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High Pesticide Exposure Events and Olfactory Impairment among U.S. Farmers

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Background: Olfactory impairment (OI) is common among older adults and independently predicts all-cause mortality and the risk of several major neurodegenerative diseases. Pesticide exposure may impair olfaction, but empirical evidence is lacking.

Objective: We aimed to examine high pesticide exposure events (HPEEs) in relation to self-reported OI in participants in the Agricultural Health Study (AHS).

Methods: We conducted multivariable logistic regression to examine the associations between HPEEs reported at enrollment (1993–1997) and self-reported OI at the latest AHS follow-up (2013–2015) among 11,232 farmers, using farmers without HPEEs as the reference or unexposed group.

Results: A total of 1,186 (10.6%) farmers reported OI. A history of HPEEs reported at enrollment was associated with a higher likelihood of reporting OI two decades later {odds ratio (OR) = 1.49 [95% confidence interval (CI): 1.28, 1.73]}. In the analyses on the HPEE involving the highest exposure, the association appears to be stronger when there was a >4-h delay between HPEE and washing with soap and water [e.g., OR = 2.07 (95% CI: 1.48, 2.89) for 4–6 h vs. OR = 1.39 (95% CI: 1.11, 1.75) for <30 min]. Further, significant associations were observed both for HPEEs involving the respiratory or digestive tract [OR = 1.53 (95% CI: 1.22, 1.92)] and dermal contact [OR = 1.47 (95% CI: 1.22, 1.78)]. Finally, we found significant associations with several specific pesticides involved in the highest exposed HPEEs, including two organochlorine insecticides (DDT and lindane) and four herbicides (alachlor, metolachlor, 2,4-D, and pendimethalin). HPEEs that occurred after enrollment were also associated with OI development.

Conclusions: HPEEs may cause long-lasting olfactory deficit. Future studies should confirm these findings with objectively assessed OI and also investigate potential mechanisms. https://doi.org/10.1289/EHP3713

Introduction

The human sense of smell decreases with age. Olfactory impairment (OI), or poor sense of smell, is an understudied public health problem among older adults. OI affects up to 25% of older U.S. adults overall, and the proportion may increase to more than 60% for those ≥80 y of age (Adams et al. 2017; Dong et al. 2017a; Murphy et al. 2002). OI adversely affects critical aspects of human functioning such as detecting environmental hazards (Santos et al. 2004), nutrition (Mattes and Cowart 1994), mood and behavior (Schiffman et al. 1995a, 1995b), sexuality (Bhutta 2007), emotional and physical well-being (Smeets et al. 2009), and quality of life (Croy et al. 2014). In older adults, OI also predicts both short-term (Devanand et al. 2015; Pinto et al. 2014; Wilson et al. 2011) and long-term mortality (Ekström et al. 2017; Schubert et al. 2017) even after accounting for dementia and other chronic diseases. More importantly, converging evidence suggests that OI is one of the earliest and most important prodromal symptoms for Parkinson's disease (PD) (Chen et al. 2017; Ross et al. 2008) and Alzheimer's disease (AD) (Wilson et al. 2009; Yaffe et al. 2017). If these connections involve shared risk factors (Dong et al. 2015, 2017b), OI research could have major implications for understanding the pathophysiology of early stages of neurodegeneration.

Few population-based studies have investigated potential risk factors for OI in older adults (Dong et al. 2017a; Murphy et al. 2002; Schubert et al. 2012). Except for higher prevalence with older age and male sex (Murphy et al. 2002), associations with other demographic and lifestyle factors and environmental exposures are largely unknown. Pesticides represent a common environmental exposure and may impair the human sense of smell by affecting peripheral olfactory structures (e.g., inflammation of nasal mucosa) as well as the central nervous system (e.g., PD- or AD- related neuropathology) (Doty 2015). However, little empirical evidence exists on pesticides and OI.

Acute high exposure to certain pesticides can have life-threatening neurotoxic effects within hours (Jett 2011; Kamel and Hoppin 2004; Vale and Lotti 2015) and may have lasting neurological deficits years later (Kamel and Hoppin 2004). We only know of one case report that documented olfactory dysfunction following high exposure to pesticide. Minutes after entering a poorly ventilated examination room treated by a pyrethrin-based insecticide for pest infestation, an Italian doctor developed nasal irritation and progressive loss of odor perception (Gobba and Abbacchini 2012). After days in the room, the doctor developed anosmia or a total loss of the sense of smell; the authors reported that anosmia persisted through the last clinical visit 3 y later and was therefore deemed permanent. In this study, we aimed to comprehensively examine reports of a high pesticide exposure event (HPEE), as a surrogate for acute high pesticide exposure, in relation to OI among farmers in the Agricultural Health Study (AHS). Specifically, we hypothesized that *a*) a history of HPEEs reported at AHS enrollment is associated with self-reported OI; and *b*) the strength of association may depend on the body parts exposed, promptness in washing with soap and water, and specific chemicals involved.

