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Pesticide Exposure and Self-Reported Incident Depression among Wives in the Agricultural Health Study

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Abstract

Background—Depression in women is a public health problem. Studies have reported positive associations between pesticides and depression, but few studies were prospective or presented results for women separately.

Objectives—We evaluated associations between pesticide exposure and incident depression among farmers' wives in the Agricultural Health Study, a prospective cohort study in Iowa and North Carolina.

Methods—We used data on 16,893 wives who did not report physician-diagnosed depression at enrollment (1993-1997) and who completed a follow-up telephone interview (2005-2010). Among these wives, 1,054 reported physician diagnoses of depression at follow-up. We collected information on potential confounders and on ever use of any pesticide, 11 functional and chemical classes of pesticides, and 50 specific pesticides by wives and their husbands via self-administered questionnaires at enrollment. We used inverse probability weighting to adjust for potential confounders and to account for possible selection bias induced by the death or loss of 10,639 wives during follow-up. We used log-binomial regression models to estimate risk ratios and 95% confidence intervals.

Results—After weighting for age at enrollment, state of residence, education level, diabetes diagnosis, and not dropping out of the cohort, wives' incident depression was positively associated with diagnosed pesticide poisoning, but was not associated with ever using any pesticide. Use of individual pesticides or functional or chemical classes of pesticides was generally not associated with wives' depression. Among wives who never used pesticides, husbands' ever use of individual

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pesticides or functional or chemical classes of pesticides was generally not associated with wives' incident depression.

Conclusions—Our study adds further evidence that high level pesticide exposure, such as pesticide poisoning, is associated with increased risk of depression and sets a lower bound on the level of exposure related to depression, thereby providing reassurance that the moderate levels of pesticide exposure experienced by farmers' wives likely do not increase risk.

Keywords

depression; female; incidence; pesticides; spouses

1. Introduction

The lifetime prevalence of doctor diagnosed depression among American women was recently reported as 20.2%, which was almost double the prevalence (11.1%) in American men (Strine et al., 2008). Although the cause of the higher prevalence of depression among women, and the cause of depression in general, remains unknown, it has been hypothesized to involve both biological susceptibilities and environmental risk factors (Kessler, 2003).

Higher rates of depression and other psychiatric conditions have been linked to exposure to pesticides, particularly organophosphate insecticides, and living on or near farms (Bazylewicz-Walczak et al., 1999; Beseler and Stallones, 2008; Beseler et al., 2006, 2008; Carruth and Logan, 2002; London et al., 2005; Mackenzie Ross et al., 2010; Meyer et al., 2010; Rehner et al., 2000; Salvi et al., 2003; Stallones and Beseler, 2002a, 2002b; Villeneuve et al., 2009; Wesseling et al., 2010). Only a few of the previous studies of pesticide exposure and depression, however, were prospective (Bazylewicz-Walczak et al., 1999; Beseler and Stallones, 2008; Salvi et al., 2003). The largest of these was a longitudinal study of about 600 farmers and their spouses in Colorado (Beseler and Stallones, 2008). In that study, depression was assessed annually for three years using the Center for Epidemiological Studies-Depression Scale (Beseler and Stallones, 2008), which assesses depression during the past week (Radloff, 1977). Farmers and their spouses who reported past pesticide poisoning at baseline were twice as likely to be classified as depressed during follow-up compared to those who did not report pesticide poisoning (Beseler and Stallones, 2008). However, associations for women were not reported separately from men in that study and associations between depression and specific pesticides, pesticide classes, or chronic, low-dose pesticide exposure were not assessed.

Four studies have evaluated pesticide exposure and depression in women (Bazylewicz-Walczak et al., 1999; Beseler et al., 2006; Carruth and Logan, 2002; Meyer et al., 2010). Bazylewicz-Walczak et al. (1999) administered the Profile of Mood States to 51 women working in the gardening industry in Poland (26 exposed to organophosphate insecticides for one season, March-June, and 25 not exposed) and found exposed women experienced greater tension, depression, and fatigue compared to unexposed women. A cross-sectional survey of 657 randomly sampled farm women in Louisiana found that women who reported pesticide use were more likely to report depressive symptoms than those who did not use pesticides (Carruth and Logan, 2002). Residents of an agricultural area of Brazil with an intensive use of pesticides had higher rates of hospitalization for mood disorders (International Classification of Diseases, 10th Revision codes F30-F39) than two reference areas (Meyer et al., 2010). In the Agricultural Health Study, wives who had ever received a physician-diagnosis of pesticide poisoning were more likely to report ever receiving a physician-diagnosis of depression than those without pesticide poisoning (Beseler et al.,

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2006). Relationships between specific pesticides and depression were not evaluated in any of these studies.

The Agricultural Health Study is a prospective cohort study of 57,310 licensed pesticide applicators (private and commercial) in Iowa and North Carolina and 32,345 spouses of private applicators. It was designed to assess associations between pesticides and other agricultural hazards and cancer and non-cancer endpoints (Alavanja et al., 1996). In addition to the study of wives (Beseler et al., 2006), a higher prevalence of depression was previously reported among male applicators in the Agricultural Health Study who experienced a past pesticide poisoning or who reported ever using pesticides from several different pesticide classes (Beseler et al., 2008). Neither study, however, evaluated relationships between specific pesticides and depression and both used cross-sectional designs (Beseler et al., 2006, 2008). The current analysis evaluates associations between both general and specific pesticide use and self-reported, incident depression among wives in the Agricultural Health Study.

2. Materials and Methods

2.1. Study population and case definition (Figure 1)

The Agricultural Health Study cohort was assembled in 1993-1997 by enrolling pesticide applicators who were at state facilities to receive or renew their pesticide-use licenses (Alavanja et al., 1996); 84% of eligible applicators enrolled by completing a questionnaire. Additional questionnaires were sent home with married private applicators to enroll their spouses (Alavanja et al., 1996); 32,345 spouses (75% of those eligible) enrolled. We excluded 4,380 spouses from this analysis because they were male (219; < 1%), reported having been diagnosed with depression by a physician at enrollment (2,252; 7%; prevalent depression), were missing data on depression at enrollment (1,345; 4%), or were missing covariate data (564; 2%).

Incident depression was ascertained through a follow-up telephone interview completed in 2005-2010. On average, the time between enrollment in the Agricultural Health Study and the follow-up interview was 11.9 years. Of 27,965 eligible wives, 10,639 (38%) did not complete the follow-up interview (1,342 because of death). We further excluded 433 wives because they reported an age at depression diagnosis prior to their age at enrollment in the Agricultural Health Study (402; 1%; prevalent depression) or were missing data on age at depression diagnosis (31; < 1%). In total, we included 16,893 wives in this analysis: 1,054 (6%) who reported ever having been diagnosed with depression (incident depression cases) and 15,839 (94%) who did not (non-cases) (Figure 1).

Information on depression was ascertained using four different questions (Agricultural Health Study, 2012). Prevalent depression was ascertained via the enrollment questionnaire using the question "Has a DOCTOR ever told you that you had (been diagnosed with)... [d]epression requiring medication? (No, Yes)". Incident depression was ascertained through a follow-up telephone interview via the question "Have you ever been diagnosed with depression? (No, Yes)". Age at depression diagnosis was ascertained at follow-up via the question "How old were you when you were first diagnosed with depression? (years)". We assigned any wife who reported an age at depression diagnosis that was less than her age at enrollment to have prevalent depression. Treatment of depression with medications was ascertained among incident cases at follow-up via the question "Are you currently taking any prescribed medicines for depression? (No, Yes)". We used all incident depression cases for our main analyses, but conducted a sensitivity analysis in which we refit models restricting incident depression cases to wives who had taken medication for their depression.

The Agricultural Health Study was approved by the Institutional Review Boards of the National Institutes of Health and its contractors; the current analysis involving coded data was exempted from review by the Institutional Review Board of the University of North Carolina at Chapel Hill. All participants provided implied informed consent by completing and returning the enrollment questionnaires after the study was explained to them.

