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Proximity to residential and workplace pesticides application and the risk of progression of Parkinson's diseases in Central California

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Abstract

Background: Pesticide exposure has consistently been associated with Parkinson's disease (PD) onset. Yet, fewer epidemiologic studies have examined whether pesticides influence PD motor and non-motor symptom progression.

Objectives: Using a geographic information system tool that integrates agricultural pesticide use reports and land use records to derive ambient exposures at residences and workplaces, we assessed associations between specific pesticides previously related to PD onset with PD symptom progression in two PD patient cohorts living in agricultural regions of California.

Methods: We calculated the pounds of pesticide applied agriculturally near each participant's residential or occupational addresses from 1974 to the year of PD diagnosis, using a geographic information system tool that links the California Pesticide Use Reports database to land use data. We examined 53 pesticides selected a priori as they have previously been associated with PD

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CRediT authorship contribution statement

Shiwen Li: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Project administration, Data curation. **Beate Ritz:** Conceptualization, Supervision, Project administration, Data curation, Writing – review & editing, Funding acquisition. **Yufan Gong:** Validation, Writing – review & editing. **Myles Cockburn:** Project administration, Data curation, Writing – review & editing. **Aline Duarte Folle:** Project administration, Data curation, Writing – review & editing. **Irish Del Rosario:** Project administration, Data curation, Writing – review & editing. **Yu Yu:** Project administration, Data curation, Writing – review & editing. **Keren Zhang:** Project administration, Data curation, Writing – review & editing. **Emily Castro:** Project administration, Data curation, Writing – review & editing. **Adrienne M. Keener:** Project administration, Data curation, Writing – review & editing. **Jeff Bronstein:** Project administration, Data curation, Writing – review & editing. **Kimberly C. Paul:** Conceptualization, Methodology, Supervision, Project administration, Data curation, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

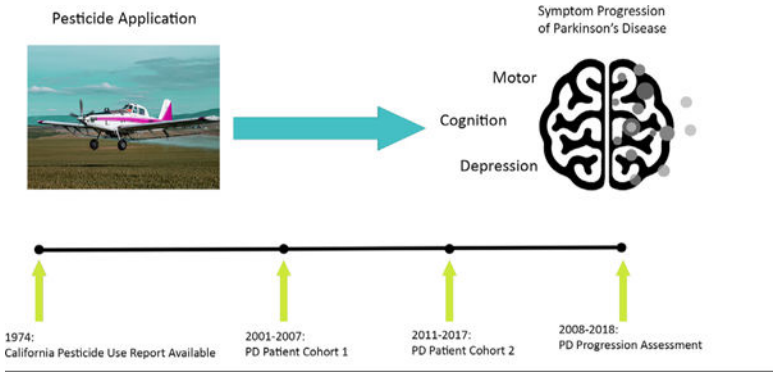
Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.160851.

onset. We longitudinally followed two PD patient cohorts (PEG1 N = 242, PEG2 N = 259) for an average of 5.0 years (SD ± 3.5) and 2.7 years (SD ± 1.6) respectively and assessed PD symptoms using the movement disorder specialist-administered Unified Parkinson's disease Rating Scale part III (UPDRS), Mini-Mental State Examination (MMSE), and Geriatric Depression Scale (GDS). Weighted time-to-event regression models were implemented to estimate effects.

Results: Ten agricultural pesticides, including copper sulfate (pentahydrate), 2-methyl-4-chlorophenoxyacetic acid (MCPA) dimethylamine salt, tribufos, sodium cacodylate, methamidophos, ethephon, propargite, bromoxynil octanoate, monosodium methanearsonate (MSMA), and dicamba, were associated with faster symptom progression. Among these pesticides, residential or workplace proximity to higher amounts of copper sulfate (pentahydrate) and MCPA (dimethylamine salt) was associated with all three progression endpoints (copper sulfate: HRs = 1.22–1.36, 95 % CIs = 1.03–1.73; MCPA: HRs = 1.27–1.35, 95 % CIs = 1.02–1.70).

Conclusions: Our findings suggest that pesticide exposure may not only be relevant for PD onset but also PD progression phenotypes. We have implicated ten specific pesticide active ingredients in faster PD motor and non-motor decline.

GRAPHICAL ABSTRACT



Keywords

Pesticide; Parkinson's disease; Motor progression; Cognitive decline; Depression

1. Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease affecting 1 % of the population over the age of 60 (Tysnes and Storstein, 2017). PD is characterized pathologically by significant and progressive loss of dopaminergic neurons within the substantia nigra (SN) and the accumulation of Lewy bodies, aberrant protein aggregates containing α-synuclein, in the midbrain (Shulman et al., 2011). Patients generally develop both motor symptoms, including tremor, rigidity, postural instability, and bradykinesia, and non-motor symptoms, including dementia, depression, sleep disorders, autonomic dysfunction, and pain (Moustafa et al., 2016; Poewe, 2008). As the disease progresses, symptoms worsen (Antonini et al., 2012; Xia and Mao, 2012). However, the course and

severity of symptom progression are highly heterogeneous (Greenland et al., 2019). Non-motor symptoms in particular are often overlooked and their impact on the patient quality of life is poorly recognized (Chaudhuri et al., 2006). Furthermore, current medications only alleviate motor symptoms but are unable to slow down or halt the progression of PD (Xia and Mao, 2012). Therefore, identifying factors that influence progression might provide insight into prevention strategies and pathways as therapeutic targets.

Pesticide exposure has been consistently associated with PD onset (Brouwer et al., 2017; Freire and Koifman, 2012; Goldman et al., 2017; Yan et al., 2018). However, few epidemiologic studies have examined whether pesticide exposure influences the rate of PD progression (Ahmed et al., 2017). The paucity of research is likely related to several challenges, including difficulties measuring the progression of PD in population-based studies and validly estimating long-term exposure to specific pesticides. Still, occupational pesticide use was associated with an increased risk of all-cause mortality in a prospective cohort of PD patients (Schneider Medeiros et al., 2020). We have also previously reported that residential or workplace proximity to higher levels of commercial, agricultural organophosphates (OP) pesticide applications contributed to faster motor and cognitive progression using a GIS-based tool linking the California Pesticide Use Reports database to land use data allowing us to investigate specific pesticides (Paul et al., 2017). We have since extended our first longitudinal cohort and conducted follow-up on a second cohort increasing the total number of PD patients followed for progression from 246 to 501. We have also recently conducted a pesticide-wide association study to more comprehensively assess ambient exposures to specific pesticides due to agricultural pesticide application in relation to PD onset (Paul et al., 2022). To do so, we started with 288 different pesticide active ingredients that we tested for associations with PD onset in an untargeted analysis of 1653 participants in our population-based case-control studies. This agnostic screening implicated 53 pesticides as associated with PD susceptibility. Many of these pesticides had not been implicated in PD before and none have been assessed for their influence on progression. For these 53 specific pesticides associated with PD risk, we now assess whether they also contribute to motor and non-motor symptom progression during prospective follow-up. Throughout the study, UCLA movement disorder specialists assessed motor features and trained staff recorded non-motor symptoms.