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Methods

Study Population

The AHS is an ongoing prospective cohort study of licensed private pesticide applicators (hereafter referred to as farmers) from Iowa and North Carolina. Details about this cohort have been published elsewhere (Alavanja et al. 1996). Briefly, 52,394 farmers enrolled in the AHS in 1993–1997 at the time of their pesticide license renewals by completing a questionnaire that asked about lifetime use of pesticides, sociodemographic characteristics, and medical history. In addition, 44% ($n = 22{,}916$) of these farmers completed a take-home questionnaire that sought further details on pesticide exposure, including a history of HPEEs. The cohort has been recontacted every 5–6 y to update exposures and health status: in 1999–2003 ($n = 33{,}457$), 2005–2010 ($n = 24{,}170$), and 2013–2015 ($n = 24{,}139$). The first two follow-ups updated HPEEs by asking about new events that had occurred after enrollment or in the previous survey year. The third (2013–2015) follow-up asked whether participants had a significantly decreased or loss of the sense of smell. AHS participants implied consent by completing study surveys. The study was approved by the institutional review boards of the National Institute of Environmental Health Sciences and the National Cancer Institute.

HPEEs and Covariates

We listed the specific questions and response options used to query HPEE at AHS enrollment and follow-up surveys in Table S1. Briefly, the enrollment take-home questionnaire asked about a history of HPEEs defined as having ever had an incident or experience while using any type of pesticide that caused unusually high personal exposure. Farmers who reported HPEEs were further asked about details of the incident that resulted in the highest exposure, including the specific pesticide involved, the decade it occurred (1990s, 1980s, 1970s, 1960s, 1950s, or 1940s), body parts exposed (head and/or face, arms, hands, cheek/back/abdomen, groin area, legs, feet, lungs and respiratory tract from breathing fumes, and digestive tract from ingesting/swallowing), and time delay between the occurrence of HPEE and washing with soap and water (<30 min, 30–59 min, 1–3 h, 4–6 h, 7–9 h, or >9 h). A slightly different question was asked in the cohort's first follow-up survey in 1999–2003 about HPEEs since enrollment: "Since [year of enrollment], did you have any incidents with fertilizers, herbicides, or other pesticides that caused unusually high personal exposure?" The questionnaire also sought information on the number of events since enrollment and details of the most recent event, including body parts exposed and promptness in washing off or changing clothes. A similar question was asked again in the 2005–2010 follow-up survey: "Since [year-of-last-interview], have you had any incidents or spills that resulted in an unusually high exposure to pesticides from contact with your skin, from breathing fumes, or dust, or from accidental ingestion?" Those who answered "yes" were asked for further details on the most recent incident, including the specific pesticide involved and whether the incident resulted in medical treatment or hospitalization. We performed separate analyses for HPEE reported at enrollment and follow-up surveys as detailed in the "Statistical Analyses" subsection of the "Methods" section.

Relevant covariate information was obtained from the enrollment questionnaires, including demographics (age, sex, race, education, marital status), smoking habit, use of smokeless tobacco (snuff and chewing tobacco), alcohol drinking in the past year, head injury, and occupational pesticide use. Participants were also asked questions about general use of pesticides: *a*) "During your lifetime, have you ever personally mixed or applied any pesticides?"; *b*) "How many years did you personally mix or apply pesticides?"; and *c*) "During those years, how many days per year did you personally mix or apply pesticides?" We calculated cumulative days of any pesticide use as the product of reported duration (years) and frequency (average days/year) of use of any pesticide. Further, all AHS surveys asked participants to report whether they had ever been diagnosed with PD by a physician, followed by collection and evaluation of medical information on PD diagnosis, symptoms, and treatments from patients and their treating physicians for diagnostic validation (Shrestha et al. 2017; Tanner et al. 2011).

Self-Reported Olfactory Impairment

In the third follow-up in 2013–2015, AHS asked participants to report whether they had a substantially decreased or loss of the sense of smell (i.e., self-reported OI) as detailed in Table S1. For those who answered "yes" to the question, the AHS further asked when they started losing the sense of smell with predefined categories: <1, 1–5, 5–10, or >10 y ago. In addition, the AHS take-home questionnaire at enrollment asked participants about the frequency of 23 nonspecific symptoms that participants might have experienced in the past 12 months, including changes in the sense of smell or taste. Although this question is not specific to a decrease in or loss of the sense of smell, we performed a sensitivity analysis excluding farmers who reported positively to this question from the analysis.

Statistical Analyses

HPEE at AHS Enrollment (1993–1997). We conducted primary analyses by examining the history of HPPEs reported at enrollment in relation to OI reported two decades later in the third follow-up. A total of 13,987 farmers participated in both surveys, and the primary analyses included 11,232 after excluding 1,457 for whom a proxy answered the 2013–2015 survey, 205 with missing data on OI, 281 with missing data on HPEE, and 812 with missing data on covariates (see Figure S1). We obtained odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression models adjusting for age at enrollment, sex, state of residence, education, marital status, smoking, alcohol drinking, and history of head injury. We selected these covariates for confounding adjustment based on the literature on their potential associations with exposure as well as with outcome.