2.2. Exposure assessment

Information on demographics, medical conditions, lifestyle, pesticide use, and other agricultural hazards and practices was collected from wives and their applicator husbands via self-administered questionnaires at enrollment in the Agricultural Health Study (Agricultural Health Study, 2012; Alavanja et al., 1996). Exposure variables used in this analysis included wives' and husbands' ever use of 1) any pesticide, 2) 11 pesticide classes (four functional: fumigants, fungicides, herbicides, and insecticides; and seven chemical: carbamates, chloroacetanilide herbicides, organochlorine insecticides, organophosphate insecticides, phenoxy herbicides, pyrethroid insecticides, and triazine herbicides), and 3) 50 individual pesticides. We present results for only those pesticides for which there were at least five exposed cases. The variables for the 11 pesticide classes were created from the responses for the individual pesticides that comprised each class. We additionally analyzed data on wives' exposure to pesticides in the non-farm job held longest and physician-diagnosed pesticide poisoning. Information on duration (years) and frequency (days per year) was collected for wives' overall use of pesticides, but not for their use of individual pesticides or pesticide classes. We also had information on duration and frequency for husbands' overall use of pesticides. We created variables representing wives' and husbands' cumulative lifetime days of overall pesticide use by multiplying the values of the duration and frequency variables and then categorizing the result into quartiles.

2.3. Statistical analyses

We evaluated associations between both general and specific pesticide use and self-reported, incident depression among wives in the Agricultural Health Study. We treated the 16,893 wives included in this analysis as a closed cohort and used log-binomial regression models to calculate risk ratios (RRs) and 95% confidence intervals (CIs) for each association. Although using Cox proportional hazards regression models to calculate hazard ratios is often preferred for analyses of prospective cohort data because they can incorporate information on censoring and the amount of time at risk for disease (Allison, 2010), we did not have information on the exact date of depression diagnosis. Even if date of depression diagnosis was available, it may not represent the earliest occurrence because depression is an ongoing condition that may begin before first recognition or diagnosis (Farr et al., 2010). Therefore, we used log-binomial regression models to calculate RRs for our main analyses, but conducted a sensitivity analysis in which we used Cox proportional hazards regression models with time on study as the time scale to calculate hazard ratios and 95% CIs for each association. For the latter analysis, we calculated time at risk for incident depression by first assigning the date corresponding to the midpoint of the year of the age at depression diagnosis as the date of depression diagnosis. We then calculated the time at risk for incident depression as the difference (in days) between the date of enrollment in the Agricultural Health Study and the approximate date of depression diagnosis (cases), date of death (non-cases who died), or date of the follow-up telephone interview (living non-cases.

We used information from the enrollment questionnaire on potential confounders identified from the previous literature, i.e., age, state, race/ethnicity, education (as a measure of socioeconomic status), number of children in family (as a measure of social connection), farm size, frequency of alcohol use in past year, cigarette smoking, number of doctor visits in past year (as a measure of general health), diabetes or heart disease diagnoses (as measures of longstanding illness, disability, or infirmity), number of years lived or worked on a farm, working a job off a farm, and solvent (other than gasoline) exposure at the non-farm job held the longest. We obtained information on number of children in the family and farm size from participants' husbands' responses. Ever diagnosed with heart disease was defined as reporting myocardial infarction, angina, or arrhythmia.

We used a directed acyclic graph (Glymour and Greenland, 2008; Greenland et al., 1999) to analyze potential confounders listed above and identified two minimally sufficient adjustment sets: 1) age, alcohol use, diabetes, smoking, solvents, and state; and 2) age, diabetes, education, and state (Supplementary Data, Figure S.1). We used the second minimally sufficient adjustment set as the final model because it had less missing covariate information than the first set.

We used stabilized inverse probability weights (a type of propensity score) to adjust for the covariates in the second minimally sufficient adjustment set and to account for the loss of the 10,639 wives who did not complete the follow-up interview (Figure 1; Cole and Hernán, 2008; Hernán et al., 2004). Specifically, we calculated two types of stabilized weights for each exposure, confounding weights and selection weights, and then calculated the overall stabilized weight as the product of the two weights (Cole and Hernán, 2008; Robins et al., 2000). We then applied the overall stabilized weight to log-binomial regression models for incident depression that contained the exposure of interest as the only explanatory variable in the same way sampling weights are applied when analyzing data from complex survey sampling designs (Cole and Hernán, 2008; Robins et al., 2000). We used robust variance estimates to calculate 95% CIs because using weights for analysis induces within-subject correlation (Hernán et al., 2000). More details regarding the rationale behind, assumptions for, and references describing inverse probability weights are provided in the Supplementary Data, p. S4.

We used linear, logistic, or polytomous logistic regression models, depending on the nature of the exposure variable, to calculate the stabilized confounding weights. Specifically, we calculated the numerators of these weights as predicted probabilities of exposure from an intercept only model and the denominators of these weights as predicted probabilities of exposure from a model including the covariates in the second minimally sufficient adjustment set as explanatory variables. In the denominator model, we fit age as a restricted, quadratic spline with three equally spaced knots at ages 36, 43, and 52 years based on percentiles of the age distribution in all cases. Diabetes, education, and state were modeled as shown in Table 1.

We used logistic regression models to calculate the stabilized selection weights. Specifically, for the numerators of the weights, we calculated the predicted probabilities of not dropping out of the cohort conditional on the exposure of interest; and, for the denominators of the weights, we calculated the predicted probabilities conditional on age, diabetes, education, state, the exposure of interest, and pairwise interaction terms between each covariate and the exposure of interest. We modeled age, diabetes, education, and state the same way as for the confounding weights.

To informally assess the bias-variance (validity-precision) tradeoff (Greenland, 2008; Winer, 1978), we progressively truncated the overall stabilized weights by resetting weights less (or greater) than a certain percentile to the value of that percentile (Cole and Hernán, 2008). Regarding the RRs derived from the untruncated weights as the "true" values, we informally evaluated the bias-variance tradeoff by looking at how features of both the weights and the corresponding RRs changed with increasing truncation. We considered nearness of the mean weight to one, reduction in number of extreme weights (e.g., < 0.05 or

> 20), and a balance between increased "bias" and reduced variance in the estimated RRs (Cole and Hernán, 2008). Truncating the overall stabilized weights at the first and 99th percentiles appeared to be the best balance of validity and precision in this analysis.

We conducted two main analyses to evaluate 1) associations between pesticide use and incident depression among all 16,893 wives and 2) associations between husbands' pesticide use (i.e., indirect exposure) and wives' incident depression among 6,830 wives who had never used any pesticides. We used within-category medians to assess linear dose-response trends in the wives' and husbands' cumulative lifetime days of pesticide use variables.

We performed additional analyses by adding race/ethnicity, number of children, farm size, number of doctor visits in past year, ever use of any pesticides, husbands' age, husbands' depression status, or husbands' use of individual pesticides to the models for the weights one-ata-time. We also added the pesticide that was the most strongly correlated with the pesticide of interest to the models for the weights to account for correlations between use of different pesticides. We refit the models for the weights adjusting for covariates in the first minimally sufficient adjustment set instead of the second set. We separately evaluated associations with cases that occurred within five years of enrollment in the Agricultural Health Study or more than five years after enrollment. Finally, we repeated analyses without weighting (i.e., using standard regression adjustment methods) and, therefore, without adjustment for potential selection bias from drop out.

We used the P1REL20100501 release of the Phase I data set, the P3REL1000.00 release of the Phase III data set, and the AHSREL201103.00 release of the demographic data set.

3. Results

After adjusting for age at enrollment, risk of incident depression was higher among wives who lived in North Carolina, had completed some high school or less compared to high school graduate, worked on a farm less than 50 acres in size compared to 50 acres or more, were a current or past cigarette smoker compared to never having smoked, visited a medical doctor more than once in the past year compared to no visits, were ever diagnosed with diabetes or heart disease, lived or worked on a farm less than 31 years compared to 31 years or more, and were exposed to solvents (other than gasoline) at the non-farm job held the longest (Table 1). Depression was inversely associated with being older than 45 years compared to 36-45, of a race/ethnicity other than non-Hispanic white, and having at least one child compared to no children (Table 1). In general, these descriptive associations were in the same directions and of similar magnitudes when we restricted analyses to wives who had never used any pesticides (Table 1). Additionally adjusting for state gave similar results except for farm size and years lived or worked on a farm, which had RRs attenuated toward 1.00 (data not shown).

