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# Pesticide use and incident Parkinson's disease in a cohort of farmers and their spouses

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ABSTRACT

*Background:* Extensive literature suggests an association between general pesticide use and Parkinson's disease (PD). However, with few exceptions, little is known about associations between specific pesticides and PD.
*Objective:* We evaluated use of pesticides and incident PD in 38,274 pesticide applicators and 27,836 of their spouses in the Agricultural Health Study cohort followed over 20 years.
*Methods:* We used self-reported information on ever-use of 50 specific pesticides as of enrollment for both applicators and spouses, and considered intensity-weighted lifetime days (IWLD) reported at enrollment and through the first 5-year follow-up among applicators. We estimated covariate-adjusted hazard ratios (HR) and 95% confidence intervals (CI) using Cox regression. We also examined heterogeneity in associations by history of head injury and chemical resistant glove use.
*Results:* A total of 373 applicators and 118 spouses self-reported incident doctor-diagnosed PD. Ever-use of the insecticide terbufos (HR:1.31, 95%CI:1.02–1.68) and the herbicides trifluralin (HR:1.29, 95%CI: 0.99–1.70) and 2,4,5-T (HR:1.57, 95%CI:1.21–2.04) was associated with elevated PD risk. On the other hand, diazinon (HR:0.73, 95%CI: 0.58–0.94) and 2,4,5-TP (HR:0.39, 95%CI:0.25–0.62) were associated with reduced risk. We observed heterogeneity in ever-use associations by head injury and chemical-resistant glove use for some pesticides, with higher risk among those who reported a history of head injury, or who did not use gloves. PD risk was also elevated for applicators in the highest category of IWLD for dichlorvos, permethrin (animal use), and benomyl.
*Conclusions:* We found evidence of increased PD risk for some pesticides. Our results also suggest higher susceptibility for pesticide-associated PD among individuals with head injury as well as protection with use of chemical resistant gloves, although further research is needed to understand the impact of head injury. Research on current and newer pesticides, including mechanisms relevant to PD, is important given widespread pesticide use.

## 1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting around 1–2% of adults over the age of 65 years (Hirtz et al., 2007). PD is associated with substantial economic burden (Kowal et al., 2013) which is likely to increase with the aging of the population (US Administration on Aging, 2012). Many pesticides are neurotoxic, and some epidemiologic studies have linked general pesticide use with PD (Goldman et al., 2017; Pezzoli and Cereda, 2013; van der Mark et al., 2012). Although most of these studies evaluated functional (i.e., fungicides, insecticides, and herbicides) or chemical (i.e., organochlorine or organophosphate insecticides) classes, rather than

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individual pesticides, some evidence from human and toxicological studies points to associations of PD with the insecticides dieldrin and rotenone and with the herbicides 2,4-dichlorophenoxyacetic acid (2, 4-D) and paraquat (Goldman et al., 2017; Kanthasamy et al., 2005; Tanner et al. 2009, 2011; Weisskopf et al., 2010). Given that some of these and other pesticides continue to be widely used, with annual usage of all pesticides totaling over one billion pounds in the United States (US) alone (Atwood and Paisley-Jones, 2017), identifying links between specific pesticides and PD can have important implications.

The Agricultural Health Study (AHS) is a prospective cohort study of farming populations from North Carolina and Iowa (Alavanja et al., 1996), with follow-up ongoing for over 20 years. Two previous investigations on pesticides and PD were conducted in the AHS. The first included data from the full cohort and examined pesticide exposure data collected at enrollment in relation to self-reported PD through the first study follow-up, approximately 5 years later (Kamel et al., 2007). The second effort, the Farming and Movement Evaluation (FAME) study, was a case-control study nested within the cohort, which assessed PD cases through the first follow-up, but with self-reported PD confirmed by in-person assessment by movement disorder specialists and with collection of additional exposure data for specific pesticides (identified *a priori*) including some not well covered in the original AHS surveys (Tanner et al., 2011). Since then, self-reported incident PD was ascertained in two additional follow-up surveys. A recent update of mortality in the AHS found that pesticide applicators experience higher than expected mortality from PD than the general populations of Iowa and North Carolina, indirectly implicating farming exposures including pesticides (Shrestha et al., 2019a). Therefore, with additional PD cases identified from extended follow-up as well as updated exposure data, we examined associations between individual pesticides and incident PD that occurred over 20 years of follow-up among private pesticide applicators and their spouses.

## 2. Material and methods

### 2.1. Study population

The AHS is described in detail elsewhere (Alavanja et al., 1996). In 1993–1997 (Phase 1), 52,394 private pesticide applicators (97.4% male, mainly farmers) completed an enrollment questionnaire at pesticide licensing locations (see Supplemental Fig. 1 for study timeline). A take-home questionnaire requesting additional pesticide use information, was completed by 22,916 (44% of those who enrolled). Applicators were also given a questionnaire to be filled out by their spouses; 32,345 spouses (75% of married spouses, 99.3% female) enrolled in the study. Enrollment questionnaires were self-administered. Computer-assisted follow-up telephone interviews were conducted in 1999–2003 (Phase 2) and 2005–2010 (Phase 3). Participants completed either self-administered mailed questionnaires or computer-assisted telephone interviews in 2013–2016 (Phase 4). Questionnaires can be found at https://aghealth.nih.gov/collaboration/questionnaires.html. The Phase 2 survey was completed by 33,456 applicators and 23,796 spouses, Phase 3 by 24,170 applicators and 19,959 spouses, and Phase 4 by 24, 145 applicators and 18,186 spouses. The institutional review boards of the National Institute of Environmental Health Sciences and the National Cancer Institute approved the study.

### 2.2. Pesticide use

The applicator enrollment questionnaire asked about ever-use of 50 pesticides, and duration and frequency of use for 22 specific pesticides. The applicator take-home questionnaire asked participants to provide duration and frequency of use for the remaining 28 pesticides, and to complete a checklist of ever-use of additional specific pesticides ("other pesticides used") that were not covered in the enrollment questionnaire. Our current analysis focuses on the 50 pesticides for which detailed information on duration and frequency of use were collected either in the enrollment or the take-home questionnaire (although other pesticides were considered in some analyses as noted). These questionnaires also sought detailed information on pesticide use practices including application methods, mixing processes, personal protective equipment use, and other workplace hygiene factors. The enrollment questionnaire asked applicators what type of personal protective equipment they generally wore when they personally handled pesticides, including respirator/gas mask, fabric/leather gloves, and chemical-resistant gloves. The enrollment spouse questionnaire only asked about ever-use of the 50 specific pesticides. All participants were asked about their overall use of any pesticides, including years and days personally mixed or applied pesticides.

We also used pesticide information collected at Phase 2 (conducted 2–10 years after enrollment, 5 years on average). At this interview, applicators and spouses were asked to provide the names and number of days of use of specific pesticides in the year prior to the interview (or most recent year used) and information on pesticide use practices. Although the Phase 2 interview asked only about pesticide use in the most recent year, when estimating cumulative exposure, we assumed that year represented pesticide use during the period since the Phase 1 exposure assessment.

We used several approaches to characterize pesticide exposures. First, we examined ever-use of the 50 specific pesticides. Exposure intensity weights were previously derived using an algorithm that incorporates information on mixing practices, application methods, repair status, and personal protective equipment use (Coble et al., 2011). We then used intensity-weighted lifetime days (IWLD) of pesticide use (i.e., the product of years of use and days used per year weighted by exposure intensity) as a measure of cumulative exposure for applicators. IWLD days were categorized using cut-points based on the exposure distribution of the full sample and number of PD cases (i.e., at least five cases) in each exposure category. Specifically, we created a four-category exposure variable (never use and three categories among users with cut-points at tertiles of IWLD). When sample size was limited, we created a three-category variable by cutting at the median of IWLD. As only applicators were asked about duration and frequency of use of specific pesticides in Phase 1, the IWLD analyses were limited to the applicators. We further restricted these analyses to male applicators due to the small number of female applicators.

In addition to examining individual pesticides, we created two ever-use pesticide groups based on potential mechanisms implicated in PD pathogenesis. The first group included use of any pesticides linked to mitochondrial complex I inhibition (namely, benomyl, permethrin, rotenone, dichlorvos, and thiabendazole) (Binukumar et al., 2010; Tanner et al., 2011); the second group included pesticides linked to aldehyde dehydrogenase inhibition (namely, benomyl, captan, folpet, aldrin, dieldrin, mancozeb/maneb, ferbam, thiram and ziram) (Fitzmaurice et al. 2013, 2014). Some pesticides of interest, including rotenone, thiabendazole, folpet, ferbam, and thiram, were not among the 50 main pesticides queried at enrollment and were only asked of applicators (not spouses) on the checklist of "other pesticides used" in the Phase 1 take home questionnaire. Although both applicators and spouses could have reported their use in the Phase 2 open-ended survey, we considered only Phase 1 exposures for these analyses to maximize the analytical sample with complete information on these pesticides and for analytical simplicity. To accommodate the fact that not all participants provided data and only a portion completed the take-home questionnaire, we conducted analyses (that focused on Phase 1 exposures only) in two different analytical subsets. We first considered only those participants with complete data on all individual pesticides in a group (so, the analysis was limited to the male applicators who returned the take-home questionnaire). In a secondary analysis in the overall sample, we considered participants as exposed if they indicated they used *at least one* of the pesticides in the group, regardless of missing information on other pesticides in that group.

### 2.3. Parkinson's disease

Potential PD cases were identified by self-report in all AHS surveys (i.e., positive response to "has a doctor ever told you that you had been diagnosed with Parkinson's disease?), as well as via linkage to the National Death Index and state death registries (with PD recorded as an underlying or contributing cause of death). Self-reported PD cases identified through Phase 2 were previously confirmed by movement disorder specialists as a part of the FAME study, via structured clinical examinations and medical records; self-reported PD was confirmed in 84% (Tanner et al., 2011). Between 2012 and 2017 (around and following the Phase 4 survey), we attempted to validate all potential PD cases (prevalent as well as incident), including those considered PD cases in FAME (n 810). Briefly, each participant with potential PD, or their proxy (if deceased or too ill), was asked to complete a detailed screening questionnaire on PD diagnosis, symptoms, characteristics, and treatment. We also requested consent to obtain medical records from their treating or diagnosing physician. Screeners were obtained for 510 prevalent and incident cases. The PD screeners were evaluated by a movement disorder specialist to adjudicate PD status using criteria analogous to clinical diagnostic criteria proposed by Gelb et al. (1999). This evaluation classified 75% as probable or possible PD, 11% as questionable or other neurological disorders, and 14% as not having PD. Among those for whom medical records were obtained (n 65), 91% were confirmed as PD by medical records and 9% were considered questionable (because of conflicting information from multiple physicians and/or physician's reporting of inadequate evidence to distinguish from other neurological disorders).

After excluding self-reported prevalent cases (age at diagnosis $\leq$ age at enrollment) and those with no information on age at diagnosis, we had 598 eligible incident potential cases (440 with and 158 without screener data; Supplemental Fig. 2). We excluded cases without supporting PD symptoms or medications (99 of 440 participants screened) and those who did not provide consistent responses across surveys (8 of the 158 without screener information), leaving 491 cases for analysis. Overall, 80.6% of the 491 cases had some confirmatory information from a validation screener, medical record, FAME evaluation, or death certificate. We used the age at diagnosis provided at the earliest survey in which age at diagnosis was reported.

### 2.4. Study sample

Participants eligible for our analysis included a total of 38,798 applicators and 28,238 spouses who completed at least one follow-up survey or the PD validation screening questionnaire (Fig. 1). After excluding prevalent cases, those with inconsistent PD information across surveys, or those lacking other supporting information, we had 38,274 applicators and 27,836 spouses for ever-use of pesticides analyses (n 66,110; 491 with PD). For IWLD analyses of the 22 pesticides for which frequency and duration of use were asked in the enrollment questionnaire, the final sample size included 37,284 male applicators (372 PD cases) and for the 28 pesticides for which frequency and duration of use were asked in the take-home questionnaire, the final sample size included 19,068 male applicators (237 PD cases).

### 2.5. Statistical analysis

#### 2.5.1. Pesticide use at enrollment

We first examined bivariate relations of incident PD with baseline covariates that included applicator status, sex, state of residence, cigarette smoking, alcohol consumption, and education. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for associations between pesticide use reported at enrollment and incident PD. We used attained age as the time scale with left truncation at enrollment and always adjusted for sex, state of residence, smoking status, and education. Models for individual pesticides were additionally adjusted for the top four pesticides among those whose Spearman correlation with the pesticide of interest was 0.40 or greater. Whenever the proportional hazards assumption failed for a pesticide (p-value for interaction between age and pesticide $\leq$ 0.10), we allowed hazards to vary by the median age (63 years). Ever-use analyses were conducted in a combined sample of applicators and spouses, and separately for male applicators (n 37,284) and female spouses (n 27,673) (female applicators and male spouses, respectively, were excluded from these analyses due to small numbers). In the IWLD analyses among male applicators, we conducted a test for trend using the median value for each exposure category as an ordinal variable in regression models.

