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# High pesticide exposures events, pesticide poisoning, and shingles: A medicare-linked study of pesticide applicators in the agricultural health study

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ABSTRACT

*Objectives:* Self-reported shingles was associated with history of high pesticide exposure events (HPEE) in licensed pesticide applicators aged >60 years in the Agricultural Health Study (AHS). In the current study, using AHS-linked Medicare claims data, we examined incident shingles in relation to pesticide-related illness and pesticide poisoning, as well as HPEE.

*Methods:* We studied 22,753 licensed private pesticide applicators (97% white males, enrolled in the AHS 1993–97), aged ≥66 years with >12 consecutive months of Medicare fee-for-service hospital and outpatient coverage between 1999 and 2016. Incident shingles was identified based on having ≥1 shingles claim(s) after 12 months without claims. At AHS enrollment, participants were asked if they ever sought medical care or were hospitalized for pesticide-related illness, and a supplemental questionnaire (completed by 51%) asked about HPEE and poisoning. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression, adjusted for age, sex, race, state, and education.

*Results:* Over 192,053 person-years (PY), 2396 applicators were diagnosed with shingles (10.5%; age-standardized rate, 13.6 cases per 1,000PY), with higher rates among those reporting hospitalization for pesticide-related illness, pesticide poisoning, and HPEE (23.2, 22.5, and 16.6 per 1,000PY, respectively). In adjusted models, shingles was associated with hospitalization for pesticide-related illness (HR 1.69; 1.18, 2.39), poisoning (1.49; 1.08, 1.46), and HPEE (1.23; 95% CI = 1.03, 1.46), especially HPEE plus medical care/poisoning (1.78; 1.30, 2.43).

*Conclusion:* These novel findings suggest that acute, high-level, and clinically impactful pesticide exposures may increase risk of shingles in subsequent years to decades following exposure.

## 1. Introduction

Shingles is a painful condition with blistering rash resulting from the symptomatic loss of latency of varicella zoster virus (VZV). A vaccine for shingles was approved for use in U.S. adults aged ≥60 years in 2006 and aged ≥50 in 2011, but uptake is not widespread (only 24% of adults ages ≥50 and 34% of those ≥60 years were covered in 2017–2018) (Lu et al., 2021). Shingles is common in older adults, with incidence of 6–8 cases per 1,000 person-years among those ages ≥60 years in the U.S., impacting up to 30% of adults who had not received shingles vaccine (Kawai et al., 2016). For unknown reasons, *overall* shingles rates have increased in recent decades, despite vaccine availability and temporally related plateaus or declines among older adults since 2007 (Lu et al., 2021; Kawai et al., 2016; Harpaz and Leung, 2019; Thompson et al., 2021). Similar increases have been seen globally, also despite differences in vaccination and populations (van Oorschot et al., 2021).

Cell-mediated immunity (CMI) plays a critical role in maintaining VZV latency, and aging-related decline in CMI is a well-established risk factor for shingles (Gershon et al., 2015). Risk is also elevated among immunosuppressed individuals, for example in those with autoimmune

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diseases and lymphoid cancers (McKay et al., 2020). Shingles is risk is associated with having a personal or family history of shingles, and is lower in males (vs. females) and African Americans (vs. whites) (Kawai and Yawn, 2017). Changes in modifiable risk factors may contribute to increasing rates; however, the role of environmental factors is not well understood, despite growing evidence of associations with external factors, such smoking, psychosocial stress, and ultraviolet radiation (Kawai and Yawn, 2017; Kawai et al., 2020; Schmidt et al., 2017; Takao et al., 2018).

A role for pesticide exposure in shingles risk was first suggested by a report of younger-onset shingles near a North Carolina superfund site containing organochlorine insecticides compared to a control area (Arndt et al., 1999). The Agricultural Health Study (AHS) is a cohort of licensed pesticide applicators (mostly farmers) and spouses enrolled in 1993–1997 from North Carolina and Iowa (Alavanja et al., 1996). Study questionnaires asked about history of pesticide use at enrollment and shingles at enrollment and during follow-up through 2005–2010. We found that incident shingles among applicators was associated with increased cumulative intensity-weighted lifetime days use of four insecticides (lindane, coumaphos, malathion, and permethrin), three herbicides (alachlor, trifluralin, and 2,4-D), and two fumigants (carbon tetrachloride/carbon disulfide and methyl bromide), indicating a potential role for chronic exposure (Parks et al., 2021). In older participants (ages ≥60 years), shingles was also associated with history of an unusually high pesticide exposure event (HPEE), suggesting that acute, high-intensity exposures may also be relevant. These novel findings comprise the only research we have identified on shingles risk and the use of specific pesticides, and on shingles as an outcome related to HPEE and pesticide poisoning. Other than the role of cell-mediated immunity, mechanisms leading to zoster reactivation are not well understood (Gershon et al., 2015). Long-term immune effects of chronic pesticide exposure are supported by literature on immunotoxicity (Mokarizadeh et al., 2015) but little is known about lasting effects of acutely toxic exposures (Bradberry et al., 2000; Andrew and Lein, 2021).

In our prior study, shingles cases were based on self-report and were not clinically confirmed. Case status was not known for participants lost to follow-up, limiting the available sample size and resulting statistical power for analyses of HPEE-related characteristics (Parks et al., 2021). Our aim in the current study was to reassess the association between high pesticide exposure events and poisonings, with more complete and valid case ascertainment. In the current study, we identify shingles among cohort participants aged ≥65 years in 1999–2016 linked to insurance claims data from Medicare, enabling ascertainment of a larger sample of clinically recognized cases and including cases occurring among participants individuals lost to active follow-up (Parks et al., 2022). Analyses investigate shingles risk among older applicators in relation to HPEE and indicators of acute health effects of pesticide exposures (e.g., hospitalization for pesticide-related illness or poisoning).

## 2. Methods

### 2.1. Study population

The AHS enrolled 52,394 private pesticide applicators (mostly farmers) in Iowa and North Carolina from 1993 to 1997 (Alavanja et al., 1996). Participant questionnaires are available online, (https://aghealth.nih.gov/collaboration/questionnaires.html), including an enrollment questionnaire and a second supplemental questionnaire (44% response). The current study also used information from a subset of participants with follow-up data in 1999–2005 and 2005–2010. All applicators provided consent, and study protocols were approved by the relevant Institutional Review Boards.

