Published in final edited form as:
Occup Environ Med. 2014 September ; 71(9): 629–635. doi:10.1136/oemed-2013-101659.

Pesticide use and incident diabetes among wives of farmers in the Agricultural Health Study

Anne P. Starling[1,2], **David M. Umbach**[3], **Freya Kamel**[1], **Stuart Long**[4], **Dale P. Sandler**[1], and **Jane A. Hoppin**[1]

[1]Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, DHHS, Research Triangle Park, NC, USA

[2]Department of Epidemiology, University of North Carolina at Chapel Hill, NC, USA

[3]Biostatistics Branch, National Institute of Environmental Health Sciences, NIH, DHHS, Research Triangle Park, NC, USA

[4]Westat, Durham, NC, USA

Abstract

Objective—To estimate associations between use of specific agricultural pesticides and incident diabetes in women.

Methods—We used data from the Agricultural Health Study, a large prospective cohort of pesticide applicators and their spouses in Iowa and North Carolina. For comparability with previous studies of farmers, we limited analysis to 13,637 farmers' wives who reported ever personally mixing or applying pesticides at enrollment (1993-1997), who provided complete data on required covariates and diabetes diagnosis, and who reported no previous diagnosis of diabetes at enrollment. Participants reported ever-use of 50 specific pesticides at enrollment and incident diabetes at one of two follow-up interviews within an average of 12 years of enrollment. We fit Cox proportional hazards models with age as the time scale and adjusting for state and body mass index to estimate hazard ratios (HR) and 95% confidence intervals (CI) for each of 45 pesticides with sufficient users.

Results—Five pesticides were positively associated with incident diabetes (n=688; 5%): three organophosphates, fonofos (HR=1.56, 95% CI=1.11, 2.19), phorate (HR=1.57, 95% CI=1.14, 2.16), and parathion (HR=1.61, 95% CI=1.05, 2.46); the organochlorine dieldrin (HR=1.99, 95% CI=1.12, 3.54); and the herbicide 2,4,5-T/2,4,5-TP (HR=1.59, 95% CI=1.00, 2.51). With phorate

Corresponding Author: Jane A. Hoppin, ScD, Department of Biological Sciences, North Carolina State University, Raleigh NC 27695, jahoppin@ncsu.edu, (919) 515-2918, (919) 515-7619 (fax).

J.H. and A.S. conceived of the analysis. J.H., A.S., F.K., D.S. and D.U. contributed to the study design. A.S., D.U. and S.L. contributed to data analysis. J.H., A.S., F.K., D.U., D.S. and S.L. all contributed to writing and editing the manuscript. J.H. is the guarantor of this work.

A poster describing these findings was presented at the 45th Annual Meeting of the Society for Epidemiologic Research in Minneapolis, MN on June 27-30, 2012, and an abstract was published in a supplement to the American Journal of Epidemiology.

CONFLICTS OF INTEREST
The authors have no conflicts of interest to report.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

and fonofos together in one model to account for their correlation, risks for both remained elevated, though attenuated compared to separate models.

Conclusions—Results are consistent with previous studies reporting an association between specific organochlorines and diabetes and add to growing evidence that certain organophosphates also may increase risk.

Keywords

pesticides; diabetes; Agricultural Health Study

Diabetes is believed to have both environmental and genetic causes, but the environmental factors that contribute to its pathogenesis are largely unknown. Recent reports implicate certain chemicals as potentially contributing to the development of diabetes. These chemicals include persistent organic pollutants such as dioxins[1], polychlorinated biphenyls[2], and organochlorine pesticides[3, 4], as well as agents with shorter biological half-lives such as organophosphate insecticides[4, 5] and chlorophenoxy herbicides[6]. The widespread use of many pesticides increases concern about the potential influence of pesticide exposures on diabetes.

Most epidemiologic studies of persistent organic pollutants and diabetes have been cross-sectional[3, 7-10], although a few have been prospective[4, 11, 12]. In cross-sectional studies based on the National Health and Nutrition Examination Survey, serum levels of a polychlorinated biphenyl, an organochlorine insecticide (p,p'-DDT) and a dioxin compound were all positively associated with self-reported diagnosed diabetes among adults[8], and the sum of all persistent organic pollutants measured in serum showed a positive dose-response relationship with diabetes[9]. Persistent organic pollutants may increase the risk of diabetes through binding to the aryl hydrocarbon receptor which, in turn, causes antagonistic effects on the peroxisome proliferator-activated receptor[13].

By contrast, most evidence for the role of relatively short-lived organophosphate insecticides in diabetes comes from laboratory studies. Organophosphate exposure may contribute to diabetes via disruption of adipokine signaling and metabolic regulation[14]. Recent experimental studies have demonstrated excess weight gain, hyperlipidemia and hyperinsulinemia persisting into adulthood in rats exposed neonatally to the organophosphate chlorpyrifos; the magnitude of these effects differs between males and females[15, 16]. The implications of such sex-specific metabolic programming in humans remain unknown.