Information on smoking (n 691) and education (n 2474) was missing for some participants, and further, some participants reported 'something else' for education (n 2625). We treated 'something else'

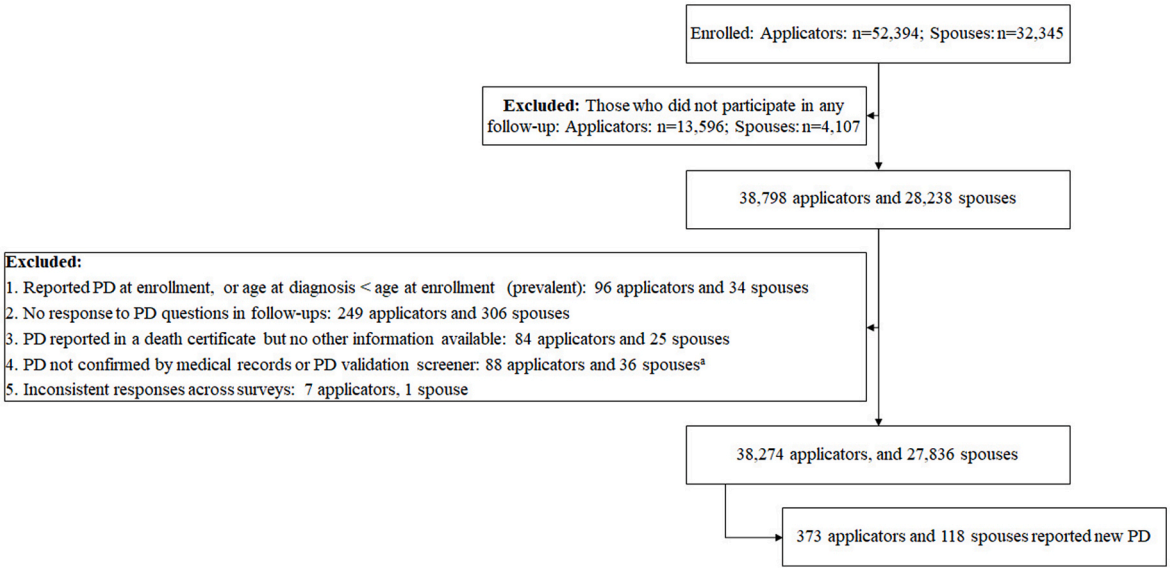


**Fig. 1.** Sample selection for pesticide and Parkinson's disease (PD) analysis in the Agricultural Health Study. [a]includes n = 2 spouses selected for validation based on FAME screening who did not report PD.

as a missing covariate and used multiple imputation to impute missing covariates (i.e., education and smoking). We created five imputed datasets, performed regression analysis in each dataset, and combined those results to estimate parameters and their standard errors using SAS PROC MIANALYZE (SAS Institute Inc, 2015).

Wearing chemical-resistant gloves was previously shown to modify PD associations with some pesticides (Furlong et al., 2015). Further, individuals with head injury may be more susceptible to pesticide-associated PD risk – the underlying hypothesis being combinations of risk factors acting in concert increase disease vulnerability (the "multiple-hit hypothesis") (Lee et al., 2012). We examined potential heterogeneity in the associations of PD with ever-use of pesticides by these characteristics (by testing for the interaction between pesticides and these characteristics), when each cross-classified category of exposure and factor contained at least five cases. Applicators were asked about a history of head injury requiring medical attention only in the take-home questionnaire, whereas all spouses were asked about head injury, and thus heterogeneity by head injury was evaluated in a smaller subset (19,222 applicators and 26,666 spouses resulting in a total of 45,888 participants). Only applicators (in the enrollment questionnaire) but not spouses were asked about chemical resistant glove use and thus heterogeneity by chemical resistant glove use was evaluated in male applicators only (n 32,816). We also stratified the analysis by follow-up time (≤10 years and >10 years) for ever-use analysis. Potential heterogeneity was not examined for IWLD due to limited sample size.

To examine the potential impact of loss-to-follow up, we performed a sensitivity analysis using inverse probability of censoring weights (Howe et al., 2016). Briefly, we used weighted Cox models to estimate HRs and 95% CIs, adjusting for covariates and using stabilized inverse probability weights. For stabilized weight estimation, first we transformed our data from a single record per person into person-year data (i.e., with multiple records per person). Then, we used logistic regression analyses to calculate the denominator of the weights, or probability of overall participation in Phase 4 conditional on exposure, year and baseline covariates (age, sex, education, smoking, alcohol use, state of residence; missing values imputed for covariates whenever applicable), as well as to calculate the numerator of the weights, or probability of overall participation in Phase 4 conditional only on year. We estimated stabilized weights as the ratio of cumulative conditional probabilities.

Lastly, we used logistic regression to analyze two other groups of cases (i) all "confirmed" prevalent and incident PD cases (n 66,216 with 597 PD cases), and (ii) all "potential" prevalent and incident PD cases (any self-reported cases or reported on death certificates) (n 84,739, with 860 PD cases). Statistical significance was determined using two-sided tests with α of 0.05. We performed statistical analyses using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

#### 2.5.2. Pesticide use through Phase 2

We also examined associations between cumulative pesticide use through Phase 2 and incident PD. However, given the lower exposure and outcome prevalence in spouses, we performed this analysis only in male applicators. About 14% of the applicators included in our analysis were missing Phase 2 exposure data due to Phase 2 non-response. To account for the missing exposure data due to non-response, we used a multiple imputation approach developed specifically for AHS applicators (Heltshe et al., 2012). This approach used information on several factors including demographics, farm characteristics, prior pesticide use, and medical conditions that predicted missingness to impute use of specific pesticides for the Phase 2 non-responders. We created five imputed datasets which were then converted to person-year datasets allowing pesticide exposure information (ever-use and IWLDs) through Phase 2 to vary until their time at risk. We applied a Cox model applied to each imputed dataset and combined those results to obtain an HR and 95% CI using SAS PROC MIANALYZE (SAS Institute Inc, 2015). This analysis was limited to the previously described 50 specific pesticides. Information on smoking and education was missing for only 1% and 4% of the sample, and we used a missing indicator category for this analysis.

## 3. Results

Characteristics of participants at enrollment differed by PD status (Table 1). Older participants, applicators, males, and those from North Carolina were more likely to develop PD, while current smokers and alcohol drinkers were less likely to develop PD. Chemical resistant glove use and a history of head injury requiring medical attention were similar between the two groups, although when adjusted for age, sex, state, education, and smoking status, we found an inverse association between having a head injury and incident PD (HR: 0.71, 95% CI: 0.46, 1.09).

### 3.1. Phase 1 pesticides

In the analysis examining lifetime days of *any* pesticide use in relation to incident PD in the overall sample, we generally observed positive HRs for higher lifetime days compared to never use, although we did not see a monotonic increasing trend (for example, HRs for the third and the fourth quartiles compared to never use were 1.27 (95% CI: 0.82, 1.98) and 1.07 (95% CI: 0.69, 1.67), respectively, Supplemental Table 1). In the female spouses only analysis, we observed increased risk (HR: 1.58,

**Table 1**
Characteristics of Agricultural Health Study participants at enrollment (n = 66,110).

| Characteristics | No PD (n (%))[a] (n 65,619) | Incident PD (n (%))[a] (n 491) |
|---|---|---|
| Age (years) | | |
| ≤45 | 31,843 (48) | 53 (11) |
| 46–55 | 16,479 (25) | 109 (22) |
| 56–65 | 12,382 (19) | 206 (42) |
| >65 | 4915 (7) | 123 (25) |
| Participant | | |
| Spouse | 27,718 (42) | 118 (24) |
| Applicator | 37,901 (58) | 373 (76) |
| Sex | | |
| Female | 28,546 (44) | 117 (24) |
| Male | 37,073 (56) | 374 (76) |
| State of residence | | |
| Iowa | 43,319 (66) | 299 (61) |
| North Carolina | 22,300 (34) | 192 (39) |
| Education[b] | | |
| ≤ High school graduate | 31,301 (50) | 300 (64) |
| 1–3 years beyond high school | 16,507 (26) | 94 (20) |
| College graduate or more | 12,732 (20) | 77 (16) |
| Something else | 2624 (4) | 1 (0) |
| Smoking status[c] | | |
| Never smoker | 40,305 (62) | 296 (61) |
| Former smoker | 16,573 (26) | 159 (33) |
| Current smoker | 8056 (12) | 30 (6) |
| Alcohol consumption (past 12 months)[d] | | |
| No | 23,979 (38) | 221 (49) |
| Yes | 38,420 (62) | 230 (51) |
| Chemical resistant glove use[e] | | |
| No | 6193 (19) | 65 (20) |
| Yes | 26,299 (81) | 259 (80) |
| Head injury requiring medical attention[f] | | |
| No | 41,911 (92) | 316 (93) |
| Yes | 3638 (8) | 23 (7) |

[a] % may not add to 100% due to rounding.
[b] Education missing for n = 2474.
[c] Smoking status missing for n = 691.
[d] Alcohol consumption missing for n = 3260.
[e] Chemical resistant glove use information was not sought from spouses and missing for n = 5458 applicators.
[f] Applicators provided information on head injury only in the take-home questionnaire.

95% CI: 1.00, 2.50) in those exposed to more than the median days as compared to never use. In the male applicators only analysis, associations for higher quartiles of lifetime days compared to the lowest quartile were slightly inverse. In a combined analysis of applicators and spouses (Table 2), we found positive associations for the organophosphate insecticide terbufos (HR:1.30, 95% CI: 1.02, 1.68) and the herbicides trifluralin (HR:1.29, 95% CI: 0.99, 1.70) and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) (HR:1.57, 95% CI: 1.21, 2.04), and inverse associations for ever-use of the organophosphate insecticide diazinon (HR: 0.73, 95% CI: 0.58, 0.94), the fumigant ethylene dibromide (HR: 0.35, 95% CI: 0.14, 0.84), and the herbicide 2,4,5-TP [2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid] (HR: 0.39, 95% CI: 0.25, 0.62). These associations remained when analyses were performed separately for male applicators (Supplemental Table 2). Separate analyses for female spouses (Supplemental Table 2) were limited to only a few pesticides due to fewer PD cases; elevated (HR $>$ 1.40), yet imprecise, risk was observed for the herbicides glyphosate, trifluralin, and cyanazine.

We found heterogeneity in associations for ever-use of some pesticides and PD risk by head injury (Table 3). We found higher PD risk for the three organochlorine insecticides chlordane, dichlorodiphenyltrichloroethane (DDT), and toxaphene, the two organophosphate insecticides diazinon and phorate, the insecticide permethrin (animal and crop use combined), the fumigant methyl bromide, and the herbicides paraquat and pendimethalin among those who reported a history of head injury as compared to reduced or null associations among those did not report a history of head injury (p for heterogeneity $\leq$0.10). For example, the HR for paraquat among those with a history of head injury was 3.20 (95%CI: 1.38, 7.45) versus 1.00 (95%CI: 0.71, 1.41) for those without a history (p for heterogeneity 0.01).

Similarly, we found that five herbicides (dicamba, imazethapyr, metolachlor, trifluralin, and metribuzin) were associated with elevated PD risk among those who did not use chemical-resistant gloves as compared to reduced or null associations among glove users, although directions were reverse for metalaxyl (Table 3). In the analyses stratified by follow-up time ($\leq$10 years and $>$10 years), we found that HRs for some herbicides including alachlor, butylate, chlorimuron ethyl, trifluralin, 2,4-D, and atrazine were elevated for the first 10 years of follow-up, but not for later years (Supplemental Table 3).

In the analyses examining IWLD through Phase 1 in male applicators (Table 4), we saw no clear monotonic exposure-response for pesticides associated with elevated PD risk. There were a few suggestive patterns. Specifically, we saw elevated HRs for individuals in the highest category of IWLD of the insecticides dichlorvos [HR:1.46 (95% CI: 0.98, 2.19), p-trend:0.06] and permethrin (animal use)[HR:1.44 (95% CI: 0.85, 2.44), p-trend: 0.21], and the fungicides benomyl (HR: 1.34 (95% CI: 0.64, 2.80), p-trend:0.31], captan [(HR: 1.27 (95% CI: 0.74, 2.20), p-trend:0.36], and chlorothalonil [HR: 1.29 (95% CI: 0.66, 2.56), p-trend:0.41] as compared to those who never used those pesticides, although risk estimates were very imprecise as reflected by the wide confidence intervals. For the herbicides terbufos and trifluralin (for which we observed significant positive association in the ever-use analysis), HRs were generally elevated for all tertiles as compared to never use. For heptachlor, HRs were higher for the two lower tertiles than for the upper. HRs in the higher tertiles of the insecticides aldrin, toxaphene, carbaryl, diazinon, and malathion were lower than in the never use category. The results (odds ratio estimates) were similar when we included "confirmed" prevalent cases (Supplemental Tables 4 and 5), or any "potential" PD cases (data not shown). The HR estimates using inverse probability weights were also similar (Supplemental Table 6).