After weighting for age, diabetes diagnosis, education, state, and not dropping out of the cohort, wives' incident depression was not associated with ever use or cumulative lifetime days of use of any pesticide, but physician-diagnosed pesticide poisoning was positively, albeit imprecisely, associated with depression (Table 2). Wives' depression was inversely associated with ever use of chloroacetanilide, phenoxy, and triazine herbicides (Table 2) as well as use of several individual pesticides, especially herbicides (Table 3). Ever use of metalaxyl and permethrin (for crops) were significantly positively associated with depression (Table 3).

Among wives who reported never using any pesticides, husbands' ever use of carbamates was the only functional or chemical pesticide class significantly positively associated with wives' depression, although RRs for husbands' ever use of insecticides, chloroacetanilide herbicides, organochlorine insecticides, and organophosphate insecticides were elevated (Table 4). With the exception of a few individual herbicides, wives' depression was not associated with husbands' use of most individual pesticides (Table 5).

Adding race/ethnicity, number of children, farm size, number of doctor visits in past year, ever use of any pesticides, husbands' age, husbands' depression status, husbands' use of individual pesticides, or the pesticide that was the most strongly correlated with the pesticide of interest to the models for the weights one-at-a-time did not meaningfully change results (data not shown). Restricting cases to wives who had taken medication for their depression (n = 742; 70%) did not change results qualitatively (data not shown). Refitting the models for the weights adjusting for covariates in the first minimally sufficient adjustment set (age, alcohol use, diabetes, smoking, solvents, and state) gave similar results to those observed when we adjusted for the covariates in the second set (age, diabetes, education, and state) (data not shown). Inverse associations between use of individual herbicides and depression that occurred within the first five years of enrollment in the Agricultural Health Study were generally stronger in magnitude than were those with depression that occurred more than five years after enrollment (data not shown). Finally, results were similar when we used Cox proportional hazards regression models (data not shown) or log-binomial regression models with standard regression adjustment methods (Supplementary Data, Tables S.1-S.4).

4. Discussion

We found evidence for a positive association between self-reported, incident depression and a history of physician-diagnosed pesticide poisoning among wives in the Agricultural Health Study. However, depression was generally not associated, or it was inversely associated, with wives' personal pesticide use on the farm. Among wives who never used pesticides, husbands' ever use of pesticides was generally not associated with wives' depression.

Our finding of a moderate, positive association between physician-diagnosed pesticide poisoning and depression, although based on only five poisoned cases, agrees with results of several other studies (Beseler and Stallones, 2008; Stallones and Beseler, 2002a, 2002b; Wesseling et al., 2010) and had previously been reported among applicators and wives of applicators in the Agricultural Health Study (Beseler et al., 2006, 2008). Pesticide poisoning may be a good measure for acute, high-level pesticide exposure because it indicates the occurrence of an exposure sufficient to cause a physical reaction. Poisoning may not, however, be a good measure for chronic exposure at lower levels.

The null and inverse associations we observed between reported pesticide use overall or use of specific pesticides and depression contrast with findings from several other studies (Bazylewicz-Walczak et al., 1999; Beseler et al., 2008; Carruth and Logan, 2002; London et al., 2005; Mackenzie Ross et al., 2010; Meyer et al., 2010; Rehner et al., 2000; Salvi et al., 2003; Villeneuve et al., 2009; Wesseling et al., 2010). These contradictory results may be explained by differences in the populations, designs, methods, sample sizes, or focus of our study relative to others. Some studies lacked data on pesticide use by individuals or use of specific pesticides (Meyer et al., 2010; Villeneuve et al., 2009). Instead, they compared hospitalization rates for mood disorder between an agricultural area with intensive pesticide use and two reference areas (Meyer et al., 2010) or used distance from individuals' homes to a large hog farming operation as a measure of exposure (Villeneuve et al., 2009). Several studies used ecological (London et al., 2005; Meyer et al., 2010), case study (London et al., 2005), or cross-sectional designs (Beseler et al., 2008; Carruth and Logan, 2002; Mackenzie Ross et al., 2010; Rehner et al., 2000; Villeneuve et al., 2009; Wesseling et al., 2010). One small study (Rehner et al., 2000) focused on methyl parathion exposure in the home, which may be very different from occupational or agricultural pesticide use. Four studies

(Bazylewicz-Walczak et al., 1999; Mackenzie Ross et al., 2010; Salvi et al., 2003; Wesseling et al., 2010) on organophosphate insecticide exposure among workers in the gardening, farming, and agricultural industries included farm workers who may have experienced substantially higher levels of pesticide exposure than the wives of farm owners in our study. Thus, our results place a lower bound on the level of pesticide exposure related to depression.

We did not expect the inverse associations we observed between wives' incident depression and use of individual herbicides or the pesticide classes chloroacetanilide, phenoxy, and triazine herbicides, but they remained apparent across a range of analytic strategies. This is may be just a chance finding, but it is also possible that women who applied herbicides may be healthier or more physically active that those who did not. Results were similar, however, when we added number of doctor visits in past year to models for the weights. Because depression is a condition that may occur and persist without diagnosis (Farr et al., 2010), it is also possible that undiagnosed or unreported depression at the time of enrollment, when exposure was assessed, might cause wives who later reported depression not to use pesticides, thus creating the appearance of an inverse association. This may be the case because inverse associations between use of individual herbicides and depression that occurred within the first five years of enrollment in the Agricultural Health Study were generally stronger in magnitude than were those with depression that occurred more than five years after enrollment.

The prevalence of depression reported by wives at enrollment in the Agricultural Health Study (overall: 7.3%; Iowa: 6.9%; North Carolina: 8.3%) is lower than that recently reported for American women (20.2%) and residents of Iowa (men and women together; 14.7%) (Strine et al., 2008). There are a couple of possible explanations for the lower prevalence of depression in our study. First, married individuals have lower rates of depression than unmarried individuals (Centers for Disease Control and Prevention, 2010; Kessler et al., 2003; Strine et al., 2008) and all women in our study were married, by design. For comparison, the prevalence of depression at enrollment in the Agricultural Health Study among unmarried, female pesticide applicators was 14.7% (Iowa: 15.2%; North Carolina: 14.5%), which is much closer to the general population—married and unmarried women together—prevalence of depression. Additionally, residents of farming communities may be less likely to seek help for depression due to the stigma sometimes associated with mental problems (Fraser et al., 2005; Gregoire, 2002). Unfortunately, we were unable to determine if the relationships between pesticide use and incident depression among wives observed in our study were different in unmarried females due to small numbers.

Animal studies have assessed the neurological effects of some of the individual pesticides for which we observed positive associations with depression in our study. Toxaphene inhibited acetylcholinesterase in the brains of guinea pigs and affected dopamine binding to brain synaptosomes in rats (Chandra and Durairaj, 1993; Trottman and Desaiah, 1983). Metalaxyl did not affect acetylcholinesterase activities in rat brains (Naidu and Radhakrishnamurty, 1988), but permethrin affected acetylcholinesterase activities throughout the brains of rats (Abdel-Rahman et al., 2004) and increased striatal levels of dopamine transporter protein in mice (Gillette and Bloomquist, 2003). The positive associations we observed in our study, however, were not consistent across wives' and husbands' pesticide use, chemicals in the same pesticide class [e.g., wives' use of permethrin (for animals) and permethrin (for crops)], or with the results of prior epidemiological studies. Similar discrepancies in associations between wives' and husbands' pesticide use were observed in a study of pesticide use and breast cancer in the Agricultural Health Study (Engel et al., 2005). Despite these inconsistencies, the lack of knowledge about the exact mechanisms of depression and the effects of pesticides on these mechanisms precludes firm conclusions about the biological plausibility of the positive associations observed in our study.