The goal is to provide information on specific pesticides that may affect PD progression and severity, stimulate future mechanistic and toxicologic research into how pesticides contribute to PD phenotypes, and ultimately, inform public health policy surrounding commercial pesticide application.

2. Methods

2.1. Study population

This study uses a community-based, longitudinal cohort of PD patients, recruited as part of the Parkinson's Environment and Genes (PEG) study in two study waves (PEG1 N = 242, 5.0 years (SD ± 3.5) of follow-up on average; PEG2 N = 259, 2.7 years (SD ± 1.6)) (Ritz et al., 2016). The PEG studies were designed as population-based case-control studies with accompanying prospective follow-up of PD patients to assess symptom development.

Briefly, a total of 833 idiopathic PD patients were recruited through the two independent study waves, referred to as PEG1 (with a baseline study visit between 2001 and 2007) and PEG2 (with a baseline study visit between 2011 and 2017). Patients were recruited from three Central California counties (Kern, Tulare, and Fresno) through neurologists, large medical groups, public service announcements, and eventually the California PD registry. The patients were early in their disease course at enrollment (mean PD duration at baseline = 2 years SD = 2 years for PEG1; mean = 4 years, SD = 3 years for PEG2). Eligibility criteria included: living in California for five years at minimum, having been diagnosed with PD for less than or equal to three years for PEG1 and less than or equal to five years for PEG2, and agreeing to participate in the study.

All patients were seen in person by a UCLA movement disorder specialist (lead by J.B., A.M.K.) to confirm PD diagnosis and assess symptoms using United Kingdom Brain Bank and Gelb criteria (Hughes et al., 1992; Gelb et al., 1999; Kang et al., 2005). The United Kingdom Brain Bank criteria define a parkinsonian syndrome as: 1) having bradykinesia and at least rigidity, (resting) tremor, or postural stability, 2) not meeting exclusion criteria, and 3) supportive positive criteria for PD (Hughes et al., 1992). Gelb's criteria require the diagnosis of at least two cardinal features including rest tremor, bradykinesia, rigidity and unilateral onset (Gelb et al., 1999). Of the 833 PD patients recruited at baseline for the case-control study (n = 356 and 477 recruited as part of PEG1 and PEG2 respectively), 332 patients (114 and 218 in PEG1 and PEG2) were not assessed for follow-up (no second exam scores for any outcome of interest) and these patients were excluded from the analysis. Of the 332 not followed, 56 % (n = 187) had died or were too ill to participate at first re-contact, 23 % (n = 75) refused or could not be re-contacted, and 21 % (n = 70 PEG2 patients) are pending an examination due to scheduling conflicts and Covid-19 related impact on patient exams (Duarte Folle et al., 2019). In total, n = 501 PD patients (242 PEG1 and 259 PEG2) were followed prospectively at least once for any of the outcomes of interest and included in this study (See Fig. 1). More details have been previously published (Duarte Folle et al., 2019).

2.2. Pesticide exposure assessment and selection

The PEG study is based in a highly agricultural region of Central California with industrial levels of commercial pesticide applications. We estimated separately ambient exposure to specific pesticides due to living or working near pesticide applications. Commercial pesticide applications are recorded in the California pesticide use reports (CA-PUR) database mandated by law since 1974. Detailed descriptions of the ambient exposure assessment methodology can be found in our previous publication (Cockburn et al., 2011). In brief, we estimated exposure with data from the CA-PUR database (CDPR, 2018) and land-use survey data (CDWR, 2022) linked to each study participant. For each year since 1974, we estimated the total pounds of each pesticide applied per acre within a 500 m buffer around the participants' residential or workplace addresses. We then calculated the average pounds of each pesticide applied within the buffer (pounds/acre/year), averaged from 1974 to the year of PD diagnosis. This time interval (1974 to PD diagnosis) was selected because long-term chronic exposure is likely most relevant for PD, which takes decades to develop and then progresses in a currently unpredictable manner. We also assessed different exposure

windows prior to diagnosis as part of sensitivity analyses, described below, to understand whether more recent exposure periods are more important than those in the distant past.

We originally determined that 288 different pesticides were commercially applied near PEG participants' residential or workplace locations in a sufficient amount to allow investigation, as ≥25 individuals were considered exposed (Paul et al., 2022). In total, 53 pesticides were selected for analysis here based on prior association with PD onset at a false discovery rate (FDR) <0.05, which was used to account for multiple testing (Paul et al., 2022). A list of the pesticides along with exposure descriptive information are provided in Supplemental Tables 1 and 2.

2.3. Outcome

We assessed motor symptoms using the Unified Parkinson's disease Rating Scale, part III (UPDRS-III). Patients were seen in person by a UCLA movement disorder specialist who assessed symptoms with the UPDRS-III at each exam, including speech, facial expression, tremor, rigidity, hand, arm, and leg movements, posture, gait, postural stability, and bradykinesia. All patients were assessed in a functional off state for PD medications (before taking their daily first medications) when possible and a subset of patients were assessed both on and off medications. For patients who could only be assessed on PD medication, we imputed the off score by taking the difference between the mean off-medication score and mean on-medication score from the study population with both on and off exams and added this difference to the individual on-medication score (Ritz et al., 2012). High motor impairment was defined as a UPDRS-III score reaching ≥35, a cut-point used previously, as it indicates that patients have developed more advanced functionally important motor symptoms (Duarte Folle et al., 2019; Shulman et al., 2010).

We also evaluated two domains of non-motor symptoms, cognition and depression, with the Mini-Mental State Examination (MMSE), performed by trained interviewers, and the self-administered 15-item Geriatric Depression Scale (GDS) at baseline and each follow-up exam. The MMSE is a test for cognitive function in the elderly population including orientation, attention, memory, language, and visual-spatial skills. High cognitive dysfunction was defined as a drop in MMSE score to ≤24. We chose a cutoff point of ≤24 as this is a widely used cutoff shown to have good specificity in predicting clinically diagnosed dementia (specificity = 0.96, sensitivity = 0.63) (Kukull et al., 1994). The short form GDS is a screening tool to assess depressive symptoms among the elderly population using 15 questions. We and others have validated the use of the GDS-15 for measuring depressive symptoms for minor (GDS-15 score 5–9) and major depression (GDS-15 score > 9) with clinical assessment in our study population (85 % sensitivity and 79 % specificity in PEG) (Thompson et al., 2011; Yesavage and Sheikh, 1986). Other studies have shown similarly high sensitivity and specificity with the GDS-15's 4/5 cutoff points (Shah et al., 1996). Therefore, we defined high levels of depressive symptoms as a GDS-15 score of ≥5.

