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## Original Contribution

# Incident Diabetes and Pesticide Exposure among Licensed Pesticide Applicators: Agricultural Health Study, 1993–2003

**M. P. Montgomery[1], F. Kamel[1], T. M. Saldana[2], M. C. R. Alavanja[3], and D. P. Sandler[1]**

[1] Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC.
[2] Social & Scientific Systems, Durham, NC.
[3] Occupational and Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD.

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Exposure to certain environmental toxicants may be associated with increased risk of developing diabetes. The authors' aim was to investigate the relation between lifetime exposure to specific agricultural pesticides and diabetes incidence among pesticide applicators. The study included 33,457 licensed applicators, predominantly non-Hispanic White males, enrolled in the Agricultural Health Study. Incident diabetes was self-reported in a 5-year follow-up interview (1999–2003), giving 1,176 diabetics and 30,611 nondiabetics for analysis. Lifetime exposure to pesticides and covariate information were reported by participants at enrollment (1993–1997). Using logistic regression, the authors considered two primary measures of pesticide exposure: ever use and cumulative lifetime days of use. They found seven specific pesticides (aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor, and cyanazine) for which the odds of diabetes incidence increased with both ever use and cumulative days of use. Applicators who had used the organochlorine insecticides aldrin, chlordane, and heptachlor more than 100 lifetime days had 51%, 63%, and 94% increased odds of diabetes, respectively. The observed association of organochlorine and organophosphate insecticides with diabetes is consistent with results from previous human and animal studies. Long-term exposure from handling certain pesticides, in particular, organochlorine and organophosphate insecticides, may be associated with increased risk of diabetes.

agrochemicals; diabetes mellitus; environmental exposure; hydrocarbons, chlorinated; insecticides; pesticides; phosphoric acid esters

Abbreviations: CI, confidence interval; OR, odds ratio.

Identifying modifiable risk factors for diabetes is important, given that approximately 8.7 percent of all Americans over 20 years of age have diabetes (1). In addition to diet and obesity, there is increasing evidence that environmental exposures should also be considered as potential risk factors. Dioxins and other persistent organic pollutants have received particular attention (2, 3). As a result of findings of a positive association between dioxin, a contaminant of some herbicide formulations, and diabetes, the Department of Veterans Affairs now offers compensation to veterans who were involved in the application of herbicides during the Vietnam War and subsequently developed type 2 diabetes (4). Other studies have demonstrated that organophosphate insecticides disrupt glucose homeostasis in animal models and can lead to hyperglycemia after poisonings in humans. However, the effects of chronic exposure to more moderate levels of organophosphate insecticides on glucose metabolism and diabetes in humans and the extent to which exposure to pesticides in other classes may contribute to diabetes risk are unclear.

Correspondence to Dr. Dale P. Sandler, Epidemiology Branch, National Institute of Environmental Health Sciences, P.O. Box 12233, 111 T. W. Alexander Drive, Research Triangle Park, NC 27709 (e-mail: sandler@niehs.nih.gov).

A previous study among spouses of pesticide applicators in the Agricultural Health Study found an association between gestational diabetes and agricultural use of pesticides during pregnancy (5). Here, we have examined the risk of incident adult onset diabetes associated with lifetime pesticide exposure in licensed pesticide applicators. In particular, we have assessed diabetes risk associated with general agricultural pesticide use and use of specific pesticides.

## MATERIALS AND METHODS

### Population

The Agricultural Health Study is a prospective study of licensed pesticide applicators and their spouses in Iowa and North Carolina. Study details have been reported previously (5), and questionnaires are available on the study website (http://aghealth.nci.nih.gov/). The institutional review boards of the National Institutes of Health (Bethesda, Maryland), Westat, Inc. (Rockville, Maryland; coordinating center), the University of Iowa (Iowa City, Iowa; Iowa field station), and Battelle (Durham, North Carolina; North Carolina field station) approved the study. Between 1993 and 1997, private pesticide applicators applying for a license to use restricted-use pesticides were invited to participate. Approximately 82 percent of eligible applicators ($n = 52{,}393$) enrolled by completing a baseline survey on lifetime pesticide application practices and exposures and a brief medical history (enrollment questionnaire). Additionally, 44 percent of enrolled pesticide applicators completed a more detailed, self-administered questionnaire by mail (take-home questionnaire).

Participants were recontacted between 1999 and 2003 for a follow-up telephone interview. In this second phase, 33,457 applicators (64 percent) provided updated information on medical conditions. Participants who did not complete the follow-up interview were more likely to be older, to have less education, and to have had diabetes at enrollment. However, applicators who were lost to follow-up were similar to those who completed the interview with respect to the cumulative days of pesticide use and the number of acres farmed in the year before enrollment (data not shown). This study focused on the private pesticide applicators who participated in the follow-up interview and who were predominantly non-Hispanic White (97 percent) and male (97 percent).

For this analysis, we excluded 1,330 participants who had diabetes at baseline. Of the 32,127 participants at risk, 238 participants (0.7 percent) were missing information on diabetes, and 102 participants (0.3 percent) were missing information on at least one key covariate (age, state, or body mass index). Thus, 31,787 applicators were included in the analysis.

### Study outcome

The primary outcome was self-reported, incident diabetes. Participants were asked, "Has a doctor ever told you that you had been diagnosed with diabetes (other than while pregnant)?" on the enrollment questionnaire, on the take-home questionnaire, and in the follow-up interview. Age (in years) at diagnosis was reported during the follow-up interview. To define diabetes as incident, we excluded participants who reported diabetes on either the enrollment or take-home questionnaire. We also considered the age at diagnosis and excluded participants whose diagnosis occurred more than 1 year prior to enrollment. Excluding diabetics who were diagnosed in the year preceding enrollment ($n = 47$) had only a negligible influence on the results. Although we cannot be certain, it is likely that most diabetics (>95 percent) were type 2, given the predominance of type 2 over type 1 incidence in adults. Nondiabetics included all participants who reported never having had a diagnosis of diabetes.

### Exposure assessment

We used questionnaire responses at baseline (either at enrollment or on the take-home questionnaire) to estimate lifetime exposure to pesticides. On the enrollment questionnaire, participants reported ever personally mixing or applying any pesticide as well as 50 individual pesticides. For 22 of these pesticides, participants also reported, in categories, the duration (years) and frequency (days per year) of use. Duration and frequency of use of the remaining 28 pesticides were reported on the take-home questionnaire. The percentage of agreement between repeated interviews in this cohort for self-reporting pesticide exposure typically ranged from 70–90 percent for ever use and from 50–60 percent for duration and frequency (6).