In the male applicators returning take-home questionnaires, none of the pesticide groups – mitochondrial complex I inhibitors [HR: 0.96 (95%CI: 0.71, 1.29)] or aldehyde dehydrogenase inhibitors [(HR: 0.84 (95%CI: 0.65, 1.11)] – were associated with increased PD risk, although we observed heterogeneity by head injury for ever-use of mitochondrial complex I inhibitors with higher HR among those who experienced head injury [HR: 2.42 (95%CI: 0.91, 6.47)] vs reduced HR among those

**Table 2**
Ever-use of pesticide reported at enrollment and Parkinson's disease (PD) risk in all participants (n = 66,110).

| Pesticide | No PD, n (%)[a] | PD, n (%)[b] | HR (95% CI)[c] |
|---|---|---|---|
| **Organochlorine insecticide** | | | |
| Aldrin | 6507 (11.1) | 98 (23.7) | 0.91 (0.68, 1.23) |
| Chlordane | 9758 (16.5) | 125 (29.8) | 1.05 (0.82, 1.34) |
| Dieldrin | 2440 (4.1) | 38 (9.2) | 0.88 (0.60, 1.30) |
| DDT | 8954 (15.4) | 143 (34.8) | 0.86 (0.67, 1.12) |
| Heptachlor | 5442 (9.4) | 87 (21.3) | 1.01 (0.74, 1.38) |
| Toxaphene | 5160 (8.7) | 59 (14.1) | 0.80 (0.60, 1.08) |
| Lindane | 7250 (12.1) | 74 (17.7) | 0.92 (0.71, 1.19) |
| **Carbamate insecticide** | | | |
| Aldicarb | 3809 (6.5) | 28 (6.9) | 1.05 (0.68, 1.62) |
| Carbaryl | 27,180 (45.5) | 231 (55.4) | 1.09 (0.87, 1.37) |
| Carbofuran | 10,017 (16.7) | 110 (26.6) | 0.95 (0.74, 1.21) |
| **Organophosphate insecticide** | | | |
| Chlorpyrifos | 16,700 (26.8) | 143 (30.7) | 0.92 (0.74, 1.13) |
| Coumaphos | 3423 (5.7) | 35 (8.4) | 1.04 (0.73, 1.47) |
| Diazinon | 13,979 (23.3) | 105 (25.1) | 0.73 (0.58, 0.94) |
| Dichlorvos | 4425 (7.3) | 48 (11.5) | 1.12 (0.83, 1.53) |
| Fonofos | 8219 (13.6) | 75 (17.7) | 0.91 (0.70, 1.19) |
| Malathion | 28,496 (48.7) | 253 (62.6) | 1.01 (0.78, 1.30) |
| Parathion | 5661 (9.5) | 62 (14.8) | 0.98 (0.74, 1.30) |
| Phorate ($\leq$63 y)[d] | 5618 (18) | 39 (36.1) | 1.33 (0.85, 2.08) |
| >63 y | 5786 (22.1) | 73 (26.1) | 0.71 (0.52, 0.97) |
| Terbufos | 13,718 (23.8) | 138 (35.4) | 1.30 (1.02, 1.68) |
| **Permethrin insecticide** | | | |
| Permethrin (Crops) | 5263 (8.8) | 36 (8.8) | 0.99 (0.70, 1.40) |
| Permethrin (Animals) | 5696 (9.4) | 41 (9.8) | 1.07 (0.77, 1.48) |
| **Fumigant** | | | |
| Carbon disulfide/Carbon tetrachloride | 2099 (3.5) | 31 (7.3) | 1.03 (0.71, 1.50) |
| Aluminum phosphide | 1707 (2.8) | 16 (3.8) | 1.08 (0.65, 1.78) |
| Ethylene dibromide | 1294 (2.2) | 5 (1.2) | 0.35 (0.14, 0.84) |
| Methyl bromide | 5707 (9.5) | 46 (10.8) | 0.86 (0.59, 1.25) |
| **Fungicide** | | | |
| *Benomyl*[e] | *3492 (6)* | *26 (6.4)* | *0.80 (0.48, 1.31)* |
| *Benomyl ($\leq$ 63y)*[d, e] | *1664 (5.3)* | *4 (3.6)* | *0.35(0.11, 1.10)* |
| *> 63y* | *1828 (6.8)* | *22 (7.5)* | *0.99 (0.58, 1.68)* |
| Captan | 4617 (7.7) | 33 (8) | 0.84 (0.59, 1.20) |
| Chlorothalonil | 2899 (4.8) | 21 (5) | 0.97 (0.59, 1.60) |
| Maneb ($\leq$63 y)[d] | 1685 (5.2) | 8 (7) | 1.43 (0.63, 3.22) |
| >63 y | 2030 (7.3) | 21 (7) | 0.75 (0.44, 1.25) |
| Metalaxyl | 7968 (13.6) | 58 (14.3) | 0.85 (0.61, 1.18) |
| **Herbicide** | | | |
| Alachlor | 19,057 (32.1) | 187 (45.6) | 1.13 (0.88, 1.45) |
| Butylate ($\leq$63 y)[d] | 5750 (18.3) | 38 (34.9) | 1.31 (0.86, 2.01) |
| >63 y | 5245 (19.7) | 65 (23.4) | 0.87 (0.64, 1.20) |
| Chlorimuron ethyl | 12,693 (21.8) | 101 (25.6) | 1.04 (0.80, 1.36) |
| Dicamba | 17,945 (31) | 161 (41.2) | 0.94 (0.72, 1.22) |
| EPTC | 7049 (12.2) | 54 (14.1) | 0.84 (0.61, 1.15) |
| Glyphosate | 35,406 (58.6) | 291 (67.4) | 1.10 (0.87, 1.39) |
| Imazethapyr | 15,124 (26.3) | 126 (32.6) | 1.04 (0.79, 1.37) |
| Metolachlor | 16,114 (27.9) | 127 (32.6) | 0.80 (0.62, 1.03) |
| Paraquat | 8526 (14.2) | 87 (20.4) | 1.09 (0.84, 1.41) |
| Pendimethalin | 15,250 (26.1) | 127 (31.9) | 1.07 (0.83, 1.37) |
| Petroleum distillate | 16,756 (28.9) | 146 (37) | 0.93 (0.73, 1.18) |
| Trifluralin | 18,665 (32.2) | 182 (46.8) | 1.29 (0.99, 1.70) |
| 2,4-D | 28,871 (49.8) | 262 (66.7) | 1.06 (0.79, 1.43) |
| 2,4,5-T | 7264 (12.5) | 116 (28.3) | 1.57 (1.21, 2.04) |
| 2,4,5-TP | 3287 (5.5) | 23 (5.5) | 0.39 (0.25, 0.62) |
| Atrazine | 25,297 (42.8) | 237 (58.2) | 1.03 (0.77, 1.38) |
| Cyanazine | 14,641 (25.2) | 133 (33.6) | 0.90 (0.69, 1.18) |
| Metribuzin | 15,500 (26.8) | 137 (35.7) | 0.86 (0.65, 1.14) |

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; HR, Hazard Ratio; PD, Parkinson's disease.

[a] Exposed individuals who did not develop PD.

[b] Exposed individuals who developed PD.

[c] HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation $\geq$ 0.40 with the ever-use variable of the target pesticide).

[d] Hazard ratio allowed to vary by the median age (i.e., 63 years) for pesticides that did not meet proportional hazards assumption (p $\leq$ 0.10).

[e] Proportional hazards assumption did not meet for those in italics, but there was not adequate sample size meeting the criteria of at least five exposed cases in cross-classified categories.

without head injury [HR: 0.83 (95%CI: 0.61, 1.12), p for heterogeneity: 0.04]. The results were similar (i.e., no independent associations for the pesticide groups but heterogeneity by head injury for the mitochondrial complex I inhibitors), when we also considered participants as exposed if they indicated they used *at least one* individual pesticide in the group in the overall sample.

### 3.2. Pesticide exposure through Phase 2

Among male applicators, associations between ever-use of individual pesticides through Phase 2 were similar to the results using information reported at enrollment; specifically, PD risk was reduced among those who ever-used diazinon, ethylene dibromide, and 2,4,5-TP, and elevated among those who ever-used terbufos, 2,4,5-T, and trifluralin (Supplemental Table 7). Results that used IWLD through Phase 2 were also similar (Table 4).

## 4. Discussion

In this study, we found that ever-use of the insecticide terbufos and the herbicides trifluralin and 2,4,5-T was associated with elevated PD risk. Positive associations of PD with ever-use of the herbicides trifluralin and 2,4,5-T are consistent with the prior AHS-wide analysis based on 78 self-reported incident PD cases identified through Phase 2 (Kamel et al., 2007). We also found lower PD risk for ever-use of some pesticides including diazinon and 2,4,5-TP. In IWLD analyses, however, we did not see evident monotonic exposure response gradients for these pesticides, although HRs for higher exposure categories reflected findings of ever-use analyses. We observed heterogeneity in the pesticide-PD associations by head injury and chemical-resistant gloves use, indicating higher PD risk for use of certain organochlorine insecticides (chlordane, DDT, and toxaphene), organophosphate insecticides (diazinon and phorate), insecticide permethrin, and herbicides (paraquat and pendimethalin) among those who reported head injury and for use of certain herbicides (dicamba, imazethapyr, and trifluralin) among those who did not use chemical-resistant gloves.

To the best of our knowledge, no studies have linked the insecticide terbufos with PD, although a few prior studies have linked other individual organophosphate insecticides that also act by inhibiting the enzyme acetylcholinesterase with PD (Gatto et al., 2009; Wang et al., 2014). We also found elevated PD risk in AHS applicators who were exposed to higher IWLD of the organophosphate insecticide dichlorvos. Chronic dichlorvos exposure in rats has been shown to induce degeneration of nigrostriatal dopaminergic neurons and alpha-synuclein aggregation, the hallmarks of PD pathogenesis, as well as to inhibit mitochondrial complexes and alter mitochondrial structures (Binukumar et al., 2010). We are aware of only one study on dichlorvos and PD, and in that study, individuals in the lower, although not the highest, exposure-day category of dichlorvos had elevated PD risk as compared to the individuals who were never exposed (van der Mark et al., 2014). On the other hand, we saw an inverse association between the organophosphate insecticide diazinon and PD risk in the overall sample and among those without head injury but saw elevated yet not statistically significant risk among those with head injury. A few prior studies, although not all, have linked diazinon with increased PD risk (Firestone et al., 2010; Gatto et al., 2009; Narayan et al., 2013). We observed

**Table 3**
Ever-use of pesticides reported at enrollment and Parkinson's disease (PD) risk by head injury status and chemical resistant glove use.

| Pesticide | Head injury | Exposed/Unexposed PD cases | HR (95% CI)[a] | P[b] |
|---|---|---|---|---|
| Chlordane | No | 77/206 | 1.10 (0.81, 1.51) | 0.01 |
| | Yes | 16/6 | 4.08 (1.58, 10.55) | |
| Diazinon | No | 57/223 | 0.64 (0.47, 0.88) | 0.07 |
| | Yes | 10/11 | 1.48 (0.62, 3.51) | |
| DDT | No | 87/189 | 0.86 (0.62, 1.19) | 0.06 |
| | Yes | 15/7 | 2.12 (0.85, 5.31) | |
| Methyl bromide | No | 22/265 | 0.67 (0.40, 1.11) | 0.01 |
| | Yes | 6/15 | 2.85 (1.06, 7.65) | |
| Paraquat | No | 45/239 | 1.00 (0.71, 1.41) | 0.01 |
| | Yes | 10/12 | 3.20 (1.38, 7.45) | |
| Pendimethalin | No | 65/207 | 0.90 (0.65, 1.25) | 0.03 |
| | Yes | 10/6 | 2.85 (1.02, 7.91) | |
| Permethrin (animal and crop use combined) | No | 33/260 | 0.79 (0.54, 1.14) | 0.08 |
| | Yes | 6/12 | 2.04 (0.76, 5.44) | |
| Phorate | No | 60/205 | 0.74 (0.53, 1.04) | 0.03 |
| | Yes | 10/6 | 2.47 (0.89, 6.89) | |
| Toxaphene | No | 31/248 | 0.69 (0.46, 1.03) | 0.08 |
| | Yes | 7/15 | 1.64 (0.66, 4.04) | |
| | Chemical resistant glove[c] | | | |
| Dicamba | No | 21/20 | 2.10 (1.11, 3.98) | 0.008 |
| | Yes | 127/100 | 0.85 (0.63, 1.15) | |
| Imazethapyr | No | 18/23 | 3.34 (1.75, 6.39) | 0.0002 |
| | Yes | 100/127 | 0.92 (0.69, 1.24) | |
| Metalaxyl | No | 8/39 | 0.44 (0.20, 0.96) | 0.05 |
| | Yes | 48/191 | 1.00 (0.70, 1.43) | |
| Metolachlor | No | 18/26 | 1.60 (0.88, 2.94) | 0.01 |
| | Yes | 98/132 | 0.70 (0.54, 0.91) | |
| Metribuzin | No | 17/25 | 1.48 (0.78, 2.81) | 0.06 |
| | Yes | 110/109 | 0.78 (0.58, 1.06) | |
| Trifluralin | No | 25/18 | 2.64 (1.42, 4.92) | 0.03 |
| | Yes | 144/80 | 1.24 (0.91, 1.68) | |

Abbreviation: CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; HR, Hazard Ratio; PD, Parkinson's disease.

