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DEPRESSION AND PESTICIDE EXPOSURES IN FEMALE SPOUSES OF LICENSED PESTICIDE APPLICATORS IN THE AGRICULTURAL HEALTH STUDY COHORT

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Abstract

Objective—This nested case control study evaluated the association between depression and pesticide exposure among women.

Methods—The study population included 29,074 female spouses of private pesticide applicators enrolled in the Agricultural Health Study between 1993–1997. Cases were women who had physician diagnosed depression requiring medication. Lifetime pesticide use was categorized as never mixed/applied pesticides, as low exposure (up to 225 days), high exposure (>225 days) and a history of diagnosed pesticide poisoning.

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Results—After adjustment for state, age, race, off-farm work, alcohol, cigarette smoking, physician visits and solvent exposure, depression was significantly associated with a history of pesticide poisoning (OR 3.26; 95% CI 1.72, 6.19) but not low (OR 1.09; CI 0.91, 1.31) or high (OR 1.09; 95% CI 0.91, 1.31) cumulative pesticide exposure.

Conclusion—Pesticide poisoning may contribute to risk of depression.

Keywords

pesticides; depression; Agricultural Health Study; female farm residents

Studies over the past forty years show an association between neurological effects and exposure to organophosphate (OP) insecticides [1–3]. In the past decade, several studies have suggested a possible association between pesticide exposure and depressive symptoms, particularly among cases of acute poisoning [4–7]. Depression associated with a pesticide poisoning may persist for years after the poisoning [4,8]. Some studies have shown long-term effects on mood in the absence of an acute pesticide poisoning [6,9–11], but others have not [12–14]. Thus reported effects of pesticide exposure on depression are inconsistent, and information on effects from low-dose, long-term exposure is especially meager.

The association of depression with pesticide exposure has been demonstrated primarily in studies of men, and the few studies of women have suffered from limited power [4,5,11]. The epidemiology of depression in women is different than in men [15]. Women have a lifetime prevalence rate of depression of 20% compared to 10% in men [16], and depression in women occurs at younger ages, lasts longer, and is more frequently associated with stressful life events than depression in men [15–18]. Risk factors for depression in women include a family or personal past history of mood disorders, loss of a parent before age 10, a childhood history of physical or sexual abuse, persistent psychosocial stresses and the loss of social support [15, 16]. Female farm spouses have additional burdens associated with financial hardship, heavy seasonal workloads, working off as well as on the farm, and exposures to chemicals that may be associated with depression [19,20].

A few studies have characterized the chemical and environmental exposures of farm spouses. In a cross-sectional survey conducted in Colorado between 1993 and 1997, 37% of female spouses of principal farm operators reported working in crop production [21]. A cross-sectional survey of 657 farm women in southeast Louisiana reported that 88.9% were involved in the management and oversight of the farm operation, 60.3% cared for farm animals, 70.8% cared for and used farm equipment and 42.5% were involved in crop management [19]. Previously published data from the Agricultural Health Study (AHS), a longitudinal study of commercial pesticide applicators and farm residents, showed that 68% of Iowa spouses and 54% of North Carolina spouses mixed or applied pesticides with a median cumulative exposure of 50 lifetime days [22].

The AHS provided the opportunity to study pesticide exposures occurring in the course of farm work undertaken by women and to evaluate whether cumulative pesticide exposure, or a history of acute pesticide poisoning, was associated with physician diagnosed depression.

METHODS

Data for this study come from spouses of private pesticide applicators, mainly farmers, enrolled in the AHS, a cohort study of 89,658 participants designed to study effects of agricultural exposures on health outcomes [23]. A total of 32,347 spouses of private farmer applicators enrolled in the study between 1993 and 1997 in Iowa and North Carolina [23]. They completed

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detailed questionnaires and returned them by mail (81%) or responded by phone (19%) [22]. Details of the questionnaire can be obtained at the AHS website (www.aghealth.org).

Because the epidemiologic characteristics of depression differ in women and men, and because few spouses were men, male spouses were excluded from the analyses. Spouses who were missing responses to the diagnosed depression question, who reported a previous lead or solvent poisoning [24] or head injury [25], or who were under 18 years of age were also excluded. A total of 29,074 women were available for analysis after these exclusions.

Cases were defined as female spouses of private applicators who responded "yes" to the question "Has a *DOCTOR* ever told you that you had been diagnosed with depression requiring medication". Controls were female spouses who responded "no". For those responding "yes", age of diagnosis was obtained in 20-year categories.

Based on associations reported in the literature on depression, and to control for potential confounding, factors chosen for inclusion in the analyses were age at enrollment, state of residence, education, race, Hispanic ethnicity, cigarette smoking and alcohol use. Visits to a physician during the past 12 months was also considered because frequent visits to a physician may increase the probability of being diagnosed with depression (26). Race was dichotomized into white and non-white with whites being the reference group. Education was categorized as whether or not the respondent finished high school, age into four groups (less than 40 years, 40 to 49 years, 50 to 59 years and greater than 59 years, with those under 40 as the reference group), current alcohol use into never/rarely, monthly, weekly or daily, and cigarette smoking status as never, past, or current.

