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Original Contribution

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Pesticides are ubiquitous neurotoxicants, and several lines of evidence suggest that exposure may be associated with depression. Epidemiologic evidence has focused largely on organophosphate exposures, while research on other pesticides is limited. We collected detailed pesticide use history from farmers recruited in 1998–2000 in France. Among 567 farmers aged 37–78 years, 83 (14.6%) self-reported treatment or hospitalization for depression. On the basis of the reported age at the first such instance, we used adjusted Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals for depression (first treatment or hospitalization) by exposure to different pesticides. The hazard ratio for depression among those who used herbicides was 1.93 (95% confidence interval (CI): 0.95, 3.91); there was no association with insecticides or fungicides. Compared with nonusers, those who used herbicides for <19 years and ≥19 years (median for all herbicide users, 19 years) had hazard ratios of 1.51 (95% CI: 0.62, 3.67) and 2.31 (95% CI: 1.05, 5.10), respectively. Similar results were found for total hours of use. Results were stronger when adjusted for insecticides and fungicides. There is widespread use of herbicides by the general public, although likely at lower levels than in agriculture. Thus, determining whether similar associations are seen at lower levels of exposure should be explored.

agricultural workers; depression; herbicides; pesticides

The public health burden of depression is tremendous. World Health Organization worldwide estimates for 2000 rank depression fourth among all causes of disability-adjusted life-years lost (4.4%) and first among all causes of years lived with disability (11.9%) (1). The Americas and Europe have higher percentages, approaching 25% for disability-adjusted life-years and 43% for years lived with disability (1). Depression increases the risk for suicide and all-cause mortality; detrimentally affects physical, mental, and social functioning; is associated with worse cognitive functioning; and leads to greater health-care-service use and costs (2). Improved understanding of the role of modifiable risk factors for depression could help in addressing the public health burden of these disorders.

Some pesticides are neurotoxic (3), and experimental evidence indicates effects on neural systems known to underlie depression (3–6). Recent epidemiologic evidence also shows associations between pesticide exposures and depression (7–10). Some studies have considered pesticide exposures in general, while others have targeted specific compounds, in particular organophosphates. Only within the Agricultural Health Study has this question been explored with detailed data on exposures to different pesticide families (11, 12). These studies found depression associated with exposure to several pesticide families, although the extent to which any individual result was driven by correlation with other pesticides was not clear. Therefore, we explored the association between professional pesticide exposures and lifetime history of depression among agricultural workers in France exposed to a wide variety of pesticides.

MATERIALS AND METHODS

Participants

This study was conducted among participants of a case-control study originally aimed at investigating the relation between pesticides and Parkinson's disease (PD). The original

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study's details, from which all the data for the current study derive, have been described previously (13). We describe the core study methods below; additional details are provided in the Web Appendix available at http://aje.oxfordjournals.org/. Participants were active or retired workers in agriculture and related occupations recruited through their membership in Mutualité Sociale Agricole from 1998 to 2000, the French health insurance for such workers. PD patients 18–75 years of age and up to 3 controls per case matched on age (within 2 years), sex, and region of residence were recruited (participation rates: cases, 83%; controls, 75%). Although not representative of all France, the PD controls were representative of the French population with the age and sex distribution typical of PD patients. PD cases or PD controls with a record of free health care for dementia were not eligible. The research protocol was approved by the ethics committee of Hôpital du Kremlin-Bicêtre, and all subjects signed an informed consent.

Pesticide exposure assessment

Pesticide exposure was assessed by using a 2-phase procedure (14, 15) that consisted of initial self-reported occupational history followed by extensive in-home interviews of all who professionally used pesticides to obtain detailed pesticide use data (13). The in-home interviews consisted of a half-day or more of detailed questioning by a Mutualité Sociale Agricole occupational health physician. Detailed pesticide use for each of the farm/crop/animal combinations was obtained including pesticides used, specific years used, and hours/year used. Interviewers visited farms, discussed technical issues, examined old pesticide containers and packages, and reviewed bills and farming calendars. Data were reviewed by 2 epidemiologists, 2 occupational health physicians, and an agronomist to check for consistency on issues such as pesticide availability at the reported date of use, likelihood of use for the target crop/animal, and likelihood of duration/frequency of use given the land size or number of animals. When some information was deemed implausible, the occupational health physician recontacted the participant. Pesticides were coded on the basis of chemical similarities by using a pesticide dictionary (http://www.alanwood.net/pesticides), and individual pesticide families were grouped into 3 main pesticide classes: insecticides, herbicides, and fungicides.

