

# Parkinson's disease mortality and pesticide exposure in California 1984–1994

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<b>Background</b>	In the last two decades reports from different countries emerged associating pesticide and herbicide use with Parkinson's disease (PD). California growers use approximately 250 million pounds of pesticides annually, about a quarter of all pesticides used in the US.
<b>Methods</b>	We employed a proportional odds mortality design to compare all cases of PD recorded as underlying (1984–1994) or associated causes (1984–1993) of death occurring in California with all deaths from ischaemic heart disease (ICD-9 410–414) during the same period. Based on pesticide use report data we classified California counties into several pesticide use categories. Agricultural census data allowed us to create measures of percentage of land per county treated with pesticides. Employing logistic regression models we estimated the effect of pesticide use controlling for age, gender, race, birthplace, year of deaths, and education.
<b>Results</b>	Mortality from PD as the underlying cause of death was higher in agricultural pesticide-use counties than in non-use counties. A dose response was observed for insecticide use per county land treated when using 1982 agricultural census data, but not for amounts of restricted pesticides used or length of residency in a country prior to death.
<b>Conclusions</b>	Our data show an increased PD mortality in California counties using agricultural pesticides. Unless all of our measures of county pesticide use are surrogates for other risk factors more prevalent in pesticide use counties, it seems important to target this prevalent exposure in rural California in future studies that use improved case finding mechanisms and collect pesticide exposure data for individuals.
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In the last two decades, case reports and experimental and epidemiological research have accumulated data suggesting that pesticides play a role in the neuro-degenerative process leading to idiopathic Parkinson's disease (PD).<sup>1–15</sup> Agricultural use of modern pesticides has become widespread after World War II.<sup>16</sup> A commonly used herbicide, paraquat, is structurally similar to the neurotoxic chemical MPP+, a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and known to be able to induce parkinsonism. Endo *et al.*<sup>17</sup> demonstrated a long-lasting reduction of catecholamines in the midbrain of mice

after oral treatment with a paraquat-containing herbicide. Other pesticides also have been proposed as potential causative agents for PD and questions about the biological interaction of various pesticides have arisen. For example, some carbamate fungicides are known to enhance the neurotoxicity of MPTP and methamphetamine<sup>18–20</sup> and were also implicated as potential causal agents in a Canadian epidemiological study.<sup>11</sup> Fleming<sup>1</sup> assaying post-mortem brain samples found higher levels of the organochlorine pesticide dieldrin in PD patient's brains.

This issue—whether pesticide use might be causing PD—is of great interest to rural Californian residents, since about a quarter of all pesticides used in the US are applied by Californian growers, approximately 250 million pounds of pesticides annually, of which two-thirds are herbicides (Cal Pesticide use reporting system). Ames *et al.*<sup>21</sup> reported that about 10 000 workers apply agricultural pesticides in California for some portion of the year and in 1985 more than 2000 applicators required medical supervision of their blood cholinesterase levels. Thus, we conducted a proportionate odds mortality study to examine whether there

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is any indication that PD in California could be associated with living in counties in which large amounts of agricultural pesticides are applied. Our analyses are solely based on three statewide record systems: (1) mortality records; (2) the California pesticide use registry data; and (3) data obtained from the agricultural census.

## Materials and Methods

### Study subjects

Employing California Vital Statistics division computerized records we identified 7516 cases of PD (ICD-9 332) reported as underlying cause of death that occurred between 1984 and 1994 and 15 222 cases reported as associated cause between 1984 and 1993 (the associated cause of death data was not available for 1994). Furthermore, we selected as controls 498 461 individuals who died between 1984 and 1994 from ischaemic heart disease (IHD) (ICD-9 410–414), a disease that has not been associated with pesticide exposure. Cases listed with IHD as the underlying cause of death who, in addition, had PD mentioned as an associated cause of death were excluded from the control series ( $N = 4392$ ). Note that these cases contributed to the associated cause of death PD category.