We calculated lifetime cumulative days of use by multiplying the midpoints of the reported categories for duration and frequency. For use of any pesticide, applicators were divided into quartiles of cumulative days of use. Categories for cumulative days of use for specific pesticides were 0.01–10 days, 10.01–100 days, and more than 100 days, with never use as the referent category. These cutpoints were selected to retain a sufficient number of observations in each category for analysis and to be consistent across most pesticides. For a few pesticides characterized by infrequent use, the two highest categories were combined into a single category of "more than 10 days."

Pesticide applicators reported using multiple pesticides in their lifetime. In practice, over a lifetime, applicators may substitute use of one pesticide with another in the same functional group. We were interested, therefore, in considering the effect of pesticide groups in addition to the effect of the individual pesticides. We considered four functional groups (herbicides, insecticides, fumigants, and fungicides) and three insecticide classes (organochlorines, organophosphates, and carbamates).

### Statistical analyses

Analyses were performed with SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina) and the Agricultural Health Study data sets P1REL0506.01 and P2REL0506.03. Odds ratios and 95 percent confidence intervals were calculated by use of multiple logistic regression. A Wald chi-square test was used to calculate $p_{\text{trend}}$ values. Some analyses included information from the take-home questionnaire. These analyses were restricted to the subset

**TABLE 1. Characteristics of incident diabetics and nondiabetics among licensed private pesticide applicators enrolled in the Agricultural Health Study, 1993–2003**

| Characteristic | Diabetics | | Nondiabetics | | Adjusted odds ratio* | 95% confidence interval |
|---|---|---|---|---|---|---|
| | No.† | % | No.† | % | | |
| Age (years) at enrollment | | | | | | |
| <40 | 147 | 13 | 10,611 | 35 | 1.00 | Referent |
| 40–49 | 327 | 28 | 8,489 | 28 | 2.44 | 2.00, 2.98 |
| 50–59 | 394 | 34 | 6,542 | 21 | 3.90 | 3.21, 4.73 |
| 60–69 | 261 | 22 | 3,990 | 13 | 4.59 | 3.73, 5.66 |
| ≥70 | 47 | 4 | 979 | 3 | 3.68 | 2.62, 5.18 |
| Sex | | | | | | |
| Male | 1,153 | 98 | 29,802 | 97 | 1.00 | Referent |
| Female | 23 | 2 | 809 | 3 | 0.67 | 0.43, 1.02 |
| State | | | | | | |
| North Carolina | 659 | 56 | 10,691 | 35 | 1.00 | Referent |
| Iowa | 517 | 44 | 19,920 | 65 | 0.44 | 0.39, 0.49 |
| Body mass index (kg/m$^2$) | | | | | | |
| <25 | 89 | 8 | 8,169 | 27 | 1.00 | Referent |
| 25–29 | 514 | 44 | 15,717 | 51 | 3.01 | 2.40, 3.79 |
| 30–32 | 222 | 19 | 3,177 | 10 | 6.54 | 5.08, 8.41 |
| >32 | 351 | 30 | 3,548 | 12 | 9.77 | 7.69, 12.4 |
| Summer exercise (hours/week)‡ | | | | | | |
| None | 203 | 37 | 3,920 | 26 | 1.00 | Referent |
| >0–2 | 177 | 32 | 5,476 | 37 | 0.77 | 0.62, 0.95 |
| ≥3 | 176 | 32 | 5,542 | 37 | 0.76 | 0.61, 0.93 |
| Education | | | | | | |
| Did not complete high school | 186 | 16 | 2,446 | 8 | 1.18 | 0.98, 1.41 |
| Completed high school or GED§ | 554 | 49 | 13,795 | 47 | 1.00 | Referent |
| At least some college | 392 | 35 | 13,265 | 45 | 0.86 | 0.75, 0.99 |
| Smoking status at enrollment | | | | | | |
| Never | 484 | 43 | 16,597 | 56 | 1.00 | Referent |
| Former | 477 | 42 | 8,988 | 30 | 1.17 | 1.03, 1.34 |
| Current | 168 | 15 | 4,249 | 14 | 1.18 | 0.98, 1.42 |
| Cumulative days of any pesticide use | | | | | | |
| 0–64 | 265 | 25 | 7,551 | 26 | 1.00 | Referent |
| 65–200 | 186 | 17 | 6,065 | 21 | 0.91 | 0.75, 1.11 |
| 201–396 | 260 | 24 | 7,480 | 26 | 1.04 | 0.87, 1.25 |
| 397–7,000 | 368 | 34 | 7,709 | 27 | 1.17 | 0.99, 1.38 |
| Acres¶ farmed in year prior to enrollment | | | | | | |
| Didn't work on farm | 31 | 3 | 549 | 2 | 1.17 | 0.73, 1.89 |
| None | 41 | 4 | 445 | 2 | 2.21 | 1.41, 3.45 |
| >0–<5 | 46 | 5 | 1,062 | 4 | 1.00 | Referent |
| 5–49 | 144 | 14 | 2,630 | 9 | 1.18 | 0.83, 1.66 |
| 50–199 | 213 | 21 | 4,955 | 18 | 1.32 | 0.94, 1.85 |
| 200–499 | 248 | 24 | 7,994 | 29 | 1.31 | 0.93, 1.85 |
| 500–999 | 177 | 17 | 6,261 | 23 | 1.31 | 0.92, 1.88 |
| ≥1,000 | 116 | 11 | 3,903 | 14 | 1.48 | 1.02, 2.15 |
| Mixed herbicides in the military‡ | | | | | | |
| Never served in military | 136 | 26 | 4,392 | 30 | 1.00 | Referent |
| No | 384 | 73 | 9,951 | 69 | 0.95 | 0.77, 1.18 |
| Yes | 6 | 1 | 83 | 1 | 1.46 | 0.61, 3.48 |

* Variables for age (<40, 40–49, 50–59, 60–69, ≥70 years), state, and body mass index (<25, 25–29, 30–32, >32) were included in all adjusted models.

† There were ranges in the numbers of diabetics ($n$ = 1,016–1,176) and nondiabetics ($n$ = 27,799–30,611) because of missing data.

‡ Asked on take-home questionnaire. There were ranges in the numbers of diabetics ($n$ = 526–556) and nondiabetics ($n$ = 14,426–14,938) because of missing observations.