[a] HR adjusted for state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation $\geq 0.40$ with the ever-use variable of the target pesticide); HR for head injury also adjusted for sex.

[b] P-value for test for heterogeneity.

[c] Male applicators only.

similar heterogeneity by head injury for the organophosphate phorate. One prior study has reported an association between phorate exposure and elevated PD risk (Wang et al., 2014). Apart from a common pathway for pesticidal action, i.e., inhibition of acetylcholinesterase, individual organophosphate insecticides may exert neurotoxicity through a wide range of mechanisms including oxidative stress and neuroinflammation (Terry, 2012) resulting in varying degrees of toxicity. We are uncertain, however, about the reasons underlying the observed inverse association for some pesticides in the overall sample or among those without head injury.

Besides the prior AHS reports (Furlong et al., 2015; Kamel et al., 2007), we are not aware of other epidemiologic evidence linking the herbicides trifluralin and 2,4,5-T and PD, although an *in vitro* study has shown that trifluralin accelerates the formation of alpha-synuclein fibrils, a finding relevant to PD pathogenesis (Uversky et al., 2002). In another analysis, AHS applicators who experienced high pesticide exposure events involving trifluralin were also more likely to report olfactory impairment, one of the important prodromal symptoms of PD (Shrestha et al., 2019b). To our knowledge, the only other study (based on only four and seven exposed cases and controls respectively) that examined 2,4,5-T in relation to PD did not find any association (Dhillon et al., 2008). We found that the herbicide dicamba was associated with increased PD risk among those who did not use chemical-resistant gloves during handling of pesticides. Dicamba, structurally similar to the phenoxy herbicide 2,4,5-T (Bradberry et al., 2004), was associated with increased, although statistically non-significant, PD risk in the prior AHS investigation in the overall sample (Kamel et al., 2007). We observed an unexpected inverse association with the herbicide 2,4,5-TP, another phenoxy pesticide structurally similar to 2,4,5-T. Use of both 2,4,5-T and 2,4,5-TP was suspended in the US in 1979 due to potential contamination by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and associated health concerns (Gintautas et al., 1992; Lilienfeld and Gallo, 1989; Ware, 1988).

We found that ever-use of certain individual pesticides and the pesticide group mitochondrial complex I inhibitors was associated with increased PD risk among those who reported a history of head injury requiring medical attention, although head injury itself was not independently associated with elevated PD risk. While sequelae of traumatic brain injury, including microglial activation, alpha-synuclein aggregation, mitochondrial dysfunction, and other chronic inflammatory responses have been suggested as potential mechanisms for PD predisposition (Acosta et al., 2015; Hutson et al., 2011; Lifshitz et al., 2004; Loane et al., 2014), findings of prior epidemiologic studies on head injury and PD risk have been conflicting (Gardner et al., 2015; Kenborg et al., 2015; Taylor et al., 2016). With the notion that traumatic brain injury potentially requires synergistic factors to lead to PD, a case-control study examined PD risk in relation to joint exposure to head injury and paraquat (assessed using geographical information system-based land use and historic pesticide use reporting data); it found that paraquat-associated PD risk was greater among individuals with head injury and that the joint exposure was associated with higher PD risk as compared to exposure to paraquat or head injury alone (Lee et al., 2012). An experimental study in rats also demonstrated that acute traumatic brain injury induced progressive degeneration of nigrostriatal dopaminergic neurons, microglial activation, and alpha-synuclein accumulation were exacerbated when the animals were exposed to concentrations of paraquat that alone would not induce nigrostriatal death (Hutson et al., 2011). We are not aware of reports that examined interaction between other pesticides and head injury, but potential interaction is plausible as some of these pesticides have been implicated in PD pathogenesis (Furlong et al., 2015; Wang et al., 2014). We note several limitations in this particular analysis – our questionnaire did not capture head injury not requiring medical attention, and limited information was available on age at injury which precluded analysis on the timing of injury occurrence.

Although our subgroup analysis did hint at higher PD risk for paraquat as well as for the pesticide group mitochondrial complex I inhibitors among individuals with head injury, we found limited evidence for independent associations of incident PD with these pesticides, whereas both were independently associated with PD in FAME (Tanner et al., 2011). Among other specific pesticides previously examined in FAME, we saw some suggestions of elevated PD risk for those with higher IWLD of the fungicide benomyl and the insecticide permethrin (animal use), though HR estimates were imprecise.

Limited reproducibility of FAME findings in the current study could be due to differences in study design, exposure data, and criteria for inclusion in analyses. FAME, although conducted within the AHS framework, collected more granular exposure data on some pesticides suspected to be etiologically relevant to PD, some of which were infrequently-used and therefore covered superficially at AHS enrollment (ever-use of "other pesticides"). The AHS questionnaires at enrollment focused, in part, on frequently-used pesticides. Further, AHS questionnaires differed for applicators and spouses, leading to lack of information in the AHS on certain pesticides of interest in FAME. For example, information on rotenone (included in the group mitochondrial complex I inhibitor) was not asked of spouses and was collected only from applicators who completed the take-home questionnaire. Likewise, although all participants were asked about ever-use of paraquat, information on duration and frequency of paraquat use was not asked of spouses and was collected only from the applicators returning the take-home questionnaire. Differences in study design and outcome ascertainment also could have contributed to differences in findings. Our analysis included all cohort members with at least some follow-up information and involved a longer follow-up period, whereas FAME involved a small subset of the cohort with fewer PD cases and shorter follow-up. Our current analysis utilized pesticide data obtained before PD diagnosis; whereas the exposure data in FAME were collected retrospectively after PD diagnosis (from participants or their proxies if participants were deceased), thereby opening the possibility of bias associated with differential recall of pesticide use (for example, if cases were more likely to recall such exposures). On the other hand, FAME benefitted from more detailed exposure information on relevant pesticides. Further, in FAME, both cases and controls underwent in-person assessment, while in the current study, we mainly relied on self-reports and those who self-reported to be PD-free did not undergo additional evaluation. Since we also included the FAME cases, however, a portion of our cases had an earlier in-person exam. Disease misclassification is possible and could have led to diminish estimates of relative risk in our analyses. In fact, while pesticide-use agreement was good overall, we did see some evidence of differential reporting by cases and controls in FAME when comparing data reported in both FAME and in the main AHS enrollment questionnaire (Supplemental Table 8 presents some comparisons, although we note that exposure timeframes are different as FAME asked exposures before PD diagnosis for cases or a reference date for controls). Lastly, FAME and our current cohort-wide effort are capturing different time windows of exposure relative to disease onset. The insidious onset of PD that is difficult to capture in non-clinical settings together with limited knowledge of induction and latent periods makes determination of exposure-relevant time windows difficult.

Specifically, for the herbicide paraquat, animal and earlier human studies offer persuasive evidence for a potential link with PD, despite continuing debate (Goldman et al., 2017; Jones et al., 2014). Some subgroups, including those with specific genetic makeup, head injury, and certain dietary intake have been found particularly vulnerable to PD following paraquat exposure (Goldman et al., 2012; Kamel et al., 2014; Lee et al., 2012; Ritz et al., 2009). We cannot rule out the possibility that limited evidence of independent associations between PD and ever-use of some pesticides (including paraquat) in the current study resulted from non-differential bias attenuating HR estimates; for example, the HR for ever-use of paraquat was elevated [HR: 1.09 (95% CI: 0.84, 1.41)], but not statistically significant. Nevertheless, we were still able to observe associations among those potentially more susceptible due to head injury.

**Table 4**
Intensity-weighted lifetime days of pesticide use at enrollment and incident PD in male applicators.

| | | Pesticide exposure through enrollment | | | | Pesticide exposure through Phase 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pesticide | Lifetime days[a] | No PD, n (%) | PD, n (%) | HR (95% CI)[b] | p[c] | Lifetime days[a] | No PD, n (%) | PD, n (%) | HR (95% CI)[b] | p[c] |
| **Organochlorine insecticide** | | | | | | | | | | |
| Aldrin [d] | Never use | 13,427 (82.7) | 145 (75.5) | Ref | 0.08 | – | – | – | – | |
| | >0–≤315 | 994 (6.1) | 18 (9.4) | 0.84 (0.50, 1.42) | | | | | | |
| | >315–≤980 | 911 (5.6) | 17 (8.9) | 0.82 (0.47, 1.41) | | | | | | |
| | >980 | 905 (5.6) | 12 (6.3) | 0.56 (0.30, 1.06) | | | | | | |
| Chlordane [d] | Never use | 13,516 (80.7) | 144 (72.7) | Ref | 0.69 | – | – | – | – | |
| | >0–≤236 | 1090 (6.5) | 18 (9.1) | 1.04 (0.63, 1.71) | | | | | | |
| | >236–≤735 | 1111 (6.6) | 17 (8.6) | 0.92 (0.55, 1.53) | | | | | | |
| | >735 | 1039 (6.2) | 19 (9.6) | 1.02 (0.62, 1.68) | | | | | | |
| Dieldrin [d] | Never use | 15,739 (96.2) | 178 (93.2) | Ref | 0.61 | – | – | – | – | |
| | >0–≤338 | 307 (1.9) | 8 (4.2) | 1.24 (0.60, 2.59) | | | | | | |
| | >338 | 308 (1.9) | 5 (2.6) | 0.77 (0.31, 1.93) | | | | | | |
| DDT [d] | Never use | 12,823 (78.3) | 117 (60.6) | Ref | 0.61 | – | – | – | – | |
| | >0–≤341 | 1221 (7.5) | 21 (10.9) | 0.84 (0.52, 1.37) | | | | | | |
| | >341–≤1675 | 1175 (7.2) | 35 (18.1) | 1.39 (0.92, 2.08) | | | | | | |
| | >1675 | 1150 (7) | 20 (10.4) | 0.87 (0.53, 1.43) | | | | | | |
| Heptachlor [d] | Never use | 14,332 (87.4) | 155 (78.7) | Ref | 0.93 | – | – | – | – | |
| | >0–≤280 | 673 (4.1) | 14 (7.1) | 1.41 (0.79, 2.51) | | | | | | |
| | >280–≤882 | 729 (4.4) | 17 (8.6) | 1.44 (0.85, 2.46) | | | | | | |
| | >882 | 660 (4) | 11 (5.6) | 1.02 (0.54, 1.94) | | | | | | |
| Toxaphene [d] | Never use | 16,128 (88.6) | 200 (89.7) | Ref | 0.12 | – | – | – | – | |
| | >0–≤315 | 714 (3.9) | 7 (3.1) | 0.54 (0.26, 1.16) | | | | | | |
| | >315–≤1181 | 670 (3.7) | 8 (3.6) | 0.66 (0.32, 1.33) | | | | | | |
| | >1181 | 681 (3.7) | 8 (3.6) | 0.59 (0.29, 1.21) | | | | | | |
| Lindane | Never use | 15,591 (86.3) | 186 (85.3) | Ref | 0.56 | Never use | 15,424 (84.4) | 183 (83.6) | Ref | 0.62 |
| | >0–≤315 | 823 (4.6) | 7 (3.2) | 0.56 (0.26, 1.2) | | >0–≤341 | 944 (5.2) | 8 (3.7) | 0.59 (0.29, 1.21) | |
| | >315–≤1232 | 839 (4.6) | 16 (7.3) | 1.23 (0.73, 2.06) | | >341–≤1232 | 961 (5.3) | 18 (8.2) | 1.26 (0.76, 2.07) | |
| | >1232 | 815 (4.5) | 9 (4.1) | 0.77 (0.40, 1.51) | | >1232 | 940 (5.1) | 10 (4.6) | 0.80 (0.42, 1.51) | |
| **Carbamate insecticide** | | | | | | | | | | |
| Carbaryl | Never use | 9547 (57.8) | 111 (56.3) | Ref | 0.12 | Never use | 9194 (52) | 106 (53) | Ref | 0.11 |
| | >0–≤387 | 2432 (14.7) | 32 (16.2) | 0.96 (0.65, 1.44) | | >0–≤441 | 2904 (16.4) | 37 (18.5) | 0.90 (0.60, 1.36) | |
| | >387–≤2460 | 2403 (14.6) | 30 (15.2) | 0.81 (0.53, 1.26) | | >441–≤2320 | 2918 (16.5) | 30 (15) | 0.78 (0.50, 1.22) | |
| | >2460 | 2123 (12.9) | 24 (12.2) | 0.64 (0.38, 1.08) | | >2320 | 2675 (15.1) | 27 (13.5) | 0.63 (0.37, 1.05) | |
| Carbofuran [e] | - | – | – | – | | Never use | 23,500 (71.3) | 198 (64.5) | Ref | 0.41 |
| | | | | | | >0–≤368 | 3133 (9.5) | 41 (13.4) | 0.90 (0.60, 1.36) | |
| | | | | | | >368–≤1370 | 3200 (9.7) | 41 (13.4) | 0.78 (0.50, 1.22) | |
| | | | | | | >1370 | 3127 (9.5) | 27 (8.8) | 0.63 (0.37, 1.05) | |
| *≤ 63y* | Never use | 13,827 (76.4) | 52 (61.9) | Ref | 0.28 | – | – | – | – | |
| | >0–≤784 | 2156 (11.9) | 24 (28.6) | 1.88 (1.15, 3.05) | | | | | | |
| | >784 | 2117 (11.7) | 8 (9.5) | 0.66 (0.31, 1.4) | | | | | | |
| *>63y* | Never use | 10,581 (67.5) | 148 (66.4) | Ref | 0.93 | | | | | |
| | >0–≤784 | 2534 (16.2) | 38 (17) | 0.99 (0.69, 1.42) | | | | | | |
| | >784 | 2551 (16.3) | 37 (16.6) | 1.02 (0.71, 1.46) | | | | | | |
| **Organophosphate insecticide** | | | | | | | | | | |
| Chlorpyrifos | Never use | 18,564 (55) | 191 (58.2) | Ref | 0.60 | Never use | 19,755 (55.4) | 220 (61.1) | Ref | 0.78 |
| | >0–≤455 | 5003 (14.8) | 54 (16.5) | 1.14 (0.84, 1.55) | | >0–≤490 | 5251 (14.7) | 55 (15.3) | 1.04 (0.77, 1.41) | |
| | >455–≤1848 | 5165 (15.3) | 33 (10.1) | 0.68 (0.47, 0.99) | | >490–≤1903 | 5406 (15.2) | 38 (10.6) | 0.71 (0.5, 1.01) | |
| | >1848 | 4994 (14.8) | 50 (15.2) | 1.12 (0.82, 1.54) | | >1903 | 5243 (14.7) | 47 (13.1) | 0.99 (0.72, 1.35) | |
| Coumaphos | Never use | 29,725 (91.2) | 271 (90) | Ref | 0.99 | Never use | 29,678 (91) | 271 (90) | Ref | 0.93 |
| | >0–≤380 | 955 (2.9) | 9 (3) | 0.87 (0.45, 1.7) | | >0–≤385 | 975 (3) | 9 (3) | 0.85 (0.44, 1.65) | |
| | >380–≤1418 | 979 (3) | 12 (4) | 1.07 (0.6, 1.91) | | >385–≤1428 | 986 (3) | 12 (4) | 1.07 (0.6, 1.91) | |
| | >1418 | 938 (2.9) | 9 (3) | 0.99 (0.51, 1.92) | | >1428 | 966 (3) | 9 (3) | 0.96 (0.49, 1.87) | |
| *Diazinon*[f] | *Never use* | *13,412 (79.2)* | *162 (81)* | Ref | 0.23 | Never use | 13,202 (75.4) | 162 (79.8) | Ref | 0.11 |
| | *>0–≤328* | *1194 (7.1)* | *13 (6.5)* | *0.79 (0.45, 1.40)* | | >0–≤350 | 1443 (8.2) | 13 (6.4) | 0.68 (0.38, 1.21) | |

