nonsuicide mortality, and dementia.[2] Although much attention has been given to psychosocial factors that contribute to depression, contributions of environmental biological insults have generally been underexplored.

Pyrethroid pesticides target neurological functioning by disrupting voltage-gated channels, and exposure to this class of pesticides has been associated with health outcomes that are comorbid with or predictive of depression, including diabetes,[3,4] Parkinson's disease (PD),[5] and behavioral disorders.[6] Additionally, occupational and chronic exposure to several pesticide classes during adulthood have been associated with depression in adults.[7–10] However, most of these studies either do not focus on pyrethroids, are occupational studies, are cross-sectional measures where the exposure and outcome are concurrent, or they use a single measure of depression to assess the outcome.

Here, we explore the relationship between living near pyrethroid pesticide applications and multiple markers of depression in a population-based sample in California's Central Valley, where exposure is measured over the 5 years before depression diagnosis.

Methods

Study Population

The Parkinson's, Environment, and Genes Study (PEG1 and PEG2) is a population-based case-control study in Central California to study the environmental and genetic contributions to PD. Recruitment occurred in two waves (PEG1&2). All subjects provided informed consent, and the study was approved by the UCLA Institutional Review Board.

In the first wave (PEG1), cases included new-onset PD patients (≤3 years from diagnosis) who resided in Fresno, Tulare, and

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The authors declare that they have no conflicts of interest with regard to the content of this report.

Data replication: Interested parties may contact the corresponding authors for access to a deidentified dataset, or the code used in the analyses.

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Kern counties, California, and were recruited through clinics, neurology offices, and public service announcements. All PEG1 participants were recruited between 2001 and 2007. Inclusion criteria required that patients had lived in California for at least 5 years, were not in the final stages of a terminal illness, were >35 years of age, within 3 years of a diagnosis, and were confirmed with clinically probable or possible PD by a UCLA movement disorder specialist. Requirements for this diagnosis have been detailed elsewhere.[11] Community controls lived in the same counties. In PEG1&2, they were identified from residential parcel listings from property tax assessor records, screened for eligibility, and enrolled by mail or telephone (PEG1) or during home visits at their doorstep (PEG2). Some controls (PEG1 only) were randomly sampled from a list of Medicare enrollees. For all controls, participation was limited to one person per household. In PEG1, 403 controls and 360 cases were recruited. For PEG2, an additional 424 population controls and 475 new-onset PD cases (≤5 years from diagnosis) were recruited from 2007 to 2015. PD patients in PEG2 were identified using a population-based PD registry.[12] Inclusion criteria were the same as in PEG1. Neurological evaluations for PEG2 took place between 2011 and 2017 and PD diagnoses were confirmed by a UCLA movement disorder specialist.

Outcome Assessment

Depression was assessed primarily via self-report. At enrollment, participants reported whether they had ever been diagnosed with depression or anxiety by a doctor, the age at diagnosis, and whether they had ever been prescribed medications for depression, along with the age at which they were first prescribed depression medication. They additionally filled out a Geriatric Depression Scale short form-15 (GDS).[13] Based on prior evidence supporting categorization of the GDS, we created a binary variable using a cutoff of >4 representing a mild, moderate, or severe depression symptom score.[14,15] In sensitivity analyses, we evaluated associations with a more severe cutoff of >9 on the GDS. Because PD is strongly linked with depression,[16] we excluded participants who developed PD before they acquired any of the outcomes (depression, anxiety, or medication use). For the GDS measure at enrollment, we also excluded participants who were on depression medications at the time of the exam.

Exposure Assessment

The California Pesticide Use Registry (PUR) is a registry of all commercial pesticide applications in the state of California since 1974. We used a validated geospatially-based system[17] to assign exposure status. Briefly, the PUR reports pesticide applications using the Public Land Survey System, roughly a one-square mile resolution. We combined this PUR data with land-use and crop information to improve the spatial resolution. We then calculated the pounds per acre for all pyrethroid pesticides applied within 500 m of the participant's residence, using reported address histories, for the 5 years before the index date for each outcome. In sensitivity analyses, we included both occupational and residential address histories. The index date for participants with an outcome (depression/anxiety diagnosis or medication use) was the diagnosis or first medication use date. The index date for unaffected participants was calculated based on the average age at diagnosis by PD status and study wave for affected participants. For instance, for participants with PD and depression in PEG1, we calculated the average age at depression diagnosis (55 years). Then, for participants with PD but without depression, we used the year in which they had been 55 years old as the index year. We repeated this within the strata of control participants in PEG1 (46 years), and PD and control participants in PEG2 (51 and 48 years), and for depression medication uses, and anxiety separately. Average depression index dates for PEG1 controls and PD patients were October 1997 and September 1995, respectively, and for PEG2 controls and PD patients they were February 1999 and June 2000. Since the PUR system began recording pesticide information in 1974, we excluded participants with an index year before 1979, to allow all participants a full 5-year period of surveillance for pyrethroid exposure. For GDS score at enrollment, we used the pyrethroid exposures in the 5 years before enrollment for all participants. Then, given a high percentage (80%) of unexposed participants, exposure represents living near any pyrethroid applications, or none.