§ GED, general equivalency diploma.

¶ One acre = 0.4047 hectare.

**TABLE 2. Ever use of specific pesticides comparing incident diabetics and nondiabetics among applicators enrolled in the Agricultural Health Study, 1993–2003**

| Pesticide name | No. of diabetics ($n$ = 1,176) | % exposed | No. of nondiabetics ($n$ = 30,611) | % exposed | Age-adjusted odds ratio* | 95% confidence interval | Adjusted odds ratio† | 95% confidence interval |
|---|---|---|---|---|---|---|---|---|
| Insecticide classes (any) | 1,042 | 89 | 27,646 | 90 | 0.84 | 0.70, 1.01 | 1.03 | 0.85, 1.24 |
| Organochlorines (any) | 666 | 57 | 14,659 | 48 | 0.98 | 0.87, 1.11 | 1.03 | 0.91, 1.16 |
| Aldrin | 261 | 27 | 5,417 | 20 | 0.99 | 0.85, 1.15 | 1.14 | 0.97, 1.33 |
| Chlordane | 372 | 38 | 7,365 | 27 | 1.25 | 1.09, 1.43 | 1.16 | 1.01, 1.34 |
| DDT‡ | 409 | 41 | 7,110 | 26 | 1.26 | 1.09, 1.46 | 1.09 | 0.94, 1.27 |
| Dieldrin | 96 | 10 | 2,031 | 7 | 0.93 | 0.75, 1.16 | 1.03 | 0.83, 1.30 |
| Heptachlor | 209 | 22 | 4,569 | 17 | 0.95 | 0.80, 1.11 | 1.20 | 1.01, 1.43 |
| Lindane | 192 | 20 | 5,728 | 21 | 0.83 | 0.70, 0.97 | 0.94 | 0.80, 1.11 |
| Toxaphene | 224 | 23 | 4,011 | 15 | 1.33 | 1.14, 1.56 | 1.14 | 0.97, 1.33 |
| Organophosphates (any) | 978 | 83 | 26,329 | 86 | 0.82 | 0.70, 0.96 | 1.02 | 0.86, 1.20 |
| Chlorpyrifos | 466 | 41 | 12,707 | 43 | 0.98 | 0.87, 1.10 | 1.03 | 0.91, 1.17 |
| Coumaphos | 111 | 11 | 2,528 | 9 | 1.18 | 0.97, 1.45 | 1.26 | 1.03, 1.55 |
| Diazinon | 387 | 40 | 9,122 | 33 | 1.19 | 1.04, 1.36 | 0.98 | 0.85, 1.13 |
| Dichlorvos | 110 | 11 | 3,105 | 11 | 0.92 | 0.75, 1.13 | 1.21 | 0.98, 1.49 |
| Fonofos | 193 | 19 | 6,293 | 23 | 0.77 | 0.65, 0.90 | 1.02 | 0.86, 1.21 |
| Malathion | 766 | 75 | 20,397 | 72 | 1.05 | 0.91, 1.21 | 1.10 | 0.95, 1.27 |
| Parathion | 218 | 23 | 4,279 | 16 | 1.34 | 1.15, 1.57 | 1.03 | 0.88, 1.22 |
| Phorate | 345 | 36 | 9,310 | 34 | 0.97 | 0.84, 1.11 | 1.22 | 1.06, 1.42 |
| Terbufos | 392 | 39 | 11,277 | 40 | 0.96 | 0.85, 1.10 | 1.17 | 1.02, 1.35 |
| Trichlorfon | 13 | 1 | 169 | 1 | 2.03 | 1.15, 3.60 | 1.85 | 1.03, 3.33 |
| Carbamates (any) | 804 | 68 | 19,267 | 63 | 1.14 | 1.00, 1.29 | 1.00 | 0.88, 1.14 |
| Aldicarb | 163 | 17 | 3,011 | 11 | 1.71 | 1.44, 2.03 | 1.10 | 0.91, 1.34 |
| Carbaryl | 702 | 68 | 16,198 | 57 | 1.42 | 1.24, 1.62 | 1.10 | 0.95, 1.28 |
| Carbofuran | 330 | 33 | 7,937 | 29 | 1.06 | 0.92, 1.21 | 1.05 | 0.91, 1.20 |
| Pyrethroids (any) | 235 | 20 | 7,006 | 23 | 0.97 | 0.84, 1.13 | 1.07 | 0.92, 1.25 |
| Permethrin (crops) | 150 | 15 | 3,849 | 14 | 1.21 | 1.01, 1.44 | 1.09 | 0.91, 1.31 |
| Permethrin (animals) | 106 | 11 | 3,997 | 14 | 0.81 | 0.66, 0.99 | 1.04 | 0.84, 1.29 |
| Herbicides (any) | 1,102 | 94 | 29,184 | 95 | 0.74 | 0.58, 0.94 | 0.92 | 0.72, 1.18 |
| 2,4,5-T‡ | 273 | 28 | 6,220 | 23 | 0.99 | 0.85, 1.14 | 1.02 | 0.88, 1.19 |
| 2,4,5-TP‡ | 120 | 13 | 2,562 | 9 | 1.12 | 0.92, 1.36 | 1.04 | 0.85, 1.27 |
| 2,4-D‡ | 822 | 73 | 22,911 | 77 | 0.75 | 0.66, 0.86 | 0.92 | 0.79, 1.06 |

**Table continues**

of applicators ($n$ = 15,851) who completed the take-home questionnaire and are indicated in the Results.

## RESULTS

### Characteristics of study population

Age and body mass index were positively associated with diabetes, while hours of recreational exercise per week and education were inversely associated with diabetes (table 1). Participants from Iowa had a 56 percent reduced odds of diabetes compared with participants from North Carolina. Both former and current smokers at enrollment had a slightly higher odds of diabetes than did never smokers. The reduced odds in Iowa remained after adjustment for smoking (odds ratio (OR) = 0.46, 95 percent confidence interval (CI): 0.40, 0.52). Applicators in the highest quartile of cumulative days of use of any pesticide had an increased odds of diabetes incidence compared with those in the lowest quartile of use. The odds of diabetes increased in a dose-dependent relation with the number of acres farmed in the year prior to enrollment, although the highest odds were among those who reported farming 0 acres (1 acre = 0.4047 hectare). Although the numbers were few, participants who reported mixing or applying herbicides during military operations had an increased odds of diabetes.