(*continued on next page*)

**Table 4** (*continued*)

| Pesticide | Lifetime days[a] | Pesticide exposure through enrollment | | | | Pesticide exposure through Phase 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No PD, n (%) | PD, n (%) | HR (95% CI)[b] | p[c] | Lifetime days[a] | No PD, n (%) | PD, n (%) | HR (95% CI)[b] | p[c] |
| | *>328–≤1274* | *1213 (7.2)* | *14 (7)* | *0.78 (0.45, 1.35)* | | >350–≤1270 | 1476 (8.4) | 16 (7.9) | 0.81 (0.48, 1.36) | |
| | *>1274* | *1116 (6.6)* | *11 (5.5)* | *0.69 (0.37, 1.29)* | | >1270 | 1391 (7.9) | 12 (5.9) | 0.6 (0.32, 1.12) | |
| Dichlorvos | Never use | 29,516 (89.2) | 264 (86.3) | Ref | 0.06 | Never use | 29,409 (88.9) | 264 (86.3) | Ref | 0.06 |
| | >0–≤1344 | 1783 (5.4) | 15 (4.9) | 0.79 (0.46, 1.33) | | >0–≤1360 | 1844 (5.6) | 15 (4.9) | 0.79 (0.46, 1.33) | |
| | >1344 | 1773 (5.4) | 27 (8.8) | 1.46 (0.98, 2.19) | | >1360 | 1832 (5.5) | 27 (8.8) | 1.46 (0.98, 2.19) | |
| Fonofos | Never use | 25,838 (77.6) | 240 (77.4) | Ref | 0.32 | Never use | 25,820 (77.5) | 240 (77.4) | Ref | 0.32 |
| | >0–≤455 | 2467 (7.4) | 26 (8.4) | 1.06 (0.7, 1.61) | | >0–≤455 | 2468 (7.4) | 26 (8.4) | 1.06 (0.7, 1.61) | |
| | >455–≤1680 | 2526 (7.6) | 24 (7.7) | 0.92 (0.60, 1.42) | | >455–≤1696 | 2538 (7.6) | 24 (7.7) | 0.92 (0.6, 1.41) | |
| | >1680 | 2463 (7.4) | 20 (6.5) | 0.80 (0.50, 1.27) | | >1696 | 2470 (7.4) | 20 (6.5) | 0.8 (0.5, 1.27) | |
| Malathion | Never use | 6436 (35.7) | 76 (35) | Ref | 0.08 | Never use | 6107 (30.4) | 69 (29.2) | Ref | 0.12 |
| | >0–≤368 | 3832 (21.3) | 53 (24.4) | 1.13 (0.79, 1.61) | | >0–≤384 | 4797 (23.9) | 68 (28.8) | 1.26 (0.89, 1.79) | |
| | >368 ≤ 1440 | 3948 (21.9) | 46 (21.2) | 0.89 (0.62, 1.29) | | >384–≤1344 | 4603 (22.9) | 47 (19.9) | 0.93 (0.64, 1.35) | |
| | >1440 | 3795 (21.1) | 42 (19.4) | 0.75 (0.51, 1.10) | | >1344 | 4584 (22.8) | 52 (22) | 0.83 (0.57, 1.2) | |
| Parathion | Never use | 16,605 (92.1) | 201 (91) | Ref | 0.97 | Never use | 16,580 (91.9) | 201 (90.5) | Ref | 0.76 |
| | >0–≤882 | 718 (4) | 10 (4.5) | 0.94 (0.49, 1.78) | | >0–≤880 | 728 (4) | 10 (4.5) | 0.86 (0.44, 1.69) | |
| | >882 | 697 (3.9) | 10 (4.5) | 0.99 (0.52, 1.89) | | >880 | 726 (4) | 11 (5) | 1.05 (0.56, 1.94) | |
| Phorate | Never use | 11,467 (68.4) | 121 (61.4) | Ref | 0.55 | Never use | 11,523 (67.8) | 122 (61.3) | Ref | 0.47 |
| | >0–≤315 | 1771 (10.6) | 25 (12.7) | 1.18 (0.75, 1.86) | | >0–≤320 | 1818 (10.7) | 25 (12.6) | 1.14 (0.72, 1.79) | |
| | >315–≤1176 | 1809 (10.8) | 34 (17.3) | 1.61 (1.07, 2.41) | | >320–≤1176 | 1874 (11) | 35 (17.6) | 1.62 (1.09, 2.41) | |
| | >1176 | 1715 (10.2) | 17 (8.6) | 0.84 (0.50, 1.40) | | >1176 | 1781 (10.5) | 17 (8.5) | 0.8 (0.48, 1.34) | |
| Terbufos | Never use | 19,869 (59.8) | 168 (54.4) | Ref | 0.50 | Never use | 19,649 (59.1) | 168 (54) | Ref | 0.53 |
| | >0–≤646 | 4397 (13.2) | 46 (14.9) | 1.34 (0.96, 1.88) | | >0–≤660 | 4497 (13.5) | 48 (15.4) | 1.35 (0.97, 1.89) | |
| | >646–≤2400 | 4536 (13.7) | 54 (17.5) | 1.46 (1.06, 2.00) | | >660–≤2436 | 4623 (13.9) | 53 (17) | 1.39 (1.01, 1.91) | |
| | >2400 | 4411 (13.3) | 41 (13.3) | 1.16 (0.82, 1.65) | | >2436 | 4480 (13.5) | 42 (13.5) | 1.16 (0.82, 1.64) | |
| **Permethrin insecticide** | | | | | | | | | | |
| Permethrin (crops) | Never use | 28,383 (86.5) | 269 (89.4) | Ref | 0.21 | Never use | 27,839 (84.8) | 265 (88.3) | Ref | 0.27 |
| | >0–≤273 | 1470 (4.5) | 15 (5) | 1.30 (0.77, 2.2) | | >0–≤288 | 1639 (5) | 17 (5.7) | 1.19 (0.7, 2.01) | |
| | >273–≤1080 | 1492 (4.5) | 11 (3.7) | 1.01 (0.55, 1.84) | | >288–≤1117 | 1695 (5.2) | 11 (3.7) | 0.94 (0.51, 1.72) | |
| | >1080 | 1466 (4.5) | 6 (2) | 0.59 (0.26, 1.33) | | >1117 | 1643 (5) | 7 (2.3) | 0.66 (0.31, 1.4) | |
| Permethrin (animals) | Never use | 28,783 (86.3) | 272 (88.6) | Ref | 0.21 | Never use | 28,163 (84.3) | 270 (87.9) | Ref | 0.16 |
| | >0–≤368 | 1574 (4.7) | 11 (3.6) | 0.93 (0.50, 1.70) | | >0–≤392 | 1737 (5.2) | 11 (3.6) | 0.84 (0.46, 1.53) | |
| | >368–≤1418 | 1505 (4.5) | 9 (2.9) | 0.77 (0.40, 1.51) | | >392–≤1512 | 1781 (5.3) | 9 (2.9) | 0.68 (0.34, 1.35) | |
| | >1418 | 1493 (4.5) | 15 (4.9) | 1.44 (0.85, 2.44) | | >1512 | 1721 (5.2) | 17 (5.5) | 1.49 (0.9, 2.46) | |
| **Fumigant** | | | | | | | | | | |
| Carbon disulfide/carbon tetrachloride [d] | Never use | 17,467 (95.8) | 209 (94.6) | Ref | 0.74 | – | – | – | – | |
| | >0–≤172 | 398 (2.2) | 6 (2.7) | 0.82 (0.36, 1.86) | | | | | | |
| | >172 | 364 (2) | 6 (2.7) | 0.88 (0.39, 1.98) | | | | | | |
| Methyl Bromide | Never use | 28,072 (84.9) | 274 (85.9) | Ref | 0.58 | Never use | 28,084 (84.8) | 276 (85.7) | Ref | 0.52 |
| | >0–≤320 | 1613 (4.9) | 13 (4.1) | 0.82 (0.46, 1.47) | | >0–≤326 | 1669 (5) | 14 (4.3) | 0.78 (0.44, 1.41) | |
| | >320–≤1372 | 1670 (5.1) | 17 (5.3) | 1.03 (0.60, 1.78) | | >326–≤1395 | 1673 (5.1) | 17 (5.3) | 0.98 (0.57, 1.7) | |
| | >1372 | 1706 (5.2) | 15 (4.7) | 0.82 (0.46, 1.48) | | >1395 | 1696 (5.1) | 15 (4.7) | 0.8 (0.45, 1.42) | |
| **Fungicide** | | | | | | | | | | |
| Benomyl | Never use | 14,990 (92.8) | 174 (91.6) | Ref | 0.31 | Never use | 14,977 (92.4) | 174 (90.6) | Ref | 0.35 |
| | >0–≤868 | 591 (3.7) | 5 (2.6) | 0.62 (0.24, 1.61) | | >0–≤868 | 623 (3.8) | 6 (3.1) | 0.73 (0.31, 1.75) | |
| | >868 | 574 (3.6) | 11 (5.8) | 1.34 (0.64, 2.80) | | >868 | 613 (3.8) | 12 (6.3) | 1.34 (0.64, 2.79) | |
| Captan | Never use | 29,167 (89.8) | 274 (90.7) | Ref | 0.36 | Never use | 28,708 (88.2) | 270 (88.8) | Ref | 0.26 |
| | >0–≤9 | 1224 (3.8) | 8 (2.6) | 0.83 (0.41, 1.68) | | >0–≤10 | 1278 (3.9) | 8 (2.6) | 0.78 (0.39, 1.59) | |
| | >9–≤212 | 1046 (3.2) | 6 (2) | 0.65 (0.29, 1.46) | | >10–≤540 | 1311 (4) | 10 (3.3) | 0.83 (0.44, 1.57) | |
| | >212 | 1060 (3.3) | 14 (4.6) | 1.27 (0.74, 2.20) | | >540 | 1264 (3.9) | 16 (5.3) | 1.33 (0.80, 2.21) | |
| Chlorothalonil | Never use | 30,547 (92.8) | 293 (94.2) | Ref | 0.41 | Never use | 30,371 (92.2) | 291 (93.6) | Ref | 0.47 |
| | >0–≤1535 | 1132 (3.4) | 7 (2.3) | 0.74 (0.34, 1.61) | | >0–≤1613 | 1245 (3.8) | 7 (2.3) | 0.71 (0.32, 1.55) | |
| | >1535 | 1221 (3.7) | 11 (3.5) | 1.29 (0.66, 2.56) | | >1613 | 1312 (4) | 13 (4.2) | 1.41 (0.75, 2.66) | |
| Maneb[g] | - | – | – | – | | Never use | 15,464 (92.3) | 186 (93) | Ref | 0.34 |
| | | | | | | >0–≤1268 | 660 (3.9) | 8 (4) | 0.69 (0.31, 1.53) | |
| | | | | | | >1268 | 636 (3.8) | 6 (3) | 0.59 (0.25, 1.4) | |