### 2.2. Linkage of the AHS data to CMS

We utilized linked Medicare claims data from the Center's for Medicare & Medicaid Services (CMS) on applicators age ≥65 years between January 1, 1999, and December 31, 2016. The linkage to Medicare data, described elsewhere (Parks et al., 2022), was based on matching by social security number or last name, sex, date of birth, and most recent zip code, yielding a match for >98% of eligible participants. Linkage of the AHS data to Medicare data was approved by the CMS and other relevant entities.

Of 26,605 private applicators with linked Medicare data, we excluded 3,852 who lacked 12 months of continuous enrollment in Medicare Parts A and B (i.e., hospitalization and outpatient coverage) prior to their shingles diagnosis, leaving 22,753 for calculating rates (Fig. 1). We further excluded 2,475 with missing covariate data, leaving 20,278 for adjusted models examining cumulative pesticide use and pesticide-related medical care, 11,472 for HPEE and pesticide poisoning, and 9,677 for analyses including HPEE occurring during follow-up. Characteristics of those with and without sufficient data for shingles ascertainment or missing covariate data are shown in Supplemental Table 1. Those with insufficient claims data tended to be younger, more highly educated, had more missing data on seeking pesticide-related medical care (7.1% vs. 5.6% in those with sufficient claims data) and were less likely to complete the supplemental questionnaire (44% vs. 51%) including data on HPEE and poisoning diagnosis. Those with missing covariate data tended to be older, from North Carolina, completed fewer years of education or were missing data on education altogether (45%), and much more likely to be missing data on seeking pesticide-related medical care (33.3% vs. 3.9% in those with complete covariate data) as well as less likely to complete the supplemental questionnaire (40% vs. 53%). Among those completing the supplemental questionnaire, those missing covariate data were also more often missing data on HPEE (7.8% vs. 3.7% in those with complete covariate data) and poisoning (7.1% vs. 1.8%).

### 2.3. Case ascertainment

Shingles cases were identified using inpatient, outpatient, or carrier claims with International Classification of Diseases Clinical Modification (ICD-M) 9th and 10th Editions diagnostic codes for herpes zoster (ICD-M-9/ICD-M-10: 053.xx/B02.xx) in any position, at one or more time point(s). Claims for postherpetic complications (ICD-M-9/ICD-M-10: 0.053.12-053.13/B02.2X) were not counted to prevent overestimation due to non-shingles conditions likes herpes simplex (Harpaz and Leung, 2019; Hales et al., 2013).

### 2.4. Calculation of shingles rates

We calculated shingles rates per 1,000 person-years (PY) by dividing the number of shingles episodes by the total person-years, then multiplying by 1,000. We required 12 months of continuous enrollment in Medicare Parts A and B prior to identifying incident shingles, so the calculation of rates included participants beginning at age 66 years (Hales et al., 2013). We calculated age-standardized incidence using the 2010 U.S. standard population (United States Census Bureau: Age and Sex Composition in the United States:, 2010). Recurrent episodes contributed to calculated incidence rates after a 12-month period without shingles claims.

### 2.5. . Exposure assessment

General pesticide use: At enrollment, participants were asked if they ever mixed or applied pesticides, for how many years (≤1, 2–5, 6–10, 11–20, 21–30, and > 30 years) and on average how many days per year (<5, 5–9, 10–19, 20–30, 40–59, 60–150, >150 days). Cumulative days of general pesticide use was calculated by multiplying the midpoints of categories of duration and frequency.

HPEE: On the supplemental take-home questionnaire, applicators were asked about history of high pesticide exposure events (HPEEs), i.e.,