**TABLE 2. Continued**

| Pesticide name | No. of diabetics (*n* = 1,176) | % exposed | No. of nondiabetics (*n* = 30,611) | % exposed | Age-adjusted odds ratio* | 95% confidence interval | Adjusted odds ratio† | 95% confidence interval |
|---|---|---|---|---|---|---|---|---|
| Alachlor | 585 | 58 | 15,194 | 54 | 1.06 | 0.94, 1.21 | 1.14 | 1.00, 1.30 |
| Atrazine | 796 | 70 | 21,577 | 72 | 0.88 | 0.77, 1.01 | 1.07 | 0.93, 1.23 |
| Butylate | 328 | 34 | 9,109 | 33 | 0.98 | 0.86, 1.13 | 1.07 | 0.93, 1.24 |
| Chlorimuron-ethyl | 339 | 35 | 10,464 | 38 | 0.98 | 0.86, 1.13 | 1.01 | 0.88, 1.16 |
| Cyanazine | 408 | 40 | 12,034 | 43 | 0.86 | 0.75, 0.97 | 1.27 | 1.09, 1.47 |
| Dicamba | 43 4 | 43 | 14,639 | 53 | 0.68 | 0.60, 0.78 | 0.99 | 0.85, 1.15 |
| EPTC‡ | 180 | 18 | 5,733 | 21 | 0.89 | 0.75, 1.04 | 1.10 | 0.93, 1.31 |
| Glyphosate | 865 | 76 | 23,072 | 77 | 0.97 | 0.85, 1.12 | 0.85 | 0.74, 0.98 |
| Imazethapyr | 318 | 32 | 12,391 | 45 | 0.65 | 0.57, 0.75 | 0.92 | 0.78, 1.09 |
| Metolachlor | 444 | 44 | 13,204 | 47 | 0.91 | 0.80, 1.04 | 1.05 | 0.92, 1.20 |
| Metribuzin | 400 | 42 | 12,998 | 47 | 0.78 | 0.69, 0.89 | 0.96 | 0.83, 1.10 |
| Paraquat | 313 | 32 | 6,509 | 24 | 1.45 | 1.26, 1.66 | 1.01 | 0.87, 1.18 |
| Pendimethalin | 453 | 46 | 12,454 | 45 | 1.11 | 0.98, 1.26 | 1.04 | 0.92, 1.19 |
| Petroleum oil | 479 | 50 | 13,415 | 49 | 1.03 | 0.90, 1.17 | 1.13 | 0.99, 1.29 |
| Trifluralin | 493 | 49 | 15,132 | 54 | 0.80 | 0.70, 0.90 | 1.01 | 0.88, 1.16 |
| Fungicides (any) | 496 | 42 | 10,515 | 34 | 1.39 | 1.23, 1.56 | 1.01 | 0.88, 1.15 |
| Benomyl | 144 | 14 | 2,782 | 10 | 1.39 | 1.16, 1.67 | 0.90 | 0.74, 1.10 |
| Captan | 115 | 12 | 3,361 | 12 | 0.96 | 0.78, 1.17 | 1.00 | 0.82, 1.23 |
| Chlorothalonil | 132 | 12 | 2,277 | 8 | 1.63 | 1.35, 1.96 | 1.04 | 0.85, 1.27 |
| Maneb | 146 | 15 | 2,717 | 10 | 1.44 | 1.20, 1.72 | 0.96 | 0.79, 1.16 |
| Metalaxyl | 322 | 32 | 6,496 | 23 | 1.54 | 1.34, 1.77 | 1.02 | 0.88, 1.20 |
| Ziram | 19 | 2 | 447 | 2 | 1.14 | 0.71, 1.81 | 0.92 | 0.57, 1.47 |
| Fumigants (any) | 357 | 30 | 6,738 | 22 | 1.41 | 1.24, 1.60 | 1.04 | 0.90, 1.19 |
| Aluminum phosphide | 59 | 6 | 1,363 | 5 | 1.26 | 0.96, 1.65 | 1.18 | 0.90, 1.55 |
| Carbon tetrachloride | 73 | 7 | 1,599 | 6 | 0.99 | 0.77, 1.26 | 1.03 | 0.80, 1.33 |
| Ethylene dibromide | 43 | 4 | 990 | 4 | 1.10 | 0.81, 1.51 | 0.82 | 0.60, 1.13 |
| Methyl bromide | 268 | 24 | 4,621 | 15 | 1.60 | 1.39, 1.84 | 0.99 | 0.84, 1.16 |

* Model adjusted for age (<40, 40–49, 50–59, 60–69, ≥70 years).

† Model includes variables for age (<40, 40–49, 50–59, 60–69, ≥70 years), state, and body mass index (<25, 25–29, 30–32, >32).

‡ DDT, dichlorodiphenyltrichloroethane; 2,4,5-T, (2,4,5-trichlorophenoxy)acetic acid; 2,4,5-TP, 2-(2,4,5-trichlorophenoxy)propionic acid; 2,4-D, 2,4-dichlorophenoxyacetic acid; EPTC, *S*-ethyl dipropylthiocarbamate.

**Ever use of specific pesticides**

According to responses at enrollment, ever use of eight pesticides (two organochlorine insecticides: chlordane and heptachlor; four organophosphate insecticides: coumaphos, phorate, terbufos, and trichlorfon; and two herbicides: alachlor and cyanazine) was statistically significantly associated with incident diabetes in models accounting for age, state, and body mass index (table 2). The herbicide glyphosate was inversely associated with diabetes. Including categorical variables for education (did not complete high school, completed high school or obtained a general equivalency diploma, or beyond high school) or years of smoking (none, 1–5, 6–15, 16–25, or >25 years) had a negligible effect on the point estimates in these models.

