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Authors

Liew, Zeyan

Wang, Anthony

Bronstein, Jeff

et al.

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TITLE: Job Exposure Matrix (JEM) derived estimates of life-time occupational pesticide exposure and the risk of Parkinson's Disease.

Zeyan Liew¹, Anthony Wang¹, Jeff Bronstein², Beate Ritz^{1*}

¹ Department of Epidemiology, School of Public Health, University of California, Los Angeles, P.O. Box 951772, Los Angeles, CA 90095, USA.

² Neurology, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, CA 90095, USA.*

Author to whom correspondence should be addressed: E-mail: britz@ucla.edu; Tel.: +1-310-206-7458; Fax: +1-310-206-6039

Abstract

Background: Previous studies repeatedly suggested that [Parkinson's disease \(PD\)](#) is associated with occupational pesticide exposure, but in many studies exposures were self-reported and none adjusted for concomitant ambient pesticide exposures.

Objective: To investigate whether occupational exposure to pesticides increases the risk of [Parkinson's Disease \(PD\)](#) in California's heavily agricultural region.

Methods: We enrolled 357 incident PD cases and 750 population controls in a case-control study in California's Central Valley between 2001 to 2011. A comprehensive Job Exposure Matrix (JEM) was developed to assess participant's life-time cumulative occupational pesticide exposure based on work history and detailed job tasks information.

Results: PD risk was estimated to be more than 2-fold higher (OR=2.19 95%CI 1.25, 3.84) in men who were classified as highly occupational exposed with our data suggesting an exposure-response (trend p=0.008). Farming tasks with more direct and intense pesticide exposures such as applying, spraying and mixing of pesticides resulted in greater risks than indirect exposures from general tasks such as planting, harvesting, packing, sorting, etc. Results did not change when we adjusted for residential and occupational ambient pesticide exposures estimated based on a Geographic Information System (GIS) model.

Conclusion: We provide further evidence that occupational pesticide exposure increases the risk of PD in men and ambient exposures did not confound these associations.

Keywords: Case-control study, Job exposure matrix, Occupation, Parkinson's [Diseasedisease](#), Pesticide exposure

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder leading to motor, cognitive and mood dysfunction with a major impact on quality of life. Its etiology is widely considered to be multi-factorial, involving a combination of exposures to neurotoxicants, genetic factors, and aging . PD has been linked to farm work and pesticide exposures in general with some studies reporting on specific pesticide exposures including our own previous reports focused on ambient pesticides in proximity to agricultural applications .

However, the vast majority of previous epidemiological studies relied on retrospective self-reporting of exposures raising questions about validity due to the possibility of differential recall bias since cases may be more inclined than control subjects to report exposures to suspected toxins as suggested previously . This German study found PD risk to be increased with self-reported pesticide use but not when a job exposure matrix was employed to assess pesticide exposures. Few studies utilized methods less influenced by subject recall such as exposure matrices or expert evaluations based on job history to assess occupational pesticide exposures but most of these studies were either very small (<90 incident PD cases) or they solely classified subjects as ever/never exposed based on job titles . A French study is perhaps the most comprehensive to date in terms of occupational pesticide exposure assessment as occupational practitioners interviewed participants and conducted in-depth evaluations of exposure histories. However, this study was still relatively small and additional information from studies employing a job exposure matrix is needed to expand the existing literature.

Our study participants reside in one of the most agriculturally intensive regions in the United States where ~65 million pounds of pesticide active ingredients were sprayed in 2009 (CDPR summary of pesticide use report data 2009). This is our first report on lifetime occupational exposure to pesticides derived from a job exposure matrix in our PD case control study in the Central Valley of California. Previously, we focused solely on ambient pesticides exposure in proximity to agricultural applications which we also accounted for in some of the analyses presented here.

MATERIALS AND METHODS

All procedures described have been approved by the University of California at Los Angeles, Institutional Review Board for human subjects, and informed consent was obtained from all participants.

Study population

We conducted a population-based case-control study of PD in a largely agricultural region in California's Central Valley and collected work histories to assess occupational pesticide exposures relying on a job exposure matrix approach. We enrolled incident idiopathic PD patients between 1 January 2001 and 1 January 2007 and population-based controls from three mostly rural agricultural counties (Kern, Tulare, Fresno) in central California between 1 January 2002 and 31 December 2010. Subject recruitment methods and case definition criteria have been described in detail elsewhere.