(*continued on next page*)

**Table 4** (*continued*)

| Pesticide | Lifetime days[a] | Pesticide exposure through enrollment | | | | Pesticide exposure through Phase 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No PD, n (%) | PD, n (%) | HR (95% CI)[b] | p[c] | Lifetime days[a] | No PD, n (%) | PD, n (%) | HR (95% CI)[b] | p[c] |
| Metalaxyl | Never use | 14,301 (81.6) | 177 (82.3) | Ref | 0.14 | Never use | 14,239 (79.1) | 175 (80.6) | Ref | 0.47 |
| | >0–≤312 | 1060 (6.1) | 17 (7.9) | 1.27 (0.77, 2.11) | | >0–≤312 | 1241 (6.9) | 18 (8.3) | 1.26 (0.76, 2.08) | |
| | >312–≤1568 | 1094 (6.2) | 15 (7) | 1.18 (0.66, 2.11) | | >312–≤1488 | 1286 (7.1) | 15 (6.9) | 1.17 (0.64, 2.13) | |
| | >1568 | 1061 (6.1) | 6 (2.8) | 0.53 (0.22, 1.27) | | >1488 | 1240 (6.9) | 9 (4.1) | 0.79 (0.38, 1.65) | |
| **Herbicide** | | | | | | | | | | |
| Alachlor | Never use | 15,100 (45.7) | 127 (41.9) | Ref | 0.80 | Never use | 14,974 (45.3) | 124 (40.9) | Ref | 0.73 |
| | >0–≤809 | 5925 (18) | 63 (20.8) | 1.11 (0.82, 1.52) | | >0–≤809 | 6011 (18.2) | 65 (21.5) | 1.15 (0.85, 1.57) | |
| | >809–≤3132 | 6056 (18.3) | 55 (18.2) | 0.95 (0.69, 1.30) | | >809–≤3145 | 6121 (18.5) | 56 (18.5) | 0.97 (0.7, 1.33) | |
| | >3132 | 5927 (18) | 58 (19.1) | 1.07 (0.78, 1.46) | | >3145 | 5977 (18.1) | 58 (19.1) | 1.09 (0.8, 1.5) | |
| Butylate | Never use | 11,964 (71.9) | 144 (72.7) | Ref | 0.22 | Never use | 13,263 (73) | 164 (73.9) | Ref | 0.24 |
| | >0–≤473 | 1564 (9.4) | 25 (12.6) | 1.26 (0.81, 1.95) | | >0–≤473 | 1626 (9) | 26 (11.7) | 1.26 (0.81, 1.95) | |
| | >473–≤1519 | 1583 (9.5) | 16 (8.1) | 0.85 (0.50, 1.45) | | >473–≤1512 | 1659 (9.1) | 18 (8.1) | 0.91 (0.54, 1.53) | |
| | >1519 | 1531 (9.2) | 13 (6.6) | 0.73 (0.41, 1.30) | | >1512 | 1619 (8.9) | 14 (6.3) | 0.73 (0.41, 1.3) | |
| Chlorimuron Ethyl | Never use | 12,384 (68) | 163 (73.4) | Ref | 0.44 | Never use | 12,187 (65.4) | 162 (72.6) | Ref | 0.22 |
| | >0–≤245 | 1930 (10.6) | 25 (11.3) | 1.22 (0.80, 1.87) | | >0–≤263 | 2140 (11.5) | 30 (13.5) | 1.28 (0.85, 1.9) | |
| | >245–≤784 | 1977 (10.9) | 17 (7.7) | 0.80 (0.49, 1.33) | | >263–≤817 | 2169 (11.6) | 15 (6.7) | 0.69 (0.4, 1.18) | |
| | >784 | 1910 (10.5) | 17 (7.7) | 0.85 (0.52, 1.41) | | >817 | 2127 (11.4) | 16 (7.2) | 0.77 (0.46, 1.28) | |
| Dicamba | Never use | 15,344 (47.7) | 141 (48) | Ref | 0.33 | Never use | 14,269 (44.3) | 131 (44.4) | Ref | 0.13 |
| | >0–≤564 | 5548 (17.2) | 50 (17) | 0.90 (0.63, 1.28) | | >0–≤694 | 5897 (18.3) | 58 (19.7) | 0.99 (0.7, 1.41) | |
| | >564–≤2184 | 5761 (17.9) | 46 (15.6) | 0.81 (0.56, 1.17) | | >694–≤2380 | 6126 (19) | 43 (14.6) | 0.83 (0.56, 1.22) | |
| | >2184 | 5524 (17.2) | 57 (19.4) | 1.11 (0.79, 1.56) | | >2380 | 5950 (18.5) | 63 (21.4) | 1.25 (0.88, 1.77) | |
| EPTC | Never use | 26,190 (79.7) | 249 (83) | Ref | 0.74 | Never use | 26,155 (79.6) | 249 (83) | Ref | 0.73 |
| | >0–≤315 | 2215 (6.7) | 19 (6.3) | 0.93 (0.58, 1.49) | | >0–≤315 | 2222 (6.8) | 19 (6.3) | 0.93 (0.58, 1.49) | |
| | >315–≤1181 | 2245 (6.8) | 14 (4.7) | 0.67 (0.39, 1.15) | | >315–≤1190 | 2261 (6.9) | 14 (4.7) | 0.66 (0.39, 1.14) | |
| | >1181 | 2192 (6.7) | 18 (6) | 0.97 (0.60, 1.57) | | >1190 | 2205 (6.7) | 18 (6) | 0.97 (0.6, 1.57) | |
| Glyphosate | Never use | 8307 (23.3) | 86 (24.2) | Ref | 0.09 | Never use | 5247 (14.8) | 62 (17.5) | Ref | 0.10 |
| | >0–≤677 | 8996 (25.2) | 106 (29.8) | 1.17 (0.88, 1.55) | | >0–≤970 | 9965 (28) | 132 (37.2) | 1.21 (0.88, 1.65) | |
| | >677–≤2604 | 9313 (26.1) | 91 (25.6) | 0.99 (0.73, 1.33) | | >970–≤3352 | 10,318 (29) | 84 (23.7) | 0.92 (0.64, 1.34) | |
| | >2604 | 9015 (25.3) | 73 (20.5) | 0.85 (0.62, 1.17) | | >3352 | 10,018 (28.2) | 77 (21.7) | 0.88 (0.62, 1.25) | |
| Imazethapyr | Never use | 17,941 (55.5) | 173 (58.6) | Ref | 0.38 | Never use | 17,152 (53.1) | 169 (56.9) | Ref | 0.64 |
| | >0–≤341 | 4874 (15.1) | 42 (14.2) | 1.00 (0.70, 1.45) | | >0–≤403 | 5007 (15.5) | 47 (15.8) | 1.03 (0.72, 1.47) | |
| | >341–≤1008 | 4752 (14.7) | 41 (13.9) | 1.05 (0.73, 1.52) | | >403–≤1176 | 5205 (16.1) | 42 (14.1) | 0.92 (0.63, 1.35) | |
| | >1008 | 4733 (14.7) | 39 (13.2) | 1.18 (0.81, 1.72) | | >1176 | 4964 (15.4) | 39 (13.1) | 1.11 (0.76, 1.62) | |
| Metolachlor | Never use | 17,519 (52.8) | 182 (60.1) | Ref | 0.79 | Never use | 16,273 (49) | 174 (57.4) | Ref | 0.71 |
| | >0–≤720 | 5255 (15.8) | 35 (11.6) | 0.67 (0.46, 0.96) | | >0–≤760 | 5600 (16.9) | 41 (13.5) | 0.72 (0.51, 1.03) | |
| | >720–≤2688 | 5322 (16) | 44 (14.5) | 0.84 (0.6, 1.17) | | >760–≤2700 | 5776 (17.4) | 44 (14.5) | 0.78 (0.55, 1.1) | |
| | >2688 | 5079 (15.3) | 42 (13.9) | 0.90 (0.64, 1.26) | | >2700 | 5585 (16.8) | 44 (14.5) | 0.89 (0.63, 1.25) | |
| Paraquat | Never use | 15,305 (84.1) | 188 (82.5) | Ref | 0.45 | Never use | 15,216 (81.9) | 188 (81.7) | Ref | 0.36 |
| | >0–≤289 | 961 (5.3) | 13 (5.7) | 1.03 (0.58, 1.81) | | >0–≤308 | 1111 (6) | 13 (5.7) | 0.92 (0.51, 1.63) | |
| | >289–≤1232 | 975 (5.4) | 18 (7.9) | 1.42 (0.86, 2.33) | | >308–≤1308 | 1135 (6.1) | 20 (8.7) | 1.49 (0.92, 2.41) | |
| | >1232 | 960 (5.3) | 9 (3.9) | 0.74 (0.37, 1.49) | | >1308 | 1113 (6) | 9 (3.9) | 0.69 (0.34, 1.38) | |
| Pendimethalin | Never use | 11,440 (62.9) | 154 (68.1) | Ref | 0.25 | Never use | 10,685 (53.9) | 145 (60.9) | Ref | 0.57 |
| | >0–≤341 | 2262 (12.4) | 32 (14.2) | 1.13 (0.77, 1.66) | | >0–≤378 | 3003 (15.2) | 38 (16) | 1.1 (0.77, 1.57) | |
| | >341–≤1320 | 2263 (12.4) | 23 (10.2) | 0.90 (0.58, 1.40) | | >378 ≤ 1232 | 3114 (15.7) | 32 (13.4) | 0.97 (0.65, 1.44) | |
| | >1320 | 2227 (12.2) | 17 (7.5) | 0.76 (0.46, 1.26) | | >1232 | 3005 (15.2) | 23 (9.7) | 0.89 (0.57, 1.39) | |
| Petroleum | Never use | 14,257 (78.9) | 184 (83.6) | Ref | 0.72 | Never use | 14,169 (78.1) | 183 (82.8) | Ref | 0.59 |
| | >0–≤515 | 1266 (7) | 9 (4.1) | 0.57 (0.29, 1.11) | | >0–≤495 | 1317 (7.3) | 11 (5) | 0.67 (0.36, 1.23) | |
| | >515–≤2500 | 1286 (7.1) | 13 (5.9) | 0.91 (0.52, 1.61) | | >495–≤2408 | 1355 (7.5) | 13 (5.9) | 0.88 (0.5, 1.55) | |
| | >2500 | 1261 (7) | 14 (6.4) | 0.89 (0.52, 1.53) | | >2408 | 1312 (7.2) | 14 (6.3) | 0.85 (0.49, 1.47) | |
| Trifluralin | Never use | 14,464 (45.7) | 116 (40.4) | Ref | 0.07 | Never use | 14,106 (44.5) | 113 (39.4) | Ref | 0.10 |
| | >0–≤1008 | 5653 (17.9) | 61 (21.3) | 1.40 (1.01, 1.95) | | >0–≤1046 | 5779 (18.2) | 64 (22.3) | 1.42 (1.02, 1.97) | |
| | >1008–≤3828 | 5877 (18.6) | 47 (16.4) | 1.05 (0.73, 1.52) | | >1046–≤3906 | 6144 (19.4) | 49 (17.1) | 1.05 (0.73, 1.52) | |
| | >3828 | 5669 (17.9) | 63 (22) | 1.50 (1.06, 2.11) | | >3906 | 5672 (17.9) | 61 (21.3) | 1.48 (1.04, 2.1) | |
| 2,4-D | Never use | 8108 (22.9) | 72 (20.5) | Ref | 0.52 | Never use | 6928 (19.5) | 67 (18.9) | Ref | 0.52 |

(*continued on next page*)