The Agricultural Health Study (AHS), a large prospective cohort of pesticide applicators and their spouses in Iowa and North Carolina, presents a unique opportunity to conduct longitudinal studies of diabetes incidence among individuals with a known history of pesticide use. A previous prospective analysis[4] among predominantly male licensed pesticide applicators in the AHS found elevated risk of diabetes associated with ever-use of eight pesticides (two organochlorines: chlordane and heptachlor; four organophosphates: coumaphos, phorate, terbufos, and trichlorfon; and two herbicides: alachlor and cyanazine).

Diabetes risk also increased with cumulative lifetime days of use of seven pesticides: aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor, and cyanazine.

Among women in the AHS cohort with at least one pregnancy in the 25 years prior to enrollment, gestational diabetes was twice as likely in those who reported mixing or applying any pesticides during the first trimester of pregnancy[17]. Gestational diabetes also increased with lifetime ever-use of seven specific pesticides (two organophosphates, diazinon and phorate; the carbamate insecticide carbofuran; and four herbicides, atrazine and butylate, as well as the historically dioxin-contaminated herbicides 2,4,5-T and 2,4,5-TP)[17].

This study tests the hypothesis that use of specific pesticides, particularly organochlorine and organophosphate insecticides, by female spouses of farmers is associated with higher incidence of diabetes during the approximately 10-year follow up period.

METHODS

Study population

Spouses of licensed pesticide applicators in Iowa and North Carolina enrolled in the AHS in 1993-1997 via self-administered questionnaire (81%) or telephone interview (19%). 76% of eligible spouses enrolled in the study[18]. At enrollment, participants provided information about demographic characteristics, lifestyle and dietary habits, personal and family medical history, and lifetime use of specific pesticides. Participants were subsequently re-contacted twice, at approximately 5-year intervals, for follow-up telephone interviews. Of the 32,126 female spouses who enrolled in the study, 23,682 (74%) participated in the first follow-up interview, and 19,876 (62%) participated in the second follow-up interview. In the follow-up interviews, participants provided information regarding changes in lifestyle or medical history. Details of the study design are reported elsewhere[19] and questionnaires are available on the study website (http://aghealth.nci.nih.gov/questionnaires.html).

To make our analysis comparable to previous studies of occupational pesticide use[4, 20], we limited it to female spouses who reported ever mixing or applying any pesticides before enrollment (55% of all female spouses, n=17,628). Women who personally mixed or applied pesticides differed in many ways from women who did not. Specifically, women who never mixed or applied pesticides before enrollment had more risk factors for diabetes, including a significantly higher proportion with a high school education or less, and a significantly higher proportion who reported no recreational exercise per week as compared to women who personally mixed or applied pesticides (data not shown).

Our analysis of female spouses with a history of pesticide application at enrollment was further restricted to those who completed at least one of the follow-up interviews (n=15,034). As we were interested in incident disease, we also excluded those with prevalent diabetes (n=518). Prevalent diabetes was defined as either of the following: 1) participant responded “yes” to the following question on the enrollment questionnaire, “Has a doctor ever told you that you had (been diagnosed with) diabetes (sugar) (other than while pregnant)?”, or 2) participant reported no diabetes at enrollment, but at one of the follow-up interviews reported an age at diabetes diagnosis that was less than the age at enrollment. Individuals who were missing information on diabetes incidence (n=57) or baseline body mass index (BMI) (n=822) were also excluded from analysis. These exclusions resulted in an eligible study population of 13,637 women.

Description of variables

At enrollment, participants provided information about their lifetime personal use of pesticides. Women were asked to report the number of years and average number of days per year that they personally mixed or applied any pesticides. We multiplied the category midpoints to create a variable for cumulative lifetime days spent mixing or applying any pesticides, and we grouped this variable into 5 quintile-based categories (1-9 days, 10-25 days, 26-64 days, 65-225 days, 226-7000 days) for analysis. Approximately 25% of women did not provide information on their frequency and duration of pesticide use. Women also provided information on personal ever-use of each of 50 specific pesticides; however, the questionnaire for spouses of farmers (unlike the questionnaire for the farmers themselves) did not request information about the frequency or duration of use of specific pesticides. We combined 2,4,5-T and 2,4,5-TP into one variable because these two herbicides have similar chemical structures, similar use patterns in our cohort, and both contained dioxin at some points in time[21]. We restricted attention to pesticide exposures with five or more exposed cases, thereby eliminating trichlorfon, ziram, aluminum phosphide, and ethylene dibromide. Consequently, we evaluated 45 pesticides for association with diabetes.

Information on covariates of interest was also collected via questionnaire at enrollment. To construct our adjusted models, we produced a directed acyclic graph representing associations previously reported in the literature which indicated that adjustment for age and state of residence (Iowa, North Carolina) would reduce bias due to confounding. We additionally adjusted for BMI at enrollment (<25, 25-29.99, 30-34.99, ≥35 kg/m^2) for comparability with a previous study among applicators[4].