### Exposure assessment

Since the early 1970s, California farmers have been required to report the application of restricted pesticides to a pesticide registry. Annual published reports from this system were used previously by Schwartz and LoGerfo,<sup>22</sup> in a study of birth defects, to rank California counties according to the total amounts of restricted pesticides used countywide in 1983. Ranking counties according to countywide per square mile use of restricted pesticides in farming activities (excluding residential and industrial uses), these authors classified 15 counties as high, 9 counties as moderate, 7 as low, and 14 as non- or minimal users of agricultural pesticides, but they omitted 13 counties with very low population density. Employing published CA-pesticide-use reports for 1972–1990 we conferred with this relative ranking of CA-counties for 1983 and, in addition, concluded that these ranks remained stable over the period 1972–1990 (Figure 1). Thus, we used the Schwartz and LoGerfo<sup>22</sup> ranking and added 13 counties previously unranked to the four pesticide-use categories based on the same pesticide-use report data (San Benito and Tehama qualified as low, Glenn as moderate use and all others as non-use counties).

Secondly, we employed the 1982 agricultural census data for California to create the following exposure measures: percentage

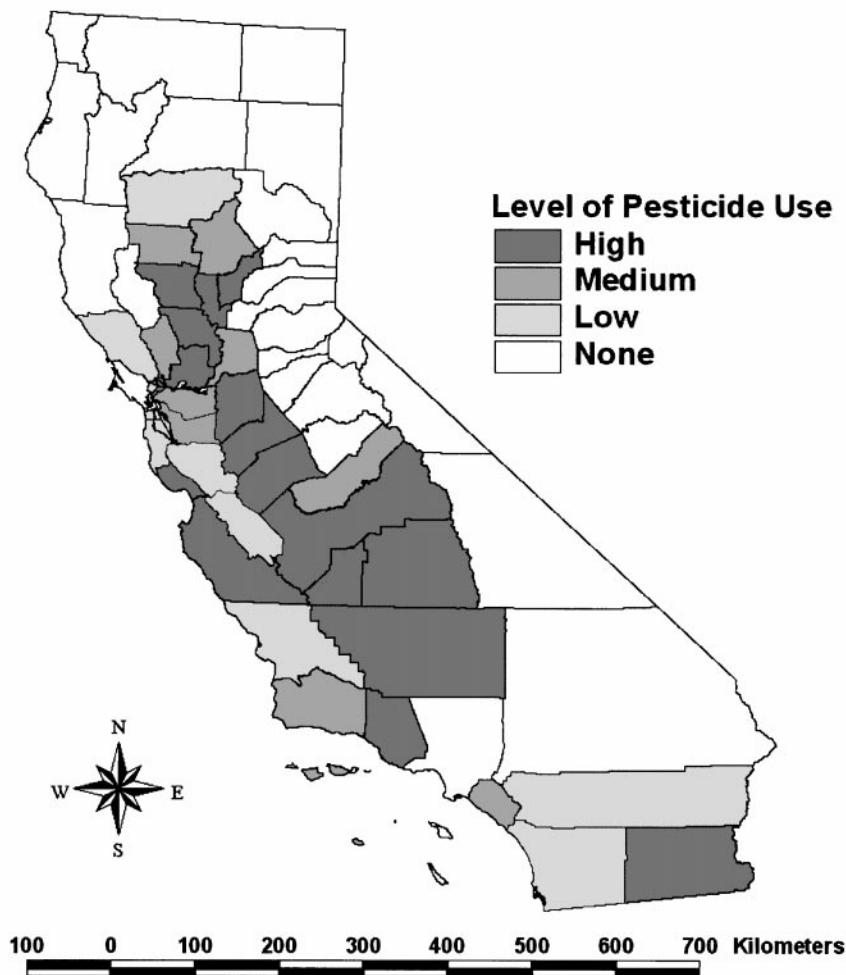


Figure 1 Pesticide use in California by county

of land in each county on which sprays, dusts, granules, and fumigants were applied to control insects, weeds, nematodes, growth and plant diseases, and the percentage of land on which fertilizers were applied. We also compared the 1982 agricultural census data with the successive censuses administered in 1987 and 1992 and found that these measures were highly correlated over time.