Farm and work history information included the number of years a person lived or worked on a farm, whether the respondent lived on a farm 10 years prior to enrollment, whether the respondent ever held a job off the farm, the amount of time spent at the job held the longest, potential exposures to pesticides, and exposure to solvents from the non-farm job held the longest. Individuals who worked with pesticides were asked whether they personally mixed or applied pesticides less than 50% or 50% or more of the time, number of years and days per year of mixing or applying pesticides, and the specific chemicals used. Information on history of pesticide poisoning was obtained by asking, "Has a *DOCTOR* ever told you that you had been diagnosed with pesticide poisoning?"

Lifetime use of any pesticide was calculated by multiplying number of years of use by the number of days per year of use. Individuals below the 90^{th} percentile of lifetime use (225 days) were classified as experiencing low-level exposure, while those above the 90^{th} percentile were assigned high-level exposure. Those with a history of pesticide poisoning were considered as a separate category, regardless of the number of lifetime days of use. Thus there were four pesticide exposure categories: never mixed or applied pesticides (referent group); low-level cumulative exposure; high-level cumulative exposure; and a history of pesticide poisoning.

Demographic, behavioral and exposure characteristics for cases and controls were evaluated by univariate analyses using logistic regression. Age, cigarette smoking, current alcohol use and visits to a doctor were coded as indicator variables (0 if no visits, 1 if one visit and 2 if more than one visit) to obtain odds ratios (OR) and 95% confidence intervals (CIs) for effects over categories. Multivariable logistic regression analysis was used to determine whether a pesticide exposure category was associated with diagnosed depression, controlling for the demographic and behavioral factors and solvents and other exposures that were significantly associated with depression in the univariate analyses. ORs with 95% CIs are reported from the univariate and multivariate analyses.

Individual pesticides were initially examined in four broad categories: as ever use of insecticides, herbicides, fumigants and fungicides. Insecticide products included permethrin, terbufos, fonofos, trichlorfon, lindane, carbofuran, chlorpyrifos, malathion, parathion, carbaryl, diazinon, aldicarb, phorate, aldrin, chlordane, dieldrin, DDT, heptachlor, toxaphene, coumaphos, and dichlorvos. Herbicide products included atrazine, dicamba, cyanazine, chlorimuron ethyl, metolachlor, EPTC, alachlor, metribuzin, paraquat, petroleum oil, pendimethalin, imazethapyr, glyphosate, 2,4,5 T P, butylate, trifluralin, 2,4-D, and 2,4,5 T. Fungicide products included benomyl, chlorothalonil, captan, maneb, metalaxyl, and ziram. Fumigant products included methyl bromide, aluminum phosphide, carbon tetrachloride/ carbon disulfide and ethylene dibromide. Secondly, a principal component analysis (PCA) was used to create groupings of related-use pesticides. Specific chemicals were considered correlated with each factor if they had a factor loading of 40 or greater, which represents approximately a 15% overlap of the variance in pesticide use with the factor. Factors were considered significant if they had eigenvalues greater than one. The factors were used in unadjusted and adjusted logistic regression models to determine whether they were associated with diagnosed depression.

All analyses were conducted using SAS, version 8.2, SAS Institute, Cary, North Carolina. The August 2, 2002, release of the AHS phase I dataset was used in these analyses. This work was conducted with approval from the Institutional Review Board of Colorado State University.

RESULTS

There were 2,051 (7.1% of the population) self-reported cases of diagnosed depression requiring medication. The prevalence of diagnosed depression was significantly higher in North Carolina (8.1%) than in Iowa (6.6 %) with an unadjusted OR of 1.25 (CI 1.14, 1.37) (Table 1). This difference was largely eliminated after adjusting for smoking, alcohol use, and number of visits to a doctor (OR 1.04; CI 0.94, 1.16).

Depression was more common among whites and older women and among those without a high school education, using alcohol or tobacco, having more doctor visits, and having worked off the farm (Table 1). The number of years lived on farms did not differ between cases and controls (mean 31.9 years with a standard deviation of 18 years). Cases were more likely to have personally mixed or applied pesticides than controls, but unadjusted ORs among those who mixed or applied pesticides more than 50% of the time were not greater than among those who mixed or applied less frequently (Table 1). Cases were more likely to have been exposed to solvents or to have personally applied pesticides to their home or lawn (Table 1).

Unadjusted ORs for depression were 1.11 (CI 1.01, 1.22) among those mixing or applying for up to 225 days, 1.22 (CI 1.02, 1.45) for greater than 225 days and 3.97 (CI 2.18, 7.21) among those reporting a history of pesticide poisoning. Depression was significantly associated with the use of insecticides, fumigants, and fungicides, and nearly significant for herbicides (Table 1).