During each of the two follow-up interviews, we asked each participant whether a doctor had ever diagnosed her with diabetes (other than while pregnant) and, if so, her age at diagnosis (given in years). Participants were not asked to report the type of diabetes diagnosed, however in adults it is estimated that 90 to 95% of all diagnosed cases of diabetes are type 2[22]. If reported age at diagnosis equaled or exceeded age at enrollment, then she was considered an incident case. Age at diagnosis, reported in years, was interval-censored. Using dates of birth, enrollment and interviews for each incident case, we established a shortest age interval containing the unknown month and day of diagnosis. Typically that interval was 365 days but might be shorter if the 365-day interval happened to contain the case's enrollment or interview dates. We defined the midpoint of the interval as the age at diagnosis in days. Non-cases were censored at their age in days at last completed interview.

Data Analysis

As described above, age at diagnosis was interval-censored and left-truncated. We are aware of no software for Cox regression that properly accommodates both these contingencies simultaneously. We opted to accommodate left-truncation and handled interval-censoring

NIH-PA Author Manuscript

NIH-PA Author Manuscript

using the midpoint of the interval. Consequently, to estimate the associations between pesticide use and diabetes risk, we fit Cox proportional hazards regression models, with age in days as the time scale, allowing for left-truncation at age at enrollment. All models were adjusted for state of residence and BMI at enrollment to produce the common base model. We checked the proportional hazards assumption for each exposure variable by including a time-varying interaction term, log(age)×exposure variable, as a covariate in the models.

To address potential confounding of individual pesticide results by correlated pesticides, we employed the following two-step procedure. First, we assessed the Spearman correlations among the pesticides which had significant associations with incident diabetes. Second, for any pair of pesticide exposure variables that were correlated at a level of $\rho>0.3$, both correlated pesticides were included as covariates in the same model.

All statistical analyses were performed with SAS, version 9.2 (SAS Institute, Inc., Cary, NC), using the Agricultural Health Study data sets P1REL0906.00, P2REL0907.00, and P3REL0901.00.

RESULTS

Among the 13,637 female spouses eligible for this study, 688 (5%) reported incident diabetes during the follow-up period. Age at enrollment ranged from 17 to 88 years (mean ± standard deviation [SD]: 47.0 ± 11.0 years). Age at diagnosis among the cases ranged from 25 to 88 years (mean ± SD: 58.3 ± 10.5 years). Women who developed diabetes were more likely to be older, to have a higher body mass index, and to be from North Carolina than those who did not (Table 1). Women who developed diabetes were also more likely to have a high school education or less, to be post-menopausal at enrollment, and to have a family history of diabetes. In addition, women who reported three or more hours of recreational physical activity per week during the summer were less likely to develop incident diabetes than those who reported no weekly recreational physical activity. The mean duration of follow-up was 10.0 years for all women; 6.7 years among women with diabetes and 10.2 years among women without diabetes.

We saw little evidence of an exposure-response relationship with measures of overall lifetime pesticide use (Table 2). There was no exposure-response relationship for frequency of pesticide use (days/year) or lifetime days of pesticide use. However, diabetes was associated with total years of use in the highest category of lifetime years of use; women who applied pesticides for more than 30 years were 60% more likely (95% confidence interval [CI]: 1.08, 2.38) to be diagnosed with diabetes than women who had applied pesticides for only one year.

Hazard ratios (HRs) for diabetes were significantly elevated for use of five of the 45 specific pesticides evaluated in models adjusted for age, state, and BMI (Table 3); no pesticide had a significantly reduced hazard ratio. Four of the five pesticides associated with diabetes risk were insecticides: the organochlorine dieldrin (HR: 1.99, 95% CI: 1.12, 3.54) and three organophosphates, fonofos (HR: 1.56, 95% CI: 1.11, 2.19), phorate (HR: 1.57, 95% CI: 1.14, 2.16), and parathion (HR: 1.61, 95% CI: 1.05, 2.46). None of the carbamate or

NIH-PA Author Manuscript

NIH-PA Author Manuscript

pyrethroid insecticides were associated with diabetes. The other pesticide significantly associated with diabetes was the herbicide 2,4,5-T/2,4,5-TP (HR: 1.59, 95% CI: 1.00, 2.51). Another chlorophenoxy herbicide, 2,4-D, was not associated with diabetes (HR: 1.07, 95% CI: 0.90, 1.27). No fumigants or fungicides were significantly associated with incident diabetes.

Two of the five pesticides significantly associated with diabetes, fonofos and phorate, were moderately correlated with each other ($\rho>=0.3$). After including both correlated pesticides in the same model, HRs were attenuated but remained elevated; the HR for fonofos was reduced from 1.56 (95% CI: 1.11, 2.19) to 1.35 (95% CI: 0.91, 2.00) and the HR for phorate was reduced from 1.57 (95% CI: 1.14, 2.16) to 1.42 (95% CI: 0.98, 2.05).

