Title

Occupational pesticide use and Parkinson's disease in the Parkinson Environment Gene (PEG) study

Authors

Narayan, Shilpa
Liew, Zeyan
Bronstein, Jeff M
et al.

Publication Date

2017-10-01

DOI

10.1016/j.envint.2017.04.010

Peer reviewed

HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Environ Int. 2017 October ; 107: 266–273. doi:10.1016/j.envint.2017.04.010.

Occupational Pesticide Use and Parkinson's Disease in the Parkinson Environment Gene (PEG) Study

Shilpa Narayan[a], **Zeyan Liew**[a], **Jeff M Bronstein**[b], and **Beate Ritz**[a,b]

[a]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles (UCLA), 650 Charles E. Young Drive, Los Angeles, California 90095-1772 USA

[b]Department of Neurology, School of Medicine, UCLA, 710 Westwood Plaza, Los Angeles, California 90095-1769 USA

Abstract

Objective—To study the influence of occupational pesticide use on Parkinson's disease (PD) in a population with information on various occupational, residential, and household sources of pesticide exposure.

Methods—In a population-based case control study in Central California, we used structured interviews to collect occupational history details including pesticide use in jobs, duration of use, product names, and personal protective equipment use from 360 PD cases and 827 controls. We linked reported products to California's pesticide product label database and identified pesticide active ingredients and occupational use by chemical class including fungicides, insecticides, and herbicides. Employing unconditional logistic regression, we estimated odds ratios and 95% confidence intervals for PD and occupational pesticide use.

Results—Ever occupational use of carbamates increased risk of PD by 455%, while organophosphorus (OP) and organochlorine (OC) pesticide use doubled risk. PD risk increased 110-211% with ever occupational use of fungicides, herbicides, and insecticides. Using any pesticide occupationally for >10 years doubled the risk of PD compared with no occupational pesticide use. Surprisingly, we estimated higher risks among those reporting use of personal protective equipment (PPE).

Conclusions—Our findings not only provide additional evidence that occupational pesticide exposures increase PD risk, but do so even after controlling for other sources of pesticide exposure; specifically, occupational use of carbamates, OPs, and OCs, as well as of fungicides, herbicides, or insecticides as a group increased risk. Interestingly, PPE use, particularly use of gloves, did not provide protection in this population.

Correspondence and reprint requests to: Beate Ritz, M.D., Ph.D., Professor and Chair, Department of Epidemiology, Fielding SPH, UCLA, 650 Charles E. Young Drive, Los Angeles, CA 90095-1772 USA. Telephone: (310) 206-7458. Fax: (310) 206-6039. britz@ucla.edu.

Competing Interests: Dr. Narayan, Dr. Liew, and Dr. Ritz declare no competing interests. Dr. Bronstein reports grants from the National Institute of Environmental Health Sciences during the conduct of the study.

Ethics Approval: This research was reviewed and approved by the UCLA Institutional Review Board. All enrolled participants provided written informed consent.

Keywords

occupational pesticide use; Parkinson's disease; case control study

Introduction[1]

Parkinson's disease (PD) is a chronic and progressive movement disorder. Many previous epidemiologic investigations identified occupational pesticide exposures as risk factors for PD.[1] Studies reporting associations of PD with occupational exposures to pesticides, herbicides, insecticides, and fungicides, however, are of varying quality, size, and consistency in terms of the agents they examined. Also, some studies assessed exposures rather crudely (ever/never occupational exposure), or employed self-reports only,[1] with little more than a handful of studies creating job exposure matrixes (JEMs) based on various types of information and levels of detail,[2-7] and the Agricultural Health Study (AHS) being the only cohort of licensed pesticide applicators and spouses with a prospective design and detailed assessment of pesticide use.[8]

In our California based case control study of PD,[9, 10] we conducted a detailed historical assessment of active occupational use of pesticides and personal protective equipment (PPE) use which we are reporting on for the very first time, while our previous reports relied on extensive information for other sources of pesticide exposure for this population, specifically, ambient pesticide exposures from agricultural applications at work places and residences and household pesticide use. Here, we present results for primarily farming-related occupational pesticide use self-reported by participants and complemented by information on chemicals from the California pesticide registration system. Thus, different from previous studies, we are able to adjust for other pesticide exposures (gardening and household use and ambient bystander exposures) common in agricultural environments and are only the second study to examine whether PPE use modifies risk from occupational pesticide use.

Materials and Methods

Study subjects

The Parkinson Environment Gene (PEG) study is a population-based case-control study of Parkinson's disease, with participants recruited from the mostly rural California counties Kern, Fresno, and Tulare. Cases were enrolled within three years of PD diagnosis, from 2001 through 2007, and population controls were enrolled between 2001 and 2011. Descriptions of PD case diagnostic criteria[9] and subject recruitment[11] can be found in our prior publications.

[1]Abbreviations: PD, Parkinson's disease; OP, organophosphorus; OC, organochlorine; PPE, personal protective equipment; HIPAA, Health Insurance Portability and Accountability Act; MMSE, Mini-Mental State Examination; CAPIT, Core Assessment Program for Intracerebral Transplantation; CDPR, California Department of Pesticide Regulation; PAN, Pesticide Action Network; DDT, Dichlorodiphenyltrichloroethane; TEPP, Tetraethyl pyrophosphate; GIS, geographic information system; DTC, dithiocarbamate; PQ, paraquat

Briefly, through local neurologists, medical groups, and public service announcements, we identified 1167 PD patients. We excluded 397 diagnosed >3 years before contact, 134 not living in the target counties, 51 without a PD diagnosis, and 22 who were too ill to participate. Of 563 remaining eligible cases, 90 declined, moved, became too ill or died before we could examine them. We further excluded 107 who did not meet criteria for idiopathic PD at exam,[9] and six withdrew prior to interview leaving us with 360 patients.