Statistical Approach

We first report demographic characteristics at enrollment, and evaluate whether participants excluded due to having index dates before 1979 were different from included participants. Next, to estimate associations between pyrethroids and depression, we used logistic regression models and report both crude and adjusted odds ratios (aORs). We also considered a continuous GDS score, which exhibited a log normal distribution. We set GDS scores of 0–0.001, and modeled associations of pyrethroids for a log-transformed-GDS total score using linear regression. We a-priori selected covariates hypothesized to be important for depression from the literature. These included smoking status (never, former, current), age at interview, PD, sex, race/ethnicity (indicator variable for non-Hispanic white), and a four-level study wave/case status variable (PEG1 PD and control, PEG2 PD and control).

We also checked interactions for pyrethroid exposure with the study wave/case status variable with a likelihood ratio test, to assess whether associations differed by study wave or PD status. For this interaction test, we set the alpha at 0.15.

Results

In total, 1654 participants were included in at least one of the analyses of pyrethroid associations with depression/anxiety measures. Some participants had an index year before 1979; thus, total participants were lower in analyses of medically diagnosed depression (n = 1,306), depression medications (n = 1,458), and medically diagnosed anxiety (n = 1,296). Participants with an index year before 1979 for depression were not different from participants with a later index year in terms of education or gender, but were older, did not have PD, and were more often recruited in PEG1.

We observed elevated effect estimates for pyrethroids with doctor-diagnosed depression or anxiety, and the first use of depression medications (Figure 1). There was no association between pyrethroids and high/low GDS score at enrollment (Figure 1), and associations with a continuous GDS score were similarly null (Beta coefficient = 0.03, 95% CI −0.38, 0.44). In sensitivity analyses, associations based on a higher cutoff for GDS (>9) were similarly null.

The interaction *P* value suggested that effect estimates may vary by study group for MD-diagnosed depression (interaction $P = 0.14$, Figure 2). However, all stratum-specific effect estimates for this outcome were above the null. For all other measures, there was no evidence of heterogeneity by study group (chi^2 interaction *P* value was >0.15 for all other measures) (Figure 2).

Sensitivity analyses using exposures at both residential and occupational address histories resulted in similar effect estimates.

Discussion

We report consistently positive associations for residential ambient pyrethroid exposures in the 5 years before a depression