DISCUSSION

Individual pesticides may influence diabetes risk among farm women who apply them. Ever-use of five pesticides was positively associated with incident diabetes. Organochlorines and dioxins have been associated with diabetes previously[10, 11, 13, 23], and we saw associations with the organochlorine insecticide dieldrin and the potentially dioxin-contaminated 2,4,5-T/2,4,5-TP. Organophosphate insecticides have been connected in animal studies to hyperlipidemia and hyperinsulinemia, conditions related to diabetes[5]. We saw an increased risk of diabetes with the organophosphates fonofos, phorate, and parathion. Our results on exposure-response for total lifetime pesticide use suggested that women with 30 or more years of pesticide use had higher risk of diabetes, but the number of days of use did not increase risk.

The incidence of diabetes in this study was 5% over approximately 10 years of follow-up, which was comparable to the national incidence of diabetes among women during the study period. The annual age-adjusted incidence of diabetes among women in the United States rose from 4.9 per 1,000 in 1993 to 7.0 per 1,000 in 2003[22].

Several persistent organic pollutants, including organochlorine pesticides and dioxins, have been previously associated with adult-onset diabetes. In non-occupationally exposed adults, serum levels of the organochlorine pesticides oxychlordane and trans-nonachlor were associated with insulin resistance[24] and the sum of three organochlorine pesticides (p,p'-DDE, trans-nonachlor, and hexachlorobenzene) was associated with incident diabetes[11]. While we had data on seven organochlorines, only dieldrin was significantly associated with an increased diabetes risk. Heptachlor, but not dieldrin, was associated with increased diabetes risk among the AHS licensed pesticide applicators[4]. We provide the previously published associations from studies of diabetes in applicators and gestational diabetes in spouses in Table 4 in order to facilitate comparison of those previous findings with our results. Heptachlor and dieldrin are both cyclodienes, a category of structurally similar organochlorine insecticides. Chlordane, another cyclodiene, was associated with increased diabetes risk in the previous study of AHS applicators (Table 4). The remaining cyclodiene insecticide examined here, aldrin, was associated with somewhat elevated risk of diabetes in both the present study and the previous study of applicators, although neither estimate reached statistical significance (Table 4).

The herbicides 2,4,5-T and 2,4,5-TP which were associated with diabetes here, were historically contaminated during production with dioxins[25]. Dioxins have been previously linked with incident diabetes in highly exposed populations[21, 26]. 2,4,5-T was associated with gestational diabetes among women in the AHS[17], however there was no association with (non-gestational) diabetes among applicators[4]. A previous study of high dioxin exposure in Seveso, Italy, showed positive associations with diabetes in women only[23], raising the possibility that dioxin-contaminated pesticides may have different effects in men and women. Another study of persistent organochlorine pesticides 2,2'4,4'5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (p,p'-DDE) observed that the strength of association between each chemical and diabetes differed between men and women[10]. The possible biological mechanisms responsible for sex-specific associations between persistent organic pollutants and diabetes have not been established.

Notably, the organochlorine and dioxin-contaminated pesticides associated with diabetes in this study have been off the market in the US for 30 years or more. Consequently, use was more common among older cohort members. Because age was the time scale in our analyses, however, confounding by age is unlikely to explain the observed associations of specific organochlorines with incident diabetes.

Organophosphate pesticides have also been linked with diabetes and associated conditions. In animal studies, exposure to the organophosphate pesticides parathion, diazinon, and chlorpyrifos during the neonatal period produced insulin resistance and altered lipid metabolism later in life[5]. In the AHS, certain organophosphate pesticides have been associated with diabetes previously (Table 4). Ever-use of the organophosphate phorate was associated with gestational diabetes among women who used any pesticides during their first trimester of pregnancy[17] and also with incident diabetes among predominantly male licensed pesticide applicators[4]. While the gestational diabetes analysis was also conducted among female spouses in the AHS, it is unlikely that the current results are driven by those findings. Only 40% of the spouses in this analysis were included in the previous analysis and only 3.6% of the gestational diabetes cases from that analysis were among the 688 incident diabetes cases included here. Two other organophosphates, coumaphos and terbufos, were also associated with increased diabetes risk in this analysis; these associations did not reach statistical significance in the present study, but the findings are consistent with the previous study of licensed pesticide applicators[4] (Table 4).

We considered BMI as a confounder due to its strong association with the outcome, and for the purpose of comparability with the previous study of applicators. However, some researchers have hypothesized that certain environmental pollutants may act as "obesogens" and promote weight gain in exposed individuals[27]. If pesticides had obesogenic effects, then BMI could actually be a causal intermediate in a hypothesized causal relationship between pesticide use and diabetes. In this scenario, adjustment for body mass index could bias the effect estimate, typically (though not always) toward the null[28]. Even after adjusting for BMI, however, we observed positive associations between individual pesticides and incident diabetes.