**Statistical analyses**

Logistic regression analysis, recommended for the analysis of proportional odds mortality studies,<sup>23,24</sup> was used to estimate odds ratios and 95% CI for crude and adjusted countywide pesticide use related PD mortality. Breslow *et al.*<sup>25</sup> have shown that—conditional on exposure not causing death from the comparison disease—a prevalence odds ratios (POR) case-control analysis controlling for age and calendar year of death can yield valid estimates of the relative risk (rate ratio) for exposure on death from the disease of interest. This modelling approach allowed us to control for multiple confounding risk factors while estimating the effect of county pesticide use. The computerized death tapes contain information on personal characteristics such as gender, race, age, place of death and birth, year of death, and, starting in 1989, education and duration of living in the county of residence prior to death. In our regression analyses we used these data for the adjustment of the estimates of countywide pesticide use as described above. We furthermore conducted some stratified analyses to examine effect modification by age-at-death, gender, and ethnicity. Lastly, we examined whether chronic diseases for which pesticides are not suspected to be causal show a similar mortality pattern when using county pesticide-use categories or agricultural census reports of pesticide applications. For these comparisons we selected deaths

from multiple sclerosis (ICD-9 340) and all diseases of the intestinal tract (ICD-9 520–577).

**Results**

Californians who died from PD between 1984 and 1994 were on average more often male and slightly older than those who died from ischaemic heart disease. They were also more often of white and less often of African American race, and had attained higher educational levels (Table 1). The educational and gender differences were larger for individuals for whom PD was reported as the underlying cause than for those for whom PD was mentioned as an associated cause only. About 70% of all subjects included in this study had lived in the county of death for >20 years and only 10% for <5 years prior to their death (average duration of residence in the county before death was >30 years).

Mortality from PD mentioned as the underlying cause of death was 19–47% higher in counties reporting the use of restricted agricultural pesticides compared to PD mortality in counties reporting no use of restricted pesticides for agricultural purposes (Table 2). Moreover, adjusting for gender, race, age, place of birth, and education, the prevalence odds ratios (POR) of long-term residents (defined as having lived in the county for >40 years prior to death) for dying from PD (as underlying cause) between 1989 and 1994 in low, moderate, or high restricted pesticide-use counties compared to long-term residents of no agricultural pesticide-use counties were 1.52 (95% CI: 1.35–1.72), 1.49 (95% CI: 1.31–1.69), and 1.49 (95% CI: 1.30–1.71) (Table 3). We observed no dose-response trend with increasing rank for countywide restricted pesticide usage. When we examined PD mentioned on death certificates as an

**Table 1** Demographic characteristics of the study population

	Underlying cause of death Parkinson's disease (ICD-9 332)	Associated cause of death Parkinson's disease (ICD-9 332)	Underlying cause of death ischaemic heart disease (ICD-9 410–414) <sup>a</sup>
	1984–1994	1984–1993	1984–1994
<b>No. of deaths</b>	7516	15 222	498 461
<b>Mean age (years)</b>	79.8	80.9	76.9
<b>Gender</b>			
Female	39.2%	43.1%	48.9%
<b>Ethnicity</b>			
White	94.6%	94.1%	90.4%
African-American	2.4%	2.8%	5.9%
Asian	2.8%	2.8%	2.2%
Other	0.2%	0.1%	1.5%
<b>Born in California</b>	18.5%	15.1%	15.9%
	<b>1989–1994</b>	<b>1989–1993</b>	<b>1989–1994</b>
<b>No. of deaths</b>	4533	7876	262 200
<b>Educational attainment (years)<sup>b</sup></b>			
<12	25.6%	30.4%	33.9%
12–15	51.9%	51.6%	52.6%
>15	22.5%	18.0%	13.5%
<b>Median duration lived in county of residence prior to death (years)<sup>b</sup></b>	30	33	30

<sup>a</sup> Excluding ischaemic heart disease cases for whom Parkinson's disease was mentioned on the death certificate as an associated cause.

