Original research

Allergic and non-allergic wheeze among farm women in the Agricultural Health Study (2005–2010)

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ABSTRACT

Background Farms represent complex environments for respiratory exposures including hays, grains and pesticides. Little is known about the impact of these exposures on women's respiratory health. We evaluated the association of farm exposures with allergic and non-allergic wheeze among women in the Agricultural Health Study, a study of farmers and their spouses based in Iowa and North Carolina.

Methods We used self-reported data (2005–2010) on current use (≤12 months) of 15 pesticides (selected based on frequency of use) and occupational farm activities from 20 164 women. We defined allergic wheeze as reporting wheeze and doctor-diagnosed hay fever (7%) and non-allergic wheeze as wheeze but not hay fever (8%) in the past 12 months. Using polytomous logistic regression, we evaluated associations of wheeze subtypes with pesticides and other farm exposures (eg, raising farm animals) using no wheeze/hay fever as the referent, adjusting for age, body mass index, state, current asthma, glyphosate use and smoking.

Results Current use of any pesticide, reported by 7% of women, was associated with both allergic (OR: 1.36, 95% CI: 1.10 to 1.67) and non-allergic (OR: 1.25, 95% CI: 1.04 to 1.51) wheeze. Four pesticides were associated with at least one wheeze subtype: glyphosate, with both wheeze subtypes; diazinon and fly spray with only allergic wheeze; carbaryl with only non-allergic wheeze. Working weekly with mouldy hay was associated with allergic (OR: 1.88, 95% CI: 1.26 to 2.80) and non-allergic wheeze (OR: 1.69, 95% CI: 1.18 to 2.42).

Conclusion Use of specific pesticides and certain farm activities may contribute to wheeze among farm women.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Use of specific pesticides is associated with respiratory symptoms including asthma and wheeze in men. Epidemiologic studies and studies using animal models suggest that associations with pesticides are stronger in individuals with allergy.

WHAT THIS STUDY ADDS

⇒ Specific pesticides that are commonly used in agricultural and residential settings, including glyphosate, were associated with both allergic and non-allergic wheeze in women. Working with mouldy hay may also contribute to allergic and non-allergic wheeze among farm women.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the widespread use of these pesticides in both agricultural and residential settings, pesticides should be considered respiratory risk factors by healthcare providers.

INTRODUCTION

Farms represent a complex exposure environment; the multiple concurrent exposures may include pesticides, grains, animals and dust.[1] Pesticides have documented negative effects on respiratory health[2] and are important occupational and environmental exposures for those working and living on farms. Pesticides are also commonly used in residential settings; in the USA, 5% of herbicides and 23% of insecticides are used residentially, underscoring the potential impact of pesticide use in the general population.[3] Epidemiological studies of adults, mostly farmers, farmworkers and commercial pesticide applicators, have documented associations between certain pesticides and adverse respiratory outcomes, including asthma and wheeze.[2 4–11] Analyses from the Agricultural Health Study (AHS), a large cohort study of private pesticide applicators and their spouses in Iowa (IA) and North Carolina (NC), have demonstrated that pesticide use, particularly use of organophosphate insecticides, is positively associated with wheeze among both farmers[12] and commercial pesticide applicators.[13] Specific pesticide exposures, including glyphosate, have been linked with both allergic and non-allergic wheeze among male farmers.[7]

Evaluation of allergic and non-allergic respiratory outcomes separately is important because allergy may contribute to different aetiology. Results from animal studies suggest that organophosphates induce airway hyper-responsiveness,[14] potentially at doses below those causing acetylcholinesterase inhibition,[15 16] and have differential effects for allergen-sensitised animals.[17] Animal models have also demonstrated that prior exposure to organophosphate and organochlorine insecticides may increase the allergic potential of environmental allergens, potentially due to an increase of T-cell surface antigen expression.[18]

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Large epidemiologic studies of respiratory outcomes in occupationally exposed individuals provide the opportunity to focus on specific pesticides and other occupational exposures rather than general categories of pesticides such as herbicides. The AHS provides a unique resource to evaluate how pesticides and other agricultural exposures may contribute to women's respiratory health. Earlier analyses of women's respiratory outcomes in the AHS have found that specific pesticides may contribute to asthma and that growing up on a farm is a protective factor against allergic respiratory disease in adult farm women.[11] To date, no studies in women have evaluated the association of pesticide exposure with wheeze. We took advantage of the wealth of data in the AHS on occupational and environmental exposures to investigate whether farm exposures, including current pesticide use, are associated with allergic and non-allergic wheeze among women.