In multivariable models, items significantly associated with the risk of depression included race, age, alcohol use, cigarette smoking, number of doctor visits in the past year, solvent exposure and history of pesticide poisoning (Table 2). Adjusting percent of time personally mixing or applying pesticides by the same covariates used in Table 2 in separate analyses, showed a reduction in the size and precision of the association of (applying < 50%: OR 1.06 CI 0.94–1.20 applying ≥ 50%: OR 1.08 CI 0.95–1.23; mixing < 50%: OR 1.13 CI 1.00–1.28 mixing > 50%: OR 1.06 CI 0.91–1.24). In adjusted models, ORs (95% CIs) were elevated but statistically insignificant for insecticides (1.09, 0.99–1.20), herbicides (1.07, 0.97–1.18), fumigants (1.25, 0.91–1.72) and fungicides (1.12, 0.91–1.38). The risk of depression from

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pesticide poisoning was relatively unaffected by adjusting for different covariates or stratifying by state (Table 3).

A separate analysis was conducted excluding the 27 women who reported a history of pesticide poisoning but responded negatively to the question about personal use of pesticides, although ten of these women reported that they personally treated their homes or lawns for pests in another section of the questionnaire. ORs for history of pesticide poisoning and diagnosed depression remained elevated after excluding the 27 women, but both effect size and precision were reduced in univariate models (OR 1.74, CI 0.61, 4.92) and after adjusting for state of residence, race, age, ever worked a job off the farm, doctor visits, cigarette smoking, current alcohol use and solvent exposure (OR 1.56, CI 0.54, 4.56).

The PCA identified four significant factors (Table 4). Factor 1, which explained most of the variance of pesticide use with an eigenvalue of 14.9, was composed of thirteen herbicides, three OP insecticides and one carbamate. This factor was not associated with diagnosed depression in a univariate logistic regression model, or after adjustment for state of residence, race, age, ever worked a job off the farm, doctor visits, cigarette smoking, current alcohol use and solvent exposure (Table 5). Factor 2 was correlated with four organochlorine insecticides, Factor 3 with two OP insecticides, one carbamate insecticide and two herbicides and Factor 4 with one fumigant and three fungicides (Table 5). In unadjusted analyses, Factors 3 and 4 showed weak, but statistically significant, associations with depression (Table 5). After adjustment for the above covariates, none of the factors were associated with depression (Table 5).

DISCUSSION

In this study, a history of pesticide poisoning was significantly associated with self-reported physician diagnosed depression among female spouses of private pesticide applicators, after controlling for other risk factors. The association was observed in both Iowa and North Carolina. The association with depression was considerably stronger among individuals with past pesticide poisoning episodes than among individuals with no such reported episodes. This finding is similar to the reports on neuropsychological outcomes that addressed mood disorders [13,14,26–28] where individuals with pesticide exposure, but no history of poisoning, showed few mood disorders, but mood disorders have been observed in those with a history of a high level of exposure or a history of poisoning [4–6,29].

At the low and high cumulative exposure levels observed in this study, no association was observed with depression in adjusted models. Potential misclassification of exposure is always a concern and it is impossible to know whether a history of depression would create a differential bias, which could either inflate or reduce the OR in the two-level exposure variable.

The prevalence of self-reported physician diagnosed depression in this study (7.1%) was similar to the prevalence of 6% to 8% of diagnosed depression found in studies of primary care medical practices. Using diagnosed depression as the outcome may select for those with major depression, rather than dysthymic disorder or intermittent, milder episodes of depression [18,30]. Previous work has shown that major depression is the type most frequently diagnosed by a physician [31]. Physicians tend to under-recognize depression in their patients, and only one-third to two-thirds of depressed individuals are diagnosed with depression by a primary care physician [32–34]. Because symptoms may be transitory, previous cross-sectional studies using standardized scales may have identified a broader range of depression types. Agricultural workers may underutilize mental health resources due to the complexities of farm life, further contributing to failure to detect mild depression [35]. Under diagnosis of depression in this farming population would result in the misclassification of cases of depression as non-cases and attenuate the OR observed in this study.

Non-pesticide risk factors for depression in this population were similar to those in previous studies of farm residents. Age, health status, current smoking, binge drinking, involvement with farm work, and working a job off the farm have been associated with depressive symptoms in several farming communities [19,36–38].

Although the frequency and duration of pesticide exposure among female spouses in the AHS was generally lower than among the licensed applicators, the cohort includes a subset of spouses who may have pesticide exposures quite similar to those of their applicator husbands [22]. Women who reported at least one lifetime application day, and those with no history of pesticide poisoning had a median number of lifetime-exposure days of 50.8 while those who reported a pesticide poisoning had a median number lifetime-exposure days of 8.8. The low median number of days in the poisoned groups makes it unlikely that low-dose, long-term exposure is acting as a confounder of pesticide poisoning [14], particularly since 27 of the 63 women with poisonings reported no use of pesticides and another 25 had < 225 days of use.