<sup>b</sup> This information was not always available on death certificates prior to 1989.

**Table 2** Prevalence odds ratios (POR) and (95% confidence interval [CI]) for Parkinson's disease as the underlying cause of death (ICD-9 332) compared to ischaemic heart disease deaths (ICD-9 410–414) in California by county pesticide use, 1984–1994

Risk factors	1989–1994 <sup>a</sup>			1984–1988 <sup>b</sup>		
	No. of cases	POR		No. of cases	POR	
		Crude (95% CI)	Adjusted (95% CI)		Crude (95% CI)	Adjusted (95% CI)
<b>County pesticide use</b>						
none	1372	1.00	1.00	981	1.00	1.00
low	1333	1.55 (1.44–1.67)	1.45 (1.34–1.56)	870	1.47 (1.34–1.62)	1.42 (1.29–1.56)
moderate	1125	1.44 (1.33–1.56)	1.36 (1.26–1.48)	729	1.40 (1.27–1.54)	1.37 (1.24–1.50)
high	703	1.42 (1.30–1.56)	1.45 (1.32–1.59)	403	1.23 (1.09–1.38)	1.19 (1.06–1.34)
<b>Total N</b>						
cases	4533			2983		
controls	259 999			238 462		

<sup>a</sup> Adjusted for: age, gender, race (white, black, Asian, other), birth place California, year of death, education ( $\leq 12$ , 13–15,  $> 15$  years).

<sup>b</sup> Adjusted for: age, gender, race (white, black, Asian, other), birth place California, year of death.

**Table 3** Prevalence odds ratios (POR) (and 95% confidence interval [CI]) for Parkinson's disease as the underlying cause of death (ICD-9 332) compared to ischaemic heart disease (ICD-9 410–414) by duration of residency in pesticide use counties; (case N = 4502, control N = 256 660)

County pesticide use	Duration lived in country of death (years)					
	0–5		5–40		>40	
	No. of cases	POR <sup>b</sup> (95% CI)	No. of cases	POR <sup>b</sup> (95% CI)	No. of cases	POR <sup>b</sup> (95% CI)
None	130	1.07 (0.88–1.31)	557	0.97 (0.87–1.09)	679	1.00 <sup>a</sup>
Low	164	1.44 (1.21–1.72)	733	1.41 (1.26–1.56)	436	1.52 (1.35–1.72)
Moderate	149	1.45 (1.21–1.74)	582	1.26 (1.13–1.41)	394	1.49 (1.31–1.69)
High	89	1.65 (1.32–2.08)	303	1.36 (1.19–1.56)	311	1.49 (1.30–1.71)

<sup>a</sup> Reference group.

<sup>b</sup> Adjusted for age, gender, race (white, black, Asian, other), birth place California, year of deaths, education ( $\leq 12$ , 13–15,  $> 15$  years).

associated cause of death only, we observed a much weaker effect (10% increase), and, this small increase in mortality was attributable to long-term residents ( $> 40$  years in county) in pesticide-use counties (results not shown).

Employing agricultural census data, we observed an almost two-and-a-half-fold increase in risk of dying from PD (as underlying cause) during the 1989–1994 period if insecticides were reported to be applied to more than 37% of the county's area and a 50% increase when 5–37% of the county's land was treated. We controlled for the percentage of other pesticides and fertilizers used per acre of land in the model. The effect estimates for insecticide use were smaller for underlying causes reported in 1984–1988 and for associated causes reported during 1984–1993. However, a dose-response was suggested for all three outcome categories employing a continuous exposure measure of percentage of land treated with insecticides (results not shown) and for underlying causes using percentile categories during the period 1989–1994 (Table 4). Crop specific analyses showed an increased risk for PD in counties in which more than

10% of the agricultural land was used for vegetable gardening (POR = 1.45, 95% CI: 1.24–1.70). No consistent pattern was found for other types of crops.