METHODS

Study population

The AHS is a prospective cohort of licensed private pesticide applicators, mostly farmers (n=52 394) and their spouses (n=32 345) from IA and NC,[19] and has been described in detail elsewhere.[19 20] Briefly, in 1993–1997, applicators seeking pesticide licenses were recruited at licensing sites. At enrolment, private applicators, mostly farmers, were given a questionnaire for themselves and an enrolment questionnaire for their spouses. Approximately 75% of the spouses of married applicators enrolled. Since enrolment, private applicators and their spouses have completed follow-up telephone interviews approximately 5 years apart. Data were collected during a phone interview from November 2005 to February 2010. Individuals were eligible for the 2005–2010 interview if they had not previously refused future contact, were able to do a phone interview and, most importantly, had participated in some prior AHS activity in addition to the enrolment questionnaire. Further study details are available at the Agricultural Health Study NIH (https://aghealth.nih.gov/about/index.html) website for review.

Our cross-sectional study population consisted of 20 164 female participants (nearly all spouses of farmer applicators) with complete information on age, body mass index (BMI), state of residence (IA/NC), current asthma, smoking status, self-reported wheeze and doctor diagnosed hay fever. Questionnaires are available at the Agricultural Health Study NIH (http://aghealth.nih.gov/collaboration/questionnaires.html) website for review. Consistent with rules at the time, participants provided implied consent by completing the enrolment questionnaires.

Respiratory outcome

We created separate categories for allergic and non-allergic wheeze based on previous evidence suggesting that allergic and non-allergic wheeze might have different aetiologies, using a three-level outcome variable similar to our earlier analysis of men in the AHS.[7] Our outcome was wheeze by subtype: no wheeze (referent), allergic wheeze (self-report of wheeze and doctor diagnosis of hay fever) and non-allergic wheeze (wheeze without hay fever). We defined a participant as having wheeze if she reported having at least one episode of wheeze or whistling in her chest in the past year. We assigned allergic status based on self-report of doctor-diagnosed hay fever.

Exposures

We used cross-sectional questionnaire responses to assign both pesticide use and other farm exposures. Between 2005 and 2010, participants provided information on their current pesticide use (defined as within the past 12 months) through open-ended questions about pesticide use since their last interview (1999–2003). Regardless of applicator status, women were asked questions regarding pesticide use designed to measure the women's own self-reported use of pesticides. Pesticide use was assessed using the following question: 'we would like now to ask about your use of pesticides since your last interview, including herbicides, insecticides, fungicides, fumigants or other chemicals used to kill plants, insects, fungi, moulds or rodents. Please do not include the use of antibiotics sanitisers, antimicrobial soaps or fertilisers. Since your last interview, have you personally mixed, loaded, handled or applied these chemicals for use on crops, animals or any other purpose not including home and garden use?' Individuals reported names (usually trade names) of the pesticides that they used for crops, animals and non-crop purposes. These verbatim names were linked to the pesticides' active ingredients using the US Environmental Protection Agency Pesticide Classification Code (see https://www.epa.gov/ingredients-used-pesticide-products/how-search-information-about-pesticide-ingredients-and-labels) to generate a list of 515 pesticides used by participants since the last interview.[21] Participants also provided information on the frequency (days/year) and duration (years) of use in their lifetime. Women also provided information on farm activities, work with farm animals and the frequency of these activities in the past 12 months.