To our knowledge, this study is the largest to date of diabetes among women who applied pesticides, particularly agricultural pesticides. Its prospective design allowed us to assess incident diabetes reported 5-10 years after enrollment. Women provided detailed information on their pesticide use, so we were able to evaluate individual pesticides rather than chemical classes. The large number of women who used pesticides in this cohort allows an informative comparison with previous studies of diabetes among predominantly male pesticide users. The pesticides most frequently used by spouses in the AHS are glyphosate, carbaryl, malathion, 2,4-D, and diazinon[18]. None of these commonly-used pesticides were associated with diabetes in the present study.

We relied on self-reported pesticide use information, which may result in some exposure misclassification. However, the reliability of self-reported ever use of specific pesticides by applicators in the AHS was high, ranging from 79 to 88% exact agreement based on two questionnaires completed 1 year apart in a sample of the cohort[29]. We expect that the reliability of reporting among spouses involved in pesticide application would be similar. We see no reason to suspect that exposure misclassification would be differential with respect to subsequent diabetes diagnosis. There is little potential for recall bias in exposure reporting because pesticide exposure was recorded at enrollment, before the onset of incident diabetes.

The outcome of this study was self-reported diabetes diagnosis. The validity of self-reported diabetes among post-menopausal women was assessed in another cohort[30]. In that study, 74% of women who reported a diagnosis of diabetes at baseline were also found on examination to have elevated fasting glucose that met the diagnostic criterion for diabetes (at least 126 mg/dL). This result suggests that self-reported diabetes in the AHS cohort may have a similar positive predictive value for clinical diabetes.

Our model building strategy relied on the use of a common base model to evaluate each individual pesticide exposure, in order to facilitate comparison of the results across pesticides. The base model used age as the time scale and included state and BMI, all three of which are known to be strongly associated with diabetes risk. If forty-five independent statistical tests were run with a type 1 error rate of 0.05, between two and three of these tests would be expected to appear statistically significant by chance alone, of which approximately half would be in the inverse direction. We observed five statistically significant adjusted associations between ever-use of pesticides and incident diabetes. None of these associations were in the inverse direction. Of course, our tests were not fully independent. However, correlation among pesticides did not explain our findings.

CONCLUSION

Overall, our findings suggest that in women, as well as men, increased risk of diabetes is associated with the use of specific pesticides. Our results are consistent with previous studies reporting an association between organochlorines and diabetes and add to growing evidence that the use of certain organophosphates also may be associated with diabetes risk. The consistent associations between ever-use of specific pesticides (such as phorate) and diabetes across multiple studies in this cohort should provoke more focused investigation of these chemicals. Further research should also examine whether a dose-response relationship may exist between the use of specific pesticides and incident diabetes in women.

Acknowledgments

FUNDING

This research was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01 ES049030) and National Cancer Institute (Z01 CP044008). Ms. Starling was supported by an extramural award (1-F30-ES022126-01) from the National Institute of Environmental Health Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Longnecker MP, Daniels JL. Environmental contaminants as etiologic factors for diabetes. Environ Health Perspect. 2001; 109(Suppl 6):871–6. [PubMed: 11744505]
2. Patel CJ, Bhattacharya J, Butte AJ. An Environment-Wide Association Study (EWAS) on type 2 diabetes mellitus. PLoS One. 2010; 5:e10746. [PubMed: 20505766]
3. Rignell-Hydbom A, Rylander L, Hagmar L. Exposure to persistent organochlorine pollutants and type 2 diabetes mellitus. Hum Exp Toxicol. 2007; 26:447–52. [PubMed: 17623770]
4. Montgomery MP, Kamel F, Saldana TM, et al. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003. Am J Epidemiol. 2008; 167:1235–46. [PubMed: 18343878]
5. Slotkin TA. Does early-life exposure to organophosphate insecticides lead to prediabetes and obesity? Reprod Toxicol. 2011; 31:297–301. [PubMed: 20850519]
6. Schreinemachers DM. Perturbation of lipids and glucose metabolism associated with previous 2,4-D exposure: a cross-sectional study of NHANES III data, 1988-1994. Environ Health. 2010; 9:11. [PubMed: 20187939]
7. Airaksinen R, Rantakokko P, Eriksson JG, et al. Association between type 2 diabetes and exposure to persistent organic pollutants. Diabetes Care. 2011; 34:1972–9. [PubMed: 21816981]
8. Everett CJ, Frithsen IL, Diaz VA, et al. Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999-2002 National Health and Nutrition Examination Survey. Environ Res. 2007; 103:413–8. [PubMed: 17187776]
9. Lee DH, Lee IK, Song K, et al. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. Diabetes Care. 2006; 29:1638–44. [PubMed: 16801591]
10. Rylander L, Rignell-Hydbom A, Hagmar L. A cross-sectional study of the association between persistent organochlorine pollutants and diabetes. Environ Health. 2005; 4:28. [PubMed: 16316471]
11. Lee DH, Lind PM, Jacobs DR Jr, et al. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study. Diabetes Care. 2011; 34:1778–84. [PubMed: 21700918]
12. Turyk M, Anderson H, Knobeloch L, et al. Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers. Environ Health Perspect. 2009; 117:1076–82. [PubMed: 19654916]
13. Remillard RB, Bunce NJ. Linking dioxins to diabetes: epidemiology and biologic plausibility. Environ Health Perspect. 2002; 110:853–8. [PubMed: 12204817]
14. Lassiter TL, Ryde IT, Levin ED, et al. Neonatal exposure to parathion alters lipid metabolism in adulthood: Interactions with dietary fat intake and implications for neurodevelopmental deficits. Brain Res Bull. 2010; 81:85–91. [PubMed: 19615431]