Lastly, we examined whether other chronic diseases not suspected to be caused by pesticide exposures showed a similar mortality pattern when using county pesticide-use categories or insecticide application based on the agricultural census. When comparing mortality from multiple sclerosis and intestinal diseases to ischaemic heart disease mortality we observed no consistent pattern comparable to our results for PD (results not shown).

## Discussion

Mortality from PD (as underlying cause) was generally increased by about 40% in all Californian counties reporting some use of restricted agricultural pesticides since the early 1970s compared to those reporting none. We did not observe a dose-response pattern with intensity of restricted pesticide use or

**Table 4** Prevalence odds ratios (POR) (and 95% confidence interval [CI]) for Parkinson's disease as underlying or associated causes of death (ICD-9 332) compared to ischaemic heart disease (ICD-9 410–414) by percentage of county land treated with chemicals to control insects according to the 1982 agricultural census

Percentage of county land treated with insecticides	1989–1994 (underlying causes)		1984–1988 (underlying causes)		1984–1993 (associated causes)	
	(Case n = 4533, control n = 259 999)	POR <sup>a</sup> (95% CI)	(Case n = 2983, control n = 238 462)	POR <sup>b</sup> (95% CI)	(Case n = 15 222, control n = 467 238)	POR <sup>b</sup> (95% CI)
<5.4 (50th percentile)	2407	1.00	1688	1.00	8952	1.00
5.4–37.1 (50–90th percentile)	1880	1.46 (1.27–1.68)	1167	1.35 (1.13–1.62)	5531	1.08 (1.00–1.17)
37.1–70.0 (90th percentile)	246	2.41 (1.77–3.27)	128	1.49 (0.99–2.26)	739	1.23 (1.04,1.46)

<sup>a</sup> Adjusted for age, gender, race (white, African American, Asian, other), birth place California, year of death, education ( $\leq 12$ , 13–15,  $> 15$  years [for 1989–1994 only]), use of fertilizer, and chemicals to control nematodes, weeds, growth, and plant diseases (50–90th, 90th percentile).

<sup>b</sup> Adjusted for age, gender, race (white, African American, Asian, other), birthplace California, year of death, use of fertilizers, and use of chemicals to control nematodes, weeds, growth, and plant diseases (50–90th, 90th percentile).

length of residency in the county of death. Intensity or acreage treated with restricted pesticides might, however, not adequately reflect potential harm to humans since the EPA criteria designating a pesticide as a restricted material were broad, including harm to public health, farm workers, domestic animals, honeybees, the environment, wildlife, or other crops. However, the risk of dying from PD (as underlying and associated cause of death) compared to the risk of dying from ischaemic heart disease increased with the percentage of agricultural land treated with any kind of insecticide as reported in the 1982 agricultural census. Furthermore, the census data suggested that intensive vegetable gardening might be related to an increased PD mortality. A comparable association of PD with market gardening was previously reported by Barbeau *et al.*<sup>3</sup> and with employment in the agricultural tree fruit industry by Hertzman *et al.*<sup>6</sup>

Previous epidemiological studies investigating the association between PD and pesticide exposure employed both ecologic and case-control designs. The first epidemiological study that suggested pesticides as a likely causal agent in rural environments was conducted by Barbeau *et al.*<sup>3</sup> in the early 1980s. In this ecologic study the prevalence of PD in nine rural regions of Quebec was found to be unevenly distributed throughout the province, varying according to drinking water source. Regions with higher PD prevalence were found to be predominantly agricultural and were characterized by intensive market gardening and pesticide use. This ecologic study employed a comprehensive regional case ascertainment method and identified more than 5000 cases who lived or died in Quebec between 1980 and 1984. Exposure, however, was assigned solely on grounds of regional drinking water source. Thus, this study could only speculate which rural drinking water contaminant might be associated with PD and it might have been biased if other PD risk factors were differentially distributed between exposed and unexposed regions.