Statistical analysis

We used polytomous logistic regression to estimate associations of the nominal three-level wheeze outcome with pesticide use and farm activities after adjustment for potential confounders, including age at interview (categories: <50, 50–59, 60–69, 70–97 years), BMI (<25, ≥25–<30, >30), state where enrolled (IA, NC), current asthma diagnosis (yes, no) and smoking status (current, past, never). Confounders were selected a priori based on expert input and prior analyses conducted in the AHS to evaluate the impact of pesticide exposures on respiratory outcomes.[7 12 13] Among women in the study who currently used any pesticide, the proportion of glyphosate users was about 60%. As glyphosate was the most commonly used pesticide, we adjusted for glyphosate use in analyses of any other pesticide significantly associated with either wheeze outcome to evaluate whether glyphosate was driving these associations. We defined current asthma based on self-reported doctor's diagnosis of asthma and a positive response to 'do you still have asthma?' We formally tested the differences between the ORs for allergic and non-allergic wheeze using a Wald test for the contrast between the two log OR parameters.

For pesticide exposures, we evaluated both use of any pesticide and use of specific pesticides. We constructed separate models for each pesticide. Current pesticide use was parameterised in two ways: (a) any current use and (b) frequency of current use in categories. We limited our analysis to the 15 pesticides with 5 or more exposed cases of allergic wheeze or non-allergic wheeze: 8 herbicides (2,4-D, atrazine, dicamba, glyphosate, metolachlor, picloram, triclopyr and trifluralin) and seven insecticides (carbaryl, cyfluthrin, diazinon, fly spray, malathion, permethrin and pyrethrins). For exposure response modelling, we split subjects exposed to each pesticide into three approximately equally sized groups based on frequency of use, ensuring that at least five exposed cases were in each group. Those with no exposure were considered as referent. Besides overall pesticide use, 2,4-D, carbaryl, glyphosate, and malathion had enough users for exposure-response modelling. For malathion, we combined the two highest categories to achieve the minimum number of cases (n=5) per category.

For current farming activities, we fit separate models for frequency of each of the queried farming activities: using machines to till/disc the soil, using machines for harvesting crops, operating diesel-powered tractors, applying natural fertilisers, harvesting crop by hand, cleaning grain bins, and handling mouldy hay or straw. These frequencies were categorised based on the number of days per year; categories were collapsed to ensure at least five observations in each category by wheeze subtype. We evaluated exposure to farm animals using a binary categorisation (yes/no) for each of the following animals: dairy cattle, beef cattle, hogs, sheep, horses, layer poultry and broiler poultry. We also created the following groupings: any livestock (cattle, sheep, or hogs), any poultry (layers or broilers) and any cattle (dairy or beef cattle).

As wheeze is the most important symptom of asthma, most asthmatics report wheeze therefore we assessed whether inclusion of asthmatics impacted the effect estimates. Consequently, we reran models excluding those who reported a current asthma diagnosis. All analyses were conducted using SAS software (V.9.4) using version P2REL201701.00 of the AHS dataset.

RESULTS

Among the 20 164 eligible women, 1495 (7.4%) met criteria for allergic wheeze and 1779 (8.8%) for non-allergic wheeze, while about 84% had no wheeze. Both older participants (70 years and older) and current smokers were more likely to report non-allergic wheeze (table 1). Overall use of any pesticide was associated with both allergic (OR=1.36, 95% CI: 1.10 to 1.67) and non-allergic (OR=1.25, 95% CI: 1.04 to 1.49) wheeze (table 2). Allergic wheeze was significantly associated with the current use of three pesticides, including the herbicide glyphosate (OR: 1.49, 95% CI: 1.15 to 1.93) and two insecticides: diazinon (OR: 2.91, 95% CI: 1.49 to 5.69) and fly spray (OR: 2.41, 95% CI: 1.18 to 4.92). Non-allergic wheeze was associated with current use of the following herbicides: glyphosate (OR: 1.31, 95% CI: 1.04 to 1.65) and the insecticide carbaryl (OR: 1.49, 95% CI:

Table 1 Characteristics by wheeze subtype of 20 164 women in the Agricultural Health Study, 2005–2010