We first examined history of HPEEs at enrollment as a dichotomous variable and then examined details of the HPEE that resulted in the highest exposure to the extent that sample size allowed. Specifically, we determined potential routes of exposures using information on "body parts exposed" (see Table S1), which was grouped into three categories: no HPEE, HPEE involving the respiratory (from breathing fumes) or digestive tract (from ingesting/swallowing), and HPEE resulting in dermal contact only (all other body parts). For time delay until washing with soap and water, we used a six-level variable: no HPEE, within <30 min, 30–59 min, 1–3 h, 4–6 h, or >6 h after HPEE. For the decades when the HPEE occurred, we grouped exposures into five categories: no HPEE, 1990s, 1980s, 1970s, 1960s, or earlier. For the specific pesticide that was involved in the highest exposure HPEE, we only examined those pesticides with at least five exposed OI cases. In all analyses, we used farmers who did not report HPEE as the reference group.

We further conducted four sensitivity analyses to examine the robustness of study results: *a*) further adjusting for cumulative days of any pesticide use because farmers who reported HPEEs were also more likely to report higher occupational use of pesticides (Alavanja et al. 1999); *b*) excluding PD cases diagnosed through the third follow-up (115 excluded, final $n = 11{,}117$) from analysis because OI is one of the most common nonmotor symptoms of PD (Chen et al. 2017; Shrestha et al. 2017); *c*) excluding

farmers ($n = 689$) who reported changes in the sense of smell or taste during the 12 months before enrollment, or with missing information ($n = 122$), as justified above (final $n = 10{,}421$); and *d*) using inverse probability weighting to account for the loss to follow-up in order to make inferences about all eligible farmers (i.e., those who returned the take-home questionnaire at enrollment) because, of the 22,916 participants who filled out the take-home questionnaire at enrollment, only about 61% participated in the third (2013–2015) follow-up survey (Hernán et al. 2000). Details on inverse probability weighting are presented in Table S2 (see also Supplemental Material, "Supplemental methods: Details on inverse probability weighting"). Briefly, we used logistic regression analyses to estimate probabilities of overall participation in the third AHS follow-up: *a*) conditional on exposure and baseline adjustment covariates (age, sex, state of residence, education, marital status, smoking, alcohol consumption, head injury, and pair-wise interactions between exposure and covariates) for the denominator of the stabilized weights; and *b*) conditional only on exposure for the numerator of the stabilized weights. Finally, we estimated stabilized weights as the ratio of conditional probabilities and applied the weights to logistic regression models examining HPEEs in relation to OI.

HPEE at the First (1999–2003) and the Second (2005–2010) Follow-Up Surveys. For HPEEs that occurred after enrollment (1993–1997) but before the 1999–2003 survey, we estimated associations with OI with onset reported ≤10 y before the 2013–2015 follow-up (see Figure S1). Briefly, a total of 20,077 participated in both the 1999–2003 and the 2013–2015 follow-up surveys; this included both those who returned and who did not return the take-home questionnaire at AHS enrollment in 1993–1997. After restricting to those with complete exposure, outcome, and covariate data and excluding individuals who reported OI onset >10 y ago, we had 14,847 individuals for our analysis.

For HPEEs that occurred after the 1999–2003 survey but before the 2005–2010 survey, we estimated associations with OI with onset reported ≤5 y before the 2013–2015 follow-up. For this analysis, we had a total of 9,546 farmers after restricting to those who participated in both the 2005–2010 and the 2013–2015 follow-ups and those with complete data and excluding those who reported OI onset >5 y ago.

For both analyses, we adjusted for age, sex, state, education, marital status, smoking, alcohol drinking, and history of head injury; however, we did not exclude those who reported having prior HPEE [e.g., we did not exclude HPEE reported before enrollment (1993–1997) for analysis that examined HPEE reported at 1999–2003]. Instead, we conducted sensitivity analyses adjusting for prior HPEE. Because these analyses depended on HPEE data from previous surveys and there were substantial missing observations, we created a missing indicator for this variable in both sensitivity analyses to retain sample sizes. We did not conduct analyses on details of the most recent incidents reported in the two follow-up surveys due to small sample sizes.

We used AHS data releases AHSREL20150600, P1REL201209_00, P2REL20120900, P3REL20120900, and Final_06172015. We conducted statistical analyses using SAS (version 9.3; SAS Institute, Inc.). Statistical significance was determined using two-sided tests with $\alpha = 0.05$.

Results

HPEE at Enrollment (1993–1997)

A total of 1,186 (10.6%) of the eligible participants reported OI at the follow-up survey in 2013–2015 (Table 1). Compared with farmers who did not report OI, those who did were older at enrollment and were more often from Iowa, divorced/widowed, and past or current smokers. They were also more likely to report snuff use, an education beyond high school, a history of head injury, and high levels of cumulative use of any pesticide. Sex and race (race definition does not consider Hispanic/Latino ethnicity) were not significantly associated with OI, but few farmers were women (2.5%) or nonwhites (0.9%). As expected, most PD patients (62.6%) reported OI with a multivariable OR of 15.19 (95% CI: 10.17, 22.71).