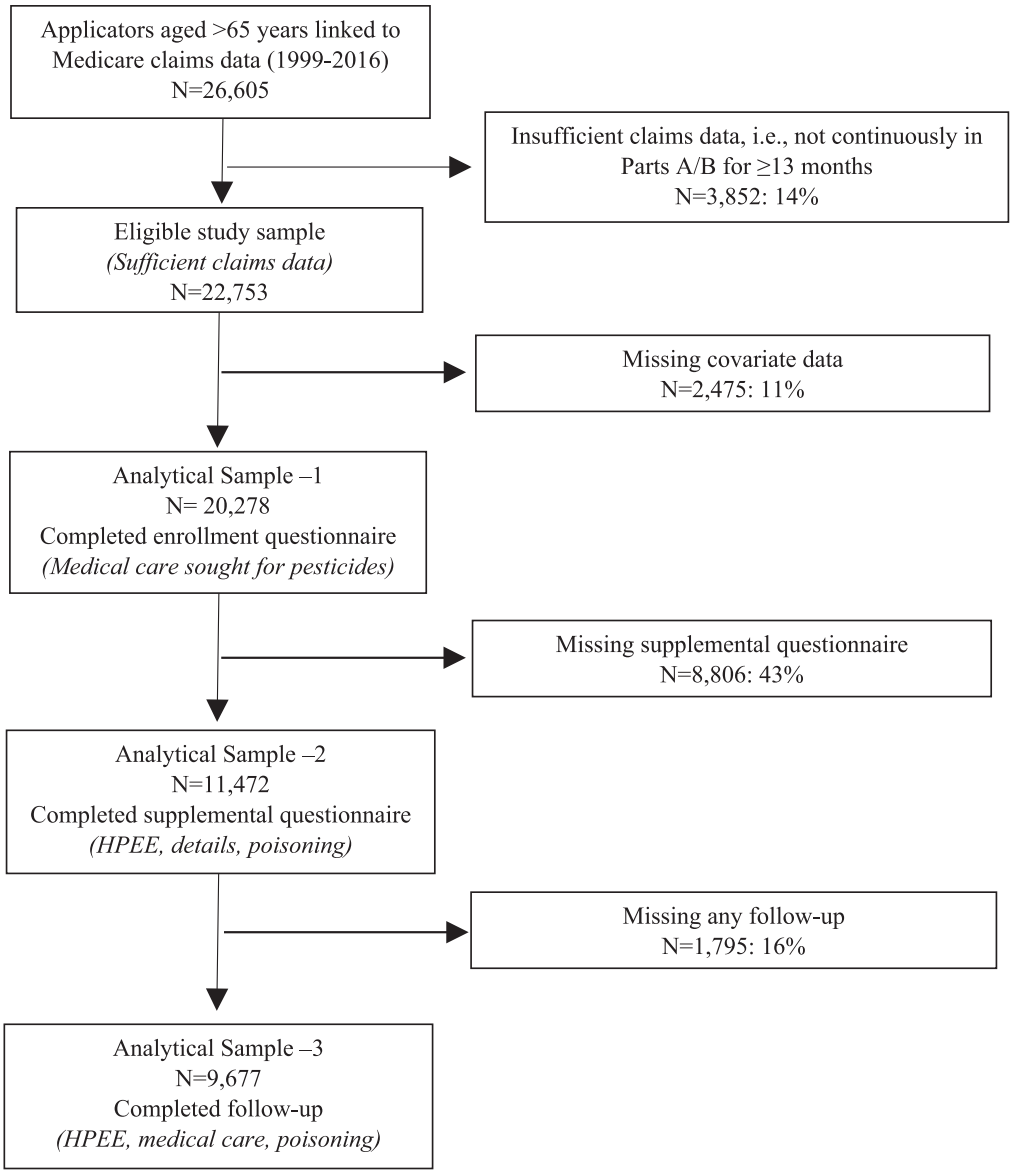


**Fig. 1.** Flowchart showing derivation of study sample for calculating rates and analyses.

ever had an incident or experience while using any type of pesticide that caused unusually high pesticide exposure. For affirmative responses, additional questions asked for the highest exposure event, including the decade in which event occurred (1990s, 1980s, 1970s, 1960s, 1950s, or 1940s), time elapsed before washing exposed body parts (with soap and water) (<30 mins, 30–59 mins, 1–3 h, 4–6 h, 7–9 h, or 9 h), exposure routes (e.g., dermal, respiratory, or digestive tract), and verbatim information on the specific pesticide associated with the event. Abstracted data on specific pesticides were grouped into nine classes (organophosphate, organochlorine, pyrethroids, carbamates, fungicides, fumigants and triazine/triazinone, phenoxy, or analides/analines herbicides) and specific pesticides previously associated with shingles in the AHS (Parks et al., 2021). When the HPEE included multiple pesticides, participants could contribute observations to more than one type. Only pesticides/classes with >10 exposed cases were analyzed, so this limited specific pesticide analyses to the herbicides 2,4-Dichlorophenoxyacetic acid (2,4-D) and alachlor.

Follow-up questionnaires in 1999–2002 (first follow-up) and 2005–2010 (second follow-up) also asked about pesticide-related incidents. In the first follow-up, participants were asked if they experienced any incidents leading to an unusually high personal exposure to fertilizers, herbicides, or other pesticides, since their enrollment year. In the second follow-up, they were asked if they had any incidents or spills since the year of last interview resulting in an unusually high exposure to pesticides from contact with skin, breathing fumes, or dust, or from accidental ingestion. Responses in follow-up were combined with enrollment HPEE to identify HPEE at enrollment only, follow-up only, or both time periods. Verbatim pesticide data was abstracted, but specific pesticides/groups were too rare to be analyzed separately. Instead, they were added to the enrollment HPEE pesticides/groups in combined supplemental models.

Healthcare due to pesticides/poisoning: At enrollment, applicators were asked if they ever sought medical care, i.e., seen a doctor or been hospitalized, due to pesticide-related illness. The supplemental take-home questionnaire asked whether they had ever been diagnosed with pesticide poisoning. Seeking medical care for pesticide-related illness or a diagnosis of pesticide poisoning diagnosis implies greater acute effects and physiologic response due to an unusually high exposure, so we derived a combined variable to identify those reporting HPEE only, medical care/poisoning only, both, and neither. In follow-up questionnaires, participants reporting HPEE in the past year were asked if they sought medical care following the incident, and in the third follow-up

they were asked about pesticide poisoning and diagnosis age.

### 2.6. Covariates

Covariates included sociodemographic (i.e., age, state, sex, race, and education) and enrollment lifestyle factors (i.e., smoking status and alcohol consumption in past 12 months at enrollment). We used claims data to identify diagnoses of systemic autoimmune diseases and lymphoid cancers preceding shingles, as both are known to be associated with shingles risk as a consequence of disease (Yenikomshian et al., 2015; Chen et al., 2014). Using linked claims data and the Medicare Chronic Conditions Warehouse algorithm we ascertained leukemia/lymphoma (Chronic Conditions Data Warehouse, xxxx), and identified 16 systemic autoimmune diseases with 2 or more claims (≥30 days apart; ICD-9/10 codes)(grouped as "any" autoimmune for analyses). Vaccination prior to shingles diagnosis was determined for those enrolled in Medicare ≥2006, using Current Procedural Terminology (CPT) code 90,736 and the National Drug Code (NDC) for the zoster vaccine (00006-4963-41; i.e., purchased vaccine) (Zhang et al., 2012).

### 2.7. Statistical analyses

All analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina), with AHS data releases: P1REL201701.00, P2REL201701.00, P3REL201809.00, AHSREL201706.00.

We derived age-standardized shingles rates by covariates and exposures assessed at AHS enrollment. Statistical tests were not conducted, given subsequent adjusted modeling. Instead, we calculated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate covariate-adjusted associations with incident shingles; time at risk was accrued until shingles diagnosis, death, or end of follow-up. The Andersen-Gill model, an extension of the standard Cox proportional hazard regression model, was used to account for recurrent episodes of shingles (Cox, 1972; Andersen and Gill, 1982; Redeker et al., 2022). The proportional hazards assumption was evaluated based on graphical observation of Kaplan-Meier plots to confirm parallel lines.

Potential confounders were identified from the literature and considering factors previously associated with shingles and HPEE in the cohort (McKay et al., 2020; Kawai and Yawn, 2017; Payne et al., 2012; Mage et al., 2000). These included AHS enrollment age (40–49, 50–59, 60–69, ≥70), state (Iowa, North Carolina), gender (male/female, education (≤high school, >high school), race (Black, White, other), smoking status (past, current, none), alcohol use in the past 12 months (any, none), and shingles vaccination (unvaccinated pre-2006, unvaccinated or vaccinated starting in 2006). Cumulative pesticide use (days per year), while previously associated with higher risk of HPEE in the AHS (Mage et al., 2000), was not considered as a confounder due to a lack of association with shingles in the current and prior analysis (Parks et al., 2021).

We examined potential confounders by adding them to the model and using a change-in-hazard ratio estimate criterion cutoff of 10%, and determined that smoking status, alcohol consumption, and vaccination did not confound the observed effect estimates. Thus, all HRs presented are adjusted for sociodemographic variables: age, state, sex, race, and education. Results shown are based on a complete-case analysis, so final models did not include those missing education (4.9% non-cases, 5% cases). We accounted for potential competing risk due to death using the Fine-Gray competing risk model (Fine and Gray, 1999).

### 2.8. Sensitivity analyses

Because repeat shingles episodes were more common among those with HPEE and poisoning, we also calculated age-standardized shingles rates and revaluated associations censoring person-time at the first episode of shingles.