A number of fungicides and fumigants were related to diabetes risk in age-adjusted models but not after further adjustment for state and body mass index. Because these chemicals are used more frequently in North Carolina, we carried out state-stratified analyses. We found no significant association between any of these chemicals and diabetes in either state. Dichlorodiphenyltrichloroethane (DDT), aldicarb, carbaryl, and paraquat use were also proportionately more common in North Carolina (data not shown). The odds of diabetes did not differ substantially between North Carolina and Iowa for either carbaryl (OR = 1.06 (95 percent CI: 0.83, 1.35) and OR = 1.13 (95 percent CI: 0.94, 1.35), respectively) or paraquat (OR = 0.95 (95 percent CI: 0.79, 1.15) and OR = 1.14 (95 percent CI: 0.89, 1.47), respectively). Dichlorodiphenyltrichloroethane and aldicarb were associated with nonsignificantly increased odds of diabetes in Iowa (OR = 1.21 (95 percent CI: 0.97, 1.50) and OR = 1.41 (95 percent CI: 0.87, 2.27), respectively) but not in

**TABLE 3. Dose-response for specific pesticides among incident diabetics and nondiabetics enrolled in the Agricultural Health Study, 1993–2003**

| Pesticide name* | Cumulative days of use | No. of diabetics | No. of nondiabetics | Adjusted odds ratio† | 95% confidence interval | $p_{trend}$‡ |
|---|---|---|---|---|---|---|
| Insecticides | | | | | | |
| Organochlorines | | | | | | |
| Aldrin§ | Never | 429 | 12,213 | Referent | | 0.08 |
| | 0.01–10 | 39 | 1,197 | 0.84 | 0.59, 1.19 | |
| | 10.01–100 | 55 | 1,100 | 1.21 | 0.89, 1.65 | |
| | >100 | 16 | 225 | 1.51 | 0.88, 2.58 | |
| Chlordane§ | Never | 392 | 11,922 | Referent | | 0.05 |
| | 0.01–10 | 92 | 1,881 | 1.15 | 0.90, 1.46 | |
| | 10.01–100 | 43 | 762 | 1.18 | 0.85, 1.65 | |
| | >100 | 15 | 159 | 1.63 | 0.93, 2.86 | |
| Heptachlor§ | Never | 454 | 12,969 | Referent | | 0.02 |
| | 0.01–10 | 41 | 946 | 1.31 | 0.93, 1.85 | |
| | 10.01–100 | 32 | 753 | 1.26 | 0.85, 1.85 | |
| | >100 | 11 | 147 | 1.94 | 1.02, 3.69 | |
| Toxaphene§ | Never | 440 | 13,172 | Referent | | 0.80 |
| | 0.01–10 | 45 | 825 | 1.28 | 0.93, 1.77 | |
| | 10.01–100 | 38 | 569 | 1.30 | 0.91, 1.85 | |
| | >100 | 13 | 237 | 0.82 | 0.46, 1.46 | |
| Organophosphates | | | | | | |
| Chlorpyrifos | Never | 672 | 17,126 | Referent | | 0.04 |
| | 0.01–10 | 141 | 4,154 | 0.96 | 0.80, 1.16 | |
| | 10.01–100 | 185 | 5,661 | 0.95 | 0.80, 1.12 | |
| | >100 | 123 | 2,695 | 1.24 | 1.02, 1.52 | |
| Coumaphos | Never | 865 | 24,668 | Referent | | 0.79 |
| | 0.01–10 | 40 | 1,053 | 1.12 | 0.81, 1.56 | |
| | 10.01–100 | 49 | 931 | 1.60 | 1.18, 2.17 | |
| | >100 | 16 | 440 | 0.94 | 0.56, 1.56 | |
| Diazinon§ | Never | 393 | 11,612 | Referent | | 0.006 |
| | 0.01–10 | 39 | 1,499 | 0.68 | 0.48, 0.95 | |
| | 10.01–100 | 70 | 1,149 | 1.30 | 0.99, 1.71 | |
| | >100 | 36 | 435 | 1.59 | 1.09, 2.31 | |
| Dichlorvos | Never | 880 | 24,466 | Referent | | 0.15 |
| | 0.01–10 | 30 | 921 | 1.15 | 0.78, 1.67 | |
| | 10.01–100 | 32 | 917 | 1.19 | 0.82, 1.72 | |
| | >100 | 44 | 1,187 | 1.26 | 0.91, 1.73 | |
| Phorate§ | Never | 396 | 10,264 | Referent | | 0.68 |
| | 0.01–10 | 50 | 1,879 | 0.97 | 0.71, 1.34 | |
| | 10.01–100 | 71 | 1,959 | 1.14 | 0.86, 1.49 | |
| | >100 | 27 | 644 | 1.05 | 0.70, 1.58 | |
| Terbufos | Never | 610 | 16,572 | Referent | | 0.19 |
| | 0.01–10 | 81 | 2,779 | 1.08 | 0.85, 1.38 | |
| | 10.01–100 | 181 | 5,020 | 1.23 | 1.03, 1.47 | |
| | >100 | 116 | 3,236 | 1.14 | 0.93, 1.41 | |

**Table continues**

**TABLE 3. Continued**

| Pesticide name* | Cumulative days of use | No. of diabetics | No. of nondiabetics | Adjusted odds ratio† | 95% confidence interval | $p_{trend}$‡ |
|---|---|---|---|---|---|---|
| Trichlorfon | Never | 968 | 27,180 | Referent | | 0.02 |
| | 0.01–10 | 5 | 61 | 1.92 | 0.75, 4.94 | |
| | >10 | 7 | 75 | 2.47 | 1.10, 5.56 | |
| Carbamates | | | | | | |
| Aldicarb§ | Never | 492 | 13,745 | Referent | | 0.90 |
| | 0.01–10 | 12 | 370 | 0.62 | 0.34, 1.12 | |
| | 10.01–100 | 23 | 410 | 1.00 | 0.64, 1.57 | |
| | >100 | 15 | 259 | 0.97 | 0.56, 1.68 | |
| Carbaryl§ | Never | 254 | 8,393 | Referent | | 0.67 |
| | 0.01–10 | 89 | 2,532 | 1.03 | 0.80, 1.32 | |
| | 10.01–100 | 101 | 2,147 | 0.98 | 0.75, 1.26 | |
| | >100 | 94 | 1,600 | 0.95 | 0.72, 1.25 | |
| Herbicides | | | | | | |
| Alachlor | Never | 431 | 12,716 | Referent | | 0.001 |
| | 0.01–10 | 110 | 3,421 | 1.00 | 0.81, 1.25 | |
| | 10.01–100 | 208 | 6,312 | 1.05 | 0.88, 1.25 | |
| | >100 | 240 | 4,974 | 1.31 | 1.11, 1.55 | |
| Atrazine | Never | 340 | 8,342 | Referent | | 0.02 |
| | 0.01–10 | 118 | 3,778 | 0.95 | 0.77, 1.19 | |
| | 10.01–100 | 285 | 8,529 | 0.99 | 0.83, 1.17 | |
| | >100 | 370 | 9,005 | 1.15 | 0.98, 1.36 | |
| Cyanazine | Never | 609 | 15,817 | Referent | | 0.004 |
| | 0.01–10 | 104 | 3,618 | 1.04 | 0.83, 1.30 | |
| | 10.01–100 | 173 | 5,003 | 1.32 | 1.09, 1.60 | |
| | >100 | 115 | 3,179 | 1.38 | 1.10, 1.72 | |
| EPTC¶ | Never | 805 | 21,707 | Referent | | 0.56 |
| | 0.01–10 | 77 | 2,488 | 1.08 | 0.84, 1.38 | |
| | 10.01–100 | 65 | 2,145 | 1.15 | 0.88, 1.50 | |
| | >100 | 31 | 949 | 1.07 | 0.74, 1.56 | |
| Metribuzin§ | Never | 351 | 9,104 | Referent | | 0.06 |
| | 0.01–10 | 80 | 2,759 | 1.02 | 0.78, 1.32 | |
| | 10.01–100 | 81 | 2,337 | 1.22 | 0.93, 1.58 | |
| | >100 | 25 | 574 | 1.44 | 0.94, 2.21 | |
| Petroleum oil§ | Never | 436 | 11,551 | Referent | | 0.72 |
| | 0.01–10 | 28 | 1,035 | 0.87 | 0.58, 1.29 | |
| | 10.01–100 | 42 | 1,226 | 0.99 | 0.71, 1.38 | |
| | >100 | 30 | 882 | 0.93 | 0.63, 1.37 | |
| Fumigant | | | | | | |
| Aluminum phosphide | Never | 524 | 14,345 | Referent | | 0.69 |
| | 0.01–10 | 11 | 282 | 1.15 | 0.62, 2.15 | |
| | >10 | 10 | 231 | 1.10 | 0.57, 2.12 | |