Controls 65 years or older were initially from Medicare enrollee lists for all three counties but after the Health Insurance Portability and Accountability Act (HIPAA) was instated, controls were randomly selected from residential parcel listings on tax assessor records. We used two strategies to enroll controls. First, we mailed letters to selected residential units and enrolled through mail and phone only. Using a second strategy, we recruited controls from randomly selected clusters of five neighboring households from parcel listings, and trained field staff conducted home visits to determine eligibility and enrolled controls at the door step. Only one eligible person per household was allowed to enroll as a control in our study. [4]

Using the first sampling strategy, we contacted 1,212 potential controls of whom 457 were ineligible (409 were < 35 years of age, 44 too ill to participate, and 4 lived outside target counties). We recruited 346 controls via phone and mail, since an additional 409 eligible controls declined, became too ill, or moved after screening and prior to interview. Through an early mailing, for which the number of eligible subjects who declined remains unknown, we recruited and interviewed 62 controls. We screened 4,753 individuals for eligibility at their door step and found 3,512 to be ineligible (88% due to age criteria), leaving 1,241 eligible controls, of whom 634 declined participation and 607 enrolled. Of the 607 controls enrolled through the second sampling strategy, 183 subjects agreed to participate in an abbreviated interview only and did not provide occupational information. Altogether, we have 827 controls available.

This study was approved by the University of California, Los Angeles (UCLA) Institutional Review Board, and we obtained written informed consent from all participants.

Data collection

Trained interviewers collected information by telephone on demographic characteristics, smoking, household pesticide use, lifetime residential addresses, lifetime occupations and addresses, and screened for jobs with exposures of interest, i.e., fertilizers, pesticides, metals, wood, paint strippers, and solvents. PD cases (290 out of 360) and controls (619 out of 827), who screened positive, i.e., reported (1) ever having worked with any one of the agents of interest or who reported having ever (2) lived on a farm, or (3) worked on a farm, were invited for an additional interview to collect more details on specific occupational exposures.

Of those who screened positive for fertilizers or pesticide use, or ever working or living on a farm (N=754), 78.7% (192/244) of cases and 80% (408/510) of controls agreed to participate in the detailed occupational interview. Of the 228 cases and 457 controls who participated in the detailed interview, there are 36 cases and 49 controls who screened

positive for using chemicals other than pesticides, i.e., metals, wood, paint strippers and solvents and did not report ever working on a farm or living on a farm. Of these, 3/36 (8.3%) cases and 4/49 (8.2%) controls reported pesticide exposures on the supplemental occupational questionnaire. Therefore, it is unlikely that those who screened positive for using other chemicals only (metals, wood, paint strippers, and solvents), who also reported not living on a farm and not working on a farm, and refused to participate in occupational interviews (10 cases and 60 controls) would have used pesticides occupationally.

All of our PD patients were seen at least once – many multiple times over a period of 10 years – by our UCLA movement specialists to confirm idiopathic PD according to United Kingdom Brain Bank, Core Assessment Program for Intracerebral Transplantation (CAPIT) rating scale, and Gelb criteria.[9] We also conducted a Mini-Mental State Examination (MMSE) over the phone or in person, with phone scores converted into predicted in-person scores as recommended.[12]

Occupational pesticide exposures

Here, we utilize extensive information from the additional interview in which participants self-reported occupational pesticide use of fungicides, herbicides, insecticides, and other pesticides (rodenticides, defoliants) including the name of pesticide products used, purpose or site of usage (e.g., crop, plant, animal, insect), duration (years) of use, location of use (Fresno, Kern, or Tulare counties; California; United States or abroad), whether subjects mixed or loaded pesticides, application methods (tractor with/out an enclosed cab, hand sprayer, backpack or aerial application, etc.), and PPE use (gloves, mask, coveralls, boots, goggles, respirator, etc.). In order to reduce subject burden and recall issues, we limited collection of all data to pesticide group (fungicides/herbicides/insecticides/other pesticides).

We identified the main active ingredient of each self-reported pesticide product, relying on the California Department of Pesticide Regulation (CDPR) product label database,[13] which lists the active ingredients of all pesticide products sold on the California market, with over 70% of products having registrations dated 1970 and later. We obtained the main active ingredient (in terms of product weight), by comparing the reported pesticide product name and purpose of use with CDPR database names, purposes (e.g., crop, plant, animal, insect), use types (e.g., fungicides, herbicides, insecticides), and product registration dates during the years of reported use.

When information on product composition was not available through CDPR (i.e., use prior to 1970), the most probable main active ingredient was identified based on products with the same brand names (e.g., Lannate) and purposes/sites of usage (e.g., cotton, alfalfa). If the chemical composition of a product varied over time, we considered the user as exposed to all main active ingredients the product contained in the period of its use. To identify the chemical classes of the main active ingredients (e.g., dicarboximide, inorganic, amide, etc.), we used the Pesticide Action Network (PAN) pesticide database[14] and the Compendium of Pesticide Common Names.[15] When the reported information was inadequate to identify chemical class we still were able to identify pesticide use type (fungicide/insecticide/herbicide/other pesticides).

From the self-reported occupational pesticide use information we derived ever/never use for each main active ingredient. We additionally summarized over the categories of all pesticides, pesticide use types (fungicides, insecticides, herbicides, and other pesticides), and chemical classes (carbamates, organochlorines, organophosphorus). We considered 'ever users' those who used products containing any ingredient within the category prior to the index time (year of diagnosis for cases and year of interview for controls). Carbamates we identified in reported products include aldicarb, carbaryl, methomyl, benomyl, and propoxur. Organochlorines include DDT, chlordane, dicofol, lindane, toxaphene, aldrin, dieldrin, chlorothalonil, dicofol, and methoxychlor. Organophosphorus pesticides include chlorpyrifos, diazinon, dimethoate, malathion, methyl parathion, parathion, phorate, acephate, demeton, bensulide, TEPP, phosmet, mevinphos, tribufos, disulfoton, naled, methamidophos, and ethion.

Since our screening process for the additional occupational interview included other chemical exposures (i.e., metals, wood, paint strippers, and solvents), participants screening positive did not necessarily use pesticides occupationally. We considered subjects who screened negative (68 cases, 201 controls), refused to participate in the occupational interview (60 cases, 159 controls), or who participated but did not provide responses to questions about pesticide use (15 cases, 15 controls) as never occupational pesticide users if during screening they reported no regular work (i.e., once a week or more) with fertilizers or pesticides. Participants lacking information on occupational pesticide use from either the screening question or additional interview (7 cases, 13 controls) were excluded from analyses of ever versus never occupational pesticide use.