To assess potential biases due to missing covariate and exposure data, we performed analyses using multiple imputation and addressed potential selection bias using inverse probability weighting to account for incomplete outcomes data among those meeting the criteria of 12 months or more of continuous A/B coverage (e.g., due to enrollment in part C). These methods, including citations, are described, and results shown, in the Supplemental materials.

We did not conduct analyses of effect measure modification by vaccination status due to limited statistical power (<5% of cases were vaccinated), but instead modeled associations excluding participants known to be vaccinated. Some could have been vaccinated prior to Medicare enrollment or 2006. We also excluded those with systemic autoimmune diseases or leukemia/lymphoma prior to shingles, which may increase shingles risk through a shared causal pathway or the effects of immune-modulating treatments. In those completing follow-up questionnaires, we considered the potential impact of more recent HPEE and poisoning on associations with shingles.

## 3. Results

In 22,753 applicators with 192,053 person-years of follow-up since Medicare enrollment (median 8.3 years ± 5.1 years per person follow-up), we identified 2,396 individuals with 2,606 episodes of shingles, for an overall age-standardized rate of 13.6 per 1,000 PY (Table 1) (Tseng et al., 2020). Annual rates are shown in Supplemental Fig. 1; average rates increased with age: >65–69 years (11.7 cases/1,000PY), 70–74 (13.7), 75–79 (14.3), 80–84 (15.5), and 85+ (15.0). Rates were higher in NC (15.4 per 1,000PY) and in women (18.3 per 1,000PY), and lower in Black participants (7.7 per 1,000PY), college graduates (12.4 per 1,000PY), and never-smokers (12.7 per 1,000PY). Shingles rates were higher in those with prior systemic autoimmune diseases or leukemia/lymphoma (22.8 and 23.9 per 1,000PY) and lower for those with claims for shingles vaccination prior to diagnosis (106 vaccinated cases [18.9% of cases with Part D starting in 2006, and 4.4% of the total], 9.9 per 1,000PY) (Supplemental Table 2).

As shown in Table 2, shingles rates were not elevated for greater cumulative days mixed or applied any agricultural pesticides but were higher among participants who sought medical care (5.3% of cases; 14.6 per 1,000PY) or were hospitalized (1.6% of cases; 23.8 per 1,000PY) due to pesticide-related illness. Based on the supplemental questionnaire, shingles rates were higher in those reporting a diagnosis of pesticide poisoning (3.4% of cases; 22.5 per 1,000PY) or who experienced an unusually high pesticide exposure event (HPEE, 12.9% of cases; 16.6 per 1,000 PY). The highest rates were seen for those reporting HPEE together with poisoning or medical care/hospitalization for a pesticide related illness (3.7% of cases; 24.4 per 1,000PY), and less so for those reporting poisoning or medical care/hospitalization without HPEE (4.5% of cases; 14.9 per 1000PY) or HPEE alone (8.4% of cases; 13.8 per 1,000PY). Sensitivity analyses including only the first episode showed slightly lower rates, but relative differences remained.

Based their highest exposure incident (Table 3), compared to those with no HPEE, rates were higher for HPEE in the 1970 s (19.9 cases per 1,000PY), washing up within the first 30 min (19.0 per 1,000PY), 30–59 min (14.3 per 1000PY), or after 6 h (18.2 per 1,000PY), and for respiratory or digestive tract exposures (18.9 per 1,000PY). Higher rates were seen for organophosphate or organochlorine insecticides (18.2 and 19.1 per 1,000PY), phenoxy herbicides; 19.0 per 1,000PY), 2,4-D (17.6 per 1000PY, analine/analide herbicides (22.3 per 1,000PY) and alachlor (31.1 per 1,000PY). Similar patterns were seen limited to the first shingles episode, except that rates were slightly attenuated for cleaning up in the first 30 min.

Fig. 2 shows adjusted hazard ratios (HR) after adjusting for sociodemographic factors, confirming no associations of shingles with greater cumulative pesticide use (HRs 0.97–1.03), but elevated HRs for seeking medical care (1.21; 95%CI 1.00, 1.46) and hospitalization (1.69; 1.19, 2.39) due to pesticide-related illness. In those completing the supplemental questionnaire, shingles risk was associated with pesticide

**Table 1**
Age-standardized shingles incidence among eligible private pesticide applicators with Medicare, overall and by enrollment characteristics.

| Enrollment characteristics | Shingles | | | | Person-years (PY) | Episodes | Age-standardized |
|---|---|---|---|---|---|---|---|
| | Yes | | No | | | | Rate (per 1000PY) All / First episode[2] |
| | N | % | N | % | | | |
| Eligible sample[1] | 2,396 | 10.5 | 20,357 | 89.5 | 192,053 | 2606 | 13.6 / 13.3 |
| Age (years) | | | | | | | |
| 40–49 | 115 | 4.8 | 3,928 | 19.3 | 10,768 | 117 | 10.9 / 10.8 |
| 50–59 | 930 | 38.8 | 8,440 | 41.5 | 77,001 | 1007 | 13.0 / 12.7 |
| 60–69 | 1,097 | 45.8 | 5,965 | 29.3 | 84,605 | 1195 | 14.0 / 14.0 |
| 70+ | 254 | 10.6 | 2,024 | 9.6 | 19,679 | 287 | 14.7 / 13.7 |
| State | | | | | | | |
| Iowa | 1,319 | 55.1 | 12,021 | 59.1 | 115,101 | 1421 | 12.4 / 12.1 |
| North Carolina | 1,077 | 44.9 | 8,336 | 40.9 | 76,952 | 1185 | 15.4 / 15.0 |
| Gender | | | | | | | |
| Male | 2,308 | 96.3 | 19,820 | 97.4 | 186,887 | 2510 | 13.5 / 13.2 |
| Female | 88 | 3.7 | 537 | 2.6 | 5166 | 96 | 18.3 / 18.1 |
| Race | | | | | | | |
| White | 2,360 | 98.5 | 19,732 | 96.9 | 187,248 | 2565 | 13.8 / 13.5 |
| Black | 27 | 1.1 | 507 | 2.5 | 3856 | 31 | 7.7 / 6.9 |
| Other | NS | NS | 113 | 0.6 | 933 | NS | 11.1 / 11.1 |
| Education | | | | | | | |
| < High school | 399 | 16.7 | 3,010 | 14.8 | 31,078 | 440 | 13.5 / 13.1 |
| High school/GED | 1,227 | 51.2 | 9,859 | 48.4 | 98,828 | 1342 | 13.8 / 13.5 |
| Some college | 381 | 15.9 | 3,691 | 18.1 | 29,987 | 406 | 13.7 / 13.4 |
| College graduate | 266 | 11.1 | 2,794 | 13.7 | 22,576 | 282 | 12.4 / 12.5 |
| Missing | 123 | 5.1 | 1,003 | 4.9 | 9583 | 136 | 14.8 / 14.5 |
| Health Behaviors | | | | | | | |
| Smoking | | | | | | | |
| Never | 988 | 41.2 | 8,863 | 43.5 | 84,736 | 1083 | 12.7 / 12.3 |
| Former | 1,110 | 46.3 | 8,467 | 41.6 | 84,682 | 1195 | 14.1 / 14.0 |
| Current | 240 | 10.0 | 2,514 | 12.3 | 18,383 | 260 | 15.2 / 14.6 |
| Missing | 58 | 2.4 | 513 | 2.5 | 4252 | 68 | 16.5 / 15.4 |
| Current alcohol | | | | | | | |
| No | 1,053 | 43.9 | 8,084 | 39.7 | 80,493 | 1147 | 14.0 / 13.8 |
| Yes | 1,138 | 47.5 | 10,605 | 52.1 | 95,999 | 1236 | 13.2 / 12.7 |
| Missing | 205 | 8.6 | 1,668 | 8.2 | 15,560 | 223 | 14.2 / 14.1 |