15. Slotkin TA, Brown KK, Seidler FJ. Developmental exposure of rats to chlorpyrifos elicits sex-selective hyperlipidemia and hyperinsulinemia in adulthood. Environ Health Perspect. 2005; 113:1291–4. [PubMed: 16203236]
16. Lassiter TL, Brimijoin S. Rats gain excess weight after developmental exposure to the organophosphorothionate pesticide, chlorpyrifos. Neurotoxicol Teratol. 2008; 30:125–30. [PubMed: 18166376]
17. Saldana TM, Basso O, Hoppin JA, et al. Pesticide exposure and self-reported gestational diabetes mellitus in the Agricultural Health Study. Diabetes Care. 2007; 30:529–34. [PubMed: 17327316]
18. Kirrane EF, Hoppin JA, Umbach DM, et al. Patterns of pesticide use and their determinants among wives of farmer pesticide applicators in the Agricultural Health Study. J Occup Environ Med. 2004; 46:856–65. [PubMed: 15300138]
19. Alavanja MC, Sandler DP, McMaster SB, et al. The Agricultural Health Study. Environ Health Perspect. 1996; 104:362–9. [PubMed: 8732939]
20. Morgan DP, Lin LI, Saikaly HH. Morbidity and mortality in workers occupationally exposed to pesticides. Arch Environ Contam Toxicol. 1980; 9:349–82. [PubMed: 7396557]
21. Flesch-Janys D, Berger J, Gurn P, et al. Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. Am J Epidemiol. 1995; 142:1165–75. [PubMed: 7485063]
22. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.
23. Pesatori AC, Zocchetti C, Guercilena S, et al. Dioxin exposure and non-malignant health effects: a mortality study. Occup Environ Med. 1998; 55:126–31. [PubMed: 9614398]
24. Lee DH, Lee IK, Jin SH, et al. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetes Care. 2007; 30:622–8. [PubMed: 17327331]
25. Milnes MH. Formation of 2,3,7,8-tetrachlorodibenzodioxin by thermal decomposition of sodium 2,4,5,-trichlorophenate. Nature. 1971; 232:395–6. [PubMed: 16063057]
26. Henriksen GL, Ketchum NS, Michalek JE, et al. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology. 1997; 8:252–8. [PubMed: 9115019]
27. Grun F, Blumberg B. Endocrine disrupters as obesogens. Mol Cell Endocrinol. 2009; 304:19–29. [PubMed: 19433244]
28. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology. 2009; 20:488–95. [PubMed: 19525685]
29. Blair A, Tarone R, Sandler D, et al. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology. 2002; 13:94–9. [PubMed: 11805592]
30. Margolis KL, Lihong Q, Brzyski R, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clin Trials. 2008; 5:240–7. [PubMed: 18559413]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

What this paper adds

- Previous studies have suggested that exposure to certain pesticides is associated with incident diabetes; most of these studies have been conducted among men.
- Women who apply agricultural pesticides may differ from men in their response to pesticide exposure.
- Among 13,637 farmers' wives who personally mixed or applied pesticides, five specific pesticides (fonofos, phorate, parathion, dieldrin, and 2,4,5-T/2,4,5-TP) were associated with incident diabetes during a 10-year follow-up period.
- The findings provide additional evidence of an association between certain organochlorines and adult onset diabetes, and also support hypothesized associations between the use of specific organophosphates and incident diabetes among women.

Table 1

Characteristics of 13,637 farmers' wives enrolled in the Agricultural Health Study.