Ambient pesticide exposures

A geographic information system (GIS) was used to obtain estimates of ambient workplace and ambient residential pesticide exposures prior to the index date. The lifetime workplace and residential addresses for the period 1974-1999 were geocoded and combined with data on pesticide use records from CDPR and land use maps from the California Department of Water Resources.[11] We estimated the pounds per acre per year of pesticides applied within a 500 meter radius surrounding each address. We then summed the exposures over the years in the 26-year period during which participants worked or lived in California and calculated 26-year average exposures. Participants who were missing a workplace or residential address were considered unexposed during that time. Those subjects with exposure at workplace or residential addresses greater than or equal to the median 26-year average exposure in exposed controls for four types of pesticides (organochlorines (OC), organophosphorus (OP), dithiocarbamates (DTC) and paraquat (PQ)) were assigned a value of 1 for workplace and residential exposure, respectively. Those with exposures at workplace or residential addresses below the median 26-year average exposure in exposed controls for all four types of pesticides were considered unexposed and assigned a 0 for workplace and residential exposure, respectively.

Household pesticide exposures

We previously created a measure of household pesticide use frequency,[16] identifying main active ingredients of reported home and garden use pesticide products from the CDPR

product label database in the manner described for occupational products. We calculated the lifetime average frequency of any household pesticide use (personal application indoors or outdoors in yards, on lawns, or in gardens) prior to index age, considering use at or above the median value in exposed controls 'frequent use' and use below the median 'never/ infrequent use'.

Statistical analyses

We calculated odds ratios (OR) and 95% confidence intervals (CI) using unconditional logistic regression for ever occupational use of any pesticide, pesticide use types (i.e., fungicides/insecticides/herbicides/ other pesticides), and exposure to specific chemicals and classes. To allow for comparison to prior studies on occupational pesticide exposures, we used a reference group of never occupational pesticide users throughout, which included participants with other sources of pesticide exposures (i.e., frequent household pesticide use and/or ambient pesticide exposures). We report on chemicals and chemical classes with at least 5 exposed cases and 5 exposed controls for analyses and specifically examined carbamates, OPs, and OCs. We conducted analyses of self-reported duration of work with pesticides in years, examining those with 1) >0 and ≤ 10 years and 2) >10 years of work with pesticides, and calculating a p-trend based on the median of each category. We also analyzed household pesticide use frequency, ambient residential and workplace exposures to pesticides, PPE use (yes/no, type of PPE used, frequency of PPE use), and job tasks of mixing, loading, or applying pesticides at work.

We adjusted analyses for sex, smoking (ever/never), age at index date (continuous), education (<12 years, 12 years, and >12 years), and race (white/non-white). In separate sensitivity analyses, we additionally adjusted for PD family history (yes/no), MMSE scores, other farming related exposures (includes regular, i.e., once a week or more, work with metals, wood, chemical solvents, or paint strippers), estimated associations for males only, excluded controls who were interviewed later than cases (i.e., between 2009-2011), excluded the 62 controls from an unknown base population, and excluded participants with low MMSE scores (less than 27).

We used two methods to address co-exposures of different types of pesticides from various exposure sources. First, when estimating the effect of occupational pesticide use we adjusted for other sources of pesticide exposure (frequent household use, ambient workplace, ambient residential) or mutually adjusted for occupational use (yes/no) of other types of pesticides (i.e., OPs, OCs, DTCs, paraquat, rotenone, carbamates, triflumizole, captan, and propargite, pesticides for which we have previously seen associations of ambient exposures or frequent household use with PD[10, 11, 16]). Second, we created different exposure categories combining different pesticide exposure measures. Participants in the reference category for this analysis 1) did not use pesticides occupationally, 2) were unexposed to ambient residential and workplace OP, OC, DTC pesticides and paraquat (i.e., exposed below the median of exposed controls), and 3) were never/infrequent users of household pesticides. Of note, this reference group includes individuals with some pesticide exposures i.e., low ambient exposures to pesticides at workplaces or residences or low household pesticide exposures from infrequent use. All analyses were conducted in SAS version 9.3.

Results

The majority of our participants were older than 60 years of age and of European ancestry. Cases were more often male, less educated than controls, and more likely to be never smokers than controls (Table 1). Participants using pesticides for occupational purposes were almost exclusively men (86.7%; versus 13.3% women).

We found frequent household pesticide use, ambient residential exposure to pesticides, and ambient workplace exposure to pesticides each to be associated with PD, increasing PD risk between 46 to 68%. Those ever occupationally using any pesticides, fungicides, insecticides, and herbicides had 29 to 89% increased risk for PD (Table 2). On average, cases used pesticides longer than controls, and most effect estimates were much larger for those having used pesticides for more than 10 years. Adjusting for other sources of pesticide exposure (i.e., frequent household use, ambient residential and ambient workplace) attenuated our estimates. Concerning pesticide groups, we estimated the strongest association for use of carbamates (OR=3.45, 95% CI: 1.19, 10.02).

Active occupational users who also reported using PPE were at increased risk, especially those using gloves, while our data suggested a smaller risk increase for ever pesticide users without PPE, and the highest OR for those always using PPE (Table 3). We also saw a positive association for the job tasks of mixing and loading pesticides (OR=1.62, 95% CI: 1.00, 2.60).

When we conducted analyses combining different sources of pesticide exposure, we found ORs for PD to be elevated for all categories of occupational pesticide use compared with the reference including never pesticide users having likely low exposures from ambient and household use pesticides (Table 4).

In sensitivity analyses additionally adjusting for PD family history, MMSE scores, or other farming related exposures results did not change. Associations were also similar when we excluded females, controls who were interviewed later than cases, and some controls from an unknown base population.