Depression and covariate assessment

Participants were administered in-person questionnaires by a Mutualité Sociale Agricole physician who asked if they had ever been treated (antidepressants, lithium, sismotherapy) or hospitalized for depression as a single question. For brevity, we refer to this as "depression." If they had, they were asked to provide their age at the first such instance. Questionnaire data also included date of birth, lifetime cigarette smoking (including start and end year), age of the participant when he/she ended schooling, history of stroke, and history of head trauma with loss of consciousness. All participants were also asked about use of home-gardening pesticides.

Statistical methods

Because there are important differences between farmers and nonfarmers with respect to lifestyle factors that may be associated with different rates of depression, as well as possible differences in health-seeking behavior for psychiatric conditions, and because nonfarmers were not professionally exposed to pesticides, analyses were restricted to participants who reported working in agriculture (mainly farm owners and workers) at least once in order to restrict analyses to a more homogeneous group and to reduce the risk of residual confounding (16).

Because of the time-dependent nature of both exposure and outcome, the analytical data set was created with multiple lines per subject, one for each year of age from birth up to the age of first depression or year of PD diagnosis (for PD cases) or the age at interview (for PD controls), whichever came first. Therefore, in PD cases, first depression occurring after PD onset was not included in the analysis. Each line included an indicator variable for ever/never exposed to each of the different pesticide families and pesticide classes and updated cumulative hours and cumulative years of individual pesticide family and class use. Similarly, cigarette smoking, history of head trauma with loss of consciousness, history of stroke, and gardening pesticide use were updated for each year. Analyses of specific families of pesticides were restricted to those used by >5% of nondepressed farmers.

We used Cox proportional hazards models for time-dependent variables, stratified by region and using age as the time scale, to estimate hazard ratios and 95% confidence intervals for depression by pesticide exposure status. Participants contributed follow-up time from birth to age at first depression, age at PD onset (for PD cases), or age at interview (for PD controls), whichever came first. Continuous pesticide use variables were split into 3 groups: 1) no use, 2) groups below the median, and 3) groups at or above the median among users. Trend tests were performed by using a continuous variable created by assigning to each participant the median value of his/her group. Our main analyses included all farmers and were adjusted for sex, PD status, education (age at end of schooling: <11 years, 11–13 years, >13 years), cigarette smoking, and history of head trauma with loss of consciousness. The last 2 were included in the model as time-dependent variables. In sensitivity analyses, we additionally included history of stroke and use of pesticides for gardening as time-dependent variables, as well as an additional stratification variable for the calendar year time period (before 1971, 1971–1980, 1981–1994, after 1994) all in the same model. We performed additional sensitivity analyses restricted to males, because they apply pesticides considerably more frequently than women, and restricted to PD controls, because depression may be an early PD nonmotor symptom. Behavioral changes related to other early PD symptoms could affect exposure before depression.

We first conducted complete-data analyses in which observations with missing information for any of the predictors are deleted from the analyses (17). This approach is appropriate when missingness is low, which was the case for the pesticide classes (insecticides, fungicides, herbicides; missingness <3%). For analyses of pesticide families, we also used multiple imputation to impute missing use values (13, 17, 18). For

each pesticide family, multiple imputation was done independently of that for other pesticides, as joint imputation across 50 pesticide families is computationally intractable. We used SAS PROC multiple imputation to generate 10 imputed use history data sets; each of these was then reduced to a use summary data set and an analytical data set including time-dependent variables. Each data set was analyzed separately, and the 10 sets of results were pooled by using SAS PROC MIANALYZE. Note that multiple imputation allows multivariable exposure analyses because each of the data sets analyzed is complete. SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina) was used for all analyses.

RESULTS

Of 781 participants (224 PD cases, 557 PD controls), 15 had missing data for depression treatment or hospitalization or age at which that first occurred. Of the remaining 766 participants, 567 (74%; 177 cases, 390 controls) had held a farming occupation at least once, of whom 83 (14.6%; 26 cases, 57 controls) reported having been treated or hospitalized for depression. Among 335 (101 cases, 234 controls) male farmers and 232 (76 cases, 156 controls) female farmers, 33 men (9.8%; 10 cases, 23 controls) and 50 women (21.6%; 16 cases, 34 controls) had been treated or hospitalized for depression. The mean age at study recruitment was 67.6 (standard deviation, 6.8; range, 37–78) years and, at first treatment or hospitalization for depression, was 48.9 (standard deviation, 14.2; range, 15–77) years.