We defined time to event (high level of cognitive, depressive, or motor dysfunction) as the time difference in decimal years between the date of the baseline exam and the date of the first follow-up exam in which the event was present. We excluded prevalent events at baseline (MMSE ≤ 24, GDS ≥ 5 or UPDRS ≥ 35) from analysis of the relevant outcome.

2.4. Statistical analysis

We log- and z-transformed the exposure estimates (average pounds applied/acre/year across the study window) for each pesticide due to the differences in pounds applied per acre for different chemicals and skewness of the exposure data. Skewness was assessed by plotting exposure data in a histogram and then determining the skewness, kurtosis, and *p*-value from a goodness-of-fit test, testing whether there is skewness and kurtosis that do not match a normal distribution.

We estimated the association for each of the 53 pesticides separately at residential and workplace addresses for the three measures of PD progression (UPDRS ≥ 35, MMSE ≤ 24, and GDS ≥ 5 events) relying on separate, weighted Cox Proportional Hazards time to event models with the follow-up time starting from the baseline interview. We adjusted for the following variables: sex (male, female), age of PD diagnosis (continuous), Hispanic ethnicity (yes, no), year of interview (continuous), education (<12 years, ≥12 years), PD disease duration at baseline (continuous), and amount of levodopa equivalent dose taken in mg (continuous). We considered a 0.05 statistical significance level.

We excluded participants with levels of exposure determined to be outliers i.e. exposures (log and z-transformed yearly average pounds/acre applied) > 3 standard deviations from the mean among participants with any exposure (>0). Outliers were determined separately for each pesticide. Fewer than five individuals, specific to each pesticide, were removed due to outlier values.

For time to event analyses, we restricted our population to those with follow-up exams and accounted for potential selection bias due to informative loss to follow-up using an inverse-probability of censoring weight (IPCW) (Hernán and Robins, 2020). Patients without any follow-up exams collecting MMSE, GDS, and UPDRS data were considered lost to follow-up. The patients lost were on average somewhat older at baseline than those with follow-up, had a slightly longer disease duration, and scored higher on the baseline MMSE and GDS exams (Supplemental Table 3). Therefore, we used the IPCW to create a pseudo-population that mimics the total population before censoring according to the distribution of these measured covariates (i.e., we weighted the censored population with follow-up data such that the distribution of these measured factors is the same as in the original uncensored population). A weight was generated for all participants with follow-up data. The numerator of the weight was generated by estimating the probability of loss to follow up given pesticide exposure in order to stabilize the weight. The denominator of the weight was generated by modeling the probability of loss to follow up given pesticide exposure, age of diagnosis, disease duration at baseline, baseline MMSE score, and baseline GDS score. As no other co-variates were associated with loss to follow up, they were not included in the weight. Each of the weights was specific to the pesticide included in the model. The weight calculation is shown below:

$$\frac{P(LosstoFollowUp = 1 \mid Pesticide)}{P(LosstoFollowUp = 1 \mid Pesticide, \text{AgeofDiagnosis}, \text{DiseaseDurationatBaseline}, \text{BaselineMMSEScore}, \text{andBaselineGDSscore})}$$

Additionally, to assess the rate of disease progression, we used a linear mixed model for repeated measures to further investigate pesticides found to be associated with one of the progression outcomes via the time to event models. We did not adjust for multiple testing as our pesticides were selected a priori in hypothesis-driven analysis due to their previous association with PD onset.

2.5. Sensitivity analysis

We performed several sensitivity analyses. First, assessing exposure in different periods, specifically, during the 10 years prior to diagnosis only or averaged from 1974 to 10 years before the year of diagnosis, i.e., lagging exposure by 10 years prior to diagnosis to account for a prodromal period in PD. We also assessed models with more confounders, including an indicator for participation in competitive sports over lifetime, a polygenetic risk score based on aggregating genome-wide association study-single-nucleotide polymorphisms for PD genetic risk (Paul et al., 2018), and a history of high blood pressure. Additionally, as cognitive and motor symptoms may decline in parallel, we also ran models including baseline cognitive symptom scores (MMSE) in the motor time to event analyses and baseline motor symptom scores (UPDRS-III) in the cognitive time to event analyses.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1 and Supplemental Table 1. Among those included in our analyses (n = 501), patients were predominantly male (62 %), of European ancestry (77 %), and never smokers (57 %). The mean years of education was 14 (SD = 4.6; Median = 14). The mean age at PD diagnosis was 66 years of age (SD = 10; Median = 68) and the mean time since PD diagnosis at baseline was 3 years (SD = 3; median = 2). Distribution of ambient pesticide exposure among patients is shown in Supplemental Table 2 and cross-tabulations of patients who had the event of interest (high levels of cognitive, depressive, and motor dysfunction) with any ambient exposure (>0) to the 53 pesticides of interest are shown in Supplemental Table 3.

The outcome measures were moderately correlated as some patients progressed in parallel across multiple symptom domains (Spearman correlation coefficients: MMSE ≤ 24 and GDS ≥ 5, $R = 0.23$, $p = 1.25e{-}07$; MMSE ≤ 24 and UPDRS ≥ 35, $R = 0.25$, $p = 1.31e{-}08$; GDS ≥ 5 and UPDRS ≥ 35, $R = 0.20$, $p = 4.22e{-}06$). In total, there are 97 incident cognitive, 212 incident depression, and 167 incident motor events during follow-up. Sixteen patients experienced all three outcomes, 13 cognitive decline and depression, 19 motor decline and depression, and 9 motor and cognitive decline.

Among patients who experienced both cognitive decline and depression events, the average time to outcome was longer for cognitive than for depression outcomes (average time to event = 4.2 ± 2.0 and 3.0 ± 1.9 years respectively). For patients who experienced both cognitive and motor outcomes or motor and depression outcomes, the time to event was similar (cognitive and motor time = 5.4 ± 1.8 and 5.2 ± 2.1 years; motor and depression time = 5.6 ± 3.0 and 5.2 ± 2.1 years). Finally, among patients who had all three outcomes during

follow-up, similar patterns were observed with shorter average time to event for depression and motor decline (5.3 ± 2.3 and 5.5 ± 1.6 years) and slightly longer time for cognitive decline (5.9 ± 1.9 years).