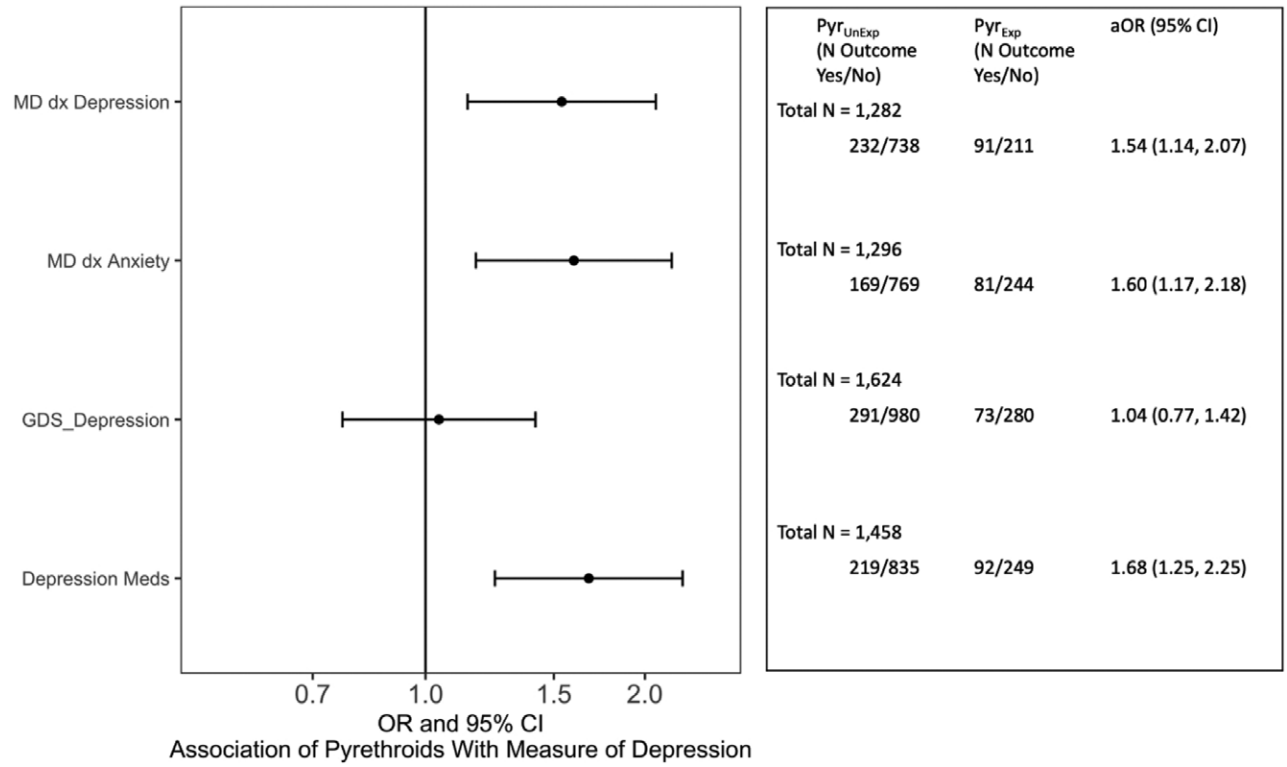

Figure 1. Associations of residential proximity to agricultural use of pyrethroid pesticides with self-reported measures of depression and anxiety. Models adjusted for smoking status, age, PD, sex, race/ethnicity, and study status. Depression Meds indicates history of medications for depression; GDS_Depression, met mild/moderate depression score cut off on Geriatric Depression Scale at enrollment; MD Dx Depression, doctor diagnosed depression; MD Dx Anxiety, doctor diagnosed depression; Pyr_{unexp}, unexposed to pyrethroids; Pyr_{Exp}, exposed to pyrethroids.