Characteristics of the nondepressed study population by sex and professional pesticide use are shown in Table 1. Use was much more common among men (87%) than women (16%). Table 2 shows the 26 specific families of pesticides used by >5% of nondepressed farmers, grouped by insecticides, fungicides, and herbicides. There was substantial correlation in use of the different classes of pesticides (Web Table 1).

There was little association between insecticides or fungicides and depression, with only a slightly elevated hazard ratio for use of any pesticide in adjusted analyses (Table 3). However, the hazard ratio for herbicide use was almost 2 and was slightly higher in analyses restricted to only PD controls or men. Further adjustment for history of stroke and gardening pesticide use, as well as including time period as an additional stratification variable, gave similar results (hazard ratio (HR) = 1.77, 95% confidence interval (CI): 0.80, 3.90). In analyses mutually adjusted for the other pesticide classes, there remained no association with insecticides or fungicides, while the results for herbicides were stronger (HR = 3.30, 95% CI: 1.12, 9.73). Similar results were found in analyses restricted to PD controls or men.

There was an increasing hazard ratio for depression with increasing cumulative years of herbicide use. Those reporting the median 19 years or more of use had a hazard ratio of 2.31 (95% CI: 1.05, 5.10) compared with nonusers (Figure 1). A similar dose-response relationship was seen for cumulative hours of use (Figure 1). In trend analyses, the hazard ratio for 10 years of herbicide exposure was 1.34 (95% CI: 1.01, 1.76) and for 100 hours of herbicide exposure was 1.25 (95% CI: 1.00, 1.55). No dose-response relationship was seen for insecticides or fungicides, but additional adjustment for use of these led to stronger results for duration (<19 years, HR = 2.24, 95% CI: 0.80, 6.25; ≥19 years, HR = 3.65, 95% CI: 1.31, 10.17) and intensity (<137 hours, HR = 2.39, 95% CI: 0.89, 6.41; ≥137 hours, HR = 4.14, 95% CI: 1.42, 12.12) of herbicide use.

In complete data analyses of specific herbicide family use, we found an increased hazard ratio for depression for use of carbamates, picolinic acid, and dinitrophenol in particular (Table 4). Missing data for these individual herbicide families ranged from 9.1% to 18.2% at the end of follow-up among nondepressed farmers. In analyses based on multiple imputation, the hazard ratio for these herbicides was somewhat reduced (Table 4). Of these, exposure to dinitrophenol was most common and, thus, this hazard ratio had the narrowest confidence interval. Results were essentially unchanged when additional adjustment was made for insecticides and fungicides.

Table 1. Characteristics by Sex and Professional Pesticide Use Among Study Farmers Without Depression, France, 1998–2000

Characteristic	Males				Females			
	Professional Pesticide Use				Professional Pesticide Use			
	No (n = 42)		Yes (n = 260)		No (n = 156)		Yes (n = 26)	
	No.	%	No.	%	No.	%	No.	%
PD case	11	26.2	80	30.8	49	31.4	11	42.3
Never smoker	20	47.6	137	52.7	151	96.8	25	96.2
Education (age at end of schooling)								
<11 years	10	23.8	64	24.6	30	19.2	7	26.9
11–13 years	17	40.5	131	50.4	98	62.8	14	53.9
>13 years	15	35.7	65	25.0	28	18.0	5	19.2
Head trauma with LOC	3	7.1	24	9.2	9	5.8	3	11.5
Stroke	1	2.4	14	5.4	5	3.2	1	3.9
Gardening pesticide exposure	20	47.6	123	47.3	50	32.1	17	65.4

Abbreviations: LOC, loss of consciousness; PD, Parkinson's disease.

Table 2.   Pesticides to Which Nondepressed Farmers Were Exposed[a] by Class, France, 1998–2000

	% Exposed (n = 484)
Insecticide	
Carbamate	13
Organochlorine	32
Organophosphorus	29
Pyrethroid	21
Arsenic	12
Fungicides	
Amide	6
Aromatic	6
Carbamate	14
Dicarboximide	8
Dithiocarbamate	20
Triazole	14
Copper	43
Sulfur	42
Herbicides	
Amide	15
Carbamate	6
Dinitroaniline	9
Dinitrophenol	18
Nitrile	5
Organophosphorus	24
Phenoxy compounds	30
Picolinic acid	11
Quaternary ammonium	18
Triazine	38
Triazole	9
Uracil	9
Urea	22

[a] Only those pesticide families (n = 26) to which >5% of non-depressed farmers were exposed.