3.2. Progression-related pesticides

Overall, among the 53 pesticides we assessed, 10 (19 %) were associated with faster time to symptom progression among our PD patients. The 10 pesticides include: copper sulfate (pentahydrate), S,S,S-tributyl phosphorotrithioate (aka tribufos), 2-methyl-4-chlorophenoxyacetic acid (MCPA) (dimethylamine salt), sodium cacodylate, methamidophos, ethephon, propargite, bromoxynil octanoate, dicamba (dimethylamine salt, other related), and monosodium methanearsonate (MSMA). Two pesticides, copper sulfate (pentahydrate) and MCPA (dimethylamine salt), were associated with all three progression outcomes, while five pesticides were associated with two outcomes each (Fig. 2A). The associated pesticides represent a range of use types and chemical classes, shown in Fig. 2A. Pesticides are often applied in combination to the same agricultural sites during the same season, either sequentially or as part of the same product. Thus, correlation between pesticide exposures is expected. Pairwise Pearson correlation coefficients for all pesticides associated with progression events are shown in Fig. 2B and C and Supplemental Table 4. The heatmaps indicate pairs or groups of highly correlated pesticides. The correlation structure was similar for residential or workplace-based exposure estimates.

3.3. Time to motor function decline

Table 2 shows the six pesticides associated with faster time to motor function decline measured by UPDRS ≥ 35. Over the 1974 to diagnosis exposure window, residential proximity to higher levels of copper sulfate (pentahydrate), MCPA (dimethylamine salt), bromoxynil octanoate, and methamidophos application was associated with faster time to motor function decline (all HRs ≥1.20 per SD increase in exposure). Workplace proximity to MSMA application was also associated with an increased risk (HR = 1.22 per SD, 95 % CI = 1.03, 1.45). In repeated measures analysis (Supplemental Table 5), proximity to higher levels of MCPA (dimethylamine salt), methamidophos, dicamba (dimethylamine salt, other related) and MSMA was also associated with a higher UPDRS score.

Supplemental Table 6 shows the results of sensitivity analyses using the recent 10 years prior to diagnosis exposure window and the 10-year lagged long-term exposure window. Overall, compared to the 1974-diagnosis exposure window estimates, the hazard ratios were somewhat attenuated for exposure in the recent 10-year window, except for MSMA which showed a stronger association (HR = 1.27 per SD, 95 % CI = 1.05, 1.54).

3.4. Time to cognitive dysfunction

Table 3 details the main findings for each pesticide that showed an association with cognitive dysfunction. Of the 53 pesticides, long-term exposure (1974-diagnosis) to 8 individual pesticides at either residence or occupation was associated with faster time to the cognitive dysfunction event (MMSE ≤ 24). S,S,S-tributyl phosphorotrithioate (aka tribufos), which is a defoliant used almost exclusively on cotton, was associated with cognitive decline based on both residential and workplace proximity measures (HR = 1.29 per SD applied

near the residence, 95 % CI = 1.01, 1.66, and HR = 1.38 per SD applied near workplaces, 95 % CI = 1.12, 1.70).

The following 6 pesticides were associated with faster time to cognitive decline based on workplace proximity to pesticide application: MCPA (dimethylamine salt), sodium cacodylate, methamidophos, ethephon, bromoxynil octanoate, and propargite (HRs ≥1.23 per SD, 95 % CIs ≥ 1.00, ≤1.69). On the other hand, long-term residential but not workplace proximity to agricultural copper sulfate (pentahydrate) applications were associated with faster time to cognitive decline (HR = 1.36 per SD, 95 % CI = 1.07, 1.73). In repeated measures analysis (Supplemental Table 5) proximity to higher amounts of tribufos, sodium cacodylate, methamidophos, propargite, and ethephon were also associated with a lower MMSE score.

In sensitivity analysis, when we considered two different exposure windows, results were quite similar (see Supplemental Table 6). Additionally, workplace proximity to the pesticides dicloran, DSMA, azinphos-methyl, and mevinphos (other related) were associated with the outcome only in the recent 10-year exposure window (HRs ≥ 1.23, 95 % CIs ≥ 1.00, ≤1.76) and dicamba (dimethylamine salt) was associated with the outcome in both the recent 10-year and the 10-year lagged exposure window (HR = 1.36, 95 % CI = 1.00, 1.83).

3.5. Time to depression

Table 4 shows results for the five pesticides associated with faster time to depression measured by GDS ≥ 5. Sodium cacodylate and tribufos were associated with faster time to depression symptoms among PD patients with workplace proximity-based exposures (HR = 1.26 per SD, 95 % CI = 1.05, 1.52 and HR = 1.22 per SD, 95 % CI = 1.01, 1.47), while dicamba (dimethylamine salt, other related), copper sulfate (pentahydrate) and MCPA (dimethylamine salt) showed an association with residential proximity (HR = 1.44 per SD, 95 % CIs = 1.10, 1.80, HR = 1.22 per SD, 95 % CIs = 1.03, 1.45, and HR = 1.27 per SD, 95 % CIs = 1.02, 1.58). Copper sulfate (pentahydrate) and MCPA (dimethylamine salt) exposures were also associated with an increase in the GDS over follow-up in repeated measures analysis (Supplemental Table 5).

In sensitivity analysis considering two different exposure windows, associations with workplace address-based exposures in the most recent 10-year window were attenuated compared with longer-term exposures, except for sodium cacodylate and copper sulfate (pentahydrate) (see Supplemental Table 6). In addition, MSMA, dicamba (dimethylamine salt) and fluazifop-butyl were associated with depression symptoms for exposures in the recent 10-year window.

Supplemental Tables 8 and 9 shows the results of further sensitivity analysis for all outcomes. The pesticide risk associations were generally similar when controlling for further covariates (physical activity proxy, PD polygenic risk score, and high blood pressure), see Supplemental Table 8. Additionally, the results were mostly robust to including the baseline MMSE score in the motor time to event models and the baseline UPDRS-III symptom score in cognitive time to event models (Supplemental Table 9). Though there was some

attenuation in the risks estimated for propargite and bromoxynil octanoate and time to cognitive dysfunction.