**Table 4** (*continued*)

| Pesticide | Lifetime days[a] | Pesticide exposure through enrollment | | | | Pesticide exposure through Phase 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No PD, n (%) | PD, n (%) | HR (95% CI)[b] | p[c] | Lifetime days[a] | No PD, n (%) | PD, n (%) | HR (95% CI)[b] | p[c] |
| | >0–≤1269 | 8944 (25.3) | 84 (23.9) | 1.07 (0.78, 1.47) | | >0–≤1440 | 9486 (26.6) | 97 (27.3) | 1.08 (0.79, 1.49) | |
| | >1269–≤5104 | 9303 (26.3) | 97 (27.6) | 1.04 (0.76, 1.43) | | >1440–≤5394 | 9767 (27.4) | 86 (24.2) | 0.87 (0.62, 1.22) | |
| | >5104 | 9035 (25.5) | 99 (28.1) | 0.96 (0.7, 1.31) | | >5394 | 9432 (26.5) | 105 (29.6) | 0.93 (0.67, 1.29) | |
| 2,4,5-T[d] | Never use | 13,328 (80.9) | 143 (71.9) | Ref | 0.71 | – | – | – | – | |
| | >0–≤289 | 1068 (6.5) | 20 (10.1) | 1.21 (0.75, 1.95) | | | | | | |
| | >289–≤1006 | 1069 (6.5) | 20 (10.1) | 1.27 (0.78, 2.05) | | | | | | |
| | >1006 | 1007 (6.1) | 16 (8) | 1.11 (0.65, 1.89) | | | | | | |
| Atrazine | Never use | 9709 (27.3) | 95 (27) | Ref | 0.64 | Never use | 8473 (23.8) | 87 (24.7) | Ref | 0.53 |
| | >0–≤1050 | 8525 (23.9) | 87 (24.7) | 1.14 (0.84, 1.54) | | >0–≤1221 | 8960 (25.2) | 97 (27.6) | 1.17 (0.86, 1.59) | |
| | >1050–≤4456 | 8826 (24.8) | 85 (24.1) | 0.99 (0.73, 1.34) | | >1221–≤4666 | 9250 (26) | 83 (23.6) | 0.95 (0.69, 1.3) | |
| | >4456 | 8556 (24) | 85 (24.1) | 0.99 (0.73, 1.34) | | >4666 | 8943 (25.1) | 85 (24.1) | 0.98 (0.72, 1.34) | |
| Cyanazine | Never use | 19,018 (57.2) | 174 (57.4) | Ref | 0.79 | Never use | 18,910 (56.9) | 173 (57.1) | Ref | 0.66 |
| | >0–≤560 | 4706 (14.2) | 40 (13.2) | 0.84 (0.59, 1.20) | | >0–≤588 | 4808 (14.5) | 39 (12.9) | 0.81 (0.57, 1.17) | |
| | >560–≤2268 | 4850 (14.6) | 45 (14.9) | 0.91 (0.64, 1.28) | | >588–≤2279 | 4792 (14.4) | 46 (15.2) | 0.94 (0.66, 1.32) | |
| | >2268 | 4665 (14) | 44 (14.5) | 1.00 (0.71, 1.42) | | >2279 | 4716 (14.2) | 45 (14.9) | 1.03 (0.73, 1.45) | |
| Metribuzin | Never use | 9599 (59.7) | 115 (61.5) | Ref | 0.33 | Never use | 9513 (58) | 115 (60.8) | Ref | 0.37 |
| | >0–≤319 | 2148 (13.4) | 30 (16) | 1.10 (0.71, 1.69) | | >0–≤341 | 2358 (14.4) | 31 (16.4) | 1.01 (0.65, 1.56) | |
| | >319–≤1024 | 2193 (13.6) | 21 (11.2) | 0.77 (0.47, 1.27) | | >341–≤1054 | 2259 (13.8) | 21 (11.1) | 0.75 (0.46, 1.23) | |
| | >1024 | 2128 (13.2) | 21 (11.2) | 0.81 (0.49, 1.33) | | >1054 | 2260 (13.8) | 22 (11.6) | 0.81 (0.50, 1.34) | |

Abbreviation: 2,4-D, 2,4-Dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-Trichlorophenoxyacetic acid; 2,4,5-T,P, 2-(2,4,5-trichlorophenoxy) propionic acid; CI, Confidence Intervals; DDT, Dichlorodiphenyltrichloroethane; EPTC, S-Ethyl dipropylthiocarbamate; HR, Hazard Ratio.

[a] Tertile cut-off and n (%) may differ between Phase 1 and Phase 2 exposure because of difference in exposure information and missingness.

[b] HR adjusted for sex, state of residence, smoking status, education, and ever-use of correlated pesticides (other pesticides whose ever-use variable had Spearman correlation $\geq 0.40$ with the ever-use variable of the target pesticide).

[c] P-value for test for trend.

[d] HR not presented if, at Phase 2, pesticide exposure since enrollment was not reported.

[e] HR allowed to vary by the median age (i.e., 63 years) for pesticides that did not meet proportional hazards assumption ($p \leq 0.10$).

[f] Proportional hazards assumption not met for those in italics, but there was no adequate sample size to provide stratified estimates by the median age.

[g] HR not presented as there were less than 5 exposed cases.

Our study also suggests that use of chemical resistant gloves may have conferred some protection against PD in pesticide applicators using certain herbicides. Chemical resistant gloves, but not other types of gloves, have been shown in the AHS to offer protection from pesticide exposure (Hines et al., 2011; Thomas et al., 2010). In FAME, associations of several pesticides including permethrin and paraquat with PD risks were greater in those who used chemical-resistant gloves less than 50% of the time compared to those who used >50% (Furlong et al., 2015).

### 4.1. Limitations and strengths

Our study has several limitations. First, pesticide-use data were self-reported; thus, some exposure misclassification is likely. However, AHS farmers have been shown to report both reliable and valid pesticide usage (Blair et al., 2002; Hoppin et al., 2002); for lifetime exposures, we used exposure intensity, which correlates better with urinary biomarkers of pesticides than uncorrected days of use (Coble et al., 2011; Hines et al., 2011). Due to our prospective design, exposure misclassification was likely non-differential for PD. Non-differential misclassification might have biased effect estimates towards the null for binary pesticide-use variables; but, for polytomous categories, directionality of bias is uncertain (Rothman et al., 2008).

Second, in the current analyses, although we incorporated pesticide usage through the first follow-up for applicators, we could not do so for spouses and we could not account for more proximal exposures for applicators because data were not available for all participants due to cohort attrition. The time duration from Phase 2 (when exposures were updated for this analysis) to Phase 4 (i.e., end of follow-up) was 13 years on average. Failure to account for exposure occurring during this window could have heightened exposure misclassification, for those pesticides that are still on the market.

Third, our effort to validate all potential PD cases using medical records suffered from low response from both participants (or their proxies) and their physicians, so we relied on PD self-report. We attempted to minimize potential PD misclassification by restricting analysis to individuals providing consistent responses on PD across surveys and for those with relevant questionnaire data, restricting to cases with supporting data on neurological symptoms and medication use. We did find that those medical records we obtained were in high agreement with self-reported PD. Further, agreement between PD self-report and clinical diagnostic evaluation was found to be high in FAME (84%) (Tanner et al., 2011) as well in other studies (Jain et al., 2015), indicating PD self-reports are, in general, reasonably reliable. Furthermore, we observed reduced PD risk in smokers [age and sex adjusted HR: 0.75 (95%CI: 0.61, 0.91) for former smoking and 0.55 (95%CI: 0.38, 0.81) for current smoking] in the current study, which is consistent with prior literature (Hernan et al., 2002) and thus indirectly supports the validity of PD self-reports in the AHS.

Fourth, we were unable to account for possible PD in participants who were lost to follow-up, although we were able to identify participants who had PD recorded on their death certificates (but did not report PD in surveys). We included such cases in our analysis if their proxy provided adequate information in the validation screener to support a PD diagnosis. We had similar results in analyses using inverse probability weighting to make inference on all enrolled participants. Nevertheless, we cannot completely rule out selection bias due to loss-to-follow up or bias due to selective mortality before enrollment resulting from higher pesticide exposures. Fifth, we found inverse associations for some pesticides which may be due to reverse causality – for instance, if individuals with symptomatic but undiagnosed PD accumulate less exposure due to reduced farming activities compared to those individuals that are "healthy" and continue farming. We know of no reason why this reverse causality would apply only to certain pesticides.

Sixth, we also did not adjust for multiple comparisons given the exploratory nature of our study and therefore some of the observed associations may be false positives and thus our findings should be interpreted with caution. Seventh, participants were exposed to multiple pesticides. Although we adjusted for several correlated pesticides, we cannot rule out lack of complete control of confounding due to other pesticides. Lastly, our current analytical approach focusing on a single exposure fails to account for the overall PD risk associated with multiple pesticide exposures. Pesticide use in the AHS is not easily addressed using current methods for the analysis of chemical mixtures. Applicators report a lifetime of use, with one or two possibly different pesticides being used in any given year. Chemicals used may have changed over time in relation to specific crops planted, environmental conditions, changes in availability of banned or restricted chemicals, pesticide costs and economic constraints, and much more. The development and application of new methods to address this complex and unique mixture situation is warranted.

Countering these limitations, the strengths for the current investigation include large sample size, prospective design, long-term follow-up, comprehensive information on lifetime use of pesticides, and detailed information on PD risk factors. Although we found evidence of increased PD risk for a few pesticides, most pesticides were not associated with PD nor, for the most part, were pesticides/groups that were previously implicated for PD. Continued research on pesticide-PD risk that can focus on specific chemicals is important because of continued widespread use of pesticides worldwide.

## Credit author statement

Srishti Shrestha and Dale P. Sandler conceptualized the investigation, led the analysis and prepared the first draft of the manuscript. Srishti Shrestha and Marie Richards-Barber conducted data analysis. Dale P. Sandler provided supervision and funding acquisition. Dale P. Sandler, Christine G. Parks, and Laura E. Beane Freeman were involved in project administration. All the authors were involved in data interpretation and in reviewing, critiquing, and editing the manuscript, and provided final manuscript approval.

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## 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.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.110186.

## References

Acosta, S.A., Tajiri, N., de la Pena, I., Bastawrous, M., Sanberg, P.R., Kaneko, Y., Borlongan, C.V., 2015. Alpha-synuclein as a pathological link between chronic