Confidence in the results of our study is increased by the fact that the associations between depression and participant characteristics shown in Table 1 followed patterns observed in other studies. Specifically, in previous studies, depression differed by state (Centers for Disease Control and Prevention, 2010; Kessler et al., 2003; Strine et al., 2008) and was less common among wives who were older (Beseler and Stallones, 2008; Centers for Disease Control and Prevention, 2010; Hölzel et al., 2011; Kessler et al., 2003; Strine et al., 2008), were of a race/ethnicity other than non-Hispanic white (Kessler et al., 2003; Strine et al., 2008), and had more children/greater social connection (Hölzel et al., 2011; Stallones and Beseler, 2002b). Depression was more common among wives who had less than a high school education (Centers for Disease Control and Prevention, 2010; Strine et al., 2008), were current or past smokers (Strine et al., 2008), visited a medical doctor in the past year/ had poorer health (Beseler and Stallones, 2008; Carruth and Logan, 2002; Stallones and Beseler, 2002b), and had heart disease or diabetes (Clarke and Currie, 2009; Strine et al., 2008).

One limitation of our study is that data on pesticide use was self-reported, so exposure misclassification is likely. We also did not have information on wives' duration and frequency of use of individual pesticides. Using husbands' pesticide use as a measure of wives' indirect exposure likely introduced exposure misclassification and could have overestimated the number of wives actually exposed. Self-reports of pesticide use are likely more accurate than those based on husband's use or the ecological or geographical indicators of exposure that have been used in some previous studies (London et al., 2005; Meyer et al., 2010; Villeneuve et al., 2009).

There is some information on reliability and validity of self-reported pesticide use in the literature. Engel et al. (2001), using data from orchardists in Washington State reported 25 years earlier as the gold standard, found sensitivities for reporting ever use of pesticides were 1.00 for any pesticides, 0.87-1.00 for pesticides classes included in our study, and 0.80-0.94 for individual pesticides included in our study. A validation study in Kansas found pesticide use was reported similarly between cancer cases and controls (Blair and Zahm, 1993). Although a reliability study in Iowa (Brown et al., 1991) found that wives could provide useful information on their husband's use of pesticides, there was considerable misclassification. A recent study in the Agricultural Health Study reported that misclassification was likely to be non-differential with respect to outcome(s) under study (Blair et al., 2011). This would typically bias associations toward the null.

Use of self-report to assess incident depression in the Agricultural Health Study might result in some misclassification, but the accuracy of self-reported depression has been evaluated and appears to be quite good. Williams et al. (1999) found using a single question to assess depression had similar sensitivity (0.85), but slightly lower specificity (0.66), compared to the Center for Epidemiological Studies-Depression Scale 20-Item instrument (sensitivity: 0.88; specificity: 0.75) when using diagnostic interviews as the gold standard. Two other studies (Kroenke et al., 2003; Whooley et al., 1997) found similar or higher sensitivities and specificities to those reported by Williams et al. (1999) when using a two question depression screening instrument. It should be noted, however, that the depression screening instruments evaluated in these studies assessed depression in the past two weeks (Kroenke et al., 2003), month (Whooley et al., 1997), or year (Williams et al., 1999), whereas we assessed ever depression in the current study. Nevertheless, misclassification of depression would typically bias risk ratios toward the null unless the amount of misclassification differed by pesticide exposure status, which is possible because pesticide exposure has been linked to decrements in memory (Ismail et al., 2012) and depression was reported after the pesticide exposures occurred. This explanation seems unlikely, however, and restricting incident depression cases in the present study to wives who had taken medication for their depression did not change results qualitatively (data not shown), which suggests that any bias resulting from misclassified incident depression was likely small.

Strengths of our study include the large sample size and prospective design, alleviating concern regarding study power and differential misclassification of exposure. Moreover, we had extensive information on wives' exposures, including ever use of any pesticides, pesticide classes, individual pesticides, and husbands' pesticide use. We were able to control for many confounders and demonstrated the robustness of our results to additional potential confounders not included in the original models. Finally, we used inverse probability weighting to account for any potential selection bias resulting from wives dropping out of the Agricultural Health Study. Overall, the effect of drop outs on our results appears to be small because results were similar when we used standard regression adjustment methods.

5. Conclusions

In conclusion, depression in women remains a major public health problem. Our study adds further evidence that high level pesticide exposure, such as physician-diagnosed pesticide poisoning, is associated with increased risk of depression. Our study provides little support, however, for positive associations between pesticide exposure and self-reported, incident depression among wives in the Agricultural Health Study. The few positive associations that we observed with individual pesticides were not consistent across wives' and husbands' pesticide use. Reverse causality or chance may be possible explanations for the inverse associations we observed between use of some individual herbicides and depression. Our results set a lower bound on the level of exposure related to depression, thereby providing reassurance that the moderate levels of pesticide exposure experienced by farmers' wives likely do not increase risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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The Agricultural Health Study was approved by the Institutional Review Boards of the National Institutes of Health and its contractors; the current analysis involving coded data was exempted from review by the Institutional Review Board of the University of North Carolina at Chapel Hill. All participants provided implied informed consent by completing and returning the enrollment questionnaires after the study was explained to them.

Abbreviations

2,4-D	2-(2,4-Dichlorophenoxy)acetic acid
2,4,5-T	2-(2,4,5-Trichlorophenoxy)acetic acid
2,4,5-TP	2-(2,4,5-Trichlorophenoxy)propanonic acid

CI	confidence interval
DDT	1,1'-(2,2,2-Trichloroethylidene)bis[4-chlorobenzene]
EPTC	N,N-Dipropylcarbamothioic acid S-ethyl ester
IQR	interquartile range
NIEHS	National Institute of Environmental Health Sciences
RR	risk ratio

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Highlights

- A few small, prospective studies exist of pesticide use and depression among women.
- We used data on 16,893 farmers' wives in the Agricultural Health Study.
- We evaluated associations between use of 50 pesticides and incident depression.
- Depression was not associated with ever use of individual or classes of pesticides.
- Depression was positively associated with physician-diagnosed pesticide poisoning.