A positive history of HPEEs at enrollment was associated with a 49% higher odds of reporting OI about two decades later (95% CI: 1.28, 1.73) (Table 2). Detailed analyses of the highest exposure event showed that, relative to those who reported no history of HPEE at enrollment, farmers whose highest exposure HPEEs occurred during the 1970s and 1980s had significantly elevated odds of reporting OI. Although nonsignificant, the magnitude of the association with highest exposure HPPEs that occurred during the 1960s or earlier was comparable to that for the 1970s. Further, compared with no history of HPEE, the association with highest exposure HPEE was stronger when there was a longer delay (≥4 h) between the HPEE and washing with soap and water compared with a shorter delay (≤3 h). On the other hand, we found little difference in associations between highest exposure HPEEs involving the respiratory or digestive tract [OR = 1.53 (95% CI: 1.22, 1.92)] and HPEEs resulting in dermal contact only [OR = 1.47 (95% CI: 1.22, 1.78)]. Sensitivity analyses further adjusting for cumulative days of any pesticide use, excluding PD cases or farmers who reported changes in the sense of smell or taste before enrollment, or accounting for loss to follow-up, generated similar results (see Tables S3 and S4). Further, we also examined association between time delay between the HPEE and washing, separately for those who had dermal-only exposures and for those who had internal exposures (see Table S5). Although potential beneficial effect of early washing was found in both groups, the benefit seems to be more apparent among those who had dermal-only exposure.

In the analyses of associations between OI and HPEEs defined by the specific pesticide involved in the highest exposure incident (Table 3), we found statistically significant associations of OI with two organochlorine insecticides {dichlorodiphenyltrichloroethane (DDT) [OR = 2.39 (95% CI: 1.04, 5.51)] and lindane [OR = 2.83 (95% CI: 1.13, 7.09)]} and four herbicides {alachlor [OR = 1.73 (95% CI: 1.17, 2.55)], metolachlor [OR = 3.20 (95% CI: 1.69, 6.06)], 2,4-dichlorophenoxyacetic acid (2,4-D) [OR = 1.50 (95% CI: 1.01, 2.24)], and pendimethalin [OR = 3.24 (95% CI: 1.58, 6.66)]}. When we combined pesticides by chemical or functional groups, among those with at least five exposed cases, we found significant associations for organochlorine and organophosphate insecticides and chloroacetanilide and phenoxy herbicides. However, these analyses were mostly based on a small number of exposed cases, and estimates are therefore imprecise. For the same reason, some other pesticides showed relatively large ORs but no statistical significance.

HPEE at the First (1999–2003) and the Second (2005–2010) Follow-Up Surveys

HPEEs reported at later surveys were also associated with higher odds of reporting incident OI first noticed in the corresponding time frame (Table 4). The multivariable OR for the association between new HPEEs reported at the 1999–2003 follow-up and OI with onset reported within 10 y before the 2013–2015 follow-up was 1.72 (95% CI: 1.27, 2.33). When additionally adjusted for history of HPEEs reported at enrollment (1993–1997), the corresponding OR was 1.67 (95% CI: 1.23, 2.26).

The OR for new HPEEs reported at the 2005–2010 follow-up in relation to OI within 5 y before the 2013–2015 follow-up was 1.66 (95% CI: 1.10, 2.50). This was slightly attenuated to 1.56

Table 1. Study population characteristics at enrollment (1993–1997) according to self-reported olfactory impairment (OI) in 2013–2015, and odds ratios (95% CIs) among farmers in the Agricultural Health Study ($n = 11,232$).

	No OI [n (%)] ($n = 10,046$)	OI [n (%)] ($n = 1,186$)	Age/sex adjusted OR (95% CI)[a]	Multivariable adjusted OR (95% CI)[b]
Age at enrollment (y)				
≤45	4,909 (48.9)	438 (36.9)	Reference	Reference
46–55	2,747 (27.3)	308 (26)	1.26 (1.08, 1.46)	1.16 (0.98, 1.36)
56–65	1,986 (19.8)	332 (28)	1.87 (1.61, 2.18)	1.81 (1.52, 2.15)
>65	404 (4.0)	108 (9.1)	3.00 (2.37, 3.79)	3.04 (2.35, 3.95)
Sex				
Women	261 (2.6)	25 (2.1)	Reference	Reference
Men	9,785 (97.4)	1,161 (97.9)	1.23 (0.81, 1.86)	1.09 (0.70, 1.69)
Race[c]				
Others	91 (0.9)	10 (0.8)	Reference	Reference
White	9,946 (99.1)	1,176 (99.2)	1.10 (0.57, 2.13)	1.02 (0.48, 2.15)
Missing	9	0		
State				
Iowa	7,342 (73.1)	889 (75)	Reference	Reference
North Carolina	2,704 (26.9)	297 (25)	0.87 (0.75, 1.00)	0.79 (0.67, 0.93)
Marital status				
Never married	1,078 (10.7)	77 (6.5)	Reference	Reference
Married/living as married	8,516 (84.8)	1,044 (88)	1.21 (0.95, 1.56)	1.34 (1.04, 1.72)
Divorced/widowed	452 (4.5)	65 (5.5)	1.50 (1.05, 2.13)	1.55 (1.08, 2.24)
Education				
High school or lower	5,188 (51.6)	610 (51.4)	Reference	Reference
1–3 y beyond high school	2,632 (26.2)	322 (27.2)	1.22 (1.06, 1.42)	1.19 (1.02, 1.39)
College graduate or more	2,226 (22.2)	254 (21.4)	1.13 (0.96, 1.32)	1.17 (1.00, 1.39)
Smoking status				
Never smoker	5,878 (58.5)	606 (51.1)	Reference	Reference
Former smoker	3,142 (31.3)	422 (35.6)	1.09 (0.95, 1.25)	1.11 (0.96, 1.28)
Current smoker	1,026 (10.2)	158 (13.3)	1.53 (1.27, 1.85)	1.59 (1.30, 1.94)
Snuff use on a regular basis for ≥6 (month)				
No	9,592 (95.5)	1,120 (94.4)	Reference	Reference
Yes	454 (4.5)	66 (5.6)	1.34 (1.03, 1.75)	1.38 (1.05, 1.82)
Chewing tobacco on a regular basis for ≥6 (month)				
No	8,750 (87.1)	1,032 (87)	Reference	
Yes	1,296 (12.9)	154 (13)	1.07 (0.89, 1.28)	1.05 (0.87, 1.28)
Alcohol drinking during the past 12 months				
No	3,243 (32.3)	384 (32.4)	Reference	Reference
Yes	6,803 (67.7)	802 (67.6)	1.14 (1.00, 1.30)	0.99 (0.86, 1.15)
Ever diagnosed with head injury requiring medical attention				
No	8,773 (87.3)	991 (83.6)	Reference	Reference
Yes	1,273 (12.7)	195 (16.4)	1.42 (1.20, 1.68)	1.30 (1.10, 1.55)
Cumulative days of any pesticide use (days)[d]				
0–64	2,620 (26.1)	252 (21.2)	Reference	Reference
>64–225	3,390 (33.7)	338 (28.5)	1.04 (0.88, 1.24)	1.03 (0.86, 1.23)
>225–457	2,161 (21.5)	293 (24.7)	1.35 (1.13, 1.62)	1.32 (1.09, 1.59)
>457	1,875 (18.7)	303 (25.5)	1.45 (1.21, 1.73)	1.43 (1.18, 1.72)
Parkinson's disease[e]				
No	9,983 (99.6)	1,109 (93.9)	Reference	Reference
Yes	43 (0.4)	72 (6.1)	12.70 (8.63, 18.7)	15.19 (10.17, 22.71)
Missing	20	5		
Change of sense of smell or taste during the past 12 months				
No	9,409 (94.6)	1,012 (86.9)	Reference	Reference
Yes	536 (5.4)	153 (13.1)	2.93 (2.41, 3.55)	2.76 (2.26, 3.38)
Missing	101	21		