No association with depression was seen for any individual insecticide and fungicide family, with or without adjustment for herbicides (Web Table 2).

For all pesticides considered, results were similar in analyses of PD controls or men only, although confidence intervals were wider because of reduced numbers (data not shown). Results were similar when we considered different "farmer" definitions in forming our base study population, specifically: whether the participant was a farmer after age 20, was a farmer whose longest-held occupation was farming, or was a farmer whose last occupation was farming (data not shown).

DISCUSSION

We found an elevated depression rate among farmers who used herbicides and a marked dose-response relationship with

Table 3.   Hazard Ratio[a] for Depression by Professional Exposure to Different Classes of Pesticides Among Farmers, France, 1998–2000

	Any Pesticide				Insecticides				Fungicides				Herbicides			
	No. of Depression Cases	Person-Years	HR	95% CI	No. of Depression Cases[b]	Person-Years	HR	95% CI	No. of Depression Cases[b]	Person-Years	HR	95% CI	No. of Depression Cases	Person-Years	HR	95% CI
All subjects																
Never	47	22,830	1.00	Referent	53	25,540	1.00	Referent	52	24,771	1.00	Referent	53	26,790	1.00	Referent
Ever	36	14,321	1.36	0.66, 2.79	28	10,867	1.01	0.62, 1.96	29	11,650	1.15	0.55, 2.41	30	10,361	1.93	0.95, 3.91
PD controls only																
Never	34	16,118	1.00	Referent	37	18,039	1.00	Referent	36	17,500	1.00	Referent	37	18,711	1.00	Referent
Ever	23	9,913	1.38	0.57, 3.38	19	7,446	1.31	0.59, 2.94	19	8,058	1.48	0.56, 3.93	20	7,259	2.42	1.00, 5.86
Males only																
Never	5	9,319	1.00	Referent	9	11,726	1.00	Referent	8	10,862	1.00	Referent	6	12,460	1.00	Referent
Ever	28	12,969	1.22	0.41, 3.62	23	9,907	0.77	0.31, 1.93	24	10,808	1.10	0.41, 2.92	27	9,824	2.60	0.94, 7.21

Abbreviations: CI, confidence interval; HR, hazard ratio; PD, Parkinson's disease.

[a] Adjusted for age (time scale), region (stratification variable), PD status, sex, cigarette smoking, age at end of schooling, and history of head trauma with loss of consciousness.
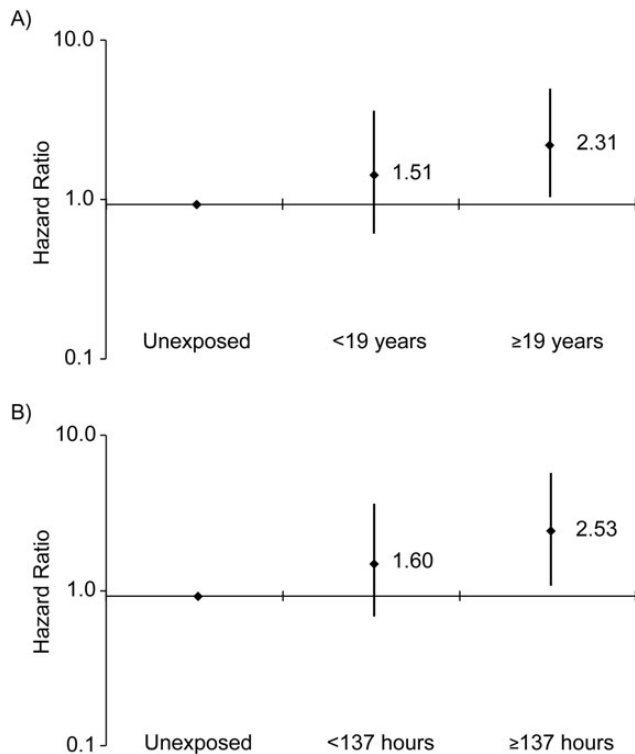
[b] Cases do not sum to 83 because of missing data.