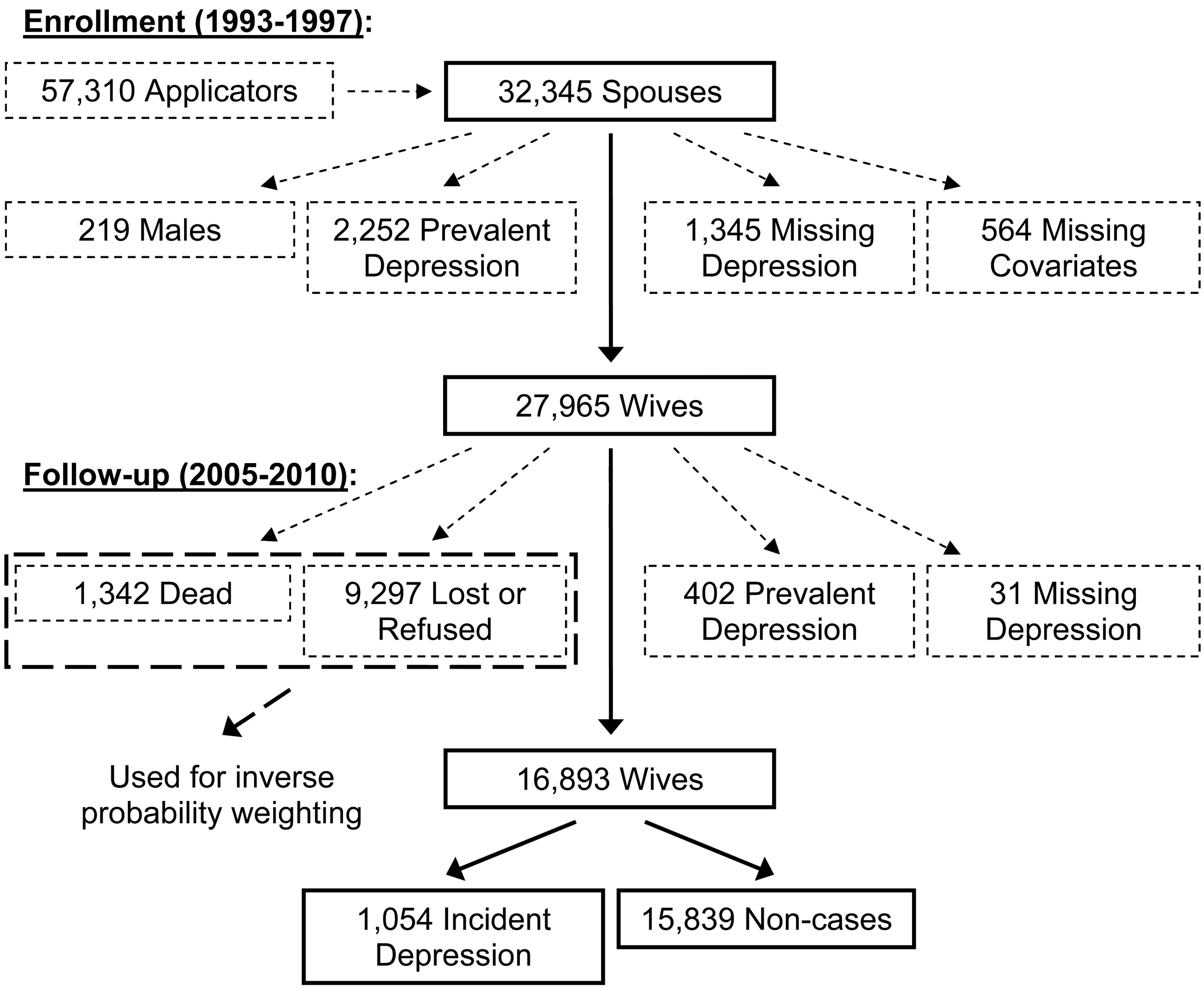

Figure 1.
Flow diagram depicting the study population for an analysis of pesticide use and self-reported, incident depression in wives from Iowa and North Carolina enrolled in the Agricultural Health Study. Boxes or lines marked with solid lines represent individuals who remained in the study after each step shown, whereas boxes or lines marked with small dashes represent individuals who were excluded after each step shown (see "2.1. Study population and case definition" for more details). Boxes or lines marked with large dashes represent individuals who, although not directly included in the analysis, were incorporated into the analysis via inverse probability weighting (see "2.3. Statistical analyses" for more details).

Table 1

Association of incident depression with characteristics of wives enrolled in the Agricultural Health Study.

	All wives						Wives who never used pesticides					
	Cases (n = 1,054)		Total (n = 16,893)		Adjusted[a]		Cases (n = 444)		Total (n = 6,830)		Adjusted[a]	
Characteristic	**No.**	**%**	**No.**	**%**	**RR**	**95% CI**	**No.**	**%**	**No.**	**%**	**RR**	**95% CI**
Age at enrollment (years)												
≤ 25	19	2	266	2	0.99	0.64, 1.55	11	2	162	2	0.86	0.48, 1.55
26-35	211	20	2,739	16	1.07	0.91, 1.26	107	24	1,338	20	1.01	0.80, 1.28
36-45	370	35	5,138	30	1.00	Referent	155	35	1,964	29	1.00	Referent
46-55	259	25	4,648	28	0.77	0.66, 0.90	89	20	1,612	24	0.70	0.54, 0.90
56-65	153	15	3,230	19	0.66	0.55, 0.79	60	14	1,304	19	0.58	0.44, 0.78
> 65	42	4	872	5	0.67	0.49, 0.91	22	5	450	7	0.62	0.40, 0.96
State of residence												
Iowa	718	68	12,146	72	1.00	Referent	291	66	4,483	66	1.00	Referent
North Carolina	336	32	4,747	28	1.28	1.13, 1.46	153	34	2,347	34	1.12	0.93, 1.36
Race/Ethnicity												
Non-Hispanic white	1,036	98	16,508	98	1.00	Referent	428	96	6,586	96	1.00	Referent
Other	18	2	367	2	0.82	0.52, 1.29	16	4	240	4	1.11	0.68, 1.79
Missing	0		18				0		4			
Education level												
Some high school or less or something else	177	17	2,238	13	1.32	1.11, 1.57	70	16	821	12	1.42	1.08, 1.86
High school graduate or General Equivalency Diploma	341	32	5,867	35	1.00	Referent	149	34	2,535	37	1.00	Referent
1-3 years of vocational education beyond high school, some college, or college graduate	473	45	7,743	46	0.95	0.83, 1.10	202	45	3,040	45	0.99	0.81, 1.23
One or more years of graduate or professional school	63	6	1,045	6	0.97	0.75, 1.26	23	5	434	6	0.82	0.54, 1.26
Number of children in family												
0	90	9	914	6	1.00	Referent	44	10	441	7	1.00	Referent
1	97	9	1,547	9	0.66	0.50, 0.88	53	12	771	12	0.73	0.50, 1.08
2	390	38	5,511	34	0.79	0.63, 0.98	169	39	2,280	35	0.83	0.60, 1.14
3-4	382	37	6,857	42	0.64	0.51, 0.80	138	32	2,516	38	0.64	0.46, 0.90
> 4	67	7	1,489	9	0.56	0.41, 0.77	26	6	557	8	0.60	0.37, 0.98

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	All wives						Wives who never used pesticides					
	Cases (n = 1,054)		Total (n = 16,893)		Adjusted[a]		Cases (n = 444)		Total (n = 6,830)		Adjusted[a]	
Characteristic	No.	%	No.	%	RR	95% CI	No.	%	No.	%	RR	95% CI
Missing	28		575				14		265			
Size of farm worked last year (acres)												
Didn't work on a farm or < 5	67	7	855	5	1.46	1.15, 1.85	32	8	420	7	1.36	0.96, 1.94
5-49	90	9	1,216	8	1.35	1.09, 1.66	36	9	566	9	1.10	0.79, 1.54
> 49	817	84	13,609	87	1.00	Referent	338	83	5,250	84	1.00	Referent
Missing	80		1,213				38		594			
Frequency of alcohol consumption during past 12 months												
Never	432	41	7,341	44	1.00	Referent	182	41	3,274	48	1.00	Referent
< 1 time a month	327	31	4,706	28	1.07	0.93, 1.24	135	31	1,807	27	1.19	0.95, 1.49
1 time a month to 1 time a week	232	22	3,794	23	0.93	0.80, 1.09	97	22	1,403	21	1.09	0.86, 1.40
> 1 time a week	58	6	929	6	1.01	0.78, 1.32	27	6	294	4	1.56	1.06, 2.29
Missing	5		123				3		52			
Cigarette smoking status												
Never	694	67	12,411	75	1.00	Referent	292	68	5,035	76	1.00	Referent
Past	194	19	2,685	16	1.31	1.12, 1.53	82	19	1,016	15	1.39	1.10, 1.75
Current	142	14	1,357	8	1.82	1.54, 2.17	55	13	593	9	1.57	1.19, 2.06
Missing	24		440				15		186			
Times visited a medical doctor or medical assistant about a health concern in past 12 months												
0	170	16	3,521	21	1.00	Referent	70	16	1,474	22	1.00	Referent
1	267	25	5,120	30	1.10	0.91, 1.32	117	27	2,063	30	1.21	0.91, 1.62
> 1	614	58	8,216	49	1.60	1.36, 1.89	254	58	3,272	48	1.70	1.32, 2.20
Missing	3		36				3		21			
Ever diagnosed with heart disease[b]												
No	957	91	15,750	93	1.00	Referent	406	91	6,421	94	1.00	Referent
Yes	97	9	1,139	7	1.55	1.27, 1.90	38	9	405	6	1.68	1.22, 2.31
Missing	0		4				0		4			
Ever diagnosed with diabetes (other than while pregnant)												