Note: Data were complete for all variables unless indicated. All characteristics were assessed at enrollment (1993–1997) except for Parkinson's disease, which include diagnosis at, as well as after, enrollment. CI, confidence interval; OI, olfactory impairment; OR, odds ratio.
[a]Age modeled as continuous variables for all age- and sex- adjusted models except for when ORs are presented for age categories.
[b]All covariates were mutually adjusted.
[c]Both white and other races are defined without regard to Hispanic/Latino ethnicity.
[d]Cumulative days of any pesticide use was obtained as a product of years of use (based on enrollment question: "How many years did you personally mix or apply pesticides?") and days of use (based on enrollment question: "During those years, how many days per year did you personally mix or apply pesticides?").
[e]Parkinson's disease was based on self-reports as well as evaluation of medical information on PD from patients and their treating physician.

(95% CI: 1.03, 2.37) with additional adjustment for the history of HPEEs reported at enrollment (1993–1997) and the 1999–2003 follow-up survey.

Discussion

To the best of our knowledge, this is the first epidemiologic study to assess the association of OI with acute high pesticide exposures. We found that a history of HPEEs reported at study enrollment were associated with 49% higher odds of reporting OI approximately two decades later; further, our data suggest a pattern that a longer delay between the HPEE and washing with soap and water was associated with higher odds of reporting OI. Finally, we linked OI to several specific pesticides that were involved in the highest exposed HPEE, including two organochlorine insecticides (DDT and lindane) and four herbicides (alachlor, metolachlor, pendimethalin, and 2,4-D). In all analyses, we adjusted for several demographic and lifestyle factors, and multiple sensitivity analyses further support the robustness of our study results.

Table 2. Adjusted odds ratios (95% CIs) for self-reported olfactory impairment (OI) in 2013–2015 in association with a history of any high pesticide exposure event (HPEE) at enrollment (1993–1997), and with specific characteristics of the HPEE that resulted in the highest exposure, relative to OI in farmers without any history of HPEE at enrollment.

Characteristic	No OI [*n* (%)]	OI [*n* (%)]	OR (95% CI)[a]
Any HPEEs			
No	8,458 (84.2)	929 (78.3)	Reference
Yes	1,588 (15.8)	257 (21.7)	1.49 (1.28, 1.73)
Details about the highest HPEE			
The decade it occurred			
No HPEE	8,458 (85.4)	929 (80.5)	Reference
1990s	262 (2.6)	25 (2.2)	1.08 (0.71, 1.64)
1980s	598 (6)	96 (8.3)	1.66 (1.31, 2.09)
1970s	428 (4.3)	69 (6)	1.36 (1.04, 1.78)
1960s or before	162 (1.6)	35 (3)	1.42 (0.97, 2.07)
Missing[b]	138	32	
Time delay between the HPEE and washing with soap and water			
No HPEE	8,458 (84.7)	929 (78.7)	Reference
<30 min	687 (6.9)	96 (8.1)	1.39 (1.11, 1.75)
30–59 min	256 (2.6)	39 (3.3)	1.38 (0.98, 1.96)
1–3 h	308 (3.1)	49 (4.2)	1.38 (1.01, 1.88)
4–6 h	188 (1.9)	46 (3.9)	2.07 (1.48, 2.89)
>6 h	94 (0.9)	21 (1.8)	1.90 (1.17, 3.09)
Missing[b]	55	6	
Exposure route[c]			
No HPEE	8,458 (84.4)	929 (78.5)	Reference
Respiratory or digestive tract	564 (5.6)	100 (8.5)	1.53 (1.22, 1.92)
Dermal only	1,000 (10)	154 (13)	1.47 (1.22, 1.78)
Missing[b]	24	3	