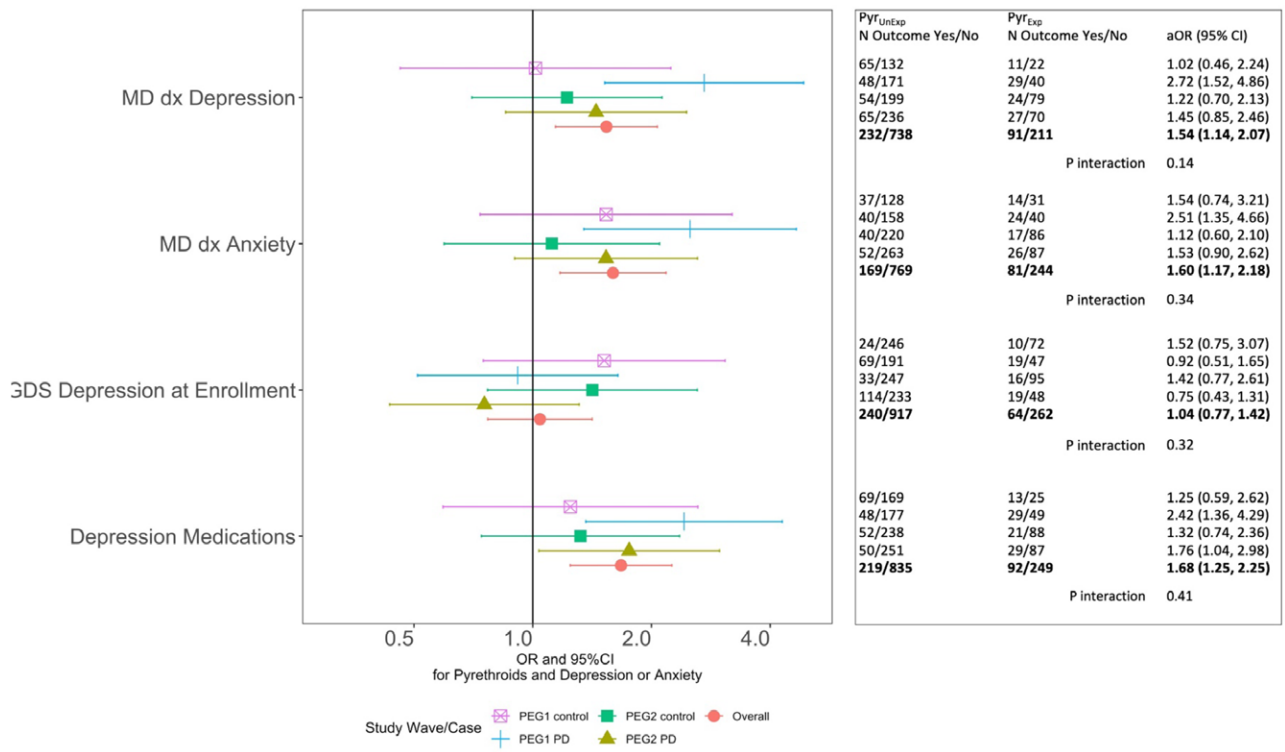

Figure 2. Associations of residential proximity to agricultural use of pyrethroid pesticides with self-reported measures of depression/anxiety by PD status and study wave. Models adjusted for smoking status, age, sex, race/ethnicity, with an interaction between pyrethroids and study wave/case status. Estimates for the overall models did not have an interaction term. Depression Meds indicates history of medications for depression; GDS_Depression, met mild/moderate depression score cut off on Geriatric Depression Scale at enrollment; MD Dx Depression, doctor diagnosed depression; MD Dx Anxiety, doctor diagnosed depression; Pyr_{unexp}, unexposed to pyrethroids; Pyr_{Exp}, exposed to pyrethroids.

Table 1.

Characteristics of the study participants

	All participants (N = 1,654)
Age at interview (mean, sd)	68.4 (11.2)
Pyrethroid exposures	
Any pyrethroid exposure in 5 years preceding enrollment	263 (20.4 %)
Smoking, n (%)	
None	850 (51.4)
Former	678 (41.0)
Current	126 (7.6)
Sex, n (%)	
Female	749 (45.3)
Male	905 (54.7)
PD/study wave, n (%)	
PEG1 PD	360 (21.8)
PEG1 control	401 (24.2)
PEG2 PD	470 (28.4)
PEG2 control	423 (25.6)
Race/ethnicity, n (%)	
Non-Hispanic White	1204 (72.8)
Other	450 (27.2)

index year, with depression and anxiety diagnoses, and medication use, but not GDS scores at enrollment.

Although associations were not modified by PD status and study wave, effect estimates tended to be stronger among PEG1 cases. However, as we did not observe the same phenomenon for cases in PEG2, we believe that this may be a chance finding. We observed associations with all measures except the GDS score at enrollment. GDS scores are measures of current depressive states only and this may reflect a reluctance to enroll in and participate in research while acutely depressed.

These associations are in line with prior literature on pyrethroids and behavior. For instance, in animals, pyrethroids have been associated with changes in open-field behaviors[18–20] and social interactions and emotionality,[19,21] along with reduced striatum dopamine levels.[18,22] In humans, the literature on pesticide exposures in adulthood and mental illness are scant, although pyrethroid exposure during pregnancy has been suggested to disrupt fetal programming related to mood and behavior.[6,23–25] We additionally previously reported that pyrethroid exposures were associated with changes in epigenetic pathways that are consistent with depression and alterations in mood.[26]

Strengths of the study include the measure of chronic pyrethroid exposure preceding outcomes, the consistency of the associations across several measures of depression, and a population living near relatively high agricultural applications. Limitations include that proximity to agricultural applications does not capture exposures through residential use or diet. However, in adulthood, exposures are difficult and impractical to measure over long periods with biomarkers, as this would be both expensive and even repeated measures may not correlate well over a long time period.[27]

This study provides preliminary support for exploring the relationship between pyrethroid pesticide exposure in adults and mental illness, specifically depression and anxiety, in older adults.