		Cases (n=688)*		**Non-cases (n=12,949)***	
Base model covariates		**N**	**%**	**N**	**%**
Age at enrollment (years)	<40	95	14	3699	29
	40-49	179	26	4101	32
	50-59	271	39	3356	26
	>=60	143	21	1793	14
State of residence	Iowa	471	68	9866	76
	North Carolina	217	32	3083	24
Body mass index (kg/m^2)	<25	113	16	6549	51
	25-29.99	244	35	4291	33
	30-34.99	218	32	1597	12
	>=35	113	16	512	4
Other covariates		N	%	N	%
Race	White, non-Hispanic	681	99	12852	99
	All others	7	1	79	1
Education	High school or less	314	46	4703	37
	More than high school	363	53	8108	63
Smoking status	Never	485	72	9289	74
	Past	122	18	2204	17
	Current	68	10	1139	9
Post-menopausal at enrollment	Yes	371	59	4736	40
	No	261	41	7249	60
Family history of diabetes mellitus at enrollment	Yes	307	45	3095	24
	No	369	55	9667	76
Servings of fruit per day	< 1 serving per day	247	44	4357	42
	1-2 servings per day	267	47	5164	49
	>= 3 servings per day	53	9	915	9

NIH-PA Author Manuscript
NIH-PA Author Manuscript

		Cases (n=688)*		Non-cases (n=12,949)*	
Base model covariates		**N**	**%**	**N**	**%**
Recreational exercise during the summer	None	122	21	1960	19
	<= 2 hours per week	216	38	3886	37
	3-5 hours per week	129	23	2776	26
	>= 6 hours per week	101	18	1840	18

*Columns may not add up to total N due to missing information for some covariates.

Table 2

Associations between time spent personally mixing or applying any pesticides and incident diabetes, among 13,637 farmers' wives enrolled in the Agricultural Health Study.

	Cases (N=688)*		Non-cases (N=12,949)*				
	N	**%**	**N**	**%**	**HR†**	**95% CI‡**	
Years mixed and applied any pesticide							
1 year	40	8	956	10	1.		
2-5 years	102	21	2604	27	1.06	0.73,	1.53
6-10 years	79	16	1870	19	1.11	0.76,	1.64
11-20 years	102	21	2271	23	1.04	0.72,	1.51
21-30 years	77	16	1204	12	1.11	0.75,	1.64
> 30 years	86	18	762	8	1.60	1.08,	2.38
Days per year mixed or applied any pesticides							
< 5 days	232	48	4822	50	1.		
5-9 days	111	23	2239	23	0.85	0.68,	1.07
10-19 days	93	19	1641	17	1.02	0.80,	1.30
20-39 days	36	7	685	7	0.85	0.60,	1.21
40-59 days	9	2	126	1	1.16	0.60,	2.27
> 60 days	5	1	167	2	0.54	0.22,	1.32
Lifetime days mixing or applying any pesticides							
1-9 days	94	19	2559	27	1.		
10-25 days	69	14	1434	15	1.28	0.94,	1.75
26-64 days	103	21	2004	21	1.22	0.92,	1.62
65-225 days	106	22	2114	22	1.07	0.81,	1.42
226-7,000 days	111	23	1504	16	1.28	0.96,	1.70

* Approximately 25% of women did not report this information.

† Hazard ratios adjusted for state (IA, NC), and body mass index at enrollment (<25, 25-29.99, 30-34.99, ≥35 kg/m^2). Proportional hazards models were fitted with attained age in days as the time scale.

‡ 95% confidence interval.

Table 3

Hazard ratios for the association between ever-use of each individual pesticide and incident diabetes, among 13,637 farmers' wives enrolled in the Agricultural Health Study.

	Cases (N=688)		Non-cases (N=12,949)				
Insecticides	**N**	**%**	**N**	**%**	**HR***	**95% CI†**	
Organochlorines							
Aldrin	18	3	176	1	1.34	0.83	2.14
Chlordane	62	10	965	8	0.95	0.73	1.23
DDT	82	13	795	7	1.23	0.97	1.56
Dieldrin	12	2	77	1	1.99	1.12	3.54
Heptachlor‡	18	3	170	1	1.48	0.92	2.37
Lindane	25	4	352	3	1.13	0.76	1.68
Toxaphene	14	2	148	1	1.07	0.63	1.82
Organophosphates							
Chlorpyrifos	53	8	896	7	1.15	0.87	1.52
Coumaphos	21	3	287	2	1.20	0.77	1.85
Diazinon	116	18	2359	19	0.88	0.72	1.08
Dichlorvos	41	6	613	5	0.96	0.70	1.33
Fonofos	36	6	410	3	1.56	1.11	2.19
Malathion	272	41	4560	36	1.05	0.90	1.23
Parathion	22	3	218	2	1.61	1.05	2.46
Phorate	41	6	416	3	1.57	1.14	2.16
Terbufos	43	7	638	5	1.20	0.87	1.63
Carbamates							
Aldicarb	8	1	106	1	1.29	0.64	1.61
Carbaryl	387	59	7042	56	0.90	0.77	1.06
Carbofuran	28	4	415	3	1.00	0.68	1.47
Pyrethroids							
Permethrin (crops)	16	3	470	4	0.65	0.40	1.07
Permethrin (livestock)	38	6	840	7	0.88	0.63	1.23