Twenty-seven women, who reported a history of poisoning, reported never having personally mixed or applied pesticides. However, in a separate section of the questionnaire, eight of these women reported personally treating their homes and two reported personally treating their lawns for pests. Treating one's home for pests was associated with diagnosed depression in this study. The fact that 18.8% of the women who responded that they used pesticides in the home or on pets did not report personally mixing or applying pesticides suggests that some pesticide exposures may be missed when questions are asked in the context of agricultural use. Domestic use of pesticides may be an important source of pesticide poisoning. Excluding the 27 women who reported poisoning, but no farm-related use from the analysis reduced the association of pesticide use with depression. This suggests that domestic poisonings have important health consequences. Alternatively, it is possible that a woman with a pesticide poisoning but no pesticide use might have used pesticides in a suicide attempt.

This study suggests that the association of pesticides with depression was more likely to be related to insecticides, fungicides, or fumigants and less likely associated with herbicides or organochlorine insecticides. Thirteen herbicides loaded onto Factor 1, but three OPs and one carbamate did so also. The organochlorine insecticides loaded separately on Factor 2 with an OR of one and were least likely to be associated with depression. This supports the finding of Savage et al., 1988, where no association of neurological effects with measured organochlorine pesticide residues was observed in a group of pesticide-poisoned applicators [4]. Factors 3 and 4 showed a very weak association to depression. Perhaps this is not surprising since the factors are based on use patterns of pesticides and not on possible risk for depression. Additionally, chemical mixtures and solvents added to the pesticide may play a role in contributing to the associations observed in this study. The PCA analysis herein excluded male spouses and demographic variables, making the results of the PCA in this study different from the factor analysis of the AHS cohort published by Samanic et al., 2005 [39].

The literature implicates OPs as one candidate for depressive effects [1,4,9,40], but few studies have reported on other classes of pesticides and depression. The effects of OPs on acetylcholinesterases are well known, but animal studies also indicate that other carboxylesterases exist in the central nervous system that are more sensitive to OPs than acetylcholinesterases [41,42]. There is also evidence that certain OPs may target neuropeptide metabolism in the central nervous system [43,44]. Recently OP compounds were shown to inhibit lysophospholipases, such as neuropathic target esterase (NTE), which is the putative target of OP-induced delayed neuropathy [45–47]. This inhibition increases the levels of lysolecithin in

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the cell, resulting in demyelination of axons and alterations in signaling from the cell membrane [45,48].

The strengths of this study include the large number of cases of diagnosed depression and the detailed questionnaire containing information on pesticide use history and other risk factors for depression. Limitations include the cross-sectional study design and the use of self-reported information for both physician-diagnosed depression and diagnosed pesticide poisoning. Information on the date of diagnosis of depression and on the date of pesticide poisoning was available only in 20-year age categories restricting our ability to make inferences about temporality.

Despite these limitations, this study suggests that farm women, who are not themselves licensed applicators, and who generally spend less time mixing and applying pesticides than farmer applicators, have an increased odds of having a physician diagnosed depression in the presence of a history of pesticide poisoning. This study highlights the importance of preventing pesticide poisoning since the chronic effects of those poisonings may contribute to high rates of depression.

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References

1. Dille JR, Smith PW. Central nervous system effects of chronic exposure to organophosphate insecticides. Aerospace Med 1964;35:475–478.
2. Ray DE, Richards P. The potential toxic effects of chronic, low-dose exposure to organophosphates. Toxicol Lett 2001;120:343–351. [PubMed: 11323193]
3. Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect 2004;112:950–958. [PubMed: 15198914]
4. Savage EP, Keefe TJ, Mounce LM, Heaton RK, Lewis JA, Burcar BJ. Chronic neurological sequelae of acute pesticide poisoning. Arch Env Health 1988;43:38–45. [PubMed: 3355242]
5. Reidy TJ, Bowler RM, Rauch SS, Pedrozza GI. Pesticide exposure and neuropsychological impairment in migrant farm workers. Arch Clin Neuropsychol 1992;7:85–95. [PubMed: 14589681]
6. Amr MM, Halim ZS, Moussa SS. Psychiatric disorders among Egyptian pesticide applicators and formulators. Environ Res 1997;73:193–199. [PubMed: 9311547]
7. Stallones L, Beseler C. Pesticide poisoning and depressive symptoms among farm residents. Ann of Epidemiol 2002;12:389–394. [PubMed: 12160597]
8. Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurological sequelae to organophosphate pesticide poisoning. Am J Public Health 1994;84:731–736. [PubMed: 8179040]
9. Farahat TM, Abdelrasoul GM, Amr MM, Shebl MM, Farahat FM, Anger WK. Neurobehavioral effects among workers occupationally exposed to organophosphorous pesticides. Occup Environ Med 2003;60:279–286. [PubMed: 12660376]
10. Salvi RM, Lara DR, Ghisolfi ES, Portela LV, Dias RD, Souza DO. Neuropsychiatric evaluation in subjects chronically exposed to organophosphate pesticides. Toxicol Sci 2003;72:267–271. [PubMed: 12660361]
11. Stephens R, Spurgeon A, Calvert IA, Beach J, Levy LS, Berry H, Harrington JM. Neuropsychological effects of long-term exposure to organophosphates in sheep dip. Lancet 1995;345:1135–1139. [PubMed: 7723544]
12. Albers JW, Garabrant DH, Schweitzer SJ, Garrison RP, Richardson RJ, Berent S. The effects of occupational exposure to chlorpyrifos on the peripheral nervous system: a prospective cohort study. Occup Environ Med 2004;61:201–211. [PubMed: 14985514]
13. Daniell W, Barnhart S, Demers P, Costa L, Eaton DL, Miller M. Neuropsychological performance among agricultural pesticide applicators. Environ Res 1992;59:217–228. [PubMed: 1425511]