traumatic brain injury and Parkinson's disease. J. Cell. Physiol. 230, 1024–1032. https://doi.org/10.1002/jcp.24830.
Alavanja, M.C., Sandler, D.P., McMaster, S.B., Zahm, S.H., McDonnell, C.J., Lynch, C.F., Pennybacker, M., Rothman, N., Dosemeci, M., Bond, A.E., Blair, A., 1996. The agricultural health study. Environ. Health Perspect. 104, 362–369. https://doi.org/10.1289/ehp.96104362.
Atwood, D., Paisley-Jones, C., 2017. Pesticides Industry Sales and Usage 2008-2012 Market Estimates. United States Environmental Protection Agency, Washington, D.C.
Binukumar, B.K., Bal, A., Kandimalla, R.J., Gill, K.D., 2010. Nigrostriatal neuronal death following chronic dichlorvos exposure: crosstalk between mitochondrial impairments, alpha synuclein aggregation, oxidative damage and behavioral changes. Mol. Brain 3, 35. https://doi.org/10.1186/1756-6606-3-35.
Blair, A., Tarone, R., Sandler, D., Lynch, C.F., Rowland, A., Wintersteen, W., Steen, W.C., Samanic, C., Dosemeci, M., Alavanja, M.C., 2002. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 13, 94–99. https://doi.org/10.1097/00001648-200201000-00015.
Bradberry, S.M., Proudfoot, A.T., Vale, J.A., 2004. Poisoning due to chlorophenoxy herbicides. Toxicol. Rev. 23, 65–73. https://doi.org/10.2165/00139709-200423020-00001.
Coble, J., Thomas, K.W., Hines, C.J., Hoppin, J.A., Dosemeci, M., Curwin, B., Lubin, J.H., Beane Freeman, L.E., Blair, A., Sandler, D.P., Alavanja, M.C., 2011. An updated algorithm for estimation of pesticide exposure intensity in the Agricultural Health Study. Int. J. Environ. Res. Publ. Health 8, 4608–4622. https://doi.org/10.3390/ijerph8124608.
Dhillon, A.S., Tarbutton, G.L., Levin, J.L., Plotkin, G.M., Lowry, L.K., Nalbone, J.T., Shepherd, S., 2008. Pesticide/environmental exposures and Parkinson's disease in East Texas. J. Agromed. 13, 37–48. https://doi.org/10.1080/10599240801986215.
Firestone, J.A., Lundin, J.I., Powers, K.M., Smith-Weller, T., Franklin, G.M., Swanson, P. D., Longstreth Jr., W.T., Checkoway, H., 2010. Occupational factors and risk of Parkinson's disease: a population-based case-control study. Am. J. Ind. Med. 53, 217–223. https://doi.org/10.1002/ajim.20788.
Fitzmaurice, A.G., Rhodes, S.L., Lulla, A., Murphy, N.P., Lam, H.A., O'Donnell, K.C., Barnhill, L., Casida, J.E., Cockburn, M., Sagasti, A., Stahl, M.C., Maidment, N.T., Ritz, B., Bronstein, J.M., 2013. Aldehyde dehydrogenase inhibition as a pathogenic mechanism in Parkinson disease. Proc. Natl. Acad. Sci. U. S. A. 110, 636–641. https://doi.org/10.1073/pnas.1220399110.
Fitzmaurice, A.G., Rhodes, S.L., Cockburn, M., Ritz, B., Bronstein, J.M., 2014. Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease. Neurology 82, 419–426. https://doi.org/10.1212/WNL.0000000000000083.
Furlong, M., Tanner, C.M., Goldman, S.M., Bhudhikanok, G.S., Blair, A., Chade, A., Comyns, K., Hoppin, J.A., Kasten, M., Korell, M., Langston, J.W., Marras, C., Meng, C., Richards, M., Ross, G.W., Umbach, D.M., Sandler, D.P., Kamel, F., 2015. Protective glove use and hygiene habits modify the associations of specific pesticides with Parkinson's disease. Environ. Int. 75, 144–150. https://doi.org/10.1016/j.envint.2014.11.002.
Gardner, R.C., Burke, J.F., Nettiksimmons, J., Goldman, S., Tanner, C.M., Yaffe, K., 2015. Traumatic brain injury in later life increases risk for Parkinson disease. Ann. Neurol. 77, 987–995. https://doi.org/10.1002/ana.24396.
Gatto, N.M., Cockburn, M., Bronstein, J., Manthripragada, A.D., Ritz, B., 2009. Well-water consumption and Parkinson's disease in rural California. Environ. Health Perspect. 117, 1912–1918. https://doi.org/10.1289/ehp.0900852.
Gelb, D.J., Oliver, E., Gilman, S., 1999. Diagnostic criteria for Parkinson disease. Arch. Neurol. 56, 33–39.
Gintautas, P.A., Daniel, S.R., Macalady, D.L., 1992. Phenoxyalkanoic acid herbicides in municipal landfill leachates. Environ. Sci. Technol. 26, 517–521. https://doi.org/10.1021/Es00027a011.
Goldman, S.M., Kamel, F., Ross, G.W., Bhudhikanok, G.S., Hoppin, J.A., Korell, M., Marras, C., Meng, C., Umbach, D.M., Kasten, M., Chade, A.R., Comyns, K., Richards, M.B., Sandler, D.P., Blair, A., Langston, J.W., Tanner, C.M., 2012. Genetic modification of the association of paraquat and Parkinson's disease. Mov. Disord. 27, 1652–1658. https://doi.org/10.1002/mds.25216.
Goldman, S.M., Musgrove, R.E., Jewell, S.A., Di Monte, D.A., 2017. Pesticides and Parkinson's disease: current experimental and epidemiological evidence. In: Aschner, M., Costa, L.G. (Eds.), Advances in Neurotoxicology: Environmental Factors in Neurodegenerative Diseases. Academic Press, Cambridge, MA, pp. 83–117.
Heltshe, S.L., Lubin, J.H., Koutros, S., Coble, J.B., Ji, B.T., Alavanja, M.C., Blair, A., Sandler, D.P., Hines, C.J., Thomas, K.W., Barker, J., Andreotti, G., Hoppin, J.A., Beane Freeman, L.E., 2012. Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study. J. Expo. Sci. Environ. Epidemiol. 22, 409–416. https://doi.org/10.1038/jes.2012.31.
Hernan, M.A., Takkouche, B., Caamano-Isorna, F., Gestal-Otero, J.J., 2002. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann. Neurol. 52, 276–284. https://doi.org/10.1002/ana.10277.
Hines, C.J., Deddens, J.A., Coble, J., Kamel, F., Alavanja, M.C., 2011. Determinants of captan air and dermal exposures among orchard pesticide applicators in the Agricultural Health Study. Ann. Occup. Hyg. 55, 620–633. https://doi.org/10.1093/annhyg/mer008.
Hirtz, D., Thurman, D.J., Gwinn-Hardy, K., Mohamed, M., Chaudhuri, A.R., Zalutsky, R., 2007. How common are the "common" neurologic disorders? Neurology 68, 326–337. https://doi.org/10.1212/01.wnl.0000252807.38124.a3.
Hoppin, J.A., Yucel, F., Dosemeci, M., Sandler, D.P., 2002. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J. Expo. Anal. Environ. Epidemiol. 12, 313–318. https://doi.org/10.1038/sj.jea.7500232.
Howe, C.J., Cole, S.R., Lau, B., Napravnik, S., Eron Jr., J.J., 2016. Selection bias due to loss to follow up in cohort studies. Epidemiology 27, 91–97. https://doi.org/10.1097/EDE.0000000000000409.
Hutson, C.B., Lazo, C.R., Mortazavi, F., Giza, C.C., Hovda, D., Chesselet, M.F., 2011. Traumatic brain injury in adult rats causes progressive nigrostriatal dopaminergic cell loss and enhanced vulnerability to the pesticide paraquat. J. Neurotrauma 28, 1783–1801. https://doi.org/10.1089/neu.2010.1723.
Jain, S., Himali, J., Beiser, A., Ton, T.G., Kelly-Hayes, M., Biggs, M.L., Delaney, J.A., Rosano, C., Seshadri, S., Frank, S.A., 2015. Validation of secondary data sources to identify Parkinson disease against clinical diagnostic criteria. Am. J. Epidemiol. 181, 185–190. https://doi.org/10.1093/aje/kwu326.
Jones, B.C., Huang, X., Mailman, R.B., Lu, L., Williams, R.W., 2014. The perplexing paradox of paraquat: the case for host-based susceptibility and postulated neurodegenerative effects. J. Biochem. Mol. Toxicol. 28, 191–197. https://doi.org/10.1002/jbt.21552.
Kamel, F., Tanner, C., Umbach, D., Hoppin, J., Alavanja, M., Blair, A., Comyns, K., Goldman, S., Korell, M., Langston, J., Ross, G., Sandler, D., 2007. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am. J. Epidemiol. 165, 364–374. https://doi.org/10.1093/aje/kwk024.
Kamel, F., Goldman, S.M., Umbach, D.M., Chen, H., Richardson, G., Barber, M.R., Meng, C., Marras, C., Korell, M., Kasten, M., Hoppin, J.A., Comyns, K., Chade, A., Blair, A., Bhudhikanok, G.S., Webster Ross, G., William Langston, J., Sandler, D.P., Tanner, C.M., 2014. Dietary fat intake, pesticide use, and Parkinson's disease. Park. Relat. Disord. 20, 82–87. https://doi.org/10.1016/j.parkreldis.2013.09.023.
Kanthasamy, A.G., Kitazawa, M., Kanthasamy, A., Anantharam, V., 2005. Dieldrin-induced neurotoxicity: relevance to Parkinson's disease pathogenesis. Neurotoxicology 26, 701–719. https://doi.org/10.1016/j.neuro.2004.07.010.
Kenborg, L., Rugbjerg, K., Lee, P.C., Ravnskjaer, L., Christensen, J., Ritz, B., Lassen, C.F., 2015. Head injury and risk for Parkinson disease: results from a Danish case-control study. Neurology 84, 1098–1103. https://doi.org/10.1212/WNL.0000000000001362.
Kowal, S.L., Dall, T.M., Chakrabarti, R., Storm, M.V., Jain, A., 2013. The current and projected economic burden of Parkinson's disease in the United States. Mov. Disord. 28, 311–318. https://doi.org/10.1002/mds.25292.
Lee, P.C., Bordelon, Y., Bronstein, J., Ritz, B., 2012. Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease. Neurology 79, 2061–2066. https://doi.org/10.1212/WNL.0b013e3182749f28.
Lifshitz, J., Sullivan, P.G., Hovda, D.A., Wieloch, T., McIntosh, T.K., 2004. Mitochondrial damage and dysfunction in traumatic brain injury. Mitochondrion 4, 705–713. https://doi.org/10.1016/j.mito.2004.07.021.
Lilienfeld, D.E., Gallo, M.A., 1989. 2,4-D, 2,4,5-T, and 2,3,7,8-TCDD: an overview. Epidemiol. Rev. 11, 28–58. https://doi.org/10.1093/oxfordjournals.epirev.a036044.
Loane, D.J., Kumar, A., Stoica, B.A., Cabatbat, R., Faden, A.I., 2014. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. J. Neuropathol. Exp. Neurol. 73, 14–29, 10.1097/NEN.0000000000000021.
Narayan, S., Liew, Z., Paul, K., Lee, P.C., Sinsheimer, J.S., Bronstein, J.M., Ritz, B., 2013. Household organophosphorus pesticide use and Parkinson's disease. Int. J. Epidemiol. 42, 1476–1485. https://doi.org/10.1093/ije/dyt170.
Pezzoli, G., Cereda, E., 2013. Exposure to pesticides or solvents and risk of Parkinson disease. Neurology 80, 2035–2041. https://doi.org/10.1212/WNL.0b013e318294b3c8.
Ritz, B.R., Manthripragada, A.D., Costello, S., Lincoln, S.J., Farrer, M.J., Cockburn, M., Bronstein, J., 2009. Dopamine transporter genetic variants and pesticides in Parkinson's disease. Environ. Health Perspect. 117, 964–969. https://doi.org/10.1289/ehp.0800277.
Rothman, K.J., Greenland, S., Lash, T.L., 2008. Validity in epidemiologic studies. In: Rothman, K.J., Greenland, S., Lash, T.L. (Eds.), Modern Epidemiology. Lippincott Williams and Wilkins, Philadelphia, PA, pp. 128–147.
SAS Institute Inc, 2015. The PROC MIANALYZE Procedure. SAS/STAT 141 User's Guide, Cary, NC.
Shrestha, S., Parks, C.G., Keil, A.P., Umbach, D.M., Lerro, C.C., Lynch, C.F., Chen, H., Blair, A., Koutros, S., Hofmann, J.N., Beane Freeman, L.E., Sandler, D.P., 2019a. Overall and cause-specific mortality in a cohort of farmers and their spouses. Occup. Environ. Med. 76, 632–643. https://doi.org/10.1136/oemed-2019-105724.
Shrestha, S., Kamel, F., Umbach, D.M., Freeman, L.E.B., Koutros, S., Alavanja, M., Blair, A., Sandler, D.P., Chen, H., 2019b. High pesticide exposure events and olfactory impairment among U.S. Farmers. Environ. Health Perspect. 127, 17005. https://doi.org/10.1289/EHP3713.
Tanner, C.M., Ross, G.W., Jewell, S.A., Hauser, R.A., Jankovic, J., Factor, S.A., Bressman, S., Deligtisch, A., Marras, C., Lyons, K.E., Bhudhikanok, G.S., Roucoux, D. F., Meng, C., Abbott, R.D., Langston, J.W., 2009. Occupation and risk of parkinsonism: a multicenter case-control study. Arch. Neurol. 66, 1106–1113. https://doi.org/10.1001/archneurol.2009.195.
Tanner, C.M., Kamel, F., Ross, G.W., Hoppin, J.A., Goldman, S.M., Korell, M., Marras, C., Bhudhikanok, G.S., Kasten, M., Chade, A.R., Comyns, K., Richards, M.B., Meng, C., Priestley, B., Fernandez, H.H., Cambi, F., Umbach, D.M., Blair, A., Sandler, D.P., Langston, J.W., 2011. Rotenone, paraquat, and Parkinson's disease. Environ. Health Perspect. 119, 866–872. https://doi.org/10.1289/ehp.1002839.
Taylor, K.M., Saint-Hilaire, M.H., Sudarsky, L., Simon, D.K., Hersh, B., Sparrow, D., Hu, H., Weisskopf, M.G., 2016. Head injury at early ages is associated with risk of Parkinson's disease. Park. Relat. Disord. 23, 57–61. https://doi.org/10.1016/j.parkreldis.2015.12.005.

Terry Jr., A.V., 2012. Functional consequences of repeated organophosphate exposure: potential non-cholinergic mechanisms. Pharmacol. Ther. 134, 355–365. https://doi.org/10.1016/j.pharmthera.2012.03.001.

Thomas, K.W., Dosemeci, M., Hoppin, J.A., Sheldon, L.S., Croghan, C.W., Gordon, S.M., Jones, M.L., Reynolds, S.J., Raymer, J.H., Akland, G.G., Lynch, C.F., Knott, C.E., Sandler, D.P., Blair, A.E., Alavanja, M.C., 2010. Urinary biomarker, dermal, and air measurement results for 2,4-D and chlorpyrifos farm applicators in the Agricultural Health Study. J. Expo. Sci. Environ. Epidemiol. 20, 119–134. https://doi.org/10.1038/jes.2009.6.

US Administration on Aging, 2012. A Profile of Older Americans: 2012. US Administration on Aging.

Uversky, V.N., Li, J., Bower, K., Fink, A.L., 2002. Synergistic effects of pesticides and metals on the fibrillation of alpha-synuclein: implications for Parkinson's disease. Neurotoxicology 23, 527–536.

van der Mark, M., Brouwer, M., Kromhout, H., Nijssen, P., Huss, A., Vermeulen, R., 2012. Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. Environ. Health Perspect. 120, 340–347. https://doi.org/10.1289/ehp.1103881.

van der Mark, M., Vermeulen, R., Nijssen, P.C., Mulleners, W.M., Sas, A.M., van Laar, T., Brouwer, M., Huss, A., Kromhout, H., 2014. Occupational exposure to pesticides and endotoxin and Parkinson disease in The Netherlands. Occup. Environ. Med. 71, 757–764. https://doi.org/10.1136/oemed-2014-102170.

Wang, A., Cockburn, M., Ly, T.T., Bronstein, J.M., Ritz, B., 2014. The association between ambient exposure to organophosphates and Parkinson's disease risk. Occup. Environ. Med. 71, 275–281. https://doi.org/10.1136/oemed-2013-101394.

Ware, G.W., 1988. Silvex (2,4,5-TP). In: Ware, G.W. (Ed.), Rev Environ Contam Toxicol. Reviews of Environmental Contamination and Toxicology, vol. 104. Springer, New York, NY, pp. 195–202.

Weisskopf, M.G., Knekt, P., O'Reilly, E.J., Lyytinen, J., Reunanen, A., Laden, F., Altshul, L., Ascherio, A., 2010. Persistent organochlorine pesticides in serum and risk of Parkinson disease. Neurology 74, 1055–1061. https://doi.org/10.1212/WNL.0b013e3181d76a93.