	No wheeze (N=16 890)		Non-allergic wheeze (N=1779)		Allergic wheeze (N=1495)	
Characteristic	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Age* (years)						
<50	3818	23	382	21	352	24
50–59	5076	30	549	31	500	33
60–69	4594	27	470	26	405	27
70 and older	3402	20	378	21	238	16
Body mass index (kg/m^2)						
25 or less	7654	45	644	36	494	33
>25–30	5702	34	589	33	459	31
>30	3534	21	546	31	542	36
State of residence						
Iowa	11 876	70	1194	67	853	57
North Carolina	5014	30	585	33	642	43
Licensed applicator						
Yes	517	3	70	4	71	5
No	16 373	97	1709	96	1424	95
Hay fever or allergy diagnosis						
Yes	4075	24	0	0	1495	100
No	12 815	76	1779	100	0	0
Episodes of wheezing or whistling in the past 12 months						
1–2	0	0	627	35	405	27
3–6	0	0	487	27	387	25
7–11	0	0	234	13	250	16
12 or more	0	0	342	19	397	27
Don't know/unsure	0	0	89	5	56	4
History of living on a farm						
Yes	9924	59	1017	57	771	52
No	5975	35	633	36	590	39
Missing	990	6	128	7	134	9
Asthma						
Yes	362	2	223	13	541	36
No	16 528	98	1556	87	954	64
Smoking status						
Never	12 781	76	1187	67	968	65
Past	3296	20	372	21	379	25
Current	813	5	220	12	148	10

*Collected at the time of interview.

Table 2 Current pesticide use and odds ratios of allergic and non-allergic wheeze among 20 164 women in the Agricultural Health Study, 2005–2010

	No wheeze		Allergic wheeze				Non-allergic wheeze			
	(N=16 890)		(N=1495)				(N=1779)			
Pesticide	N	%	N	%	OR	95% CI	N	%	OR	95% CI
Current use of* any pesticide	1156	6.9	126	8.4	1.36	1.1 to 1.67	143	8.3	1.25	1.04 to 1.51
Herbicides										
Glyphosate*	688	4.1	80	5.4	1.49	1.15 to 1.93	88	5	1.31	1.04 to 1.65
2,4-D	305	1.8	32	2.1	0.98	0.61 to 1.59	34	1.9	0.89	0.58 to 1.36
Atrazine	81	0.5	6	0.4	0.59	0.23 to 1.51	11	0.6	1.05	0.53 to 2.08
Trifluralin	83	0.5	6	0.4	0.62	0.25 to 1.55	9	0.5	0.83	0.4 to 1.72
Dicamba	64	0.4	4	0.3			11	0.6	1.6	0.81 to 3.16
Picloram	72	0.4	6	0.4	0.99	0.4 to 2.45	5	0.3	0.58	0.23 to 1.48
Metolachlor	38	0.2	0	0			6	0.3	1.09	0.43 to 2.75
Triclopyr	37	0.2	4	0.3			9	0.5	1.94	0.91 to 4.18
Insecticides										
Carbaryl	221	1.3	31	2.1	1.34	0.85 to 2.11	37	2.1	1.49	1.01 to 2.22
Malathion	98	0.6	16	1.1	1.76	0.96 to 3.25	18	1	1.64	0.95 to 2.82
Permethrin	81	0.5	12	0.8	1.33	0.65 to 2.73	13	0.7	1.44	0.78 to 2.67
Cyfluthrin	43	0.3	5	0.3	1.32	0.49 to 3.52	7	0.4	1.33	0.63 to 3.29
Diazinon	50	0.3	12	0.8	2.91	1.49 to 5.69	3	0.2		
Fly spray	54	0.3	11	0.7	2.41	1.18 to 4.92	6	0.3	1.01	0.42 to 2.4
Pyrethrins	38	0.2	4	0.3			5	0.3	1.2	0.46 to 3.12

Participants with no history of current use for each specific pesticide were used as the reference group.
Models adjusted for state of residence, categorised age, body mass index, asthma, glyphosate use and smoking (never/past/current). ORs not reported if fewer than five exposed cases.
*Models evaluating Current use of pesticide and glyphosate use as exposures were not adjusted fordid not include glyphosate use in the adjustment set.

1.01 to 2.22). When we evaluated whether ORs differed between allergic and non-allergic wheeze, fly spray (p_{int}=0.08) showed evidence of differences, with the estimate being elevated for allergic wheeze and null for non-allergic wheeze. Glyphosate was the most commonly used pesticide among current pesticide users (~60%) and glyphosate influenced the results for other pesticides. We present in online supplemental table 1 the results without glyphosate adjustment.