Of 1,167 PD patients initially identified through neurologists, large medical groups, and public service announcements, 604 did not meet eligibility criteria: 397 had their initial PD diagnosis more than 3 years prior to recruitment, 134 lived outside the tri-county area at the time of recruitment, 51 had a diagnosis other than PD, and 22 were too ill to participate. Of the 563 eligible cases, 90 could not be examined (56 declined to participate or moved away, 18 had become too ill to be examined, and 16 died prior to the scheduled appointment). Of the 473 subjects examined by a University of California at Los Angeles movement disorder specialist, 94 did not meet published criteria for idiopathic PD when examined or re-examined during the initial study period, an additional 13 were reclassified as not idiopathic PD during our follow-up study, and 6 subjects withdrew between examination and interview. Of the remaining 360 cases, 357 provided all information including work history necessary for inclusion in this analysis.

Population-based controls were recruited initially from Medicare lists (2001) and, after the Health Insurance Portability and Accountability Act (HIPAA), from residential tax assessor records from the tri-county area. Controls recruitment eligibility criteria were similar to cases: 1) age 35 or older; 2) not too ill to participate; 3) had lived in California for 5 years prior to enrollment; 4) currently residing primarily at the selected residence; and 5) not being diagnosed with PD (not for cases). Two sampling strategies were implemented to increase enrollment success and achieve representativeness of the control population. First between 2001 and 2007, we randomly selected residential parcels and enrolled control subjects via mail and phone only (described in detail in). For our second control recruitment effort (2009-11), we again selected

parcels presumed to be residential units at random from tax assessors maps but this time identified a group of five residences each clustered in close proximity to each other for at the door-step recruitment. Thus, our trained field staffs who determined eligibility and enrolled controls during home visits had the opportunity to enroll as many as five controls in neighboring homes – if found eligible - at each visit. Each household was approached up to four times on weekdays and weekends. Only one member per household was allowed to enroll.

Of the 1,212 potential controls contacted through the first sampling strategy, 457 were ineligible: 409 were <35 years of age, 44 were too ill to participate, and 4 primarily resided outside the study area. From 755 eligible population controls, 409 declined, became too ill to participate, or moved out of the area after screening and prior to enrollment; 346 population controls enrolled from the first sampling strategy. Of the 4,756 individuals screened for eligibility through the second sampling strategy, 3,515 were ineligible (88% due to age criteria). Under the second sampling strategy, 1,241 population controls were found to be eligible, but 634 declined participation; 607 population controls enrolled, but 183 of those controls completed only an abbreviated questionnaire. In sum, 341 from first sampling and 409 from second sampling with a total of 750 controls provided all information including work history needed for following analyses.

Job Exposure Matrix

Trained interviewers blinded to case/control status conducted structured telephone interviews to obtain demographic and work history information such as job title, job task, company, industry, address, and duration of work (years), and hours worked per week from study participants.

We coded information on jobs and industries in 26 major occupational categories according to the Integrated Public Use Microdata Series (IPUMS-USA) 2000 Occupation Code System. Only jobs in which a subject had worked for 6-months or more throughout their lifetime were assessed. We created a job exposure matrix (JEM) to estimate occupational pesticide exposure based on work history information for job titles, job tasks and duration of work. We estimated the likelihood that an occupational exposure to pesticides had occurred in an approach similar to Young et al (2004). Job tasks were assigned weights to reflect intensity of likely pesticide exposure. Jobs unrelated to farming and those not known to involve occupational pesticide handling received a weight of zero, while pesticide-specific tasks were given corresponding

weights. Due to concerns that our effect measures may be sensitive to how the weights were chosen, we compared three weighting schemes, a standard, a conservative (lower weights assigned for general farm_work, non-fieldwork, and farming supplies job tasks), and a maximum weight emphasizing tasks with likely high intensity exposures (see Table S1 in appendix).

When a job involved multiple tasks that received different weights, we constructed an average weight across all tasks performed in this job. Years a subject reported having worked in a job multiplied by each weight were summed across all jobs reported to construct a lifetime cumulative measure of occupational pesticide exposure for each participant (see table S2 in appendix for examples).