Note: CI, confidence interval; HPEE, high pesticide exposure event; OI, olfactory impairment; OR, odds ratio.
[a]Adjusted for age (continuous variable), sex, state, education, marital status, smoking status, alcohol consumption, and head injury.
[b]Numbers with missing data among those who reported an HPEE.
[c]Participants with a history of HPEE were classified as having respiratory or gastrointestinal tract exposure if they reported that they breathed fumes or ingested or swallowed the pesticide during the HPEE event regardless of whether they might also have had dermal exposure. Participants were classified as having only dermal exposure if they reported exposure of the head and/or face, arms, hands, cheek/back/abdomen, groin area, legs, or feet but did not report breathing fumes or ingesting/swallowing the pesticide.

A poor sense of smell among older adults has been increasingly recognized as a significant public health problem (Murphy et al. 2002). Potential risk factors for OI among older adults, however, have received little investigation. Recent evidence suggests that environmental pesticides may be responsible for the loss of sense of smell in honeybees (Chakrabarti et al. 2015; Williamson and Wright 2013; Yang et al. 2012) and salmon (Engelhaupt 2008; Tierney et al. 2008; Wang et al. 2016). Studies using PD rodent models also suggest that rotenone (Sasajima et al. 2015, 2017) and paraquat (Czerniczyniec et al. 2011; Nuber et al. 2014) damage the olfactory bulb and impair olfaction. Although extrapolating these animal data to humans is difficult, these studies support the biological plausibility that pesticide exposure may adversely affect the human sense of smell (Braak et al. 2006; Doty 2015). When airborne, pesticides may lead to poor olfaction in humans by damaging the olfactory epithelium, impairing nerve function, inducing local acute or chronic inflammation, and disrupting the xenobiotic metabolism, immune system and microbiome of the olfactory mucosa (Doty 2015). Further, pesticides may find their way to the brain via olfactory structures, including the nasal cavity and olfactory nerve, thereby bypassing the blood-brain barrier (Doty 2015). Alternatively, pesticides may first enter the body via the digestive tract and initiate synucleinopathy in the gut, which may later spread to the brain as posited by the Braak hypothesis for PD (Braak et al. 2006). These purported peripheral and central mechanisms may eventually contribute to OI development.

Despite the biological plausibility of a connection between pesticide exposure and OI in humans, empirical data are sparse and indirect. In addition to the aforementioned case report of anosmia following acute exposure to pyrethroids (Gobba and Abbacchini 2012), several cross-sectional studies (Ahman et al. 2001; Gudziol et al. 2007; Holmström et al. 2008; Quandt et al. 2016; Snyder et al. 2003) compared the sense of smell between farmers or farmworkers and control subjects and have provided suggestive but inconsistent evidence. The best evidence to date comes from a recent study (Quandt et al. 2016, 2017) that compared the sense of smell of 304 Latino farmworkers and 247 non-farmworkers in North Carolina, 18–70 y of age (78% younger than 45 y of age). This study found that farmworkers were not significantly different from controls in smell identification, but they had higher olfactory thresholds that persisted throughout a 2-y follow-up period (Quandt et al. 2017). The authors speculated that this difference may not be explained by nasal epithelial damage from exposure to dust or other environmental chemicals because controls were manual laborers with comparable environmental exposures (Quandt et al. 2016). These preliminary data on farmers, although interesting, need confirmation. These studies were small and cross sectional, and most did not have data on pesticide exposures. Further, study participants were relatively young, so the results may not readily inform the role of pesticides in OI among older farmers or older adults.

The AHS offers a unique opportunity to examine associations between pesticide exposures and OI in a large cohort of farmers who were middle-aged or older at their latest follow-up. Its relatively large sample size and rich data collection allowed us to conduct comprehensive statistical analyses. In general, farmers can reliably recall their use of pesticides (Blair et al. 2002). We chose to focus on HPEEs as the primary exposure of interest because they represent isolated acute high exposure events. Further, such accidents are relatively common among farmers, and farmers may be able to more accurately report event details (e.g., specific chemical involved) than the general population. In previous AHS investigations, HPEEs have been linked to self-reported neurologic symptoms (Kamel et al. 2005, 2007) and poor performance on neurobehavioral tests (Starks et al. 2012).

With these strengths, to the best of our knowledge, our study provides the first empirical evidence that acute high exposure to pesticides may lead to poor sense of smell among older farmers.

Table 3. Adjusted odds ratios (95% CIs) for self-reported olfactory impairment (OI) in 2013–2015 and high pesticide exposure events (HPEEs) defined by the specific pesticide involved in the highest exposure HPEE relative to OI among farmers with no HPEE history at enrollment (1993–1997).