4. Discussion

Pesticide exposure has been consistently associated with Parkinson's disease across numerous epidemiologic and experimental studies (Goldman et al., 2017). However, there is little information about whether pesticides influence symptom progression among PD patients, likely because evaluating the impact of pesticides on human health through population-based research is challenging, primarily due to limitations in long-term exposure assessment. On the other hand, use and variety of pesticide products introduced by industry has been growing and changing worldwide. Currently, in California, there are 13,443 pesticide products registered, with 1072 different active ingredients (CDWR, 2022). To assess the influence of pesticides on Parkinson's more comprehensively, including on the course of progression, we have previously established a record-based exposure assessment using agricultural pesticide application records in California to screen nearly 300 specific pesticide active ingredients in an untargeted manner (Paul et al., 2022). Among the 53 pesticides we have already implicated in PD onset, we now identified 10 pesticides that are also associated with faster motor and non-motor symptom worsening. Six pesticides are especially notable as they affected multiple progression outcomes: copper sulfate (pentahydrate), MCPA (dimethylamine salt), S,S,S-tributyl phosphorotrithioate (also known as tribufos), sodium cacodylate, methamidophos, and bromoxynil octanoate. Copper sulfate (pentahydrate) and MCPA (dimethylamine salt) were associated with all progression endpoints (cognitive, depressive, and motor symptom events).

Several of the pesticides associated with PD progression here have also been experimentally linked to PD-relevant pathogenic mechanisms. Previously, we coupled our epidemiologic screening of pesticides for PD risk with experiments that tested for dopaminergic neuron toxicity. That is, 43 pesticides were systematically tested for toxicity in an induced pluripotent stem cells (iPSC) model of midbrain dopaminergic neurons (mDA) derived from PD patients (Paul et al., 2022). Ten pesticides were found to be directly toxic to mDA neurons, including copper sulfate (pentahydrate) and propargite, which we have associated with faster PD symptom progression in the current study. Furthermore, co-exposure to pesticides commonly co-applied in cotton agriculture, including tribufos and trifluralin, resulted in even more neuron death (Paul et al., 2022). For instance, trifluralin alone produced a 32 % decrease in mDA neurons compared to DMSO, while tribufos produced an 8 % decrease, but in combination they produced a 65 % decrease (Paul et al., 2022). While mDA neuron death is responsible for the cardinal motor symptoms and these experimental models indicate a number of pesticides associated with progression here are capable of direct toxicity to this cell type, it is very likely that these pesticides are not only toxic to mDA neurons but possibly also to other neurons and cell types that contribute to both motor and non-motor symptoms (Richardson et al., 2019). Furthermore, as some patients progress in parallel in multiple symptom domains, it is not unexpected to find some pesticides related to multiple domains.

Copper sulfate (pentahydrate) is primarily used agriculturally as a fungicide, though non-agriculturally it has uses as an algaecide and herbicide to control invasive aquatic plants. The copper (Cu) ion itself possesses the intended toxicologic properties in target organisms, as it binds to certain proteins resulting in denaturation and subsequent cell damage (Reregistration Eligibility Decision (RED) for Coppers, 2009). In humans, copper is an essential trace metal, present at low concentrations and tightly regulated via homeostasis. It is necessary for numerous cellular functions, including PD-relevant physiologic processes such as neural transmission, defense against oxidative stress (e.g. component of Cu/zinc superoxide dismutase), and iron metabolism (Bell et al., 2002). However, free copper ions can also generate free radicals, inducing oxidative and inflammatory stress and disrupting mitochondrial function. Furthermore, α-synuclein has a high affinity for binding with copper. Copper ions have been shown to induce oligomerization of α-synuclein and accelerate the prion-like propagation of α-synuclein fibrils by promoting cellular internalization of α-synuclein fibrils, intracellular α-synuclein aggregation, and the subsequent release of mature fibrils to the extracellular space to induce further propagation (Li et al., 2020; Montes et al., 2014). Thus, while we have not found any previous epidemiologic report of agriculturally used copper sulfate (pentahydrate) exposure and PD, Parkinson's specific neurotoxicity due to accumulation of copper ions in the central nervous system has been demonstrated in vitro and in vivo. A meta-analysis of 18 post-mortem studies (211 PD brains, 215 control brains) found copper levels to be lower in the substantia nigra of PD patients, while at the same time iron levels were higher (Genoud et al., 2020). Other studies have shown higher levels of copper in patient's cerebro-spinal fluid (Boll et al., 2008; Hozumi et al., 2011; Pall et al., 1987; Zheng and Monnot, 2012). Ultimately, copper levels are delicately maintained in equilibrium. Both too much and too little copper will lead to altered homeostasis and dysfunction (Skjørringe et al., 2012). Workplace exposure to copper has been implicated in PD etiology before (Gorell et al., 1999) and our results both corroborate these results and implicate copper sulfate (pentahydrate) exposure in symptom progression and severity across multiple domains.

MCPA (2-methyl-4-chlorophenoxyacetic acid) was also associated with all three progression endpoints. MCPA has previously been associated with PD onset in a Dutch case-control study (Brouwer et al., 2017). MCPA is one of the most widely used herbicides worldwide (Li, 2018) and considered acutely toxic. Yet, there is little experimental research connecting MCPA exposure to neurotoxicity. However, several studies have shown that the class of chlorophenoxy pesticides is linked to cell membrane damage, disruption of cell membrane transport mechanisms, damage to the blood-brain barrier, and generation of free radicals (Bjørling-Poulsen et al., 2008). In our current study, both MCPA and bromoxynil octanoate exposures were associated with cognitive and motor symptom decline. Exposure levels for these two pesticides are quite correlated as they are often co-applied or part of the same weed killer products (e.g., BRONATE® for example) (U.S. EPA, 2005). Experimental research is needed to assess whether both pesticides are mechanistically linked to PD individually or if there are synergistic effects from co-exposure.