Statistical Analysis

We used SAS 9.2 (SAS Institute Inc., Cary, NC, USA) to perform unconditional logistic regression analyses. We adjusted for age at diagnosis (cases) or age at interview (controls), sex, ethnicity (White vs. non-White), education (< 12 years, 12 years, > 12 years), having a 1st degree family member with PD (yes, no), and smoking (current, former, never). Based on percentiles from the exposure distribution in controls using the JEM-derived lifetime cumulative occupational pesticide measure we considered participants as unexposed, or if falling above 0 and below the 25th percentile as low, 26-75th percentile as medium, and above the 75th percentile as highly exposed.

Moreover, we considered participants who reported ever performing the job tasks of mixing and applying/spraying of pesticides as directly exposed to pesticides and those who reported having held farming jobs with tasks other than pesticide mixing and application as likely indirectly exposed.

In addition, in sensitivity analyses we stratified our main analyses by gender, excluded Hispanics, and restricted control groups from first or second sampling separately. We also investigated whether our JEM-derived exposure measures were sensitive to reported hours of work per week in each job. While most jobs were reported as 40 hours per week (full time) positions, we used additional weights to adjust for having held part time jobs (i.e. dividing the reported hours per week by 40); this procedure increased the exposure score for those working more than 40 hours and reduced it for part time jobs. Since 15% of all reported farm-related jobs did not report hours per week, we imputed the missing hours based on the average hours a

subject reported working in all other jobs or alternatively assumed they had worked 40 hours per week.

Moreover, we adjusted our JEM derived measures also for residential and occupational pesticide exposures based on our Geographic Information System (GIS) model that provides ambient exposure measures for addresses within 500 meter from pesticide applications recorded in the California Pesticide Use Reporting system during 1974-1999. Details have been described elsewhere . We used indicator variables for ever/never exposure to four types of pesticides (organochlorines (OC), organophosphates (OP), dithiocarbamates (DTC) and paraquat (PQ)) that have been suggested to be linked to dopaminergic cell damage and possibly PD , or we adjusted based on a propensity score that regressed the JEM-derive exposure estimate onto the indicators of ever/never exposure to residential and occupational ambient pesticide exposure and other key covariates included in main analysis.

RESULTS

Study participants were predominantly White, over the age of 60, and did not have a family history of PD (Table 1). Cases were slightly older than controls, more frequently male, and also reported to have smoked less than controls.

The distribution of occupational histories (jobs held >6 months at any time in life) by case status categorized according to the IPUM-USA 2000 occupational codes classification are shown in Table 2. The most commonly reported occupations among study populations were office/administrative support (34%), followed by farming/fishing/forestry (29%), and management occupations (28%). In our data, more cases had been employed in farming and military occupations (male dominated jobs), and more controls in education/training and food preparation related occupations (female dominated jobs) as expected due to the predominance of PD among males. Job tasks reported by those who had held agricultural jobs included: fieldwork and general tasks (25.2%), non-fieldwork related farming tasks (10.7%), planting/ploughing, pesticide application/spraying, transportation/farming supplies (2-3%), and only 3 men reported mixing of pesticides as a task (see Table 3). Also as expected, all of these farming tasks were mostly performed by men.

Based on our JEM-derived life-time cumulative occupational pesticide exposure estimates, we calculated a 56% increase in the risk of developing PD with high (OR=1.56 95%CI 0.96, 2.53), a 34% increase with medium (OR =1.34 95%CI 0.92, 1.96), and no association with low

pesticide exposure (OR=0.91 95%CI 0.54, 1.54) (Table 6). Estimated effects were much stronger for males, with a 119% risk increase with high (OR=2.19 95%CI 1.25, 3.84), 73% with medium (OR=1.73 95%CI 1.05, 2.84), and no association with low exposure (OR=1.11 95%CI 0.57, 2.14). Conversely, no associations were observed for women who were exposed (OR=0.83 95%CI 0.50, 1.40) but these estimates were based on very small numbers (only 3 female cases and 15 female controls were considered highly exposed).

Our results based on alternative conservative or maximum weights for specific job tasks were quite consistent with the results using standard weights to create our JEM measures. Since we recruited more Hispanics residents in our second home visit based control sampling, we also performed sensitivity analyses excluding Hispanics. Results were very similar to those presented (i.e. for highly exposed non-Hispanic males OR=2.06 95%CI 1.08, 3.93). Reported associations did not change in additional sensitivity analyses that incorporated weights for hours worked per week in each job (see online table I). Additionally, reported associations also did not change when we adjusted in addition for ambient residential pesticide exposures in our models (see online table II). However, effect estimates were slightly attenuated with adjustment for ambient pesticide exposures at workplaces (JEM derived highly exposed males versus unexposed OR=1.94 95%CI 1.08, 3.49).