Characteristic	No OI	OI	OR (95% CI)[a]
No HPEE	8,458	929	Reference
HPEE exposure by chemical groups[b]			
Organochlorines	96	23	1.78 (1.12, 2.84)
Organophosphates	278	46	1.46 (1.06, 2.02)
Carbamates	79	8	0.96 (0.46, 2.01)
Chloroacetanilide	259	48	1.77 (1.28, 2.44)
Triazine	218	29	1.31 (0.88, 1.95)
Phenoxy	177	32	1.51 (1.02, 2.23)
Fumigant	55	7	1.22 (0.55, 2.72)
HPEE exposure to individual pesticides[b]			
DDT	20	8	2.39 (1.04, 5.51)
Lindane	22	6	2.83 (1.13, 7.09)
Aldrin	19	5	1.86 (0.69, 5.04)
Malathion	44	7	1.44 (0.64, 3.22)
Terbufos	43	5	1.18 (0.46, 3.01)
Phorate	71	15	1.58 (0.89, 2.78)
Alachlor	181	32	1.73 (1.17, 2.55)
Metolachlor	42	13	3.20 (1.69, 6.06)
2,4-D	168	30	1.50 (1.01, 2.24)
Butylate	59	6	1.03 (0.44, 2.40)
Atrazine	144	21	1.45 (0.90, 2.31)
Pendimethalin	35	10	3.24 (1.58, 6.66)
EPTC	23	5	2.17 (0.81, 5.78)
Cyanazine	58	6	1.07 (0.46, 2.51)
Metribuzin	27	5	1.66 (0.63, 4.35)
Trifluralin	173	27	1.41 (0.93, 2.15)

Note: 2,4-D, 2,4-dichlorophenoxyacetic acid; CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; EPTC, *S*-ethyl dipropylthiocarbamate; HPEE, high pesticide exposure event; OI, olfactory impairment; OR, odds ratio.
[a]Adjusted for age (continuous variable), sex, state, education, marital status, smoking status, alcohol consumption, and head injury, using no HPEE as the reference in all analyses.
[b]Numbers in each exposure group are based on the HPEE resulting in the highest exposure if more than one HPEE was reported. Participants were excluded from individual pesticide or pesticide group analyses if their highest exposure HPEE involved a different pesticide or pesticide group (except when participants reported using combinations of pesticides during HPEE event) (thus missing n are different) or if they reported an HPEE but not the specific pesticide involved in the highest exposure incident ($n = 125$). Estimates are reported only for individual pesticides or pesticide groups with at least five participants who were exposed and reported OI.

Our findings persisted in several sensitivity analyses: for example, with additional adjustment for cumulative lifetime days of any pesticide use or exclusion of PD cases to minimize potential impact from a strong connection between OI and PD (Chen et al. 2017; Shrestha et al. 2017). The validity of our finding is further supported by the fact that we found higher ORs for a longer delay (≥4 h) than a shorter delay (≤3 h) between the HPEE and washing with soap and water when compared with no exposure to an HPEE. This observation is consistent with the general notion that washing quickly with soap and water after exposure to hazardous chemicals may help mitigate their potential detrimental effects. In contrast to our prior expectation that only HPEEs involving inhalation or ingestion are related to OI, we found that potential dermal-only exposures were also associated with a higher OR. Explanations for this unexpected finding may not be straightforward. For example, pesticides can be absorbed through skin (MacFarlane et al. 2013) and may thus contribute to OI development. Alternatively, reporting errors about the specific body parts exposed in the accident were likely. Further, because we only asked for details for the highest exposed event, we cannot exclude the possibility of confounding by other HPEEs that involved the respiratory and/or digestive tracts.

Our analyses on specific pesticides are limited to chemicals that were relatively common in accidental events. Nevertheless, two chemical groups were clearly implicated: organochlorine insecticides and chloroacetanilide herbicides. In the first group, HPEEs involving lindane or DDT were each associated with two times higher odds of reporting OI about 20 y later. Organochlorines are neurotoxic and have been consistently linked to neurodegenerative diseases such as PD (Elbaz et al. 2009; Hancock et al. 2008) and AD dementia (Hayden et al. 2010; Richardson et al. 2014). Although these organochlorines are no longer used in agriculture in the United States, they are persistent and can still be detected in the environment, in food (Chang 2018; Di Bella et al. 2018; Schecter et al. 2010), and in human biosamples (Fry and Power 2017; Kim et al. 2015; Perla et al. 2015; Pumarega et al. 2016). Of the chloroacetanilides that are still used in the United States (Fernandez-Cornejo et al. 2014; Ryberg and Gilliom 2015), both metolachlor and alachlor were associated with higher odds of reporting OI. Although these herbicides are generally considered to have low acute toxicity, multiple adverse effects, including neurotoxicity, have been suggested (Andreotti et al. 2015; Lebov et al. 2016; Lee et al. 2004; Silver et al. 2015). Interestingly, earlier experimental studies showed that alachlor induced olfactory tumors in rats probably by damaging olfactory mucosa (Genter et al. 2002, 2009). In addition, two recent ecological studies have correlated agricultural use of alachlor (Wan and Lin 2016) or ground water contamination with herbicides (including both metolachlor and alachlor) (James and Hall 2015) with the prevalence of PD. We also found an association of self-reported OI with the phenoxy herbicide 2,4-D. Exposures to phenoxy in general (Elbaz et al. 2009) and 2,4-D specifically (Tanner et al. 2009) were linked to PD in two well-designed case–control studies. Finally, we also identified an OI association for pendimethalin, another herbicide commonly used in the United States (Fernandez-Cornejo et al. 2014). A recent *in vitro* study found that pendimethalin induced fibrillation of α-synuclein, which may further contribute to Lewy pathology as observed in PD (Fazili and Naeem 2016). Overall, the present study identified associations between specific pesticides and OI, providing leads for further investigation.