References

1. SAMHSA. Results from the 2016 National Survey on drug use and health: detailed tables. Prevalence estimates, standard errors, p values, and sample sizes. 2017.
2. Aziz R, Steffens DC. What are the causes of late-life depression? Psychiatr Clin North Am. 2013;36:497–516.
3. Hansen MR, Jørs E, Lander F, Condarco G, Schlünssen V. Is cumulated pyrethroid exposure associated with prediabetes? A cross-sectional study. J Agromedicine. 2014;19:417–426.
4. Park J, Park SK, Choi YH. Environmental pyrethroid exposure and diabetes in U.S. adults. Environ Res. 2019;172:399–407.
5. Furlong M, Tanner CM, Goldman SM, et al. Protective glove use and hygiene habits modify the associations of specific pesticides with Parkinson's disease. Environ Int. 2015;75:144–150.
6. Furlong MA, Barr DB, Wolff MS, Engel SM. Prenatal exposure to pyrethroid pesticides and childhood behavior and executive functioning. Neurotoxicology. 2017;62:231–238.
7. Beard JD, Umbach DM, Hoppin JA, et al. Pesticide exposure and depression among male private pesticide applicators in the agricultural health study. Environ Health Perspect. 2014;122:984–991.
8. Kamel F, Engel LS, Gladen BC, Hoppin JA, Alavanja MC, Sandler DP. Neurologic symptoms in licensed private pesticide applicators in the agricultural health study. Environ Health Perspect. 2005;113:877–882.
9. Campos Ÿ, Dos Santos Pinto da Silva V, Sarpa Campos de Mello M, Barros Otero U. Exposure to pesticides and mental disorders in a rural population of Southern Brazil. Neurotoxicology. 2016;56:7–16.
10. Freire C, Koifman S. Pesticides, depression and suicide: a systematic review of the epidemiological evidence. Int J Hyg Environ Health. 2013;216:445–460.
11. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology. 1992;42:1142–1146.
12. Ritz BR, Paul KC, Bronstein JM. Of pesticides and men: a California story of genes and environment in Parkinson's disease. Curr Environ Health Rep. 2016;3:40–52.
13. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clini Gerontol J Aging Mental Health. 1986.
14. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriatr Psychiatry. 1999;14:858–865.
15. Lesher EL, Berryhill JS. Validation of the geriatric depression scale–short form among inpatients. J Clin Psychol. 1994;50:256–260.
16. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008;23:183–9; quiz 313.
17. Gatto NM, Rhodes SL, Manthripragada AD, et al. α-Synuclein gene may interact with environmental factors in increasing risk of Parkinson's disease. Neuroepidemiology. 2010;35:191–195.
18. Nasuti C, Gabbianelli R, Falcioni ML, Di Stefano A, Sozio P, Cantalamessa F. Dopaminergic system modulation, behavioral changes, and oxidative stress after neonatal administration of pyrethroids. Toxicology. 2007;229:194–205.
19. Farag AT, Goda NF, Shaaban NA, Mansee AH. Effects of oral exposure of synthetic pyrethroid, cypermethrin on the behavior of F1-progeny in mice. Reprod Toxicol. 2007;23:560–567.
20. Souza MF, Medeiros KAAL, Lins LCRF, et al. Intracerebroventricular injection of deltamethrin increases locomotion activity and causes spatial working memory and dopaminergic pathway impairment in rats. Brain Res Bull. 2020;154:1–8.
21. Lazarini CA, Florio JC, Lemonica IP, Bernardi MM. Effects of prenatal exposure to deltamethrin on forced swimming behavior, motor activity, and striatal dopamine levels in male and female rats. Neurotoxicol Teratol. 2001;23:665–673.
22. Tayebati SK, Di Tullio MA, Ricci A, Amenta F. Influence of dermal exposure to the pyrethroid insecticide deltamethrin on rat brain microanatomy and cholinergic/dopaminergic neurochemistry. Brain Res. 2009;1301:180–188.
23. Viel JF, Rouget F, Warembourg C, et al. Behavioural disorders in 6-year-old children and pyrethroid insecticide exposure: the PELAGIE mother–child cohort. Occup Environ Med. 2017;74:275–281.
24. Wang N, Huang M, Guo X, Lin P. Urinary metabolites of organophosphate and pyrethroid pesticides and neurobehavioral effects in Chinese children. Environ Sci Technol. 2016;50:9627–9635.
25. Quirós-Alcalá L, Mehta S, Eskenazi B. Pyrethroid pesticide exposure and parental report of learning disability and attention deficit/hyperactivity disorder in U.S. children: NHANES 1999-2002. Environ Health Perspect. 2014;122:1336–1342.
26. Furlong MA, Paul KC, Yan Q, et al. An epigenome-wide association study of ambient pyrethroid pesticide exposures in California's central valley. Int J Hyg Environ Health. 2020;229:113569.
27. Spaan S, Pronk A, Koch HM, et al. Reliability of concentrations of organophosphate pesticide metabolites in serial urine specimens from pregnancy in the Generation R Study. J Expo Sci Environ Epidemiol. 2015;25:286–294.