Moreover, we estimated that presumed direct exposures (ever mixed, applied or sprayed pesticides) increased risk of PD in males by 2 fold (OR=2.00 95%CI 0.92, 4.37) and presumed indirect exposures (ever performed farming job tasks other than pesticides mixing and application) by about 62% (OR=1.62 95%CI 1.08, 2.43) (see table 5).

DISCUSSION

We conducted a population-based case-control study of PD in a largely agricultural region of Central California confirming previous reports that occupational exposures to pesticides in farming related jobs increase the risk of developing PD. In fact, we found an exposure response trend for PD with intensity of life-time cumulative pesticide exposures based on JEM derived measures. We also found that presumed direct exposures to pesticide (e.g. applying, spraying and mixing of pesticides) resulted in greater risk of PD compared to indirect exposures from farming work. Our results for occupational pesticide exposures are restricted to men in our population.

Not only were few women engaged jobs exposing them to pesticides in this study, those women who may have worked with and around pesticides may still have been exposed to a different degree since our study was unable to capture for example type of pesticides and personal protective equipment use. [It is also possible that men are more vulnerable to pesticide exposure than women although this is not supported by other studies \(refs\).](#)

Past epidemiologic studies have linked farming in general to PD risk , and some suggested that specific occupational pesticide exposures are responsible for PD in farmers . A most recent meta-analysis that reviewed 46 previous studies reported a summary risk ratio of RR= 1.52 (95%CI 1.23, 1.88) for PD and Parkinsonism and occupational exposure to any pesticide, and a RR= 1.62 (95%CI 1.40, 1.88) for combined occupational and non-occupational pesticide exposure . Among PD case-control studies, a majority however relied on retrospectively self-reported occupational pesticide exposures, with only a few estimating occupational pesticide exposures solely based on expert assessment and job-titles to construct exposure matrixes, underscoring a lack of studies using exposure assessment methods that might not be affected by recall bias. A small case-control study conducted in southwest of France (Baldi et al, 2003) took an approach similar to our study developing a life-time occupations JEM with the help of occupational health professionals and reported ever occupational pesticide exposure to be associated with PD (OR=2.2 95%CI 1.1, 4.3). However, this study failed to find any exposure-response for life-time cumulative pesticide exposure and PD, possibly due to the small number of exposed cases (only 2 highly and 7 moderately exposed cases). Another more recent French study used case-by-case expert evaluation for exposure assessment; here professional pesticide use was positively associated with PD (OR=1.8, 95% CI 1.1, 3.1) and a exposure-response with number of years use was also observed.

Few cohort studies investigated the impact of occupational pesticide use on PD . Two studies were not informative for professional pesticide exposures due to the small number of exposed cases with PD. The Honolulu-Asia Aging Study (HAAS) employed a simple metric of years working on sugarcane or pineapple plantations and reported that men who had worked for more than 20 years approximately doubled their risk for PD (RR=1.9 95%CI 1.0-3.5). To date, the most comprehensive study on occupational pesticide use is the Agricultural Health Study (AHS) cohort of licensed pesticide applicators and their spouses. This study recently reported an increased risk for PD with self-reported cumulative days of pesticide use (OR=2.3 95%CI 1.2-4.5). This study investigated specific pesticide use but did not find any specific compounds or

functional groups to be more than weakly associated with incident PD, possibly due to the small number of cases (n=78 incident cases) and the large number of chemicals (~50) participants were asked to report. More recently, a small case controls study of 110 PD cases nested within this cohort reported increased PD risk for exposure to rotenone (OR=2.5 95%CI 1.3-4.7) and any pesticides thought to inhibit mitochondrial complex I (OR=2.0 95%CI 1.2-3.6), as well as for exposure to paraquat (OR=2.5 95%CI 1.4-4.7) or any oxidative stressors (OR=1.7 95%CI 1.0-2.8). While these results ~~corroborate~~ are consistent with some of our previous findings for specific ambient pesticides in Central California based on pesticide use report records, this nested case control study did not collect exposure data from baseline and prior to disease occurrence therefore might suffer from the same differential recall bias as any case control studies that employed retrospective exposure assessment and subjects self-reported pesticides use.