* Pesticides with no dose-response association with diabetes are not shown.
† Models include variables for age (<40, 40–49, 50–59, 60–69, ≥70 years), state, and body mass index (<25, 25–29, 30–32, >32).
‡ Wald's chi-square test.
§ Information provided on take-home questionnaire completed by 44% of enrolled applicators.
¶ EPTC, *S*-ethyl dipropylthiocarbamate.

**TABLE 4. Relation between specific pesticide use and incident diabetes stratified by age and state among applicators enrolled in the Agricultural Health Study, 1993–2003**

| Pesticide | Age (years) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <60 | | | | ≥60 | | | |
| | No. of diabetics | No. of nondiabetics | Adjusted odds ratio* | 95% confidence interval | No. of diabetics | No. of nondiabetics | Adjusted odds ratio* | 95% confidence interval |
| Insecticides | | | | | | | | |
| Organochlorines | | | | | | | | |
| Aldrin | 169 | 3,757 | 1.11 | 0.92, 1.34 | 92 | 1,660 | 1.10 | 0.82, 1.47 |
| Chlordane | 268 | 5,450 | 1.26 | 1.08, 1.48 | 104 | 1,915 | 0.88 | 0.67, 1.15 |
| Heptachlor | 140 | 3,163 | 1.25 | 1.01, 1.54 | 69 | 1,406 | 1.00 | 0.72, 1.38 |
| Organophosphates | | | | | | | | |
| Dichlorvos | 86 | 2,673 | 1.22 | 0.96, 1.54 | 24 | 432 | 1.16 | 0.74, 1.81 |
| Trichlorfon | 11 | 142 | 2.03 | 1.07, 3.86 | 2 | 27 | 1.31 | 0.30, 5.68 |
| Herbicides | | | | | | | | |
| Alachlor | 451 | 12,896 | 1.18 | 1.01, 1.37 | 134 | 2,298 | 1.00 | 0.77, 1.30 |
| Cyanazine | 322 | 10,331 | 1.33 | 1.13, 1.58 | 86 | 1,703 | 1.04 | 0.76, 1.41 |
| | State | | | | | | | |
| | North Carolina | | | | Iowa | | | |
| | No. of diabetics | No. of nondiabetics | Adjusted odds ratio† | 95% confidence interval | No. of diabetics | No. of nondiabetics | Adjusted odds ratio† | 95% confidence interval |
| Insecticides | | | | | | | | |
| Organochlorines | | | | | | | | |
| Aldrin | 82 | 956 | 1.20 | 0.93, 1.56 | 179 | 4,461 | 1.10 | 0.89, 1.34 |
| Chlordane | 210 | 3,045 | 1.14 | 0.94, 1.38 | 162 | 4,320 | 1.20 | 0.98, 1.46 |
| Heptachlor | 26 | 429 | 0.80 | 0.53, 1.22 | 183 | 4,140 | 1.34 | 1.09, 1.64 |
| Organophosphates | | | | | | | | |
| Dichlorvos | 22 | 314 | 1.08 | 0.69, 1.70 | 88 | 2,791 | 1.25 | 0.98, 1.59 |
| Trichlorfon | 8 | 89 | 1.54 | 0.73, 3.25 | 5 | 80 | 2.67 | 1.05, 6.81 |
| Herbicides | | | | | | | | |
| Alachlor | 276 | 3,898 | 1.25 | 1.04, 1.49 | 309 | 11,296 | 1.03 | 0.85, 1.24 |
| Cyanazine | 105 | 1,252 | 1.43 | 1.14, 1.79 | 303 | 10,782 | 1.17 | 0.97, 1.41 |

* Adjusted for age (continuous), body mass index (<25, 25–29, 30–32, >32), and state.
† Adjusted for age (<40, 40–49, 50–59, 60–69, ≥70 years) and body mass index (<25, 25–29, 30–32, >32).

North Carolina (OR = 1.02 (95 percent CI: 0.83, 1.25) and OR = 1.06 (95 percent CI: 0.86, 1.30), respectively).

### Cumulative days of pesticide use

Of the 16 pesticides for which ever use from the enrollment questionnaire had an increased odds of diabetes in fully adjusted models (OR > 1.10), six also demonstrated a dose response ($p_{trend} < 0.10$) (table 3). These included aldrin, chlordane, heptachlor, trichlorfon, alachlor, and cyanazine. Dichlorvos showed a moderate dose-response trend with diabetes. Additionally, four pesticides (chlorpyrifos, diazinon, atrazine, and metribuzin) showed a positive dose response with diabetes that was not detected in ever use analyses. The remaining pesticides showed no dose-response association with diabetes incidence (data not shown). Information on cumulative days of use for certain pesticides was asked only on the take-home questionnaire, as indicated in table 3. Ever use of these pesticides based on take-home questionnaire information is available from the corresponding author. In general, the estimates do not vary significantly between the two questionnaires.