This Canadian study, however, stimulated researchers to conduct case-control studies further exploring the pesticide/PD hypothesis. The case-control design promised the greatest efficiency for studying this relatively rare disease and allowed collection of individual level exposure data in patient interviews. Case-control studies reported odds ratio point estimates ranging from 0.5 to 6.4 for different types of pesticide exposure.<sup>26</sup> Many studies reported positive associations, but results lacked

precision and some reported conflicting results. In Kansas, no increase was observed when using university hospital referrals, yet, after adding a rural study site, a threefold increased risk with pesticide exposure was found.<sup>9,14</sup> Another study relying mostly on metropolitan residents found an increased risk for 'rural living', yet, no effect for pesticide applications to lawns, gardens, or neighbourhoods on PD occurrence.<sup>13</sup> Finally, a study comparing residents from Beijing and Guangzhou, reported that living in Chinese villages was associated with a decreased risk for PD,<sup>27</sup> while for Hong Kong residents past residence in rural areas and farming increased the risk for PD.<sup>15</sup>

Case-control results might have varied because of differences in exposure definition, ranging from environmental to occupational and from general pesticide use to specific product information. The most important limitation of all case-control studies conducted to date, however, is caused by what was supposed to be one of their greatest advantages: obtaining individual level exposure information through interviews with patients. Relying on study subjects to recall chemical usage over very long periods of time could have introduced substantial information bias. Moreover, such bias might be differential because cases could be more motivated than healthy controls to recall possible chemical agents which could be responsible for their disease. A finding reported by Seidler *et al.*<sup>5</sup> indicated that recall bias might have played a role: when employing self-reported occupational information, these authors found an effect of occupational exposures on PD, yet, none was seen when a job-exposure matrix was employed instead. The authors considered the job-exposure matrix a more objective measure for occupational exposures.

Second, only one Canadian study<sup>10–12</sup> can be considered population-based and thus unlikely to have suffered from a biased control selection. Third, none of the studies enrolled incident cases and some used a mixture of young- and old-onset cases. Prevalent cases of a chronic disease are dependent on factors influencing incidence and mortality and are less suitable for aetiological research and genetic factors may cause young-onset cases.<sup>28</sup> Fourth, most of the studies had limited statistical power due to the small to moderate sample sizes of 30 and 150 cases; only one study was based on a fairly large number of cases (N = 380).<sup>5</sup> Thus, most of the studies had insufficient power to address the effect of specific chemicals, chemical

mixture, and the interaction of these chemicals with other risk factors that could increase susceptibility to neuro-degeneration. Furthermore, even though a study had enough subjects, recall of chemicals was unspecific limiting the examination of more specific hypotheses: when asked to name specific compounds applied during farming operations, about 60% of all exposed cases in a Canadian and 62% of all exposed study subjects in the German study were unable to recall the name of the chemical.<sup>5,11</sup>

We conducted our study solely relying on information routinely collected for all Californian residents. Our ecologic exposure measures reflect the potential for environmental and/or occupational exposures to pesticides based on county of residence. Personal characteristics such as age, gender, and education, however, were available for each case and control. Employing this mixture of individual and ecologic data we avoided the ecologic fallacy of purely 'ecological' studies.<sup>29</sup> Nevertheless, our study might suffer greatly from exposure misclassification bias when attributing the same exposure level to all county residents, i.e. assuming that living in certain counties increased on average the likelihood of pesticide exposure for all residents homogeneously. Most likely the resulting exposure misclassification was non-differential with respect to disease status biasing the effect estimates towards the null value of no association. However, we cannot preclude that our pesticide use measure might be surrogates for another countywide risk factor for PD mortality.