In addition to HPEE, we also observed elevated OI among Iowa farmers, those ever married, current smokers, snuff users,

Table 4. Adjusted odds ratios (95% CIs) for self-reported olfactory impairment (OI) in association with high pesticide exposure events (HPEEs) that occurred between enrollment (1993–1997) and the 1999–2003 survey (for OI first noticed within 10 y of the 2013–2015 survey), and HPEE that occurred between the 1999–2003 and 2005–2010 surveys (for OI first noticed within 5 y of the 2013–2015 survey).

New HPPEs reported in	No OI [n (%)]	OI [n (%)]	OR (95% CI)[a]	OR (95% CI)[b]
1999–2003 follow-up ($n = 14,847$)				
No	13,388 (96.2)	883 (94.6)	Reference	Reference
Yes	526 (3.8)	50 (5.4)	1.72 (1.27, 2.33)	1.67 (1.23, 2.26)
2005–2010 follow-up ($n = 9,546$)				
No	8,700 (94.4)	300 (91.7)	Reference	Reference
Yes	519 (5.6)	27 (8.3)	1.66 (1.10, 2.50)	1.56 (1.03, 2.37)

Note: CI, confidence interval; HPEE, high pesticide exposure event; OI, olfactory impairment; OR, odds ratio.
[a]Adjusted for age (continuous variable), sex, state, education, marital status, smoking status, alcohol consumption, and head injury.
[b]Adjusted for age (continuous variable), sex, state, education, marital status, smoking status, alcohol consumption, head injury, and prior HPEE (missing indicator used if information on prior HPEE was missing).

those with head injury, and those reporting higher cumulative pesticide exposure. We do not know why farmers in Iowa were more likely to report OI than those in North Carolina even after accounting for education level and several other potential confounders. Residual confounding from imperfect measurements of these variables or confounding from unmeasured variables is possible. A higher prevalence of self-reported OI in those ever married may in part be explained by the possibility that their partners might have identified their problems with the sense of smell (Adams et al. 2017). Our observation on smoking and OI is consistent with the existing literature (Ajmani et al. 2017) that suggests that smoking is associated with a poor sense of smell. Further, we reported a novel observation that snuff use, but not tobacco chewing, was associated with self-reported OI, suggesting inhaled chemicals from snuff use may jeopardize the sense of smell. Head injury has been proposed as a potential risk factor for OI, but the data to date are inconsistent (Dong et al. 2017a; Schofield et al. 2014).

Despite notable strengths of the current study, it has limitations. First, we relied upon self-reported OI as the analytic outcome. Compared with the objective sense of smell tests, self-reported OI generally shows a good-to-excellent specificity (80% to >90%) but a low and unstable sensitivity (from <20% to >60%) (Adams et al. 2017; Hoffman et al. 2016; Murphy et al. 2002; Rawal et al. 2014). Therefore, some farmers with OI might have been misclassified as having normal olfaction in the analyses. This misclassification most likely would lead to an underestimation of the association; however, we cannot exclude the possibility that farmers with HPEEs were more likely to recognize and report OI decades later. Second, although we asked about the time period that famers first noticed a decrease in the sense of smell, the accuracy of this information is uncertain. However, given that the primary exposure was assessed about 20 y before the outcome, reverse causation is unlikely an explanation for the observed association. Third, we asked about OI only once at the third follow-up survey and did not ask specific details (e.g., acute vs. chronic, or temporary vs. permanent), limiting our ability to answer more details. For example, although we expect that people were more likely to remember and report permanent OI, we could not make an inference on HPEE exposure in relation to permanent as compared with a transient OI. Fourth, HPEE was self-reported and, to a large extent, farmers answered this question to their own interpretations. Fifth, our current investigation focused on HPEE as a surrogate for acute high exposures to pesticides and did not address whether long-term chronic exposures impair the sense of smell. Sixth, our participants were exposed to multiple pesticides as demanded by their regular farming tasks and thus confounding by long-term use of pesticides is possible. Seventh, only 61% of AHS participants who answered the take-home questionnaire also participated in the most recent AHS survey that collected information on OI. Although we conducted sensitivity analyses using inverse probability weighting to account for loss to follow-up, we could not entirely exclude the possibility of selection bias. Finally, because our study participants were mostly farmers with occupational pesticide exposure, the results may not be readily generalizable to other populations with lower exposure to pesticides.

Conclusions

In summary, data from this large study of farmers suggest that HPEEs may increase the risk of OI among older adults. Future studies are needed to confirm these associations using objective measurements of OI and, if confirmed, to investigate underlying mechanisms.

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