	All wives						Wives who never used pesticides					
	Cases (n = 1,054)		Total (n = 16,893)		Adjusted[a]		Cases (n = 444)		Total (n = 6,830)		Adjusted[a]	
Characteristic	No.	%	No.	%	RR	95% CI	No.	%	No.	%	RR	95% CI
No	1,023	97	16,439	97	1.00	Referent	426	96	6,610	97	1.00	Referent
Yes	31	3	454	3	1.28	0.90, 1.81	18	4	220	3	1.58	1.00, 2.50
Years lived or worked on a farm over lifetime												
< 5	84	8	925	6	1.56	1.23, 1.97	56	13	611	9	1.55	1.13, 2.13
5-10	93	9	1,127	7	1.38	1.10, 1.75	54	12	619	9	1.44	1.03, 2.00
11-20	203	19	2,716	16	1.31	1.10, 1.56	88	20	1,198	18	1.28	0.97, 1.68
21-30	211	20	3,036	18	1.25	1.06, 1.48	85	19	1,218	18	1.25	0.95, 1.63
> 30	455	44	8,924	53	1.00	Referent	155	35	3,094	46	1.00	Referent
Missing	8		165				6		90			
Ever have a job off a farm												
No	91	9	1,685	10	1.00	Referent	43	10	729	11	1.00	Referent
Yes	961	91	15,088	90	1.06	0.86, 1.31	399	90	6,032	89	0.95	0.70, 1.30
Missing	2		120				2		69			
Exposed to solvents (other than gasoline) at non-farm job held longest												
No	931	88	15,344	91	1.00	Referent	407	92	6,344	94	1.00	Referent
Yes	121	12	1,429	9	1.33	1.60	35	8	417	6	1.22	0.87, 1.70
Missing	2		120				2		69			

Abbreviations: CI, confidence interval; RR, risk ratio.

[a]Adjusted for age at enrollment (modeled with a linear term).

[b]Derived from questions regarding myocardial infarction, angina, and arrythmia.

Table 2

Pesticide use and self-reported, incident depression in wives from Iowa and North Carolina enrolled in the Agricultural Health Study.

	Cases (n = 1,054)		Total (n = 16,893)		Inverse Probability Weighted[a]	
Variable	**No.**	**%**	**No.**	**%**	**RR**	**95% CI**
Ever personally mixed or applied pesticides						
No	444	42	6,830	40	1.00	Referent
Yes	610	58	10,063	60	0.96	0.85, 1.09
Cumulative lifetime days personally mixed or applied pesticides[b]						
0 (Median = 0.00)	444	49	6,830	48	1.00	Referent
1-9 (8.75)	132	15	1,952	14	1.05	0.87, 1.27
10-51 (24.50)	121	13	1,972	14	0.95	0.78, 1.16
52-179 (108.50)	107	12	1,935	13	0.85	0.69, 1.04
> 179 (369.75)	99	11	1,667	12	0.88	0.72, 1.09
Missing	151		2,537			
Trend (IQR = 169.75)[c]					0.94	0.85, 1.04
Exposed to pesticides at non-farm job held longest						
No	1,004	95	16,177	96	1.00	Referent
Yes	48	5	596	4	1.23	0.92, 1.64
Missing	2		120			
Ever diagnosed with pesticide poisoning						
No	1,048	100	16,831	100	1.00	Referent
Yes	5	< 1	49	< 1	1.78	0.76, 4.14
Missing	1		13			
Functional pesticide classes[d]: ever personally mixed or applied						
Fumigants						
No	1,014	98	16,214	98	1.00	Referent
Yes	21	2	316	2	0.94	0.61, 1.47
Missing	19		363			
Fungicides						
No	979	95	15,606	95	1.00	Referent
Yes	54	5	905	5	0.93	0.70, 1.23
Missing	21		382			
Herbicides						
No	649	62	10,045	60	1.00	Referent
Yes	397	38	6,646	40	0.95	0.84, 1.08
Missing	8		202			
Insecticides						
No	629	60	9,622	58	1.00	Referent
Yes	420	40	7,087	42	0.96	0.85, 1.08

	Cases (n = 1,054)		Total (n = 16,893)		Inverse Probability Weighted[a]	
Variable	No.	%	No.	%	RR	95% CI
Missing	5		184			
Chemical pesticide classes[e]: ever personally mixed or applied						
Carbamates						
No	712	68	10,953	66	1.00	Referent
Yes	328	32	5,697	34	0.92	0.80, 1.04
Missing	14		243			
Chloroacetanilide herbicides						
No	979	96	15,397	94	1.00	Referent
Yes	42	4	992	6	0.72	0.52, 0.99
Missing	33		504			
Organochlorine insecticides						
No	946	93	14,886	91	1.00	Referent
Yes	67	7	1,395	9	0.84	0.65, 1.09
Missing	41		612			
Organophosphate insecticides						
No	773	74	11,922	72	1.00	Referent
Yes	269	26	4,655	28	0.95	0.83, 1.09
Missing	12		316			
Phenoxy herbicides						
No	912	89	13,779	84	1.00	Referent
Yes	118	11	2,676	16	0.71	0.58, 0.88
Missing	24		438			
Pyrethroid insecticides						
No	993	95	15,876	95	1.00	Referent
Yes	55	5	864	5	1.07	0.81, 1.40
Missing	6		153			
Triazine herbicides						
No	983	96	15,367	94	1.00	Referent
Yes	39	4	1,019	6	0.69	0.49, 0.96
Missing	32		507			

Abbreviations: 2,4-D, (2,4-dichlorophenoxy)acetic acid; 2,4,5-T, (2,4,5-trichlorophenoxy)acetic acid; 2,4,5-TP, (*RS*)-2-(2,4,5-trichlorophenoxy)propionic acid; CI, confidence interval; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; EPTC, *S*-ethyl dipropyl(thiocarbamate); IQR, interquartile range; RR, risk ratio.

[a]Weights adjusted for age at enrollment (modeled with a restricted, quadratic spline with three equally spaced knots at ages 36, 43, and 52 years based on percentiles of the age distribution in all cases), ever diagnosed with diabetes (other than while pregnant), education level, state of residence, and not dropping out of the Agricultural Health Study cohort (conditional on the exposure of interest and on the same covariates just listed as well as pairwise interaction terms between each covariate and the exposure of interest). Robust variance estimates were used to calculate 95% CIs.

[b]Category boundaries set at the quartiles of cumulative lifetime days of pesticide use among all wives who used any pesticides.

[c]Used within-category medians and scaled the RR to an IQR-unit (days) increase in cumulative lifetime days of pesticide use among all wives who used any pesticides.

[d]Fumigants included aluminum phosphide, methyl bromide, carbon tetrachloride/carbon disulfide (80/20 mix), and ethylene dibromide. Fungicides included benomyl, captan, chlorothalonil, maneb/mancozeb, metalaxyl, and ziram. Herbicides included 2,4-D; 2,4,5-T; 2,4,5-TP; alachlor; atrazine; butylate; chlorimuron-ethyl; cyanazine; dicamba; EPTC; glyphosate; imazethapyr; metolachlor; metribuzin; paraquat; pendimethalin; petroleum oil; and trifluralin. Insecticides included aldicarb, aldrin, carbaryl, carbofuran, chlordane, chlorpyrifos, coumaphos, DDT, dichlorvos, diazinon, dieldrin, fonofos, heptachlor, lindane, malathion, parathion, permethrin (for animals), permethrin (for crops), phorate, terbufos, toxaphene, and trichlorfon.

[e]Carbamates included aldicarb, benomyl, carbaryl, and carbofuran. Chloroacetanilide herbicides included alachlor and metolachlor. Organochlorine insecticides included aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, and toxaphene. Organophosphate insecticides included chlorpyrifos, coumaphos, dichlorvos, diazinon, fonofos, malathion, parathion, phorate, terbufos, and trichlorfon. Phenoxy herbicides included 2,4-D; 2,4,5-T; and 2,4,5-TP. Pyrethroid insecticides included permethrin (for animals) and permethrin (for crops). Triazine herbicides included atrazine, cyanazine, and metribuzin.