Figure 1. Hazard ratios (diamonds) and 95% confidence intervals (vertical bars) for depression by cumulative years (A) (median years, 19) and hours (B) (median hours, 137) of exposure to herbicides, adjusted for age (time scale), region (stratification variable), Parkinson's disease status, sex, cigarette smoking, education, and history of head trauma with loss of consciousness. The numbers of depression cases among the unexposed, those below the median, and those at or above the median are 53, 9, and 21 (A) and 53, 11, and 19 (B).

both increasing duration and intensity of herbicide use. These results were independent of insecticide or fungicide use—neither of which exhibited an association with depression—and independent of several other lifestyle and health variables. The dinitrophenol herbicide family was associated with depression in both complete data and multiple imputation analyses, but other herbicide families showed associations that were suggestively elevated. However, we could not adjust these analyses for all herbicide families simultaneously. We found no association with specific insecticide or fungicide families. Although this study was a secondary analysis of data from a PD case-control study, because the original study found no association between herbicides and PD (13), the analyses adjusting for PD case status provide valid estimates of the herbicide-depression association (19, 20). Similarly, the estimate from analyses among controls only is also valid—even for the insecticide association because the prevalence of PD is low—although less precise.

The lifetime prevalence of depression is an estimated 16% in the United States and 18% in France when using face-to-face interviews with the World Health Organization Composite International Diagnostic Interview (which provides diagnoses based on the *Diagnostic and Statistical Manual of*

Mental Disorders-IV), similar to the 15% found in our study (21, 22). Our sex-specific prevalence (22% women/10% men) was also similar to that in French data (24% women/12% men). This suggests that despite self-reported depression (specifically treatment or hospitalization) in our study, we still captured this outcome reasonably well. French data suggest a mean age at first depressive episode of about 30 years of age (22), which is younger than the mean of 49 years at first treatment or hospitalization for depression we found among our farmers. This likely reflects both the age distribution of our sample originally recruited for a PD study and the age distribution of the Mutualité Sociale Agricole population, which is considerably older than the French general population (23), as well as a delay between first depressive episode and treatment or hospitalization for depression.

A higher frequency of depression has been found among pesticide formulators or applicators in some studies (8, 24), and others focusing more explicitly on organophosphate exposure have found associations with greater risk of depression or depressive symptoms (9, 10). However, coexposure to other pesticides is hard to rule out. Other pesticide classes have been studied directly less often. Carbamate-poisoned banana workers did not show increased symptoms of depression and anxiety (10), but they did show an elevated odds ratio for suicidal thoughts (odds ratio (OR) = 2.57, 95% CI: 0.73, 9.81) (10). Suicide itself, however, is influenced not just by depression but also by traits like hostility and impulsivity. With that caveat in mind, however, the odds ratio for suicide in a study of Canadian farmers was not higher for insecticide spraying alone, but 71% higher (OR = 1.71, 95% CI: 1.08, 2.71) for combined herbicide and insecticide spraying compared with those who didn't spray those products (25).

The only prior study of which we are aware to specifically examine depression in relation to herbicide exposure is the Agricultural Health Study. Among pesticide applicators in the Agricultural Health Study, the odds ratios for a depression diagnosis were elevated for ever exposure to insecticides, fungicides, and fumigants and to organochlorines or organophosphates specifically (12). Intriguingly, the odds ratio for herbicides was as large as that for insecticides and larger than all other pesticides, but it had a wide confidence interval (OR = 0.05, 95% CI: 0.76, 5.54). However, there was no dose-response relationship for any specific pesticide group, and which pesticide group or groups were independently associated with depression is somewhat unclear because specific pesticide group analyses were not adjusted for the other pesticides. Furthermore, strong associations between pesticide poisoning and a high pesticide exposure event were seen, but these were not included in analyses of specific pesticides. Among female spouses of pesticide applicators in the Agricultural Health Study, use of insecticides, fungicides, and fumigants was weakly associated with depression when adjustment was made for pesticide poisonings (ORs from 1.09 to 1.25, lower 95% CIs: 0.91, 0.99), while the odds ratio for herbicides was 1.07 (95% CI: 0.97, 1.18) (11). These findings were not adjusted for other pesticide classes.