Discussion and Conclusions

Our findings for occupational pesticide use are in agreement with earlier studies showing an increase in PD risk and our own studies of increased PD risk with ambient workplace exposures to OP pesticides, dieldrin, and benomyl.[10] Our results are also consistent with expectations in terms of duration of exposure such that longer years of use were associated with higher risk, and the highest risks were estimated for job activities (mixing/loading) known to result in particularly high exposures.[17] Interestingly, those who reported PPE use, especially always use of PPE and use of gloves, were at highest risk of PD, possibly because these farm workers felt compelled to use PPE when handling toxic pesticides; however, the types of PPEs they used failed to protect them adequately. Different from previous studies, we also adjust our estimates for all other sources of pesticide exposure in addition to all major confounders.

Toxicologic studies in animals, cells, and *in vitro* experiments with pesticides provided evidence of neurotoxicity in support of the hypothesis that pesticides are involved in PD pathogenesis. Mechanisms by which pesticides may be related to PD pathogenesis include oxidative stress and inhibition of mitochondrial complex I.[18] Pesticides, including rotenone, DDT, 2,4-dichlorophenoxyacetic acid (2,4-D), dieldrin, diethyldithiocarbamate, paraquat, maneb, trifluralin, parathion, and imidazoldinethione, were found to accelerate the formation of α-synuclein fibrils *in vitro*,[19] and mice exposed to paraquat had increases in brain levels of α-synuclein and α-synuclein containing aggregates in the substantia nigra pars compacta.[20] Lab and epidemiologic studies from our group show that benomyl inhibits aldehyde dehydrogenase, which detoxifies the dopamine metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL), in mesencephalic rat neurons and inhibits the ubiquitin-proteasome system in SK-N-MC^{u} neuroblastoma cells.[10]

Previously, ten cohort studies – six occupational - examined associations between PD and occupational pesticide exposures or work in occupations involving pesticide exposures,[3, 6, 8, 21-27] and reported relative risk estimates ranging from 0.66 to 5.6. However, since PD is a rare event in all but very large cohorts, these studies relied on as few as 1 and a maximum of 134 exposed incident PD cases. Exposure assessment in these studies was based on self-report, broad occupational categories listed in national databases, and few used employee records[21, 26] or job-exposure matrices.[3, 6] The Agricultural Health Study[8] and a French (PAQUID) study[3] performed the most detailed exposure assessments, but still only had 68 and 8 exposed PD cases available for analysis, respectively. Some studies collected exposure information only once at baseline, possibly ignoring long periods of exposure during follow-up and prior to diagnosis that might be relevant.[6, 22, 23, 27] Case control studies enrolling larger numbers of PD cases might have higher diagnostic accuracy if patients are examined by experts, but many were small (<200 cases) and included prevalent cases with long (>5 years) or unspecified disease duration.[2, 5, 7, 28-38] Few included incident cases,[5, 39] raising concerns about survivor bias, differential recall due to cognitive impairment in prevalent cases, and temporal ambiguity.

Strengths of our California case control study are that it is to date among the largest in terms of the prevalence of occupational pesticide use among PD cases (21%) and that we enrolled incident PD cases diagnosed by UCLA movement disorder specialists and re-evaluated most patients at multiple follow-up occasions, limiting misclassification of disease status. Our study is one of few that evaluated risk of PD from exposure to specific pesticides and also duration and intensity/type of exposure, only the second study of occupational pesticide use which assessed use of personal protective equipment, and the first that controlled for other sources of pesticide exposures in residents of largely agricultural counties in which few can be considered completely unexposed. We had to rely on recall for our exposure assessment, which allows for non-differential misclassification bias as well as differential recall bias. Restricting analyses to subjects with high cognitive scores (i.e., MMSE) indicated that our results were not greatly affected by impaired cognition. Since participants often do not know or remember what active ingredients the product they used contained, we compared reported pesticide brand names, purposes, and dates of use with information in the CDPR database to identify the main active pesticide ingredients in reported pesticide products. We did not account for other active ingredients, which may change often and are therefore difficult to

identify, nor did we have information on inert ingredients in pesticide products. Another possible limitation is that our results may be impacted by selection bias if occupational pesticide use were related to participation in our study, since a larger proportion of eligible cases compared with controls participated in our study.

Furthermore, we collected detailed information about PPE use during occupational work with pesticides. Findings from the Agricultural Health Study (AHS)[8] and the Farming and Movement Evaluation (FAME) case-control study nested within the AHS cohort[40] suggested that PPE use in pesticide applicators may reduce PD risk and that protective glove use (chemically resistant rubber gloves, plastic gloves, and rubber gloves) more than 50% of the time while mixing and applying pesticides reduced PD risk from use of paraquat and permethrin. A family-based case-control study found PPE use to not alter associations between pesticide use at home and work and PD.[41] Our results suggest that PPE use, especially glove use, did not protect against risk but rather may even be a surrogate marker for the use of more toxic pesticides or, alternatively, the PPEs they used did not protect from exposure to the agents handled. Indeed, most of our study participants did not report using highly protective PPE (e.g., respirators, chemically resistant rubber gloves). We may have seen elevated PD risks in glove users since many did not report using chemically resistant gloves and may have used gloves inadequate for protection from exposure. We did not collect information on whether the gloves used were clean and in good condition. Additional research targeting PPEs when assessing health risks from chronic pesticide exposures is needed.

Our subjects reported occupational use of 149 different pesticides, with 42% and 40% of exposed cases and controls, respectively, reporting use of more than one pesticide up to a maximum of 29 different pesticides, limiting our ability to estimate effects for single pesticide exposures of interest for PD based on animal, cell, or previous human data. Of cases and controls who reported occupational pesticide use, 35% of cases and 25% of controls did not recall the specific products used. Chemicals that our participants commonly used include DDT, 2,4-D, malathion, and glyphosate, but these have not been previously linked to PD. Our difficulty in interpreting results as pesticide specific is due to co-exposure to multiple pesticides applied simultaneously or sequentially by study participants. When we mutually adjusted for occupational use of other pesticides we previously identified as relevant for PD, estimates for occupational carbamate use remained elevated, but confidence intervals widened (OR=4.46, 95% CI: 0.66, 30.25). Importantly, in our reference group of never occupational pesticide users, a majority were exposed to other sources of pesticides including household and gardening pesticides or ambient exposures at residences or workplaces from agricultural applications in these counties. Of note, in additional analyses we created an alternate reference group accounting for multiple exposure sources and found even more strongly increased risks with occupational use of carbamates, organochlorines, and organophosphorus pesticides (Table 4).