14. Fielder N, Kipen H, Kelly-McNeil K, Fenske R. Long-term use of organophosphates and neuropsychological performance. Am J Ind Med 1997;32:484–496.
15. Kornstein SG. Gender differences in depression: Implications for treatment. J Clin Psychiatry 1997;58:12–18. [PubMed: 9427872]
16. Bhatia SC, Bhatia SK. Depression in Women: Diagnostic and Treatment Considerations. Am Fam Physician 1999;60:225–240. [PubMed: 10414640]
17. Kornstein SG, Schatzberg AF, Yonkers KA, et al. Gender differences in presentation of chronic major depression. Psychopharmacological Bull 1996;31:711–718.
18. Aneshensel CS. The natural history of depressive symptoms. Res Commun Mental Health 1985;5:45–74.
19. Carruth AK, Logan CA. Depressive symptoms in farm women: effects of health status and farming lifestyle characteristics, behaviors and beliefs. J Community Health 2002;27:213–228. [PubMed: 12027271]
20. Engberg L. Women and agricultural work. Occup Med 1993;8:869–882. [PubMed: 8303498]
21. Stallones L, Beseler C. Farm work practices and farm injuries in Colorado. Injury Prevention 2003;9:241–244. [PubMed: 12966013]
22. Kirrane EF, Hoppin JA, Umbach DM, Samanic C, Sandler DP. Patterns of pesticide use and their determinants among wives of farmer pesticide applicators in the Agriculltural Health Study. J Occup Environ Med 2004;46:856–865. [PubMed: 15300138]
23. Blair A, Sandler D, Thomas K, Hoppin JA, Kamel F, Coble J, Lee WJ, Rusiecki J, Knott C, Dosemeci M, Lynch CF, Lubin J, Alavanja M. Disease and injury among participants in the Agricultural Health Study. J Agricult Safety Health 2005;11:141–150.
24. Walker B Jr. Neurotoxicity in human beings. J Lab Clin Med 2000;136:168–180. [PubMed: 10985495]
25. Willer BS, Allen KM, Zicht MS. Problems and coping strategies of individuals with traumatic brain injury and their spouses. Arch Phys Med Rehabil 1991;72:460–464. [PubMed: 2059116]
26. Rodnitzky RL, Levin HS, Mick DL. Occupational exposure to organophosphate pesticides. Arch Environ Health 1975;30:98–103. [PubMed: 1115534]
27. Maizlish N, Schenker M, Weisskopf C, Selber J, Samuels S. A behavioral Evaluation of Pest Control Workers with short-term, low-level exposure to the organophosphate diazinon. Am J Ind Med 1987;12:153–172. [PubMed: 3661569]
28. Ames RG, Steenland K, Jenkins B, Chrislip D, Russo J. Chronic neurologic sequelae to cholinesterase inhibition among agricultural pesticide applicators. Arch Environ Health 1995;50:440–444. [PubMed: 8572722]
29. Rosenstock L, Keifer M, Daniell WE, McConnell R, Claypole K. Chronic central nervous system effects of acute organophosphate pesticide intoxication. Lancet 1991;338:223–227. [PubMed: 1676786]
30. APA. 4th edition ed. Washington, DC: American Psychiatric Association; 1994. Diagnostic and statistical manual of mental disorders: DSM-IV.
31. Carney PA, Dietrich AJ, Eliassen MS, Owen M, Badger LW. Recognizing and managing depression in primary care: A standardized patient study. J Fam Pract 1999;48:965–972. [PubMed: 10628577]
32. Perez-Stable E, Miranda J, Munoz R, Ying Y. Depression in medical outpatients: Underrecognition and misdiagnosis. Arch Intern Med 1990;150:1083–1088. [PubMed: 2184790]
33. Coyne J, Schwenck T, Fechner-Bates S. Nondetection of depression by primary care physicians reconsidered. Gen Hosp Psychiatry 1995;17:3–12. [PubMed: 7737492]
34. Simon G, VonKorff M. Recognition, management, and outcomes of depression in primary care. Arch Fam Med 1995;4:99–105. [PubMed: 7842160]
35. May J. Agriculture: Work practices and health consequences. Semin Resp Med 1993;14:1–7.
36. Linn JG, Husaini BA. Determinants of psychological depression and coping behaviors of Tennessee farm residents. J Community Psychol 1987;15:503–513.
37. Booth NJ, Lloyd K. Stress in farmers. Int J Soc Psychiatry 1999;46:67–73. [PubMed: 14529080]
38. Stallones L, Leff M, Garrett C, Criswell L, Gillan T. Depressive symptoms among Colorado farmers. J Agricult Safety Health 1995;1:37–43.