In the present study, we did not find any association between organophosphate pesticide use and depression. Prior studies clearly showed a strong relationship with organophosphate poisonings or high pesticide exposure events. When long-term exposure was considered, either results were weak or

Table 4. Adjusted[a] Hazard Ratios and 95% Confidence Intervals for Depression by Exposure to Different Herbicide Families in Complete-Data and Multiple-Imputation Analyses, France, 1998–2000

Herbicide Family	Not Exposed		Exposed		Complete Case		Imputed	
	No. of Depression Cases[b]	Person-Years	No. of Depression Cases[b]	Person-Years	Adjusted[a] HR	95% CI	Adjusted[a] HR	95% CI
Amide	70	32,249	3	1,232	1.03	0.28, 3.78	1.28	0.40, 4.13
Carbamate	70	33,568	3	690	4.44	1.07, 18.5	2.60	0.69, 9.72
Dinitroaniline	73	33,892	2	822	0.75	0.16, 3.58	1.04	0.24, 4.44
Dinitrophenol	62	30,692	13	2,564	3.35	1.47, 7.65	2.36	1.04, 5.36
Nitrile	73	34,314	1	400	1.26	0.14, 11.2	0.85	0.13, 5.42
Organophosphorus	67	32,949	7	2,007	1.62	0.62, 4.22	1.13	0.46, 2.75
Phenoxy	64	29,509	14	4,718	1.38	0.64, 2.97	1.35	0.66, 2.77
Picolinic acid	67	32,655	6	1,052	3.07	1.05, 8.92	2.05	0.74, 5.69
Quaternary ammonium	67	31,867	8	2,190	1.55	0.64, 3.76	1.28	0.56, 2.92
Triazine	63	29,596	15	5,383	1.24	0.56, 2.76	1.37	0.63, 2.96
Triazole	78	34,069	1	1,214	0.26	0.03, 2.01	0.27	0.04, 2.04
Uracil	69	34,030	5	825	1.90	0.60, 6.00	1.70	0.55, 5.19
Urea	69	31,561	5	1,949	0.93	0.31, 2.77	1.05	0.43, 2.56

Abbreviations: CI, confidence interval; HR, hazard ratio; PD, Parkinson's disease.

[a] Adjusted for age (time scale), region (stratification variable), PD status, sex, cigarette smoking, age at end of schooling, and history of head trauma with loss of consciousness.

[b] The number of depression cases is less than 83 because of missing data for specific families of pesticide.

were not adjusted for poisonings or high exposure events, so these could have been driving the associations seen with long-term exposure. If this is the case, then the lack of association with organophosphates in our population could be explained if poisonings or high pesticide exposure events were less common. Alternatively, the organophosphorous family of insecticides includes many products that were all grouped in our analyses. If only specific organophosphorous products are related to depression, this could have obscured findings with the larger category. Exposure misclassification could also have obscured an association. Other possible explanations of the discrepancy with previous studies include different levels of exposure, differences in usage practices including use of personal protective equipment, application method, or different types of organophosphates used in France compared with other countries.

Because herbicide targets are often biochemical processes unique to plants, it is generally thought that herbicides are less neurotoxic than other classes of pesticides—in particular insecticides—although some herbicide neurotoxicity has been reported (3). Dinitrophenol is a nonspecific mitochondrial oxidative phosphorylation uncoupler, which reduces cellular adenosine triphosphate production and thereby can be neurotoxic by depleting neurons' energy stores. Many other herbicides, including paraquat, chlorophenoxy herbicides, carbamates, picolinic acid, and atrazine (a triazine), also can have neurotoxic effects (5, 26–30).

A strength of our study was the detailed data on classes and many families of pesticides, with a wide range of use. In addition, we could determine pesticide use specifically prior to first treatment or hospitalization for depression. There were also

several limitations. First, information on depression treatment or hospitalization was self-reported. However, a validation study found that 74% of a sample self-reporting physician-diagnosed depression was confirmed as meeting depression criteria using a validated instrument (31), and the overall percentages of depression in our study sample were very close to French national figures. Furthermore, because of the requirement of obtaining services from the medical system for treatment or hospitalization, our approach likely minimized false positive diagnoses. In contrast, focusing on depression, treatment, or hospitalization could have missed some participants with symptoms who did not seek treatment. There could also have been some error in reporting the timing of first treatment or hospitalization. The reliability of self-reported age at onset of depression symptoms has been found to be low (32, 33), but depression symptoms are generally episodic, and cognitive psychology research shows that information about when an episodic experience first occurred is one of the least well-remembered aspects of experience (34, 35). In contrast, memory for distinctive events, as treatment or hospitalization would be, is better, and this is borne out in studies that suggest self-reported age at physician depression diagnosis or age at onset of psychiatric conditions with more vivid onset, like panic, is adequate or better (31, 33). Importantly, however, diagnostic misclassification of depression itself or the timing of its onset is likely to be independent from pesticide exposure and would therefore bias associations toward the null.