We also observed that exposure to several highly correlated pesticides mostly applied on cotton (sodium cacodylate, tribufos, propargite, and ethephon) was associated with faster cognitive decline and depression. This cotton cluster of pesticides has been shown to be

highly toxic to dopaminergic neurons in vitro (Paul et al., 2022). However, unlike motor function decline, depression and cognitive decline in PD are not necessarily attributable to dopaminergic neuron death. They may instead involve dysfunction of noradrenergic and serotonergic neurons within the locus coeruleus and raphe nucleus (Lim et al., 2009). Damage in the serotonergic and noradrenergic neurons, which play an important role in cognition and mood, may lead to these non-motor symptoms in PD and noradrenergic neuron loss can subsequently lead to further DA neuron damage (Grosch et al., 2016; Paredes-Rodriguez et al., 2020). However, only a few well-studied OP pesticides, such as chlorpyrifos, and the herbicide paraquat are known for their impact on serotonergic (i.e. decrease in serotonin synthesis and loss of serotonergic neurons) (Aldridge et al., 2005; Xu et al., 2012), noradrenergic neurons (Sandström et al., 2017; Hou et al., 2017, 2019), along with their toxicity to dopaminergic neurons (Kang et al., 2009; Zhang et al., 2015). OP pesticides have also shown direct toxicity to cortical neurons as they can induce apoptosis or oxidative stress (Schmuck et al., 2002; Mollace et al., 2003; Caughlan et al., 2004), while some research also indicates certain OPs may deregulate microRNAs, leading to mitochondrial dysfunction, oxidative stress, and neuronal death (reviewed: Aloizou et al., 2020). Ultimately, these correlated pesticides represent co-exposure profiles of interest for future experimental research to determine whether and how each of the pesticides is neurotoxic, either individually or together in a co-exposure mixture.

Our sensitivity analysis focused on different exposure periods to determine whether more distant or recent exposures were important. However, exposures in our study area were generally moderately to highly correlated over time due to widespread and consistent commercial application, especially of sodium cacodylate and tribufos. This made it almost impossible to determine the most sensitive periods of exposure for PD progression. Discrepancies between estimated effects for residential versus occupational proximity to pesticide application and PD progression suggests the relevance of considering both exposure locations over long-term windows. For instance, for pesticides with higher levels of historical use than current use, such as sodium cacodylate which was banned in 2007 and other cotton pesticides like tribufos which has seen its use decline in the Central Valley since 2000, long-term ambient exposures at workplaces over the 30+ year window were associated with the progression events. While for pesticides that have higher current use or similar trends of use, such as copper sulfate which has seen its use greatly increase since 2000 or MCPA which has had relatively consistent use for the past several decades, more recent residential exposures were associated with the progression events. This may suggest higher historical exposures at workplace addresses as well as highlight the importance of exposure around PD onset for progression, when many patients are not employed anymore, but could still be exposed at their homes. Overall, our results suggest that some of the same pesticide exposures that we previously linked to PD onset may also contribute to PD progression.

We recognize several limitations of our study. First, patients from study wave 2 were followed for a shorter time compared to study wave 1. Therefore, it is possible that some of the outcome events did not yet develop during the shorter follow-up time. There was loss of follow-up related to PD symptom status at baseline, which also strongly predicts the rate of progression, as those with the worst symptom scores (highest UPDRS-III, GDS-15, lowest MMSE) were more likely to be lost to follow-up as a result of dying or being too

ill. Pesticide exposure was not related to loss to follow-up. We nevertheless implemented an inverse probability weight for censoring as described by Hernan and Robins to account for potential selection bias due to censoring (Hernán and Robins, 2020). However, any potential selective censoring due to exposure and outcome would likely bias results towards the null, leading to an underestimation of effects. Additionally, motor and non-motor symptoms may decline in parallel. We did in fact estimate some moderate correlation between our event outcomes, which could result in non-specific outcomes. However, our sensitivity analyses including baseline cognitive symptom scores in the motor time to event models and vice versa were quite robust. We also included various covariates to control for potential confounding, still we were unable to assess all factors that may contribute to the disease progression, like diet, comorbidities, lifestyle factors, and infection (Ascherio and Schwarzschild, 2016). We also recognize that there are other PD-related motor and non-motor symptoms that were not investigated in our study, including dysautonomia, pain, and sleep disorders (Chaudhuri et al., 2006). Future research should further assess associations with more in-depth symptom profiling. Sill, a great strength of our study is that all patients were seen and evaluated in person by movement disorder specialists across follow-up, greatly minimizing disease and progression misclassification.

In terms of exposure assessment, we used a proximity model and record-based pesticide use reports from the study region (over 5.9 million reports in the study region from the CA-PUR). This allowed us to assess 40 years of exposure to over 700 pesticide active ingredients, from which we selected those we previously associated with PD (Paul et al., 2022). Our GIS-based approach however allows for non-differential misclassification of pesticide exposure. Several geographical factors, such as wind direction and temperature, that may influence the drift of pesticides were not considered. We also assumed that study participants were in the relevant locations during the relevant exposure periods at the time when pesticide applications occurred. In fact, it has been reported that being within a certain buffer of a pesticide application is one of the strongest predictors of ambient pesticide exposure (Figueiredo et al., 2021) and we have also previously validated our pesticide exposure assessment with serum measurements (Ritz and Costello, 2006). Furthermore, in agricultural communities, where thousands of pesticide products are applied, it is not possible for the general population to know or report what pesticides they may have encountered in their ambient environment. Thus, one of the greatest strengths of this study was that we did not have to rely on self-report of pesticide use or agricultural application, rather the CA-PUR records allowed us to assess the targeted 53 specific pesticide active ingredients while limiting recall bias.

Additionally, most participants were exposed to multiple different pesticides, many as a result of the co-application of different pesticides and the same seasonal applications occurring year after year. Thus, pesticide exposures were often correlated. We consider this both a strength of the study and a limitation. Collinearity that forces us not to consider co-adjustment in regression models may allow for residual confounding due to other pesticide exposures and there is no remedy for this exposure scenario in human studies. On the other hand, such real-world co- or sequential exposures are the norm and not the exception due to intensive and changing agricultural pesticide use. While it is not possible for experimental research to target every possible pesticide mixture, our current analyses suggest some

common mixtures that should be prioritized in experimental studies. Additionally, future research could apply techniques like Bayesian profile regression (Molitor et al., 2010) or multipollutant model (Tavallali et al., 2020) to investigate pesticide co-exposure profiles specifically.

5. Conclusion

Ultimately, PD progression is highly heterogeneous and multi-faceted, with some patients rapidly deteriorating over a few years while others progress slowly over decades. Identifying modifiable risk factors for disease progression may help identify new targets for research, perhaps leading to mechanistic insights important for medication development, and importantly help revise public health policy, aiming to reduce exposure to disease-modifying agents. Our study has implicated individual pesticides in Parkinson's disease progression in several domains. For some, previous epidemiologic or experimental data are supportive of our findings. Further investigation should target both these individual pesticides and the cumulative risk of their mixtures to tease out potential synergistic effects. Pesticides are not applied in isolation and people are not singly exposed to one agent over a lifetime. Both scientists and regulators need to consider co- and sequential application hazards and human exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The data that has been used is confidential.

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HIGHLIGHTS

- Pesticide exposure is important for PD onset but may also influence progression.
- We used the California Pesticide Use Report database to estimate pesticide exposure.
- Exposure to ten pesticides was associated with faster PD symptom progression.
- Copper sulfate and MCPA were associated with motor and non-motor progression.