NS = not shown for counts ≤ 10 individuals.
[1] Eligible if alive, ≥65 years of age, and continuously enrolled in Medicare parts A and B for at least one month between 1999 and 2016 following a 1-year washout period.
[2] Per 1,000 person-years, age-standardized to the 2010 US census population (except for age, which shows crude rates per category). Rates are shown for total number of episodes diagnosed (a recurrent episode was defined after 6 months without any shingles claims), and for the first diagnosis only.

poisoning (1.49; 1.08, 2.06) and HPEE (1.23; 1.04, 1.46). Together, the strongest association was seen for those reporting an HPEE as well as poisoning or medical care (1.78; 1.30, 2.43) compared to no HPEE or poisoning. After applying multiple imputation for missing data and inverse probability weighting, these main effects were not substantially changed (Supplemental Table 3). For the highest HPEE incident, HRs were elevated for washing up within 30 min (1.40; 1.07, 1.83) and 30–60 min (1.37; 0.91, 2.06), events in the 1970s (1.40; 1.04, 1.88) or 1980s (1.26; 0.89, 1.77), and exposures via the respiratory or digestive tract (1.36; 1.08, 1.73). Four major types of specific HPEE pesticides (organophosphate and organochlorine insecticides, anilid/aniline and phenoxy herbicides), including 2 individual pesticides with sufficient Ns (2,4-D and alachlor) showed elevated HRs (>1.2) (Supplemental Table 4). The most frequently reported HPEE pesticide types in cases were organophosphate > organochlorine insecticides > anilid/aniline > phenoxy herbicides. The frequency of reporting in non-cases showed a somewhat different order (anilid/aniline herbicides > organophosphate insecticides > phenoxy herbicides > organochlorine insecticides).

In sensitivity analyses, overall results were similar after excluding participants with prior systemic autoimmune diseases or leukemia/lymphoma, or who had received the shingles vaccine (Supplemental Table 5). Among those with available follow-up questionnaire data, rates were highest in those who reported both past and a new HPEE versus those reporting only a new HPEE (i.e., 20 versus 10.8 per 1,000PY) and remained elevated for enrollment HPEE (16.6 per 1000PY)(Supplemental Table 6). New data on specific HPEE pesticides did not change associations compared to enrollment pesticides (Supplemental Table 4). Finally, incident poisonings or reports of HPEE-related healthcare were too rare (<0.5%) to estimate rates.

## 4. Discussion

Our results in AHS licensed private pesticide applicators show that having a history of and medical care or hospitalization for pesticide related illness, pesticide poisoning, or HPEE is associated with increased risk of shingles based on Medicare claims data, supporting the hypothesis that acute, clinically impactful pesticide exposures may have long-term effects on immunity to herpes zoster. These findings are

**Table 2**
Shingles rates by history of general pesticide use, high pesticide exposure events, and seeking healthcare due to pesticides or poisoning.

| | Shingles | | | | Person-years (PY) | Episodes | Age-standardized |
|---|---|---|---|---|---|---|---|
| | Yes | | No | | | | Rate (per 1000PY) All / First episode[2] |
| | N | % | N | % | | | |
| Eligible sample[1] | 2,396 | | 20,357 | | 192,053 | 2606 | 13.6 / 13.3 |
| Cumulative pesticide use (days) | | | | | | | |
| 0–64 | 549 | 22.9 | 4,667 | 22.9 | 43,665 | 599 | 13.4 / 13.0 |
| > 64–225 | 600 | 25.0 | 5,319 | 26.1 | 48,701 | 656 | 13.6 / 13.1 |
| > 225–457 | 371 | 15.5 | 3,234 | 15.9 | 31,301 | 393 | 12.5 / 12.4 |
| > 457 | 674 | 28.1 | 5,437 | 26.7 | 52,041 | 733 | 14.3 / 14.2 |
| Missing | 202 | 8.4 | 1,700 | 8.4 | 16,345 | 225 | 13.9 / 13.4 |
| Ever sought medical care due to pesticides | | | | | | | |
| Did not seek care | 2,050 | 85.6 | 17,777 | 87.3 | 167,270 | 2222 | 13.3 / 13.0 |
| Sought care | 126 | 5.3 | 956 | 4.7 | 9186 | 139 | 14.7 / 13.9 |
| Hospitalized | 38 | 1.6 | 200 | 1.0 | 2028 | 45 | 23.2 / 21.8 |
| Missing | 182 | 7.6 | 1,424 | 7.0 | 13,568 | 200 | 15.1 / 14.7 |
| Total supplemental Q[3] | 1,295 | | 10,360 | | 103,612 | 1424 | 13.6 / 13.2 |
| Ever pesticide poisoning | | | | | | | |
| No | 1,222 | 94.4 | 9,895 | 95.5 | 98,666 | 1340 | 13.4 / 13.0 |
| Yes | 44 | 3.4 | 232 | 2.2 | 2564 | 52 | 22.5 / 20.9 |
| Missing | 29 | 2.2 | 233 | 2.3 | 2383 | 32 | 13.6 / 13.0 |
| Ever HPEE | | | | | | | |
| No | 1,072 | 82.8 | 8,720 | 84.2 | 87,493 | 1172 | 13.2 / 12.9 |
| Yes | 167 | 12.9 | 1,226 | 11.8 | 11,762 | 187 | 16.6 / 15.7 |
| Missing | 56 | 4.3 | 414 | 4.0 | 4358 | 65 | 14.1 / 13.1 |
| Ever HPEE and medical care/poisoning[4] | | | | | | | |
| Neither | 935 | 72.2 | 7,636 | 73.7 | 76,603 | 1022 | 13.2 / 12.8 |
| HPEE only | 109 | 8.4 | 899 | 8.7 | 8361 | 115 | 13.8 / 14.1 |
| Care or poisoning | 58 | 4.5 | 400 | 3.9 | 4101 | 64 | 14.9 / 14.5 |
| Both HPEE and Care or poisoning | 48 | 3.7 | 260 | 2.5 | 2707 | 60 | 24.4 / 20.6 |
| Missing | 145 | 11.2 | 1,165 | 11.3 | 11,841 | 163 | 13.4 / 12.8 |