In this population based study of incident PD, we found evidence of increased PD risk with occupational pesticide use, increasing years of pesticide use, and job tasks resulting in the highest exposures to pesticides such as mixing and loading pesticides. We also found some evidence for specific pesticide groups including carbamates, OPs, and OCs. Finally, personal

protective equipment use did not result in reduced PD risk from pesticide exposures at the workplace, and our findings suggest that the equipment, especially gloves, did not protect the applicators sufficiently.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge our study participants and Dr. Myles Cockburn at the University of Southern California for assisting us with our GIS pesticide exposure assessments. This manuscript is based on work published as part of SN's dissertation, referenced directly below, which is available in ProQuest.

Narayan, Shilpa. “An Investigation into Household and Occupational Pesticide Exposures with Genetic Variants as Risk Factors for Parkinson's Disease.” Order No. 3680243 University of California, Los Angeles, 2015. Ann Arbor: ProQuest. Web.

Funding: This work was supported by the National Institute of Environmental Health Sciences [ES10544, P01ES016732, U54ES12078, 5P30 ES07048] and pilot funding received from the American Parkinson Disease Association. The funding organizations had no role in the study design, data collection, data analysis, interpretation, writing of the report, or the decision to submit the paper for publication.

References

1. Brown TP, Rumsby PC, Capleton AC, et al. Pesticides and Parkinson's disease--is there a link? Environ Health Perspect. 2006; 114(2):156–64. [PubMed: 16451848]
2. Baldi I, Cantagrel A, Lebailly P, et al. Association between Parkinson's disease and exposure to pesticides in southwestern France. Neuroepidemiology. 2003; 22(5):305–10. [published Online First: 8 August 2003]. DOI: 10.1159/000071194 [PubMed: 12902626]
3. Baldi I, Lebailly P, Mohammed-Brahim B, et al. Neurodegenerative diseases and exposure to pesticides in the elderly. Am J Epidemiol. 2003; 157(5):409–14. DOI: 10.1093/aje/kwf216 [PubMed: 12615605]
4. Liew Z, Wang A, Bronstein J, et al. Job exposure matrix (JEM)-derived estimates of lifetime occupational pesticide exposure and the risk of Parkinson's disease. Arch Environ Occup Health. 2014; 69(4):241–51. [published Online First: 18 Mar 2013]. DOI: 10.1080/19338244.2013.778808 [PubMed: 24499252]
5. Elbaz A, Clavel J, Rathouz PJ, et al. Professional exposure to pesticides and Parkinson disease. Ann Neurol. 2009; 66(4):494–504. [published Online First: 13 Apr 2009]. DOI: 10.1002/ana.21717 [PubMed: 19847896]
6. Feldman AL, Johansson AL, Nise G, et al. Occupational exposure in parkinsonian disorders: a 43-year prospective cohort study in men. Parkinsonism Relat Disord. 2011; 17(9):677–82. [published Online First: 5 Jul 2011]. DOI: 10.1016/j.parkreldis.2011.06.009 [PubMed: 21733735]
7. van der Mark M, Vermeulen R, Nijssen PC, et al. Occupational exposure to pesticides and endotoxin and Parkinson disease in the Netherlands. Occup Environ Med. 2014; 71(11):757–64. [published Online First: 7 Aug 2014]. DOI: 10.1136/oemed-2014-102170 [PubMed: 25104429]
8. Kamel F, Tanner C, Umbach D, et al. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am J Epidemiol. 2007; 165(4):364–74. [published Online First: 20 Nov 2006]. DOI: 10.1093/aje/kwk024 [PubMed: 17116648]
9. Kang GA, Bronstein JM, Masterman DL, et al. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord. 2005; 20(9):1133–42. [published Online First: 13 Jun 2005]. DOI: 10.1002/mds.20513 [PubMed: 15954133]
10. Ritz BR, Paul KC, Bronstein JM. Of Pesticides and Men: a California Story of Genes and Environment in Parkinson's Disease. Curr Environ Health Rep. 2016; 3(1):40–52. [published Online First: 9 Feb 2016]. DOI: 10.1007/s40572-016-0083-2 [PubMed: 26857251]