### Ever use stratified by age and state

Analyses stratified on age, state, and body mass index were carried out for pesticides where the odds of diabetes were increased in both ever-never and dose-response models (tables 4 and 5). We used lenient selection criteria, because prior evidence for these pesticides was lacking. With the exception of heptachlor, which was associated with diabetes only in Iowa, pesticide estimates did not differ greatly

**TABLE 5. Relation between specific pesticide use and incident diabetes stratified by body mass index among diabetics and nondiabetics enrolled in the Agricultural Health Study, 1993–2003**

| Pesticide | Under- and normal weight (<25 kg/m²) | | | | Overweight (25–29 kg/m²) | | | | Obese (≥30 kg/m²) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of diabetics | No. of nondiabetics | Adjusted odds ratio* | 95% confidence interval | No. of diabetics | No. of nondiabetics | Adjusted odds ratio* | 95% confidence interval | No. of diabetics | No. of nondiabetics | Adjusted odds ratio* | 95% confidence interval |
| Insecticides | | | | | | | | | | | | |
| Organochlorines | | | | | | | | | | | | |
| Aldrin | 10 | 1,210 | 0.53 | 0.26, 1.08 | 106 | 2,903 | 1.07 | 0.84, 1.36 | 145 | 1,304 | 1.31 | 1.05, 1.63 |
| Chlordane | 28 | 1,860 | 1.03 | 0.63, 1.68 | 165 | 3,904 | 1.16 | 0.94, 1.42 | 179 | 1,601 | 1.19 | 0.97, 1.45 |
| Heptachlor | 7 | 1,036 | 0.48 | 0.21, 1.10 | 81 | 2,408 | 1.09 | 0.83, 1.43 | 121 | 1,125 | 1.42 | 1.11, 1.81 |
| Organophosphates | | | | | | | | | | | | |
| Dichlorvos | 7 | 832 | 1.03 | 0.46, 2.32 | 44 | 1,628 | 1.15 | 0.83, 1.60 | 59 | 645 | 1.30 | 0.97, 1.75 |
| Trichlorfon | 0 | 52 | N/A† | | 9 | 83 | 3.19 | 1.56, 6.51 | 4 | 34 | 1.29 | 0.45, 3.69 |
| Herbicides | | | | | | | | | | | | |
| Alachlor | 32 | 3,659 | 0.82 | 0.51, 1.32 | 239 | 8,020 | 1.09 | 0.89, 1.327 | 314 | 3,515 | 1.24 | 1.03, 1.50 |
| Cyanazine | 18 | 2,978 | 0.62 | 0.34, 1.13 | 176 | 6,357 | 1.41 | 1.13, 1.77 | 214 | 2,699 | 1.27 | 1.03, 1.57 |

* Adjusted for age (<40, 40–49, 50–59, 60–69, ≥70 years), state, and body mass index (continuous).
† N/A, not available.

between states, although the confidence intervals widened due to smaller sample sizes. For age-specific strata, however, pesticide associations with diabetes were more obvious among applicators aged less than 60 years. In general, the associations of pesticides with diabetes were also stronger among participants with higher body mass index.

## DISCUSSION

This study is to our knowledge the largest study to evaluate the potential effects of pesticides on diabetes incidence in adults. The prospective design of the study ensures that exposures were reported prior to the diagnosis of diabetes and reduces the potential for recall bias. Of the 50 pesticides evaluated, seven displayed evidence suggesting an association with diabetes incidence in both ever-use and cumulative-days-of-use models: aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor, and cyanazine. It is noteworthy that all of these pesticides are chlorinated compounds, while only half of the pesticides investigated were chlorinated.

Few studies, if any, have considered the potential diabetogenic effects of alachlor and cyanazine, which both showed a dose-response association with diabetes in the present study. However, the biologic plausibility of a diabetogenic effect of exposure to persistent organic pollutants (e.g., dioxins, polychlorinated biphenyls, and organochlorine insecticides) and organophosphate insecticides is supported by numerous studies.

### Persistent organic pollutants (organochlorine insecticides)

Because persistent organic pollutants are lipid soluble and bioaccumulate in animal tissues, studies of the relation of chronic exposure to persistent organic pollutants to diabetes can be conducted by use of human biologic samples (3, 7, 8). Of the seven pesticides for which the odds of diabetes were increased in both ever-never and dose-response analyses, three (aldrin, chlordane, and heptachlor) are persistent organic pollutants. Although the organochlorine insecticides in this study are no longer available on the market, measurable levels of these and other persistent organic pollutants are still detectable in the general population and in food products, making these findings potentially relevant to the general population (2, 9, 10).

Studies using National Health and Nutrition Examination Survey (NHANES) data have found associations of persistent organic pollutants with both diabetes and insulin resistance and have noted, in particular, the association of diabetes with organochlorine insecticides (2, 11, 12). A metabolite and an impurity of chlordane were most strongly associated with insulin resistance in nondiabetics (12). Animal studies of exposure to chlordane have demonstrated increased lipids and triglycerides in the liver (13, 14) and altered glucose metabolism (14, 15). Our finding that chlordane exposure followed a dose-response association with diabetes incidence strengthens the chlordane-diabetes hypothesis. Heptachlor is a frequent component of chlordane mixtures and is structurally very similar (16), but few studies have considered the diabetogenic actions of heptachlor itself. There is some evidence that heptachlor affects lipid metabolism (17). Similarly, few studies have examined aldrin in relation to diabetes, although it has been shown that aldrin disrupts carbohydrate metabolism in fish (18, 19).

Dioxin, a frequenct contaminant of herbicides used for military purposes, is a persistent organic pollutant that has been studied repeatedly for its potential diabetogenic effect in humans. Studies have suggested that exposure to dioxin as a contaminant of the herbicide Agent Orange (a code name used by the military) increased the risk of diabetes and disrupted glucose and insulin homeostasis among exposed veterans (20, 21). Although the number of exposed diabetics was small, our findings that participants who reported mixing herbicides in the military had an increased odds of diabetes incidence compared with participants who did not mix herbicides in the military or who were not in the military are consistent with those of these studies.