39. Samanic C, Hoppin JA, Lubin JH, Blair A, Alavanja MCR. Factor analysis of pesticide use patterns among pesticide applicators in the Agricultural Health Study. J Exposure Anal Environ Epidemiol 2005;15:225–233.
40. Steenland K, Dick RB, Howell RJ, Chrislip DW, Hines CJ, Reid TM, Lehman E, Laber P, Krieg EF Jr, Knott C. Neurological function among termiticide applicators exposed to chlorpyrifos. Environ Health Perspect 2000;108:293–300. [PubMed: 10753086]
41. Chanda SM, Mortensen SR, Moser VC, Padilla S. Tissue-specific effects of chlorpyrifos on carboxylesterase and cholinesterase activity in adult rats: an *in vitro* and *in vivo* comparison. Fundam Appl Toxicol 1997;38:148–157. [PubMed: 9299188]
42. Chemnitius JM, Zech R. Inhibition of brain carboxylesterases by neurotoxic and non-neurotoxic organophosphorus compounds. Mol Pharmacol 1983;23:717–723. [PubMed: 6865914]
43. O'Neill JJ. Non-cholinesterase effects of anti-cholinesterases. Fundam Appl Toxicol 1981;1:154–160. [PubMed: 6192030]
44. Richards P, Johnson MK, Ray DE. Identification of acylpeptide hydrolase as a sensitive site for reaction with organophosphorus compounds and a potential target for cognitive enhancing drugs. Mol Pharmacol 2000;58:577–583. [PubMed: 10953051]
45. Quistad GB, Barlow C, Winrow CJ, Sparks SE, Casida JE. Evidence that mouse brain neuropathy target esterase is a lysophospholipase. Proc Natl Acad Sci 2003;100:7983–7987. [PubMed: 12805562]
46. Quistad GB, Casida JE. Lysophospholipase inhibition by organophosphorus toxicants. Toxicol Appl Pharmacol 2004;196:319–326. [PubMed: 15094302]
47. Zaccheo O, Dinsdale D, Meacock PA, Glynn P. Neuropathy target esterase and its yeast homologue degrade phosphatidylcholine to glycerophosphocholine in living cells. J Biol Chem 2004;279:24024–24033. [PubMed: 15044461]
48. Wang A, Dennis EA. Mammalian lysophospholipases. Biochim Biophys Acta 1999;1439:1–16. [PubMed: 10395961]

Table 1

Associations of depression with demographic, behavioral, and pesticide exposure characteristics in 29,074 Iowa and North Carolina female spouses of farmer pesticide applicators, AHS, 1993–1997; unadjusted odds ratios (ORs) with 95% confidence intervals (CIs)