	Cases (N=688)		Non-cases (N=12,949)				
Insecticides	**N**	**%**	**N**	**%**	**HR***	**95% CI†**	
Herbicides	N	%	N	%	HR	95% CI	
2,4,5-T or 2,4,5-TP	19	3	173	1	1.59	1.00	2.51
2,4-D	185	29	3415	28	1.07	0.90	1.27
Alachlor	62	10	961	8	1.10	0.84	1.43
Atrazine	65	10	1025	8	1.08	0.83	1.40
Butylate	16	2	325	3	0.82	0.50	1.34
Chlorimuron-ethyl	24	4	378	3	1.18	0.78	1.77
Cyanazine	33	5	653	5	0.90	0.63	1.28
Dicamba	54	8	916	7	1.15	0.86	1.53
EPTC	23	4	303	2	1.36	0.89	2.09
Glyphosate	397	58	7737	61	1.03	0.88	1.20
Imazethapyr	30	5	685	6	0.87	0.60	1.25
Metolachlor	32	5	758	6	0.78	0.54	1.11
Metribuzin	23	4	405	3	0.95	0.62	1.44
Paraquat	19	3	264	2	1.07	0.67	1.71
Pendimethalin	27	4	538	4	0.98	0.66	1.43
Petroleum oil	52	8	815	7	1.08	0.81	1.44
Trifluralin	65	10	1219	10	0.97	0.74	1.25
Fungicides and Fumigants	N	%	N	%	HR	95% CI	
Fungicides							
Benomyl	14	2	199	2	1.12	0.66	1.92
Captan	26	4	524	4	0.73	0.49	1.08
Chlorothalonil	11	2	224	2	0.80	0.44	1.45
Maneb	20	3	351	3	0.80	0.51	1.26
Metalaxyl	28	4	323	3	1.42	0.96	2.10
Fumigants							
Methyl bromide‡	19	3	250	2	1.21	0.76	1.94
Carbon tetrachloride/carbon disulfide (80/20 mix)	10	2	119	1	0.91	0.49	1.71

NIH-PA Author Manuscript
NIH-PA Author Manuscript

[*] Hazard ratios adjusted for state (IA, NC), and body mass index at enrollment (<25, 25-29.99, 30-34.99, ≥35 kg/m^2). Proportional hazards models were fitted with attained age in days as the time scale.

[†] 95% confidence interval.

[‡] These pesticides were the only ones that showed any evidence of non-proportional hazards (p=0.05 for heptachlor and p=0.01 for methyl bromide).

Table 4

Pesticides previously associated with gestational diabetes among spouses of applicators or with incident diabetes among applicators in the Agricultural Health Study, as compared with the results of the present study.

	Gestational diabetes among spouses*			**Incident diabetes among applicators (ever use)** †			**Incident diabetes among spouses (present study)**		
	OR	**95% CI**		**OR**	**95% CI**		**HR**	**95% CI**	
Organochlorines									
Aldrin				1.14‡	0.97,	1.33	1.34	0.83,	2.14
Chlordane				1.16‡	1.01,	1.34	0.95	0.73,	1.23
DDT				1.09	0.94,	1.27	1.23	0.97,	1.56
Dieldrin				1.03	0.83,	1.30	1.99	1.12,	3.54
Heptachlor				1.20‡	1.01,	1.43	1.48	0.92,	2.37
Organophosphates									
Coumaphos				1.26	1.03,	1.55	1.20	0.77,	1.85
Diazinon	2.35	0.95,	5.78	0.98	0.85,	1.13	0.88	0.72,	1.08
Dichlorvos				1.21‡	0.98,	1.49	0.96	0.70,	1.33
Fonofos				1.02	0.86,	1.21	1.56	1.11,	2.19
Parathion				1.03	0.88,	1.22	1.61	1.05,	2.46
Phorate	3.57	1.14,	11.17	1.22	1.06,	1.42	1.57	1.14,	2.16
Terbufos	1.74	0.60,	5.06	1.17	1.02,	1.35	1.20	0.87,	1.63
Trichlorfon				1.85‡	1.03,	3.33			
Carbamate									
Carbofuran	3.93	1.28,	12.02	1.05	0.91,	1.20	1.00	0.68,	1.47
Herbicides									
2,4,5-T or 2,4,5-TP	4.67§	1.13,	19.38	1.02§	0.88,	1.19	1.59	1.00,	2.51
Alachlor	2.05	0.79,	5.33	1.14‡	1.00,	1.30	1.10	0.84,	1.43
Atrazine	2.35	0.98,	5.67	1.07	0.93,	1.23	1.08	0.83,	1.40
Butylate	3.92	1.29,	11.93	1.07	0.93,	1.24	0.82	0.50,	1.34
Cyanazine	2.45	0.88,	6.84	1.27‡	1.09,	1.47	0.90	0.63,	1.28

* Saldana et al. 2007. Adjusted for age at pregnancy, BMI at enrollment, parity, state of residence, and five commonly used pesticides.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

[†] Montgomery et al., 2008. Adjusted for age, state of residence, BMI at enrollment.

[‡] Indicates that dose-response relationship was observed.

[§] Estimate for 2,4,5-T.