Other limitations include small numbers of exposed depression cases for many herbicide families and the lack of acute pesticide poisoning data, which has been associated with depression or suicide (7, 9–12). These studies generally targeted

poisonings by organophosphates or pesticides in general; thus, it seems unlikely that this could account for an herbicide-specific association, in particular one with a strong dose-response relationship. Another limitation is the possibility of untreated depression prior to first treatment or hospitalization influencing pesticide use patterns. Our herbicide-specific results, however, also argue somewhat against this limitation's causing a spurious association, as that would require untreated depression to lead to greater herbicide use specifically. In contrast, this limitation could potentially contribute to the null findings for insecticides and fungicides if untreated depression led to less use of pesticides in general, which would have biased results for all classes towards the null. Limited psychosocial data, which can be important predictors of depression, are an additional limitation, but the herbicide-specific findings also argue against this having caused the association.

In summary, our findings suggest an association between herbicides and depression. The possibility that environmental contaminants could affect psychological health has been generally underappreciated. Herbicide exposure in particular has received little research attention. If true, our findings have important public health implications for agricultural workers given the tremendous public health burden of depression and the fact that herbicides are widely used in agriculture and landscape management. In the United States, herbicides make up about 65% of all agricultural pesticide use (36). Our findings suggest the opportunity for public health intervention measures to educate and reduce exposures to these compounds that could have great public health impact. Of additional importance is the likelihood of widespread herbicide exposure to the general public from residential use. An estimated 40% of US households use herbicides for home and garden purposes, and the amount of herbicides applied dwarfs insecticides, fungicides, or other pesticides (36). Although exposures from such use may be less than among agricultural workers, determining whether similar associations are seen at lower levels of exposure should be explored.

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REFERENCES

1. World Health Organization. *The World Health Report 2001—Mental Health: New Understanding, New Hope.* Geneva, Switzerland: World Health Organization; 2001.
2. Roose SP, Sackheim HA. *Late-Life Depression.* New York, NY: Oxford University Press; 2004.
3. Costa LG, Giordano G, Guizzetti M, et al. Neurotoxicity of pesticides: a brief review. *Front Biosci.* 2008;13(4): 1240–1249.
4. Naismith SL, Norrie LM, Mowszowski L, et al. The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. *Prog Neurobiol.* 2012;98(1):99–143.
5. Werner FM, Covenas R. Classical neurotransmitters and neuropeptides involved in major depression: a review. *Int J Neurosci.* 2010;120(7):455–470.
6. Jones DC, Miller GW. The effects of environmental neurotoxicants on the dopaminergic system: a possible role in drug addiction. *Biochem Pharmacol.* 2008;76(5):569–581.
7. Beseler CL, Stallones L. A cohort study of pesticide poisoning and depression in Colorado farm residents. *Ann Epidemiol.* 2008;18(10):768–774.
8. Farahat TM, Abdelrasoul GM, Amr MM, et al. Neurobehavioural effects among workers occupationally exposed to organophosphorous pesticides. *Occup Environ Med.* 2003;60:279–286.
9. London L, Flisher AJ, Wesseling C, et al. Suicide and exposure to organophosphate insecticides: cause or effect? *Am J Ind Med.* 2005;47(4):308–321.
10. Wesseling C, van Wendel de Joode B, Keifer M, et al. Symptoms of psychological distress and suicidal ideation among banana workers with a history of poisoning by organophosphate or *N*-methyl carbamate pesticides. *Occup Environ Med.* 2010;67:778–784.
11. Beseler C, Stallones L, Hoppin JA, et al. Depression and pesticide exposures in female spouses of licensed pesticide applicators in the Agricultural Health Study cohort. *J Occup Environ Med.* 2006;48(10):1005–1013.
12. Beseler CL, Stallones L, Hoppin JA, et al. Depression and pesticide exposures among private pesticide applicators enrolled in the Agricultural Health Study. *Environ Health Perspect.* 2008;116(12):1713–1719.
13. Elbaz A, Clavel J, Rathouz PJ, et al. Professional exposure to pesticides and Parkinson disease. *Ann Neurol.* 2009;66(4): 494–504.
14. Clavel J, Glass DC, Cordier S, et al. Standardization in the retrospective evaluation by experts of occupational exposure to organic solvents in a population-based case-control study. *Int J Epidemiol.* 1993;22(suppl 2):S121–S126.
15. Stewart WF, Stewart PA. Occupational case-control studies. I. Collecting information on work histories and work-related exposures. *Am J Ind Med.* 1994;26(3):297–312.
16. Greenland S, Poole C. Interpretation and analysis of differential exposure variability and zero-exposure categories for continuous exposures. *Epidemiology.* 1995;6(3):326–328.
17. Klebanoff MA, Cole SR. Use of multiple imputation in the epidemiologic literature. *Am J Epidemiol.* 2008;168(4): 355–357.
18. Schafer JL. *Analysis of Incomplete Multivariate Data.* London, United Kingdom: Chapman and Hall; 1997.