[1] Eligible if alive, ≥65 years of age, and continuously enrolled in Medicare parts A and B for at least one month between 1999 and 2016 following a 1-year washout period, and must have completed the supplemental questionnaire: 54% of cases and 51% non-cases.
[2] Per 1,000 person-years, age-standardized to the 2010 US census population. Rates are shown for total number of episodes diagnosed (a recurrent episode was defined after 6 months without any shingles claims), and for the first diagnosis only.
[3] Includes participants completing the supplemental questionnaire.
[4] Combined variable can include medical care (enrollment) or poisoning (supplemental).

consistent with our prior observations for HPEE based on shingles self-report (N = 580 cases) and extend this work among older participants with a larger number of cases (N = 1093), enabling exploratory analyses care for pesticide-related illness and diagnosed pesticide poisoning, as well as the decade and other characteristics of the highest HPEE incidents.

Shingles rates in the current study sample (mostly male farmers, ages >65 years) are similar if not slightly higher than rates in the Medicare population, with 13.6 cases per 1,000PY compared to 12 per 1,000PY for males in Medicare for 2010 (Hales et al., 2013), though direct comparisons are limited by differences across study samples, designs, and years (Yawn et al., 2007; Johnson et al., 2015). We saw expected differences by age, sex, race, and prior autoimmune or leukemia/lymphoma diagnosis (Kawai and Yawn, 2017). Notably, participants reporting a hospitalization for pesticide-related illness, or a diagnosis of pesticide poisoning, had similar rates to those with a history of leukemia, lymphoma, or systemic autoimmune diseases in our sample and published rates among autoimmune disease patients on immunosuppressive medications in Medicare (McKay et al., 2020). Cases with pesticide poisoning also had more frequent shingles recurrence (18–24%), suggesting greater immune susceptibility.

These findings that effects from acute HPEE and pesticide poisoning may manifest decades later as effects on herpes zoster are consistent with findings for other long-term outcomes in the AHS; for example, associations have been shown for neurologic symptoms, end-stage renal disease, depression, and increased methylation in the promoter of glutathionone-S-transferase-p1 (GSTP1) (Beard et al., 2013; Lebov et al., 2016; Crawford et al., 2008; Kamel et al., 2005; Rusiecki et al., 2017), which has been associated with increased age-related methylation in naïve CD4+ T-cells, supporting the potential for long-term immune effects (Dozmorov et al., 2017). Few studies of pesticide poisoning have included immune markers or outcomes and follow-up data. The neutrophil to lymphocyte ratio, a marker for the acute inflammatory response that was predictive of later mortality in survivors of pesticide poisoning (Zhou et al., 2016), has also been associated with shingles risk in immunosuppressed patients (Sim et al., 2021; Mok et al., 2022). In the Bhopal pesticide plant disaster in India, long-term immune effects have been observed after two decades (Bhargava et al., 2010; Senthilkumar et al., 2017). Other potential mechanisms may not be limited to direct immunotoxicity. For example, acute pesticide toxicity due to

**Table 3**
Characteristics of highest HPEE in relation to age-adjusted shingles rates.

| | Shingles | | | | Person-years (PY) | Episodes | Rate (per 1000PY) All / First episode[2] |
|---|---|---|---|---|---|---|---|
| | Yes | | No | | | | |
| | N | % | N | % | | | |
| Total (supplemental Q)[1] | 1,295 | | 10,360 | | 103,612 | 1424 | 13.6 / 13.2 |
| Never had HPEE | 1,072 | 82.8 | 8,720 | 84.2 | 87,493 | 1172 | 13.2 / 12.9 |
| Ever had HPEE | 167 | 12.9 | 1,226 | 11.8 | 11,762 | 187 | 16.6 / 15.7 |
| | N = 167 | | N = 1226 | | | | |
| | | % | | | | | |
| Decade | | | | | | | |
| 1990s | 12 | 15.5 | 106 | 8.3 | 853 | 13 | 14.7 / 14.5 |
| 1980s | 36 | 21.5 | 323 | 26.3 | 2725 | 41 | 14.8 / 14.1 |
| 1970s | 49 | 29.3 | 345 | 28.1 | 3072 | 54 | 19.9 / 19.7 |
| 1960s or before | 44 | 26.3 | 301 | 24.5 | 3571 | 49 | 13.7 / 13.1 |
| Missing | 26 | 15.5 | 151 | 12.3 | 1541 | 95 | 24.0 / 14.6 |
| Time to washing up | | | | | | | |
| <30 mins | 58 | 34.7 | 428 | 34.9 | 3860 | 68 | 19.0 / 16.5 |
| 30–59 mins | 28 | 16.8 | 197 | 16.1 | 1930 | 33 | 17.4 / 15.8 |
| 1–3 h | 37 | 22.2 | 281 | 22.9 | 2784 | 37 | 13.6 / 14.6 |
| 4–6 h | 21 | 12.6 | 175 | 14.3 | 1724 | 21 | 11.8 / 12.7 |
| >6 h | 11 | 6.6 | 83 | 6.8 | 789 | 12 | 18.2 / 18.8 |
| Missing | 12 | 7.2 | 62 | 5.1 | 675 | 16 | 24.2 / 20.1 |
| Exposure route | | | | | | | |
| Respiratory/digestive | 81 | 48.5 | 494 | 40.3 | 5056 | 93 | 18.9 / 17.2 |
| Dermal only | 80 | 47.9 | 709 | 57.8 | 6433 | 87 | 14.6 / 14.8 |
| Missing | NS | | NS | | 273 | NS | — |
| Specific pesticides[3] | | | | | | | |
| Insecticides: | | | | | | | |
| Organochlorine | 29 | 18.4 | 145 | 12.8 | 1701 | 32 | 19.1 / 19.3 |
| Organophosphate | 34 | 21.5 | 236 | 20.8 | 2328 | 40 | 18.2 / 16.8 |
| Herbicides: | | | | | | | |
| Phenoxy | 27 | 17.1 | 160 | 14.1 | 1646 | 30 | 19.0 / 18.3 |
| 2,4-D | 24 | 15.2 | 144 | 12.7 | 1451 | 25 | 17.6 / 15.6 |
| Analide/analine | 30 | 19.0 | 252 | 22.2 | 2179 | 35 | 22.3 / 17.9 |
| Alachlor | 13 | 8.2 | 114 | 10.0 | 933 | 17 | 31.1 / 21.2 |