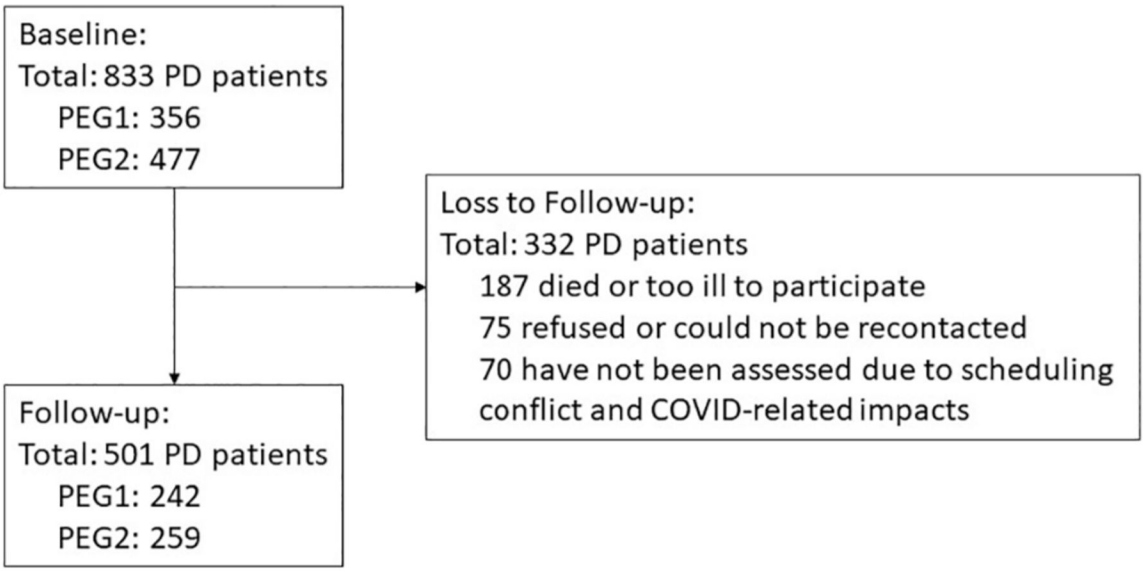

Fig. 1.
Flowchart of PD patients in baseline and follow-up.

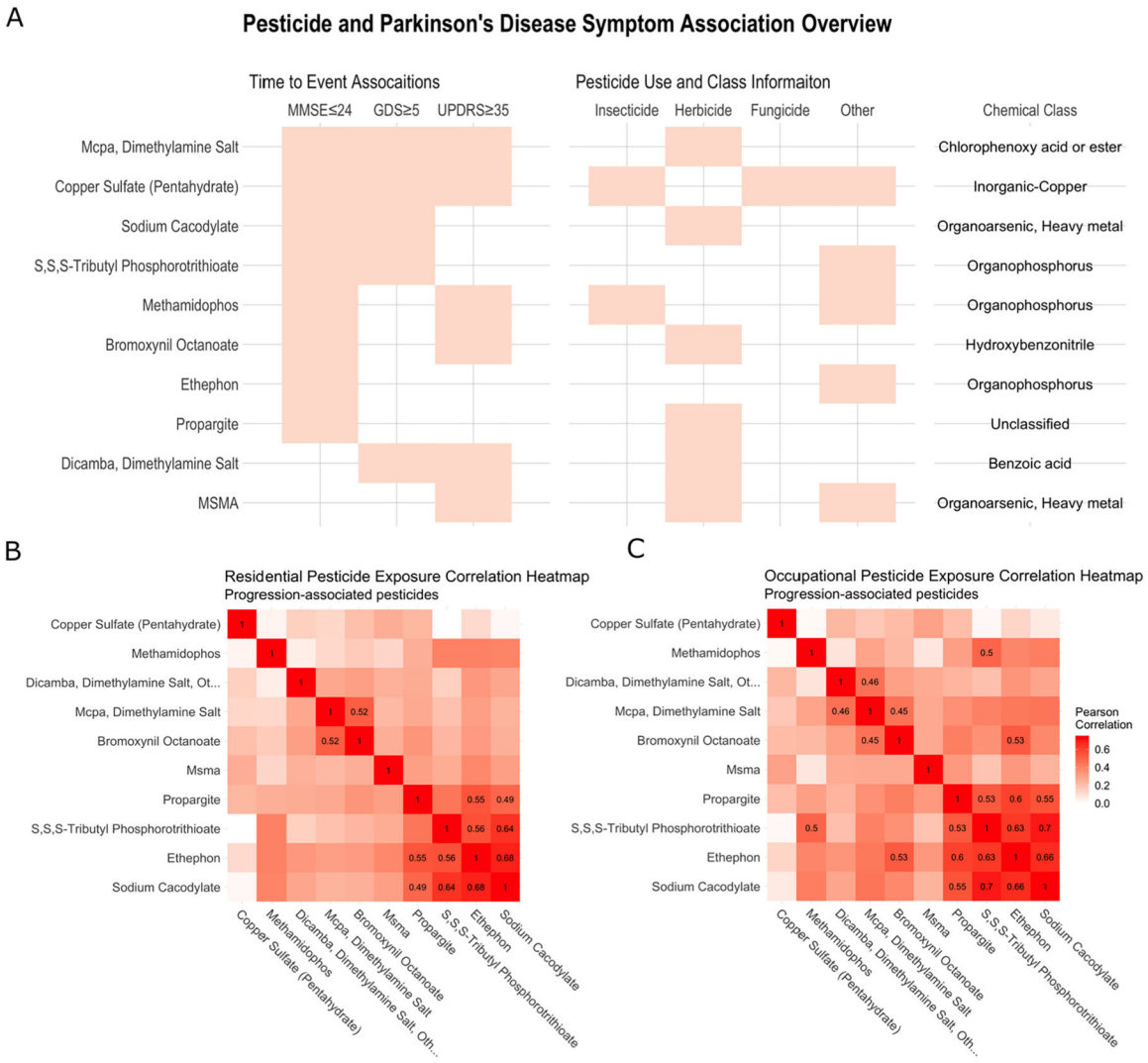

Fig. 2.

A. Overview of the time to event associations between each pesticide and symptom event outcomes. Pesticide use type and class information are shown on the right. B & C. Heatmaps displaying the pairwise correlation based on both residential (left) and occupation (right) proximity-based exposure. Coefficients >0.45 are enumerated.

Table 1

Characteristics of PD participants in PEG 1 and 2.