19. Richardson DB, Rzehak P, Klenk J, et al. Analyses of case-control data for additional outcomes. *Epidemiology*. 2007; 18(4):441–445.

20. Nagelkerke NJ, Moses S, Plummer FA, et al. Logistic regression in case-control studies: the effect of using independent as dependent variables. *Stat Med*. 1995;14(8): 769–775.

21. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602.

22. Sapinho D, Chee CC, Beck F. Prévalence de l'épisode dépressif majeur et co-morbidités [in French]. In: Chee CC, Beck F, Sapinho D, et al, eds. *La dépression en France: Enquête Anadep 2005*. Paris, France: Institut National de Prévention et d'Education pour la Santé; 2009: 35–57.

23. Moisan F, Spinosi J, Dupupet JL, et al. The relation between type of farming and prevalence of Parkinson's disease among agricultural workers in five French districts. *Mov Disord*. 2011;26(2):271–279.

24. Amr MM, Halim ZS, Moussa SS. Psychiatric disorders among Egyptian pesticide applicators and formulators. *Environ Res*. 1997;73(1-2):193–199.

25. Pickett W, King WD, Lees RE, et al. Suicide mortality and pesticide use among Canadian farmers. *Am J Ind Med*. 1998;34(4):364–372.

26. Aggett PJ, Fenwick PK, Kirk H. An in vitro study of the effect of picolinic acid on metal translocation across lipid bilayers. *J Nutr*. 1989;119(10):1432–1437.

27. Bosco MC, Rapisarda A, Massazza S, et al. The tryptophan catabolite picolinic acid selectively induces the chemokines macrophage inflammatory protein-1 alpha and -1 beta in macrophages. *J Immunol*. 2000;164(6):3283–3291.

28. Miller DB. Neurotoxicity of the pesticidal carbamates. *Neurobehav Toxicol Teratol*. 1982;4(6):779–787.

29. Smith AJ, Stone TW, Smith RA. Neurotoxicity of tryptophan metabolites. *Biochem Soc Trans*. 2007; 35(Pt 5):1287–1289.

30. US Environmental Protection Agency. *Triazine Cumulative Risk Assessment*. Washington, DC: US Environmental Protection Agency; 2006.

31. Sanchez-Villegas A, Schlatter J, Ortuno F, et al. Validity of a self-reported diagnosis of depression among participants in a cohort study using the Structured Clinical Interview for DSM-IV (SCID-I). *BMC Psychiatry*. 2008;8:43.

32. Farrer LA, Florio LP, Bruce ML, et al. Reliability of self-reported age at onset of major depression. *J Psychiatr Res*. 1989;23(1):35–47.

33. Robins LN, Regier DA. *Psychiatric Disorders in America*. New York, NY: The Free Press; 1991.

34. Rubin DC, Baddeley AD. Telescoping is not time compression: a model of the dating of autobiographical events. *Mem Cognit*. 1989;17(6):653–661.

35. Sudman S, Bradburn NM, Schwarz N. *Thinking about Answers: the Application of Cognitive Processes to Survey Methodology*. San Francisco, CA: Jossey-Bass; 1996.

36. Kiely T, Donaldson D, Grube A. *Pesticide Industry Sales and Usage, 2000 and 2001 Market Estimates*. Washington, DC: Office of Prevention Pesticides and Toxic Substances, US Environmental Protection Agency; 2004.