Exposure assessment in case-control studies of chronic diseases with a long latency like PD is challenging because exposures usually have to be assessed retrospectively and for many years before the disease occurs. As mentioned above, differential and non-differential recall bias are both major concerns since PD cases may over-report exposures and agricultural workers in general may not remember what chemicals they applied to fields, or the chemical names or frequency of application. In addition, self-reported pesticide exposures do not account for exposures in those who do not actively apply pesticides but are nevertheless potentially indirectly exposed to pesticides from drift and working in fields previously treated. A major strength of our study is the use of a job exposure matrix to uniformly and blindly estimate occupational pesticide exposure based on comprehensive lifetime occupational histories. Most likely it is easier for subjects to recall job titles and tasks than specific pesticide compounds. Differential recall bias may still arise if cases spent more effort to recall details of job tasks during their occupation history interviews, but we found that frequency and duration of reported occupations was comparable in our case and control participants.

Another important strength of our study is that unlike previous studies we were able to account for background ambient pesticide exposures due to working on or living near farms. To our knowledge, we are the first study to show that after adjusting for ambient residential and occupational pesticide exposures as well as other PD risk factors, pesticide exposures estimated through life-time farming job history remain a strong risk factor for PD. Interestingly but not unexpectedly, our measures of ambient occupational but not residential exposures derived from

GIS models using reported workplace addresses correlated moderately with our JEM-derived occupational exposure measures based on job titles and job tasks. In addition, we estimated a greater PD risk increase in those more directly exposed via handling or applying pesticide which provides additional evidence for the role of pesticide exposure over other farming related activities that result in exposures to solvents, fuels, dusts, micro-organisms that have been suggested as contributing to PD risk in farmers .

In line with previous studies , we found a PD risk increase only in men and not women occupationally exposed to pesticide. However, our previous studies in Central Valley California that used GIS and pesticide use reports to investigate ambient pesticide exposures due to living or working near pesticide applications did not observe exposure and PD risk differences by gender (Costello 2009, Wang et al, 2011). This contrast might be due to differences in exposure patterns by gender such that men are more likely to be exposed to pesticides through performing the more strenuous farming tasks involving pesticide mixing, spraying, and planting in the field, whereas ambient exposures from living or working in proximity to agricultural applications would be expected to not vary by gender.

Our study is to date the only study in which movement disorder specialists examined patients multiple times to confirm diagnoses, thus largely reducing disease misclassification. Moreover, our study enrolled a relatively large number of PD cases compared to previous studies that also used expert evaluations to assess occupational pesticide exposure. Finally, as farming is the second most common occupation in the tri-county area, the prevalence of occupational pesticide exposure in our study was sufficiently high to detect moderate size associations.

A limitation of our study is that we did not record usage of personal protective equipments with the occupational history which might modify pesticide exposure levels . Moreover, our study does not provide evidence for the association between PD and specific pesticides due to the limits of a JEM measuring exposures to specific compounds. Exposure misclassification is another concerns using a JEM because the same exposure level is being assigned to everyone reporting similar job tasks, yet in reality other factors such as methods of application and the physical or chemical properties of different pesticides may influence the true amount of pesticide exposure to farm workers . However, this exposure misclassification is likely to be non-differential by case status and bias effect estimates towards the null.

As in any case control study with less than perfect participation rates, bias may occur if cases and controls selected themselves into a study according to their potential for pesticide exposure.

Our first group of controls were recruited by mail and phone and responders tended to be somewhat more educated than cases which allows for the possibility that we enrolled less population controls potentially exposed to pesticides occupationally from farming. However, our second control group was recruited in a door-to-door approach and control participants were more likely to be of Hispanic origin and to have less formal education, i.e. they were indeed more representative of our source population in Central California. Our results however did not change when we compared our cases to either the first or the second control group separately, or excluded all Hispanics participants.

In conclusion, our study suggests that PD risk increases in men with higher lifetime cumulative pesticide exposure from farming-related jobs, as well as performing job tasks that were related to more direct and possibly intense pesticide exposures in the highly agricultural California Central Valley, even after controlling for ambient pesticide exposures.

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REFERENCE