Characteristic	Statistics	PEG 1 (N = 242)	PEG 2 (N = 259)	Total (n = 501)
Sex	n (%)			
Male		137 (57 %)	172 (66 %)	309 (62 %)
Female		105 (43 %)	87 (34 %)	192 (38 %)
Non-White race	n (%)	49 (20 %)	66 (25 %)	115 (23 %)
Age of diagnosis	n (%)	70 (62, 75)	69 (60, 75)	69 (61, 75)
Year of interview	Median (IQR)	2002 (2000 2004)	2010 (2008 2011)	2006 (2002,2010)
Years of education	Median (IQR)	14.0 (12.0, 16.0)	14.0 (12.0, 17.0)	14.0 (12.0, 16.6)
Smoking	n (%)			
Never smoker		135 (56 %)	152 (59 %)	287 (57 %)
Past smoker		99 (41 %)	104 (40 %)	203 (41 %)
Current smoker		8 (3.3 %)	3 (1.2 %)	11 (2.2 %)
Duration of PD at baseline	Median (IQR)	2 (1,3)	3 (2, 4)	2 (1, 4)
Motor outcome				
Baseline UPDRS	Median (IQR)	18 (13, 25)	19 (13, 28)	18 (13, 26)
UPDRS reaching 35	n (%)	100 (41 %)	74 (29 %)	174 (35 %)
Time for UPDRS reaching 35 (yrs)	Median (IQR)	4.95 (2.78, 6.67)	2.62 (2.03, 3.97)	3.34 (2.24, 5.00)
Cognitive outcome				
Baseline MMSE	Median (IQR)	29 (28, 30)	29 (27, 30)	29 (27, 30)
MMSE reaching 24	n (%)	68 (28 %)	35 (14 %)	103 (21 %)
Time for MMSE reaching 24 (yrs)	Median (IQR)	5.42 (3.07, 7.19)	2.90 (2.24, 4.07)	3.81 (2.39, 5.39)
Depression outcome				
Baseline GDS	Median (IQR)	2 (1, 4)	2 (1, 4)	2 (1, 4)
GDS Reaching 5	n (%)	118 (49 %)	101 (39 %)	219 (44 %)
Time for GDS reaching 5 (yrs)	Median (IQR)	3.73 (1.16, 6.21)	2.53 (1.81, 4.01)	3.05 (1.30, 4.72)

Table 2

Motor outcome: hazard ratios between yearly average from 1974 to diagnosis residential and occupational proximity to pesticide (per SD of log(yearly average pounds/acre increase) and worsening motor function among PEG PD patients.

Pesticide chemical name	Residential		Workplace	
	HR[1,2]	*P* value	HR[1,2]	*P* value
MCPA, dimethylamine salt	1.31 [1.09, 1.56]	<0.01	1.15 [0.95, 1.39]	0.17
Copper sulfate (pentahydrate)	1.29 [1.08, 1.54]	<0.01	1.04 [0.90, 1.20]	0.63
Dicamba, dimethylamine salt, other related	1.20 [1.02, 1.41]	0.03	1.16 [0.95, 1.41]	0.15
Bromoxynil octanoate	1.22 [1.02, 1.45]	0.03	1.11 [0.92, 1.33]	0.29
Methamidophos	1.31 [1.02, 1.69]	0.04	0.91 [0.76, 1.10]	0.34
MSMA	1.13 [0.95, 1.33]	0.16	1.22 [1.03, 1.45]	0.02

[1]All models were adjusted for sex, age of PD diagnosis, Hispanic ethnicity, year of interview, education, PD disease duration at baseline, amount of levodopa taken in mg.

[2]Outcome was defined as time to UPDRS score greater than or equal to 35; baseline outcome event was excluded.

Table 3

Cognitive outcome: hazard ratios between yearly average from 1974 to PD diagnosis residential and occupational proximity to pesticide (per SD of log(yearly average pounds/acre increase) and cognitive decline among PEG PD patients.

Pesticide chemical name	Residential		Workplace	
	HR[1,2]	*P* value	HR[1,2]	*P* value
Copper sulfate (pentahydrate)	1.36 [1.07, 1.73]	0.01	0.85 [0.62, 1.17]	0.32
S,S,S-tributyl phosphorotrithioate	1.29 [1.01, 1.66]	0.04	1.38 [1.12, 1.70]	<0.01
MCPA, dimethylamine salt	1.21 [0.88, 1.67]	0.25	1.35 [1.12, 1.64]	<0.01
Sodium cacodylate	1.15 [0.89, 1.49]	0.30	1.36 [1.10, 1.69]	<0.01
Methamidophos	1.05 [0.75, 1.48]	0.77	1.23 [1.04, 1.46]	0.02
Ethephon	0.98 [0.66, 1.45]	0.92	1.32 [1.03, 1.69]	0.02
Propargite	0.97 [0.68, 1.39]	0.88	1.39 [1.01, 1.90]	0.04
Bromoxynil octanoate	0.92 [0.66, 1.28]	0.63	1.25 [1.00, 1.55]	0.05

[1]All models were adjusted for sex, age of PD diagnosis, Hispanic ethnicity, year of interview, education, PD disease duration at baseline, amount of levodopa taken in mg.

[2]Outcome was defined as time to MMSE score less than or equal to 24; baseline outcome event was excluded.

Table 4

Depression outcome: hazard ratios between yearly average from 1974 to diagnosis residential and occupational proximity to pesticide (per SD of log(yearly average pounds/acre increase) and worsening depression among PEG PD patients.

Pesticide chemical name	Residential		Workplace	
	HR[1,2]	*P* value	HR[1,2]	*P* value
Dicamba, dimethylamine salt, other related	1.44 [1.10, 1.80]	<0.01	1.06 [0.80, 1.40]	0.67
Copper sulfate (pentahydrate)	1.22 [1.03, 1.45]	0.03	1.09 [0.90, 1.32]	0.36
MCPA, dimethylamine salt	1.27 [1.02, 1.58]	0.04	0.99 [0.79, 1.25]	0.95
Sodium cacodylate	1.08 [0.88, 1.33]	0.45	1.26 [1.05, 1.52]	0.01
S,S,S-tributyl phosphorotrithioate	0.95 [0.76, 1.20]	0.67	1.22 [1.01, 1.47]	0.04

[1]All models were adjusted for sex, age of PD diagnosis, Hispanic ethnicity, year of interview, education, PD disease duration at baseline, amount of levodopa taken in mg.

[2]Outcome was defined as time to GDS score greater than or equal to 5; baseline outcome event was excluded.