Table 3

Ever use of specific pesticides and self-reported, incident depression in wives from Iowa and North Carolina enrolled in the Agricultural Health Study.

	Cases[b] (n = 1,054)		Total[b] (n = 16,893)		Inverse Probability Weighted[c, d]	
Ever personally mixed or applied[a]	**No.**	**%**	**No.**	**%**	**RR**	**95% CI**
Fumigants						
Carbon tetrachloride/carbon disulfide (80/20 mix)	6	1	108	1	0.88	0.40, 1.95
Methyl bromide	16	2	202	1	1.13	0.68, 1.87
Fungicides						
Benomyl	9	1	157	1	0.87	0.45, 1.68
Captan	25	2	428	3	0.83	0.56, 1.24
Chlorothalonil	7	1	180	1	0.62	0.29, 1.31
Maneb/mancozeb	11	1	290	2	0.64	0.33, 1.25
Metalaxyl	25	2	268	2	1.61	1.03, 2.52
Herbicides						
2,4-D	118	11	2,662	16	0.72	0.58, 0.89
Alachlor	32	3	774	5	0.71	0.50, 1.03
Atrazine	28	3	828	5	0.61	0.41, 0.90
Butylate	6	1	257	2	0.48	0.21, 1.07
Chlorimuron-ethyl	13	1	304	2	0.71	0.41, 1.23
Cyanazine	16	2	517	3	0.50	0.30, 0.84
Dicamba	31	3	730	4	0.75	0.52, 1.08
EPTC	6	1	247	2	0.44	0.19, 1.00
Glyphosate	359	34	6,017	36	0.95	0.83, 1.08
Imazethapyr	17	2	517	3	0.58	0.35, 0.95
Metolachlor	23	2	586	4	0.68	0.45, 1.04
Metribuzin	8	1	324	2	0.47	0.23, 0.98
Paraquat	14	1	211	1	1.08	0.64, 1.83
Pendimethalin	15	1	408	2	0.62	0.37, 1.04
Petroleum oil	32	3	644	4	0.80	0.56, 1.14
Trifluralin	38	4	947	6	0.71	0.50, 0.99
Insecticides						
Aldrin	10	1	139	1	1.37	0.74, 2.52
Carbaryl	325	31	5,574	33	0.94	0.82, 1.07
Carbofuran	7	1	347	2	0.31	0.14, 0.67
Chlordane	34	3	766	5	0.79	0.55, 1.13
Chlorpyrifos	36	4	687	4	0.95	0.68, 1.32
Coumaphos	10	1	228	1	0.77	0.41, 1.43
DDT	28	3	659	4	0.63	0.43, 0.94
Dichlorvos	27	3	473	3	1.05	0.71, 1.56
Diazinon	101	10	1,864	11	0.87	0.71, 1.07

	Cases[b] (n = 1,054)		Total[b] (n = 16,893)		Inverse Probability Weighted[c, d]	
Ever personally mixed or applied[a]	**No.**	**%**	**No.**	**%**	**RR**	**95% CI**
Fonofos	16	2	333	2	0.87	0.52, 1.45
Heptachlor	6	1	129	1	0.68	0.31, 1.50
Lindane	14	1	276	2	0.84	0.50, 1.43
Malathion	203	20	3,563	21	0.96	0.82, 1.12
Parathion	10	1	175	1	0.89	0.48, 1.66
Permethrin (for animals)	34	3	633	4	0.83	0.58, 1.18
Permethrin (for crops)	32	3	342	2	1.44	1.02, 2.03
Phorate	16	2	338	2	0.77	0.46, 1.27
Terbufos	21	2	501	3	0.79	0.51, 1.23
Toxaphene	6	1	126	1	0.80	0.36, 1.80

Abbreviations: 2,4-D, (2,4-dichlorophenoxy)acetic acid; 2,4,5-T, (2,4,5-trichlorophenoxy)acetic acid; 2,4,5-TP, (*RS*)-2-(2,4,5-trichlorophenoxy)propionic acid; CI, confidence interval; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; EPTC, *S*-ethyl dipropyl(thiocarbamate); RR, risk ratio.

[a]Fewer than five cases ever personally mixed or applied 2,4,5-T; 2,4,5-TP; aldicarb; aluminum phosphide; dieldrin; ethylene dibromide; trichlorfon; or ziram.

[b]Information for specific pesticides was missing for 1–4% of wives.

[c]The wives who did not use each specific pesticide served as the reference group.

[d]Weights adjusted for age at enrollment (modeled with a restricted, quadratic spline with three equally spaced knots at ages 36, 43, and 52 years based on percentiles of the age distribution in all cases), ever diagnosed with diabetes (other than while pregnant), education level, state of residence, and not dropping out of the Agricultural Health Study cohort (conditional on the exposure of interest and on the same covariates just listed as well as pairwise interaction terms between each covariate and the exposure of interest). Robust variance estimates were used to calculate 95% CIs.

Table 4

Husbands' pesticide use and self-reported, incident depression in wives from Iowa and North Carolina who never used pesticides, but who were enrolled in the Agricultural Health Study.

	Cases (n = 444)		Total (n = 6,830)		Inverse Probability Weighted[b]	
Variable[a]	**No.**	**%**	**No.**	**%**	**RR**	**95% CI**
Cumulative lifetime days personally mixed or applied pesticides[c]						
0 (Median = 0.00)	8	2	82	1	1.00	Referent
1-64 (38.75)	120	27	1,829	27	0.67	0.33, 1.35
65-225 (178.50)	142	32	2,188	32	0.67	0.34, 1.34
226-457 (369.75)	95	21	1,392	20	0.71	0.35, 1.43
> 457 (767.25)	78	18	1,297	19	0.62	0.31, 1.26
Missing	1		42			
Trend (IQR = 393.50)[d]					0.95	0.83, 1.09
Functional pesticide classes[e]: ever personally mixed or applied						
Fumigants						
No	305	74	4,833	77	1.00	Referent
Yes	105	26	1,477	23	1.11	0.85, 1.44
Missing	34		520			
Fungicides						
No	266	65	4,091	64	1.00	Referent
Yes	144	35	2,260	36	0.94	0.75, 1.19
Missing	34		479			
Herbicides						
No	9	2	164	2	1.00	Referent
Yes	430	98	6,536	98	1.25	0.64, 2.47
Missing	5		130			
Insecticides						
No	17	4	342	5	1.00	Referent
Yes	405	96	6,199	95	1.42	0.88, 2.30
Missing	22		289			
Chemical pesticide classes[f]: ever personally mixed or applied						
Carbamates						
No	139	34	2,268	35	1.00	Referent
Yes	273	66	4,139	65	1.27	1.01, 1.60
Missing	32		423			
Chloroacetanilide herbicides						
No	110	27	1,914	30	1.00	Referent
Yes	296	73	4,430	70	1.16	0.93, 1.44
Missing	38		486			
Organochlorine insecticides						

Variable[a]	Cases (n = 444) No.	Cases (n = 444) %	Total (n = 6,830) No.	Total (n = 6,830) %	Inverse Probability Weighted[b] RR	Inverse Probability Weighted[b] 95% CI
No	201	50	3,013	48	1.00	Referent
Yes	198	50	3,254	52	1.17	0.94, 1.44
Missing	45		563			
Organophosphate insecticides						
No	37	9	656	10	1.00	Referent
Yes	385	91	5,897	90	1.21	0.86, 1.71
Missing	22		277			
Phenoxy herbicides						
No	91	22	1,244	19	1.00	Referent
Yes	324	78	5,262	81	0.94	0.74, 1.19
Missing	29		324			
Pyrethroid insecticides						
No	302	74	4,843	77	1.00	Referent
Yes	107	26	1,471	23	1.08	0.87, 1.36
Missing	35		516			
Triazine herbicides						
No	80	19	1,239	19	1.00	Referent
Yes	347	81	5,325	81	1.00	0.78, 1.30
Missing	17		266			

Abbreviations: 2,4-D, (2,4-dichlorophenoxy)acetic acid; 2,4,5-T, (2,4,5-trichlorophenoxy)acetic acid; 2,4,5-TP, (*RS*)-2-(2,4,5-trichlorophenoxy)propionic acid; CI, confidence interval; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; EPTC, *S*-ethyl dipropyl(thiocarbamate); IQR, interquartile range; RR, risk ratio.