We evaluated the relationship between the frequency of use and wheeze subtypes for overall pesticide use and for the four chemicals (2,4-D, glyphosate, carbaryl and malathion) with sufficient frequency of current use, defined as five or more users with the outcome of interest (table 3). For any pesticide use, 2,4-D, glyphosate, and malathion, the ORs for allergic wheeze were the largest in the highest exposure category whereas we saw no evidence of a monotonic increase with non-allergic wheeze. Specifically, the largest ORs for non-allergic wheeze were in the lowest categories for glyphosate, carbaryl and malathion.

Farming activities involving the handling of hays and grains and natural fertiliser were associated with elevated wheeze (table 4). Handling mouldy hay or straw was strongly associated with both allergic and non-allergic wheeze. Use of natural fertiliser was associated with increased odds of allergic wheeze, but the exposure-response pattern was inconsistent. Cleaning grain bins weekly or daily was associated with non-allergic wheeze (OR: 2.60, 95% CI: 1.17 to 5.77), but not significantly with allergic wheeze, although the OR was elevated (OR: 2.07, 95% CI: 0.74 to 5.78). Working with animals was also associated with wheeze (table 5). Raising any livestock (cattle, horses, hogs or sheep) on the farm was associated with allergic (OR: 1.27, 95% CI: 1.10 to 1.45) and non-allergic wheeze (OR:1.26, 95% CI:1.12 to 1.41). Raising dairy cattle was also associated with both allergic (OR: 1.45, 95% CI: 1.03 to 2.05) and non-allergic wheeze (OR: 1.79, 95% CI: 1.36 to 2.35). Additionally, raising poultry for eggs was associated with allergic (OR: 1.58, 95% CI: 1.12 to 2.24) and non-allergic wheeze (OR: 1.38, 95% CI: 1.00 to 1.91); wheeze was not associated with working with broilers.

In analyses limited to women without current asthma (n=19 038), we observed similar associations of specific pesticide use with allergic wheeze (online supplemental table 2). The association of two herbicides (dicamba and triclopyr) and one insecticide (malathion) with non-allergic wheeze no longer reached statistical significance, but the ORs remained elevated. When evaluating occupational exposures among women without asthma, we observed associations of handling mouldy hay or straw and of cleaning grain bins weekly or daily with both allergic and non-allergic wheeze (online supplemental table 3). Associations of currently raising animals on the farm showed similar results across wheeze subtypes whether women with asthma were included (online supplemental table 4).

DISCUSSION

Our study evaluated specific pesticides and farming activities in relation to allergic and non-allergic wheeze among 20 164 farm women from the AHS cohort. Current use of any pesticide and glyphosate were associated with both allergic and non-allergic wheeze. Diazinon and fly spray, both insecticides, were associated with only allergic wheeze, even after we excluded women with asthma. Although allergic and non-allergic wheeze had similar prevalence, the associations of pesticides with allergic wheeze generally were of greater magnitude; we observed a similar pattern among male farmers in the AHS.[7] Our observations in men and women of the AHS are consistent with animal models that suggest the respiratory impact of some pesticides is stronger in those with allergy.[17] Although associations differed

Table 3 Select exposure-response models for pesticides and ORs and 95% CIs of allergic and non-allergic wheeze among 20 164 women enrolled in the Agricultural Health Study, 2005–2010