Characteristic	Cases (n=2051) n (%)	Controls (n=27023) n (%)	OR (95% C.I.)
State of residence			
Iowa	1322 (64.5)	18751 (69.4)	reference
North Carolina	729 (35.5)	8272 (30.6)	1.25 (1.14, 1.37)
Race			
White	2028 (99.0)	26502 (98.2)	reference
Non-white	20 (1.0)	477 (1.8)	0.55 (0.35, 0.86)
Hispanic ethnicity			
No	1993 (99.2)	26314 (99.1)	reference
Yes	16 (0.8)	237 (0.9)	0.89 (0.54, 1.48)
Age quartiles			
< 40	485 (23.6)	8500 (31.5)	reference
40 – 49	666 (32.5)	7672 (28.4)	1.52 (1.35, 1.72)
50 – 59	575 (28.0)	6361 (23.5)	1.58 (1.40, 1.80)
> 59	325 (15.9)	4490 (16.6)	1.27 (1.10, 1.47)
High school graduate			
Yes	1682 (93.8)	23069 (94.9)	reference
No	111 (6.2)	1249 (5.1)	1.22 (1.00, 1.49)
Alcohol use in past year			
Never	979 (48.2)	11979 (44.8)	1.28 (1.09, 1.51)
≤ 3 times per month	831 (40.9)	11526 (43.1)	1.13 (0.96, 1.33)
1 – 4 times per week	184 (9.1)	2884 (10.8)	reference
Every/almost every day	36 (1.8)	360 (1.3)	1.57 (1.08, 2.28)
Cigarette smoking			
Never	1294 (64.8)	19279 (73.0)	reference
Past	417 (20.9)	4560 (17.3)	1.36 (1.21, 1.53)
Current	286 (14.3)	2572 (9.7)	1.66 (1.45, 1.90)
Doctor visits in past year			
None	137 (6.7)	5850 (21.8)	reference
Once	376 (18.4)	7955 (29.6)	2.02 (1.66, 2.46)
More than once	1530 (74.9)	13043 (48.6)	5.01 (4.19, 5.98)
Ever worked job off the farm			
No	179 (8.8)	2955 (11.0)	reference
Yes	1853 (91.2)	23785 (89.0)	1.29 (1.10, 1.51)
Lived on farm 10 years ago			
No	414 (20.2)	5168 (19.2)	reference
Yes	1631 (79.8)	21796 (80.8)	0.93 (0.84, 1.04)
Ever personally mixed or applied pesticides			
No	854 (41.6)	12047 (44.6)	reference
Yes	1197 (58.4)	14974 (55.4)	1.13 (1.03, 1.24)
% of time personally mixed pesticides			
Never	1188 (67.2)	16310 (70.1)	reference
< 50%	368 (20.8)	4231 (18.2)	1.19 (1.06, 1.35)
50% or more	212 (12.0)	2714 (11.7)	1.07 (0.92, 1.25)
% of time personally applied pesticides			
Never	918 (52.0)	12805 (55.2)	reference
< 50%	468 (26.5)	5649 (24.3)	1.16 (1.03, 1.30)
50% or more	378 (21.4)	4762 (20.5)	1.11 (0.98, 1.25)
Pesticide exposure levels*			
Never mixed/applied	1162 (56.9)	16134 (60.0)	reference
Low: 1–225 days	716 (35.0)	8980 (33.4)	1.11 (1.01, 1.22)
High: >225 days	152 (7.4)	1736 (6.4)	1.22 (1.02, 1.45)
Diagnosed poisoning	14 (0.7)	49 (0.2)	3.97 (2.18, 7.21)
Exposed to solvents			
No	1824 (88.9)	24863 (92.0)	reference
Yes	227 (11.1)	2160 (8.0)	1.43 (1.24, 1.66)
Personally treated home for pests			
No	1393 (67.9)	19533 (72.3)	reference
Yes	658 (32.1)	7490 (27.7)	1.23 (1.12, 1.36)
Personally treated lawn for pests			
No	1802 (87.9)	24130 (89.3)	reference
Yes	249 (12.1)	2893 (10.7)	1.15 (1.00, 1.32)
Ever use insecticides			
No	1189 (58.0)	16675 (61.7)	reference
Yes	862 (42.0)	10348 (38.3)	1.17 (1.07, 1.28)
Ever use herbicides			
No	1267 (61.8)	17222 (63.7)	reference
Yes	784 (38.2)	9801 (36.3)	1.09 (0.99, 1.19)
Ever use fumigants			
No	2005 (97.8)	26579 (98.4)	reference

Characteristic	Cases (n=2051) n (%)	Controls (n=27023) n (%)	OR (95% C.I.)
Yes	46 (2.2)	444 (1.6)	1.37 (1.01, 1.87)
Ever use fungicides			
No	1938 (94.5)	25821 (95.6)	reference
Yes	113 (5.5)	1202 (4.4)	1.25 (1.03, 1.53)

* The exposure categories are: never personally applied or mixed pesticides; low exposure includes those exposed to 225 days or less (the 90th percentile); the high group is comprised of those with > 225 days of exposure; diagnosed poisoning group reported a pesticide poisoning.

Table 2

Association of diagnosed depression with pesticide exposure in female spouses of private pesticide applicators, controlling for demographic and behavioral characteristics shown to be significant in the univariate analysis AHS, 1993–1997 (n=1966 cases and 25886 controls).*

Variable	Adjusted OR ** (95% CI)
State of residence	
Iowa	reference
North Carolina	1.08 (0.97, 1.21)
Race	
White	reference
Non-white	0.47 (0.29, 0.74)
Age	
< 40	reference
40 – 49	1.53 (1.35, 1.73)
50 – 59	1.51 (1.33, 1.73)
> 59	1.14 (0.97, 1.34)
Alcohol use in past year	
Never	1.28 (1.08, 1.53)
≤ 3 times per month	1.15 (0.97, 1.36)
1 – 4 times per week	reference
Every/almost every day	1.24 (0.83, 1.86)
Cigarette smoking	
Never	reference
Past	1.31 (1.17, 1.48)
Current	1.66 (1.44, 1.92)
Doctor visits	
No visits	reference
1 visit	1.99 (1.63, 2.44)
2+ visits	4.93 (4.12, 5.91)
Ever worked job off the farm	
No	reference
Yes	1.17 (0.99, 1.39)
Exposed to solvents	
No	reference
Yes	1.37 (1.18, 1.60)
Pesticide exposure levels**	
Never mixed/applied	reference
Low: 1 – 225 days	1.06 (0.96, 1.18)
High: 226–7000 days	1.09 (0.91, 1.31)
Diagnosed poisoning	3.26 (1.72, 6.19)