[a]Fewer than five cases' husbands never personally mixed or applied pesticides.

[b]Weights adjusted for age at enrollment (modeled with a restricted, quadratic spline with three equally spaced knots at ages 36, 43, and 52 years based on percentiles of the age distribution in all cases), ever diagnosed with diabetes (other than while pregnant), education level, state of residence, and not dropping out of the Agricultural Health Study cohort (conditional on the exposure of interest and on the same covariates just listed as well as pairwise interaction terms between each covariate and the exposure of interest). Robust variance estimates were used to calculate 95% CIs.

[c]Category boundaries set at the quartiles of cumulative lifetime days of pesticide use among all husbands (of wives who never used pesticides) who used any pesticides.

[d]Used within-category medians and scaled the RR to an IQR-unit (days) increase in cumulative lifetime days of pesticide use among all husbands (of wives who never used pesticides) who used any pesticides.

[e]Fumigants included aluminum phosphide, methyl bromide, carbon tetrachloride/carbon disulfide (80/20 mix), and ethylene dibromide. Fungicides included benomyl, captan, chlorothalonil, maneb/mancozeb, metalaxyl, and ziram. Herbicides included 2,4-D; 2,4,5-T; 2,4,5-TP; alachlor; atrazine; butylate; chlorimuron-ethyl; cyanazine; dicamba; EPTC; glyphosate; imazethapyr; metolachlor; metribuzin; paraquat; pendimethalin; petroleum oil; and trifluralin. Insecticides included aldicarb, aldrin, carbaryl, carbofuran, chlordane, chlorpyrifos, coumaphos, DDT, dichlorvos, diazinon, dieldrin, fonofos, heptachlor, lindane, malathion, parathion, permethrin (for animals), permethrin (for crops), phorate, terbufos, toxaphene, and trichlorfon.

[f]Carbamates included aldicarb, benomyl, carbaryl, and carbofuran. Chloroacetanilide herbicides included alachlor and metolachlor. Organochlorine insecticides included aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, and toxaphene. Organophosphate insecticides included chlorpyrifos, coumaphos, dichlorvos, diazinon, fonofos, malathion, parathion, phorate, terbufos, and trichlorfon. Phenoxy herbicides included 2,4-D; 2,4,5-T; and 2,4,5-TP. Pyrethroid insecticides included permethrin (for animals) and permethrin (for crops). Triazine herbicides included atrazine, cyanazine, and metribuzin.

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Table 5

Husbands' ever use of specific pesticides and self-reported, incident depression in wives from Iowa and North Carolina who never used pesticides, but who were enrolled in the Agricultural Health Study.

	Cases[b] (n = 444)		Total[b] (n = 6,830)		Inverse Probability Weighted[c, d]	
Ever personally mixed or applied[a]	**No.**	**%**	**No.**	**%**	**RR**	**95% CI**
Fumigants						
Aluminum phosphide	26	7	301	5	1.35	0.92, 2.00
Carbon tetrachloride/carbon disulfide (80/20 mix)	25	6	350	6	1.41	0.94, 2.12
Ethylene dibromide	12	3	228	4	0.86	0.45, 1.63
Methyl bromide	70	16	1,010	15	1.04	0.61, 1.77
Fungicides						
Benomyl	46	12	657	11	1.25	0.80, 1.96
Captan	37	9	654	11	0.85	0.61, 1.19
Chlorothalonil	42	10	547	8	1.14	0.78, 1.66
Maneb/mancozeb	47	12	609	10	1.08	0.66, 1.78
Metalaxyl	91	22	1,385	22	0.93	0.70, 1.25
Ziram	10	3	89	1	1.76	0.93, 3.31
Herbicides						
2,4-D	316	72	5,130	77	0.83	0.67, 1.03
2,4,5-T	75	19	1,392	23	1.00	0.76, 1.31
2,4,5-TP	40	10	588	10	1.24	0.89, 1.73
Alachlor	230	58	3,477	56	1.13	0.93, 1.37
Atrazine	307	70	4,889	73	0.85	0.69, 1.05
Butylate	136	35	1,986	33	1.16	0.94, 1.43
Chlorimuron-ethyl	175	44	2,298	37	1.25	1.02, 1.52
Cyanazine	173	44	2,674	43	1.00	0.80, 1.24
Dicamba	208	52	3,196	52	0.96	0.77, 1.20
EPTC	80	21	1,263	21	0.97	0.73, 1.29
Glyphosate	330	75	4,935	74	1.04	0.84, 1.30
Imazethapyr	195	49	2,720	44	1.21	0.95, 1.55
Metolachlor	213	53	3,000	48	1.21	0.99, 1.47
Metribuzin	196	50	2,825	46	1.17	0.95, 1.43
Paraquat	101	25	1,443	23	1.22	0.95, 1.56
Pendimethalin	204	51	2,766	45	1.25	1.03, 1.52
Petroleum oil	186	48	2,951	48	0.95	0.78, 1.15
Trifluralin	231	57	3,309	53	1.19	0.97, 1.45
Insecticides						
Aldicarb	41	10	699	11	1.16	0.73, 1.85
Aldrin	70	18	1,198	20	1.20	0.88, 1.64
Carbaryl	227	55	3,406	54	1.13	0.90, 1.40
Carbofuran	104	26	1,724	28	1.03	0.82, 1.29

Ever personally mixed or applied[a]	Cases[b] (n = 444)		Total[b] (n = 6,830)		Inverse Probability Weighted[c, d]	
	No.	%	No.	%	RR	95% CI
Chlordane	88	23	1,584	26	1.04	0.80, 1.36
Chlorpyrifos	190	43	2,841	43	0.97	0.81, 1.17
Coumaphos	38	10	520	9	1.14	0.82, 1.58
DDT	90	23	1,682	27	1.16	0.85, 1.58
Dichlorvos	39	10	626	10	0.97	0.69, 1.38
Diazinon	124	32	1,895	31	1.07	0.86, 1.33
Dieldrin	18	5	433	7	0.77	0.45, 1.31
Fonofos	85	21	1,394	22	0.97	0.73, 1.27
Heptachlor	53	13	990	16	1.01	0.71, 1.43
Lindane	78	20	1,181	19	1.13	0.88, 1.45
Malathion	286	71	4,501	71	1.00	0.81, 1.23
Parathion	65	17	913	15	1.20	0.89, 1.62
Permethrin (for animals)	63	16	856	14	1.08	0.80, 1.45
Permethrin (for crops)	61	15	780	13	1.21	0.92, 1.58
Phorate	131	33	2,061	34	1.05	0.85, 1.31
Terbufos	159	39	2,527	40	0.95	0.77, 1.17
Toxaphene	64	16	915	15	1.35	1.00, 1.81

Abbreviations: 2,4-D, (2,4-dichlorophenoxy)acetic acid; 2,4,5-T, (2,4,5-trichlorophenoxy)acetic acid; 2,4,5-TP, (*RS*)-2-(2,4,5-trichlorophenoxy)propionic acid; CI, confidence interval; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane; EPTC, *S*-ethyl dipropyl(thiocarbamate); RR, risk ratio.

[a] Fewer than five cases' husbands ever personally mixed or applied trichlorfon.

[b] Information for specific pesticides was missing for 2–11% of wives' husbands.

[c] The wives whose husbands did not use each specific pesticide served as the reference group.

[d] Weights adjusted for age at enrollment (modeled with a restricted, quadratic spline with three equally spaced knots at ages 36, 43, and 52 years based on percentiles of the age distribution in all cases), ever diagnosed with diabetes (other than while pregnant), education level, state of residence, and not dropping out of the Agricultural Health Study cohort (conditional on the exposure of interest and on the same covariates just listed as well as pairwise interaction terms between each covariate and the exposure of interest). Robust variance estimates were used to calculate 95% CIs.