NS = not shown for counts ≤ 10 individuals.
[1] Includes participants completing the supplemental questionnaire only.
[2] Age-standardized to the 2010 US census population for all other rates. Rates are shown for total number of episodes diagnosed (a second episode was defined after 6 months without any shingles claims), and for the first diagnosis only.
[3] Overall, 158 cases (178 episodes) and 1,135 non-cases reported any specific pesticide related to their HPEE (17.1 cases per 1000PY). Pesticide classes and specific pesticides reported by >10 exposed cases are listed. List of chemicals and adjusted hazard ratios shown in Supplemental Table 4.

organophosphates may contribute to lasting nerve damage and neuroinflammation (Andrew and Lein, 2021). Shingles risk has also been associated with history of physical trauma in older adults (with short-term effects) and traumatic brain injury in a large population-based study (with longer term effects an average of 5.9 years after initial injury) (Tung et al., 2015; Zhang et al., 2013); suggested pathways may include both immediate and persistent effects on neuroinflammation and associated changes in adaptive immunity (Braun et al., 2017; Morganti-Kossmann et al., 2007).

The temporal relationship of acute immunosuppression and shingles incidence is not well understood. After initial infection, the zoster virus establishes a lifelong latent neuronal infection and, while the mechanisms leading to reactivation are not fully understood, cell-mediated immunity plays a critical role in maintaining latency (Gershon et al., 2015). Following acute medical immunosuppression, increased shingles risk is not immediate; patients with hematopoietic stem cell transplantation, in the absence of antiviral prophylaxis, experience elevated risk of shingles in the first 3–12 months, which can persist for several years, especially in those with ongoing use of immunosuppressive medications (McKay et al., 2020; Boeckh et al., 2006). In the AHS, acute HPEE and poisoning also occur in the context of past and subsequent use of the same and other pesticides, some of which were also associated with shingles in our prior analyses of self-reported cases (Parks et al., 2021). Thus, while our findings suggest that a clinically impactful HPEE may affect future shingles, we cannot rule out immunosuppression due to past and ongoing pesticide use (Mokarizadeh et al., 2015)."

Because HPEE is not a specific causal exposure, we explored HPEE by pesticide classes and pesticides associated with shingles in our prior study. The top 2 specific HPEE pesticides in shingles cases and non-cases were 2,4-D and alachlor. This may, in part, reflect their prevalence of use, though other widely used herbicides (e.g., glyphosate) were not commonly reported as HPEE. Adjusted shingles risk was elevated only among those reporting washing up in the first 30–60 min, which could reflect an urgency related to their expected toxicity. Dermal exposure alone did not appear to be associated with shingles; exposure routes associated with shingles included ingestion or inhalation, for example in the case of 2,4-D, which is known to drift during application (Islam et al., 2018). Generally, acute toxicity is greater for ingested and inhaled routes of exposure, as greater concentrations of chemicals more readily reach the bloodstream than for dermal routes of exposure (Damalas and Koutroubas, 2016).

Our study has both strengths and limitations. Our findings may not be generalizable to the broader population at risk of HPEE and pesticide poisoning. AHS participants were similar to other farmers in the study