11. Wang A, Costello S, Cockburn M, et al. Parkinson's disease risk from ambient exposure to pesticides. Eur J Epidemiol. 2011; 26(7):547–55. [published Online First: 20 Apr 2011]. DOI: 10.1007/s10654-011-9574-5 [PubMed: 21505849]
12. Newkirk LA, Kim JM, Thompson JM, et al. Validation of a 26-point telephone version of the Mini-Mental State Examination. J Geriatr Psychiatry Neurol. 2004; 17(2):81–7. DOI: 10.1177/0891988704264534 [PubMed: 15157348]
13. California Department of Pesticide Regulation. [dates accessed 13 August 2010, 12 December 2012] California Department of Pesticide Regulation Product/Label Database. 2013. Available from: http://www.cdpr.ca.gov/docs/label/prodnam.htm
14. Kegley, SE., Hill, BR., Orme, S., Choi, AH. Pesticide Action Network; North America: PAN Pesticide Database - Chemicals 2000-2014. updated June 2014Available from: www.pesticideinfo.org/Search_Chemicals.jsp [dates accessed 3 November 2010, 12 December 2012]
15. Wood, A. [date accessed 2012 December 12] Compendium of Pesticide Common Names 1995-2016. updated 2014Available from: http://www.alanwood.net/pesticides/
16. Narayan S, Liew Z, Paul K, et al. Household organophosphorus pesticide use and Parkinson's disease. Int J Epidemiol. 2013; 42(5):1476–85. [published Online First: 20 Sep 2013]. DOI: 10.1093/ije/dyt170 [PubMed: 24057998]
17. Rutz R, Krieger RI. Exposure to pesticide mixer/loaders and applicators in California. Rev Environ Contam Toxicol. 1992; 129:121–39. [PubMed: 1410692]
18. Sherer TB, Betarbet R, Greenamyre JT. Environment, mitochondria, and Parkinson's disease. Neuroscientist. 2002; 8(3):192–7. DOI: 10.1177/1073858402008003004 [PubMed: 12061498]
19. Uversky VN, Li J, Bower K, et al. Synergistic effects of pesticides and metals on the fibrillation of alpha-synuclein: implications for Parkinson's disease. Neurotoxicology. 2002; 23(4-5):527–36. [published Online First: 9 October 2002]. DOI: 10.1016/S0161-813X(02)00067-0 [PubMed: 12428725]
20. Manning-Bog AB, McCormack AL, Li J, et al. The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. J Biol Chem. 2002; 277(3): 1641–4. [published Online First: 13 Nov 2001]. DOI: 10.1074/jbc.C100560200 [PubMed: 11707429]
21. Wastensson G, Hagberg S, Andersson E, et al. Parkinson's disease in diphenyl-exposed workers--a causal association? Parkinsonism Relat Disord. 2006; 12(1):29–34. [published Online First: 26 Oct 2005]. DOI: 10.1016/j.parkreldis.2005.06.010 [PubMed: 16256410]
22. Ascherio A, Chen H, Weisskopf MG, et al. Pesticide exposure and risk for Parkinson's disease. Ann Neurol. 2006; 60(2):197–203. [published Online First: 26 Jun 2006]. DOI: 10.1002/ana.20904 [PubMed: 16802290]
23. Petrovitch H, Ross GW, Abbott RD, et al. Plantation work and risk of Parkinson disease in a population-based longitudinal study. Arch Neurol. 2002; 59(11):1787–92. DOI: 10.1001/archneur.59.11.1787 [PubMed: 12433267]
24. Hofmann J, Guardado J, Keifer M, et al. Mortality among a cohort of banana plantation workers in Costa Rica. Int J Occup Environ Health. 2006; 12(4):321–8. [published Online First: 19 Jul 2013]. DOI: 10.1179/oeh.2006.12.4.321 [PubMed: 17168219]
25. Kenborg L, Lassen CF, Lander F, et al. Parkinson's disease among gardeners exposed to pesticides--a Danish cohort study. Scand J Work Environ Health. 2012; 38(1):65–9. [published Online First: 17 Jun 2011]. DOI: 10.5271/sjweh.3176 [PubMed: 21687921]
26. Tomenson JA, Campbell C. Mortality from Parkinson's disease and other causes among a workforce manufacturing paraquat: a retrospective cohort study. BMJ Open. 2011; 1(2):e000283.doi: 10.1136/bmjopen-2011-000283
27. Tuchsen F, Jensen AA. Agricultural work and the risk of Parkinson's disease in Denmark, 1981-1993. Scand J Work Environ Health. 2000; 26(4):359–62. DOI: 10.5271/sjweh.554 [PubMed: 10994803]
28. Koller W, Vetere-Overfield B, Gray C, et al. Environmental risk factors in Parkinson's disease. Neurology. 1990; 40(8):1218–21. [PubMed: 2381528]

29. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology. 1992; 42(7):1328–35. [PubMed: 1620342]

30. Hertzman C, Wiens M, Snow B, et al. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Mov Disord. 1994; 9(1):69–75. [published Online First: 12 Oct 2004]. DOI: 10.1002/mds.870090111 [PubMed: 8139607]

31. Chan DK, Woo J, Ho SC, et al. Genetic and environmental risk factors for Parkinson's disease in a Chinese population. J Neurol Neurosurg Psychiatry. 1998; 65(5):781–4. DOI: 10.1136/jnnp.65.5.781 [PubMed: 9810958]

32. McCann SJ, LeCouteur DG, Green AC, et al. The epidemiology of Parkinson's disease in an Australian population. Neuroepidemiology. 1998; 17(6):310–7. [PubMed: 9778597]

33. Fall PA, Fredrikson M, Axelson O, et al. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Mov Disord. 1999; 14(1):28–37. [PubMed: 9918341]

34. Baldereschi M, Di Carlo A, Vanni P, et al. Lifestyle-related risk factors for Parkinson's disease: a population-based study. Acta Neurol Scand. 2003; 108(4):239–44. [published Online First: 28 Aug 2003]. DOI: 10.1034/j.1600-0404.2003.00128.x [PubMed: 12956856]

35. Fong CS, Wu RM, Shieh JC, et al. Pesticide exposure on southwestern Taiwanese with MnSOD and NQO1 polymorphisms is associated with increased risk of Parkinson's disease. Clin Chim Acta. 2007; 378(1-2):136–41. [published Online First: 17 Nov 2006]. DOI: 10.1016/j.cca.2006.11.006 [PubMed: 17188257]

36. Petersen MS, Halling J, Bech S, et al. Impact of dietary exposure to food contaminants on the risk of Parkinson's disease. Neurotoxicology. 2008; 29(4):584–90. [published Online First: 14 Mar 2008]. DOI: 10.1016/j.neuro.2008.03.001 [PubMed: 18455239]

37. Gorell JM, Johnson CC, Rybicki BA, et al. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology. 1998; 50(5):1346–50. [PubMed: 9595985]

38. Kuopio AM, Marttila RJ, Helenius H, et al. Environmental risk factors in Parkinson's disease. Mov Disord. 1999; 14(6):928–39. [PubMed: 10584666]

39. Firestone JA, Lundin JI, Powers KM, et al. Occupational factors and risk of Parkinson's disease: A population-based case-control study. Am J Ind Med. 2010; 53(3):217–23. [published Online First: 18 Dec 2009]. DOI: 10.1002/ajim.20788 [PubMed: 20025075]

40. Furlong M, Tanner CM, Goldman SM, et al. Protective glove use and hygiene habits modify the associations of specific pesticides with Parkinson's disease. Environ Int. 2015; 75:144–50. [published Online First: 21 Nov 2014]. DOI: 10.1016/j.envint.2014.11.002 [PubMed: 25461423]

41. Hancock DB, Martin ER, Mayhew GM, et al. Pesticide exposure and risk of Parkinson's disease: a family-based case-control study. BMC Neurol. 2008; 8:6.doi: 10.1186/1471-2377-8-6 [PubMed: 18373838]