* Model adjusted for state, race, age, working a job off the farm, doctor visits, alcohol use, cigarette smoking and solvent exposure; 1,222 had missing information in multivariable analysis

** The exposure categories are: never personally applied or mixed pesticides; low exposure includes those exposed to 225 days or less (the 90th percentile); the high group has > 225 days of exposure; the diagnosed poisoning group reported a pesticide poisoning.

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Table 3

Association of diagnosed depression with pesticide exposure by state of residence, female spouses of private applicators, AHS, 1993–1997.

Exposure model*	Iowa (n=20073) OR (95% CI)	North Carolina (n= 9001) OR (95% CI)
Model 1: Exposure levels		
Never mixed/applied	reference	reference
Low: </= 225 days	1.08 (0.96, 1.22)	1.28 (1.08, 1.53)
High: 226–7000 days	1.24 (0.99, 1.54)	1.19 (0.89, 1.59)
Diagnosed poisoning	2.82 (1.25, 6.33)	7.22 (2.83, 18.4)
Model 2: Exposure levels		
Never mixed/applied	reference	reference
Low: </= 225 days	1.06 (0.94, 1.19)	1.27 (1.06, 1.51)
High: 226–7000 days	1.17 (0.93, 1.46)	1.12 (0.84, 1.50)
Diagnosed poisoning	2.72 (1.21, 6.14)	7.00 (2.73, 17.9)
Model 3: Exposure levels		
Never mixed/applied	reference	reference
Low: </= 225 days	1.03 (0.91, 1.16)	1.21 (1.01, 1.44)
High: 226–7000 days	1.15 (0.92, 1.44)	1.07 (0.80, 1.44)
Diagnosed poisoning	2.81 (1.22, 6.43)	5.72 (2.19, 15.0)
Model 4: Exposure levels		
Never mixed/applied	reference	reference
Low: </= 225 days	1.03 (0.91, 1.16)	1.15 (0.96, 1.38)
High: 226–7000 days	1.12 (0.89, 1.41)	1.04 (0.77, 1.40)
Diagnosed poisoning	2.57 (1.11, 5.95)	4.61 (1.64, 13.0)

* Model 1, unadjusted; Model 2, age-adjusted; Model 3, adjusted by age and visits to a doctor; Model 4 adjusted using all variables in Table 2.

Table 4

Factor loadings from principal components analysis of individual pesticides in female spouses of private pesticide applicators, AHS, 1993–1997.

Factor 1		Factor 2		Factor 3		Factor 4	
Herbicides:		Organochlorines:		OPs:		Fumigants:	
atrazine	68			malathion	65	methyl bromide	50
dicamba	66	aldrin	62	diazinon	48	Fungicides:	
cyanazine	70	dieldrin	56	Carbamate:		benomyl	41
metolachlor	72	DDT	40	carbaryl	58	chlorothalonil	41
EPTC	60	heptachlor	62	Herbicides:		maneb/mancozeb	49
alachlor	69			glyphosate	51	metalaxyl	60
metribuzin	64			2,4-D	47		
petroleum oil	48						
pendimethalin	62						
imazethapyr	71						
butylate	51						
trifluralin	64						
chlorimuron ethyl	55						
OPs:							
terbufos	54						
fonofos	46						
chlorpyrifos	45						
Carbamate:							
carbofuran	43						

* Results of varimax rotated factor analysis of specific pesticide exposures correlated to four significant factors and their factor loadings with the four factors. Factors with an eigenvalue of at least 1.0 were retained in the factor analysis. Pesticides with a factor loading of 40 or greater (at least a 15% overlap of the variance in pesticide use with the factor considered) are reported here. The PCA result represents 31 of the 50 pesticides considered in the AHS; the other 19 had factor loadings of less than 40.

Table 5

Association of diagnosed depression with individual factors derived from PCA of pesticides used by female spouses of private applicators, AHS, 1993–1997. *

Factor	Univariate OR (95% CI)	Adjusted OR (95% CI)
Factor 1	0.98 (0.94, 1.04)	1.01 (0.96, 1.06)
Factor 2	1.01 (0.96, 1.07)	1.00 (0.95, 1.06)
Factor 3	1.09 (1.03, 1.14)	1.05 (0.99, 1.11)
Factor 4	1.07 (1.02, 1.12)	1.03 (0.98, 1.09)

* Factor scores were compared between cases and non-cases. Separate analyses were run for each factor.

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