One such factor could be differences in smoking rates since ischaemic heart disease deaths are positively associated with smoking while PD occurrence may be negatively related to smoking.<sup>26</sup> Information about smoking is not provided on death certificates, but we obtained data for Californian counties.<sup>30</sup> When we grouped the counties into our four pesticide-use categories the percentages of smokers in 1990 in the age group 30+ years were almost identical (22.2%, 21.3%, 22.1%, and 22.3%, respectively, range 18.2–25.9% per county). Thus, it seems unlikely that differences in smoking behaviour explain the differences we found for pesticide use. Furthermore, determinants of smoking rates in the US population are period, ethnicity, sex, educational status, and age.<sup>31</sup> Since we controlled for these factors in our analyses, we may have indirectly controlled for differences in smoking behaviour. Yet, in addition, we checked whether our results hinged on the choice of our comparison group and selected a random sample from all other causes of deaths except cancers. Using this random sample, the estimates calculated for county pesticide use were almost identical to those provided in Table 2.

Mortality records were the only resource that allowed identification of PD cases comprehensively throughout California. Because PD is not, per se, a fatal disease, PD will be listed as the underlying cause only for the most severe cases and for those deceased who did not concurrently suffer from other fatal diseases, such as cancer or ischaemic heart disease. In the latter case PD may or may not be listed as an associated cause. Educational attainment was generally higher among cases with underlying cause of death PD (Table 1). This could suggest a healthy survivor effect for more educated PD patients, i.e. if education leads to a healthier lifestyle more educated individuals may be less likely to die of ischaemic heart disease. Note, however, that such a survivor effect would apply equally to residents of pesticide use and non-use counties.

American and British researchers reported that no more than 25–30% of all PD patients receive a PD diagnosis as the underlying cause of death.<sup>32,33</sup> Including associated causes of death, researchers were able to identify 63.9% of all known PD cases registered with the Ohio Parkinson Society.<sup>34</sup> Thus, even when employing all information almost 40% of PD cases are never mentioned on death certificates. Underreporting of PD will most likely cause underestimation of the effect if it is non-differential with respect to exposure, i.e. unrelated to county pesticide use. Yet, access to specialized medical care and receiving a diagnosis of PD or reporting on death certificates might be associated with our pesticide measure. Since specialized neurological care is more accessible in metropolitan than rural areas, we expect that in agricultural pesticide-use regions milder cases of PD are more likely to be underdiagnosed and reported, resulting in underestimation of the effect when relying on associated causes of death for PD. On the other hand, lack of care could exacerbate the disease causing increased mortality with the opposite effect on the effect estimate for underlying cause.

Underreporting of PD as associated cause is more likely in populations that on average are less healthy since the criteria for associated cause reporting state that these causes not only have to be present but also need to contribute to death.<sup>35</sup> Thus, even if a physician is aware of a PD diagnosis, depending on the relative severity of PD and other concurrent diseases, PD may or may not be mentioned on the death certificate. In general, the underlying cause criteria are more straightforward and probably better understood than those for associated causes.<sup>36</sup> We believe that our results for underlying causes of PD are more reliable because they are less affected by differential reporting and diagnoses that may depend on access to health care and, thus, may be different for rural and urban populations. Yet, we are not aware of any data that could support our notion.

Finally, patients with Parkinson-like syndromes (essential tremor, drug-induced parkinsonism, progressive supranuclear palsy, striatonigral degeneration) may be erroneously listed as PD. However, such cases are estimated to represent less than 7% of all idiopathic PD cases in the US.<sup>37</sup> Since mortality data are susceptible to changes of diagnostic criteria and diagnostic accuracy over time and for different age groups, we controlled for such effects by entering age and calendar time of deaths into our models.

Our data suggest that PD mortality in California is increased in counties using agricultural pesticides. We believe that the use of mortality data and ecologic exposure measurements most likely introduced bias towards the null due to non-differential misclassification. The methodological limitations of this study preclude any definitive conclusions, but our findings suggest that studies of PD aetiology should be targeting rural California. It will be important to employ improved case finding mechanisms and to add individual level exposure measures derived from the California pesticide use registry to replace the ecologic measures of countywide pesticide exposure.

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