Table 1

Characteristics of participants

	Cases (360) n (%)	Controls (827) n (%)
Age		
mean (SD)	68.3 (10.2)	66 (11.7)
<=60 years	76 (21.1)	264 (31.9)
>60 years	284 (78.9)	563 (68.1)
range	34-88	35-99
Sex		
Male	206 (57.2)	382 (46.2)
Female	154 (42.8)	445 (53.8)
Race[a]		
White	290 (80.6)	569 (68.8)
Black	3 (0.83)	28 (3.4)
Latino	47 (13.1)	160 (19.4)
Asian	4 (1.1)	25 (3)
Native American	16 (4.4)	43 (5.2)
Education		
<12 years	67 (18.6)	123 (14.9)
12 years	96 (26.7)	172 (20.8)
>12 years	197 (54.7)	532 (64.3)
Family History of PD		
positive	53 (14.7)	65 (7.9)
negative	307 (85.3)	762 (92.1)
Smoking Status		
Never	188 (52.2)	400 (48.4)
Former	152 (42.2)	333 (40.3)
Current	20 (5.6)	94 (11.4)

[a]There were 2 controls for whom we were missing information on race.

Table 2

OR (95% CI) for self-reported household pesticide use, ambient residential pesticide exposure, ambient workplace pesticide exposure, self-reported occupational pesticide use, years of use, and PD risk

	Cases (360) n (%)	Controls (827) n (%)	Unadjusted OR	Adjusted[a] OR (95%CI)	Adjusted[b] OR (95%CI)
Household Pesticide Use[c]					
Never/Infrequent Users	196 (54.4)	502 (60.7)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Frequent Users	161 (44.7)	302 (36.5)	1.37	1.46 (1.13, 1.91)	-
Ambient Residential Exposure to Pesticides[d]					
exposed below the median	102 (28.3)	312 (37.7)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
exposed at or above the median	258 (71.7)	508 (61.4)	1.55	1.56 (1.18, 2.05)	-
Ambient Workplace Exposure to Pesticides[d]					
exposed below the median	130 (36.1)	394 (47.6)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
exposed at or above the median	230 (63.9)	426 (51.5)	1.64	1.68 (1.29, 2.19)	-
Analyses of self-reported occupational pesticide use and years of use					
No Occupational Pesticide Use[e]	279 (77.5)	700 (84.6)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Occupational Pesticide Users[f]					
Any Pesticides					
Ever Use	74 (20.6)	114 (13.8)	1.63	1.50 (1.05, 2.14)	1.36 (0.95, 1.95)
Duration of use in years					
Mean (SD)	18.2 (15.4)	13.0 (13.2)	-	-	-
>0 and ≤ 10	29 (8.1)	55 (6.7)	1.32	1.27 (0.77, 2.09)	1.22 (0.74, 2.02)
> 10	35 (9.7)	40 (4.8)	2.20	1.98 (1.20, 3.28)	1.69 (1.01, 2.83)
p-trend[g]			*0.0009*	*0.0073*	*0.0426*
Pesticide Product Types[h]					
Fungicides					
Ever Use	31 (8.6)	39 (4.7)	2.00	1.89 (1.12, 3.19)	1.62 (0.95, 2.76)
Duration of use in years					
>0 and ≤ 10	14 (3.9)	18 (2.2)	1.95	1.97 (0.93, 4.17)	1.86 (0.87, 3.95)
> 10	13 (3.6)	16 (1.9)	2.04	1.82 (0.83, 3.97)	1.46 (0.66, 3.23)

	Cases (360)	Controls (827)	Unadjusted	Adjusted[a]	Adjusted[b]
	n (%)	n (%)	OR	OR (95%CI)	OR (95%CI)
p-trend[g]			*0.0363*	*0.0969*	*0.2776*
Insecticides					
Ever Use	51 (14.2)	87 (10.5)	1.47	1.29 (0.87, 1.94)	1.15 (0.76, 1.74)
Duration of use in years					
>0 and ≤ 10	20 (5.6)	41 (5.0)	1.22	1.12 (0.62, 1.99)	1.05 (0.58, 1.90)
> 10	23 (6.4)	29 (3.5)	1.99	1.71 (0.94, 3.10)	1.45 (0.79, 2.65)
p-trend[g]			*0.0146*	*0.0771*	*0.2315*
Herbicides					
Ever Use	41 (11.4)	60 (7.3)	1.72	1.51 (0.96, 2.36)	1.34 (0.84, 2.12)
Duration of use in years					
>0 and ≤ 10	8 (2.2)	31 (3.8)	0.65	0.65 (0.29, 1. 46)	0.59 (0.26, 1.35)
> 10	26 (7.2)	22 (2.7)	2.97	2.41 (1.31, 4.44)	2.07 (1.12, 3.85)
p-trend[g]			*0.0005*	*0.0070*	*0.0290*
Other Pesticides (rodenticides,defoliants,etc)					
Ever Use	20 (5.6)	37 (4.5)	1.36	1.37 (0.76, 2.47)	1.27 (0.70, 2.33)
Duration of use in years					
>0 and ≤ 10	6 (1.7)	18 (2.2)	0.84	0.98 (0.37, 2.59)	1.01 (0.38, 2.69)
> 10	9 (2.5)	8 (1.0)	2.82	2.60 (0.95, 7.12)	2.05 (0.74, 5.69)
p-trend[g]			*0.0536*	*0.0764*	*0.1829*

[a]Adjusted for sex, smoking(ever/never), age(continuous), education(<12 years, 12 years, and >12 years), race(white/non-white).

[b]Adjusted for sex, smoking(ever/never), age(continuous), education(<12 years, 12 years, and >12 years), race(white/non-white), household pesticide use frequency (frequent vs never/infrequent), and ambient residential and work address pesticide exposures.

[c]In this particular analysis only, the household pesticide use variable is lagged 10 years, i.e., it is defined based on the median value of the lifetime average frequency of any household pesticide use (personal application indoors or outdoors in yards, on lawns, or in gardens) prior to 10 years before the index age, considering use at or above the median value in exposed controls 'frequent use' and use below the median 'never/infrequent use'. We excluded 3 cases and 23 controls missing information on household pesticide use from analyses.