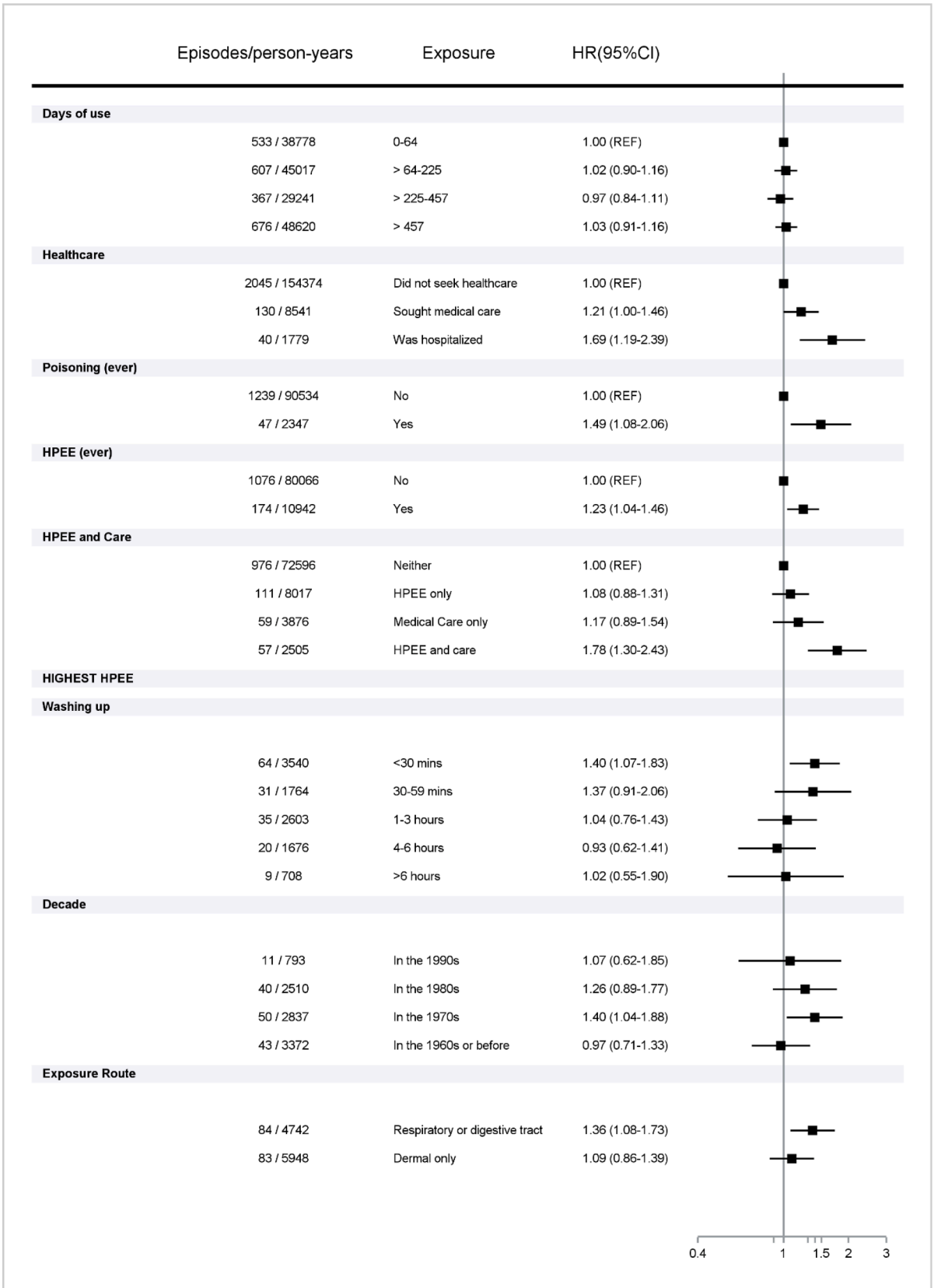


**Fig. 2.** Shingles associated with Cumulative Pesticide Use, High Pesticide Exposure Events (HPEE) and pesticide poisoning. Hazard Ratios (HR) and 95% Confidence Intervals (CI) calculated by Cox proportional hazard regression models adjusting for age, sex, race, education.

area according to the US Agricultural Census (Lynch et al., 2005). Individuals who use pesticides as an unlicensed applicator were not represented in the sample, nor are farm workers, who comprise the majority of cases of acute agricultural pesticide poisoning (Calvert et al., 2008). Data on seeking medical care for pesticide-related illness were available for most enrolled participants. However, we lacked HPEE and poisoning data for those who did not complete the supplemental questionnaire (46% of cases, 49% non-cases), which tracked with missing outcome and covariate data. Nonetheless, shingles rates were the same in those with supplemental data as in the enrolled sample and findings were unchanged in analyses imputing missing values and inverse probability weighting for potential selection bias.

A major strength of the study is the prospective design, which limits potential for recall bias among cases; however, analyses relied on self-reported questionnaire data on HPEE, medical care, and poisoning. While self-report of specific pesticide data in the AHS has been shown to be reliable (Blair et al., 2002), past HPEE and medical care or poisoning were not confirmed or validated. Recall errors may be greater for episodes in the more distant past but may also be influenced by the known toxicity of the agent or symptoms experienced. Those with less impactful (or less memorable) HPEE may therefore be included in the referent group, which could result in attenuation of the observed associations. The small number of participants with both HPEE and poisoning or care precluded examination of specific HPEE characteristics among those with a history of poisoning or seeking medical care for pesticide-related illness. Of those reporting HPEE, only a fraction (22% non-cases, 30% cases) also reported poisoning or seeking medical care, which is reasonable given differences in toxicity and interpretation of what comprised an HPEE. Conversely, not everyone reporting pesticide poisoning or seeking medical care reported an HPEE. The question specifies the incident or experience as occurring while using pesticides, but participants may have also experienced indirect acute high-level exposures, such as from ariel spraying or drift.

The current study used Medicare claims data, enabling more complete ascertainment of clinically identified cases and a considerably larger sample than our previous study, including cases among participants who had been lost to active follow-up and thus not included in our prior study based on self-report of shingles on questoinnaires. The positive predictive value (PPV) of the claims-based shingles diagnosis compared to medical record review is 85–100% (Yawn et al., 2011). Left truncation and censoring in these linked data may contribute to selection bias: some cases in our sample will have previously had shingles, while others who died from pesticide poisoning (or other morbidities) were not enrolled. In our prior study, median age of self-reported shingles diagnosis was 60 years (IQR 55–70 years) in the first 12 years of follow-up (IQR 11–13). Shingles rates based on claims data in the current study were similar when we excluded recurrent shingles episodes, overall and by most exposures in Tables 2 and 3 – so we anticipate that unobserved past episodes would not appreciably change the rates we observed. Some participants (14%) lacked sufficient claims data to assess incident shingles, and we previously found incomplete claims data to be associated with demographic factors (Parks et al., 2022); however, in the current study, those with insufficient data had a similar proportion who sought medical care for pesticides or reported pesticide poisoning, and only a slightly higher frequency of HPEE (14.5% vs. 12% in those with sufficient data). Moreover, the use of inverse probably weighting showed no evidence of bias.

The observed differences in shingles rates persisted in regression models adjusted for sociodemographic factors, and we saw no additional confounding by health covariates. We did not examine other factors, such as use of personal protective equipment, which could affect internal dose following an HPEE and the need to seek medical care. We were missing covariate data on 11% of the study sample, but saw few differences in missingness by key covariates, such as education (4.9% non-cases, 5.1% cases). Our findings were robust in sensitivity analyses excluding those with known risk (autoimmune and lymphoid cancers) or protective factors (vaccination), but we lacked vaccination data on those who may have received the vaccine prior enrollment in Medicare or who did not have Part D coverage, and the small number of vaccinated cases limited our ability to consider effect measure modification, i.e., whether associations were attenuated in vaccinated individuals.

## 5. Conclusions

Results of the current study provide novel evidence that clinically impactful HPEE may modify risk of shingles, suggesting that, similar to aging, these types of exposures could impact susceptibility to other infections or optimal response to vaccination. Replication of these findings in other populations is warranted, including studies on patients presenting with HPEE, pesticide-related illness or pesticide poisoning. Supporting evidence is needed to investigate underlying immune effects, such as markers of subclinical reactivation of shingles and other latent viral infections, immune phenotyping (lymphocytes and T-cell counts, CD4/CD8 ratios), and vaccine challenge studies, as well as other clinical outcomes such as other viral infections and infection-related chronic diseases, autoimmune conditions, and hematologic malignancies.

Shingles inflicts high costs on the population, due to health care costs and burden on quality of life. Our findings of elevated shingles risk associated with acute, clinically relevant pesticide exposures also highlights potential long term costs of unintentional high-level pesticide exposures, especially those contributing to poisoning, which is a global problem in agricultural settings.

## CRediT authorship contribution statement

**Christine G. Parks:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Darya Leyzarovich:** Software, Validation, Data curation, Formal analysis, Writing – review & editing, Visualization. **Shelly-Ann Love:** Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Stuart Long:** Software, Validation, Data curation, Writing – review & editing. **Jonathan N. Hofmann:** Resources, Writing – review & editing. **Laura E. Beane Freeman:** Resources, Writing – review & editing, Funding acquisition. **Dale P. Sandler:** Conceptualization, Resources, Writing – review & editing, Funding acquisition, Supervision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

The data that has been used is confidential.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108251.

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