### Organophosphate insecticides

Unlike persistent organic pollutants, organophosphate insecticides are readily degraded, and consequently, studies have more frequently been conducted in animal models where the outcome is typically short-term disruption of glucose homeostasis. An advantage of the Agricultural Health Study is the ability to consider the risk of diabetes in humans in relation to long-term exposure to lower levels of organophosphate insecticides. Of the 10 such insecticides investigated, we found seven (chlorpyrifos, coumaphos, diazinon, dichlorvos, phorate, terbufos, and trichlorfon) that had increased odds of diabetes, three of which (chlorpyrifos, diazinon, and trichlorfon) were associated in a dose-dependent manner.

Type 2 diabetes is characterized by insulin resistance, which initially is compensated by an increase in insulin production. Over time, the pancreas fails to produce sufficient insulin to stimulate adequate glucose uptake in adipose and muscle tissues, leading to hyperglycemia and type 2 diabetes. Pancreatic β-cells contain muscarinic acetylcholine receptors, which are involved in the glucose-dependent production of insulin (22). Organophosphate insecticides are known inhibitors of acetylcholinesterase, the enzyme responsible for the degradation of acetylcholine. Thus, exposure to sufficiently high levels of organophosphate insecticides would be expected to result in increased accumulation of acetylcholine, potentially leading to overstimulation and eventual down-regulation of its receptors (23) and reducing insulin production.

Indeed, organophosphate exposure has been shown repeatedly to be associated with hyperglycemia in animal models (24). Dichlorvos specifically has been shown to disrupt glucose homeostasis in male Wistar rats (25). We found that applicators exposed to dichlorvos had an increased odds of diabetes and that the odds increased with increasing cumulative days of use, although the test for trend was only moderately significant. Furthermore, the pesticide most strongly associated with diabetes among applicators was the organophosphate insecticide trichlorfon, which is converted to dichlorvos in mammals (26).

In addition to studies of the effects of short-term exposure to organophosphate insecticides, studies that have considered the effects of long-term, low-level exposure may be of greater relevance to our study population. Studies of long-term exposure to organophosphate insecticides with respect to diabetes in humans have not previously been conducted. However, animal studies have demonstrated that tolerance to organophosphate insecticide exposure develops over time, likely as a result of decreased expression of muscarinic receptors (27). Because these receptors mediate the production of insulin in β-cells, a decrease in muscarinic receptors could potentially lead to decreased insulin production. Additionally, prolonged stimulation by acetylcholine may reduce β-cell sensitivity to glucose (28).

Unlike that of organophosphate insecticides, the carbamate insecticide inhibition of acetylcholinesterase is reversible and short-lived, and therefore the effects of exposure would be expected to be less severe. We found that the carbamate insecticides showed very weak, if any, evidence of an association with diabetes in fully adjusted models. Pesticides from the fungicide and fumigant groups also showed no convincing association with diabetes, indicating that our findings were exclusive to organochlorine and organophosphate insecticides and a limited number of herbicides.

### The role of body mass index

Because persistent organic pollutants are lipophilic, people with higher body mass index may be more likely to store higher levels of these organic pollutants than people with lower body mass index with equivalent exposure. A study in the National Health and Nutrition Examination Survey population found that obesity and diabetes were associated only among participants with detectable levels of persistent organic pollutants (2). The diabetogenic effect of dioxin exposure has also been shown to be stronger among obese compared with lean individuals (29). The effects of the seven pesticides that showed an association in both ever-never and dose-response analyses were strongest in obese participants. Although body mass index may be related to pesticide exposure in the case of lipophilic compounds, it is not clearly in the causal pathway; that is, pesticide exposure has not been shown to cause weight gain in adults, allaying the concern that adjustment for body mass index would result in an overadjustment of the effect of pesticide exposure.

### Limitations

One limitation of this study was the use of self-reported diagnosis of diabetes. Among the 1,055 participants who indicated a diagnosis of diabetes at baseline and completed the follow-up interview, 92 percent ($n = 972$) confirmed this diagnosis in the follow-up interview. This suggests a high level of reliability in self-reporting diabetes in this cohort. Furthermore, it is reassuring that age and body mass index were associated with the outcome, as these are well established risk factors for diabetes. A second limitation was our inability to control for exercise and diet.

A drawback in studies of occupationally exposed cohorts that has been raised in previous studies is the ability of the group identified as unexposed to represent a truly low-risk group (2). Inclusion of participants exposed to other potentially diabetogenic pesticides in the unexposed group may have resulted in an underestimation of the true effects.

With regard to age, which is associated with cumulative pesticide exposure and causally associated with diabetes, there may be some concern about residual confounding. However, estimates from models with age treated as a continuous or as a quadratic term were nearly identical to those from the model using age as a categorical variable. In age-stratified analyses, the observation that pesticide effects were more prominent among younger applicators may be due to an increased number of competing risk factors for diabetes at older ages.

There was a strong relation between diabetes incidence and state of residence; applicators from North Carolina had a twofold increased odds of diabetes compared with applicators in Iowa, even after adjustment for age, body mass index, and smoking. This may reflect differences in health and lifestyle status between the states that were not completely controlled for by age, body mass index, and smoking alone. State, therefore, was included in all fully adjusted models, and state-stratified analyses were conducted when necessary.

Although we had relatively good follow-up of the cohort after 5 years, participants who did not complete the follow-up interview were more likely to have had diabetes at enrollment. Although the cumulative days of pesticide use did not differ significantly, ever use of pesticide groups was lower among participants who were lost to follow-up. The loss of prevalent diabetics does not necessarily imply the loss of incident diabetics, and it is impossible to know whether the loss of diabetics would be related to level of exposure. However, we cannot exclude the possibility that selection would have biased our results.

### Summary

Pesticide applicators who reported exposure to certain organochlorine and organophosphate insecticides and two herbicides showed an increased risk of diabetes independent of age, state of residence, and body mass index. These results extend previous findings of persistent organic pollutants and organophosphate insecticides to a much larger cohort where diabetes onset was assessed prospectively and exposure was measured in a semiquantitative manner. Although based in an occupationally exposed cohort, the findings may have relevance to the general population in the case of environmentally persistent chemicals. Apart from organochlorine insecticides, most pesticides in this study are considered general-use pesticides and are available to the general public, although the strength and formulation may vary. The increasing burden of diabetes in populations worldwide warrants our improved understanding of the possible relation of diabetes risk to long-term, low levels of pesticide exposure.

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