[d]Reference category includes those unexposed to any OP pesticides, organochlorines, dithiocarbamates, and paraquat at or above the median value in exposed controls over the 26 year period. Those considered exposed, had exposure at or above the median value in exposed controls. We excluded 7 controls missing information on ambient residential and workplace exposures to pesticides from analyses.

[e]Reference group for all comparisons. Reference group is composed of self-reported never users of pesticides occupationally. These participants may have other pesticide exposures (such as frequent household pesticide use, ambient residential, and/or ambient workplace pesticide exposures).

[f] We excluded 7 cases and 13 controls missing information on occupational pesticide use from analyses.

[g] Based on median of each category.

[h] Note that participants may be counted in multiple sub-categories (e.g., fungicides, insecticides, herbicides, other pesticides) of pesticide usage.

Table 3

OR (95% CI) for occupational pesticide use with or without personal protective equipment (PPE[a]) and PD risk

	Cases (360) n (%)	Controls (827) n (%)	Unadjusted OR	Adjusted[b] OR (95%CI)
No Occupational Pesticide Use[c]	279 (77.5)	700 (84.6)	1.00 (Ref)	1.00 (Ref)
Occupational Pesticide Users				
Used any PPE				
No	28 (7.8)	49 (5.9)	1.43	1.33 (0.80, 2.20)
Yes	46 (12.8)	65 (7.9)	1.78	1.64 (1.06, 2.53)
Used Specific Types of PPE				
Gloves				
No	34 (9.4)	61 (7.4)	1.40	1.25 (0.78, 1.99)
Yes	40 (11.1)	53 (6.4)	1.89	1.82 (1.14, 2.90)
Mask				
No	43 (11.9)	68 (8.2)	1.59	1.54 (1.00, 2.37)
Yes	31 (8.6)	46 (5.6)	1.69	1.45 (0.87, 2.41)
Coveralls				
No	50 (13.9)	77 (9.3)	1.63	1.51 (1.01, 2.27)
Yes	24 (6.7)	37 (4.5)	1.63	1.48 (0.84, 2.62)
Tractor with Enclosed Cab				
No	66 (18.3)	104 (12.6)	1.59	1.51 (1.05, 2.18)
Yes	8 (2.2)	10 (1.2)	2.01	1.42 (0.53, 3.77)
PPE use frequency[d]				
Never	28 (7.8)	49 (5.9)	1.43	1.33 (0.80, 2.21)
Sometimes	23 (6.4)	39 (4.7)	1.48	1.40 (0.79, 2.45)
Always	20 (5.6)	21 (2.5)	2.39	2.21 (1.14, 4.30)

[a] PPE includes gloves, masks, coveralls, applying pesticides in an enclosed cab, and other sorts of protection, such as boots, goggles, etc. For 14 participants who used pesticides, information on PPE use was not available, and we assigned them to the no PPE category; another 9 participants with partially missing information on PPE use were also assigned to the no PPE category as they reported no use.

[b] Adjusted for sex, smoking(ever/never), age(continuous), education(<12 years, 12 years, and >12 years), race(white/non-white).

[c] Reference group for all comparisons. Reference group is composed of self-reported never users of pesticides occupationally. These participants may have other pesticide exposures (such as frequent household pesticide use, ambient residential, and/or ambient workplace pesticide exposures).

[d] The PPE use frequency does not incorporate information on use of a tractor with an enclosed cab, since we did not collect frequency of tractor use. However, only 1 case and 1 control used a tractor with enclosed cab and no other PPE. Also, 2 cases and 4 controls reported using PPE other than a tractor with enclosed cab, but did not provide a frequency of PPE use.

Table 4

OR (95% CI) for self-reported occupational pesticide use and PD risk. Analyses combine multiple sources of pesticide exposure

	Cases (360) n (%)	Controls (827) n (%)	Unadjusted OR	Adjusted[a] OR (95%CI)
Low exposure to pesticides[b]	34 (9.4)	134 (16.2)	1.00 (Ref)	1.00 (Ref)
Exposure to other pesticide sources[c]	250 (69.4)	563 (68.1)	1.75	1.89 (1.25, 2.87)
Occupational Pesticide Users				
Any Pesticide Use	74 (20.6)	114 (13.8)	2.56	2.50 (1.50, 4.15)
Pesticide Product Types[d]				
Fungicide Use	31 (8.6)	39 (4.7)	3.13	3.11 (1.65, 5.88)
Insecticide Use	51 (14.2)	87 (10.5)	2.31	2.10 (1.22, 3.60)
Herbicide Use	41 (11.4)	60 (7.3)	2.69	2.45 (1.37, 4.36)
Other Pesticide Use (rodenticides,defoliants,etc)	20 (5.6)	37 (4.47)	2.13	2.22 (1.11, 4.44)
Chemical Class of Main Active Ingredients				
Carbamate Use	10 (2.8)	6 (0.7)	6.57	5.55 (1.81, 17.04)
Organochlorine Use	10 (2.8)	17 (2.1)	2.32	1.97 (0.81, 4.82)
Organophosphorus Use	16 (4.4)	31 (3.8)	2.03	1.92 (0.92, 4.04)

[a] Adjusted for sex, smoking(ever/never), age(continuous), education(<12 years, 12 years, and >12 years), race(white/non-white).

[b] Reference group for all comparisons. Reference category participants have low exposure to ambient residential and ambient workplace pesticides (OPs, OCs, DTCs, & paraquat; i.e., exposed below the median of exposed controls), are never/infrequent users of household pesticides, and did not use pesticides occupationally. We excluded 2 cases and 16 controls from analyses who could not be assigned to an exposure category due to missing information on occupational pesticide use, household pesticide use, exposure to ambient residential pesticides, and/or exposure to ambient workplace pesticides.

[c] These participants did not self-report occupational pesticide use but were exposed to pesticides based on other measures of pesticide exposure (frequent household pesticide use, ambient residential, and/or ambient workplace pesticide exposures).

[d] Note that participants may be counted in multiple sub-categories (e.g., fungicides, insecticides, herbicides, other pesticides, carbamates, organochlorines, organophosphorus pesticides) of pesticide usage.