Pesticide	Frequency of use (days/year)	No wheeze		Allergic wheeze				Non-allergic wheeze			
		n	%	n	%	OR	95% CI	n	%	OR	95% CI
Any pesticide*											
	None	15 753	93.3	1374	91.9			1638	92.1		
	1–4	409	2.4	43	2.9	1.32	0.94 to 1.87	53	3	1.31	0.98 to 1.76
	5–10	431	2.6	36	2.4	1.06	0.73 to 1.54	49	2.8	1.16	0.86 to 1.57
	11–275	297	1.8	42	2.8	1.63	1.13 to 2.34	39	2.2	1.3	0.92 to 1.84
2,4-D											
	None	16 591	98.2	1463	97.9			1747	98.2		
	1–3	108	0.6	8	0.5	0.88	0.39 to 1.96	10	0.6	0.8	0.4 to 1.59
	4–9	96	0.6	10	0.7	1	0.46 to 2.15	10	0.6	0.85	0.42 to 1.71
	10–60	95	0.6	14	0.9	1.11	0.55 to 2.24	12	0.7	0.87	0.45 to 1.68
Glyphosate*											
	None	16 216	96	1418	94.8			1691	95.1		
	1–4	236	1.4	27	1.8	1.56	1.01 to 2.42	33	1.9	1.46	1 to 2.11
	5–10	236	1.4	19	1.3	1.02	0.61 to 1.69	30	1.7	1.3	0.88 to 1.92
	11–215	202	1.2	31	2.1	1.81	1.19 to 2.76	25	1.4	1.23	0.8 to 1.88
Carbaryl											
	None	16 674	98.7	1465	98			1744	98		
	0–3	74	0.4	11	0.7	1.3	0.63 to 2.69	16	0.9	1.88	1.06 to 3.34
	4–8	72	0.4	9	0.6	1.28	0.59 to 2.74	11	0.6	1.34	0.69 to 2.61
	9–150	70	0.4	10	0.7	1.3	0.62 to 2.75	8	0.4	0.99	0.46 to 2.13
Malathion											
	None	16 793	99.4	1479	98.9			1761	99		
	1–2	47	0.3	6	0.4	1.66	0.68 to 4.09	10	0.6	1.91	0.93 to 3.9
	3–30	50	0.3	10	0.7	1.85	0.83 to 4.11	8	0.4	1.42	0.65 to 3.1

Models adjusted for state of residence, categorised age, body mass index, asthma, glyphosate use and smoking (never/past/current). ORs not reported if fewer than five exposed cases.
*Models evaluating current use of pesticide and glyphosate use as exposures did not include glyphosate use in the adjustment set. Models were not adjusted for glyphosate use.

between allergic and non-allergic wheeze for some exposures, we saw no strong evidence for differential associations between wheeze subtypes among women like we did among men, potentially because women used pesticides less frequently compared with men.

Prevalence of allergic wheeze in our prior study of male farmers in the AHS[7] was comparable to the prevalence we observed among women in the current study; however, the prevalence of non-allergic wheeze among women (8%) was much lower than that among men (16%) (online supplemental table 5). Women in the AHS used any particular pesticide less frequently than men. For example, glyphosate was the most commonly used pesticide in both women and men in the AHS; however, in women only 4.1% of women not reporting wheeze reported using glyphosate in the last year, whereas it was used by 56% of men not reporting wheeze. Other pesticides showed similar patterns of prevalence. Despite these differences in pesticide exposure prevalence, we observed several of the same associations in women as in men. Among both women and men, glyphosate was associated with both allergic and non-allergic wheeze. Similar to our findings, prior research has shown associations of glyphosate with atopic asthma among women farmers.[11] On the other hand, we observed elevated associations for diazinon and fly spray with allergic wheeze for women that were not observed among men.[7] Organophosphate insecticides have been associated with wheeze and asthma among adults in the AHS[11–13 22] and other populations.[6 23] Organophosphate insecticides contribute to airway hypersensitivity in animals by decreasing neuronal M2 muscarinic receptor function in the lungs.[16] Further, allergen-sensitised animals have increased vulnerability to airway hyperactivity,[17] a factor that may explain why we observed stronger associations with allergic than non-allergic wheeze.

Few studies of pesticide exposure and respiratory symptoms have focused on women. General or any pesticide use among farm women in different global regions has been associated with respiratory symptoms, including asthma and wheeze.[9 10 24 25] Among rural women in South Africa residing close to farms, organophosphate and pyrethroid pesticide exposure measured using urinary metabolites was positively associated with asthma-related cytokines, markers for airway inflammation.[26] Similarly, the organophosphate diazinon was associated with allergic wheeze in our analysis. In Costa Rica, a study of indigenous women (n=127) working on plantain plantations showed that exposure to organophosphate insecticides chlorpyrifos and terbufos was strongly associated with wheeze.[23] We were unable to assess associations with chlorpyrifos due to its limited use among AHS women; no women reported using terbufos.

Interestingly, although select pyrethroids have been associated with wheeze in prior work,[11] we did not observe any association with use of pyrethroids (permethrin, cyfluthrin and pyrethrin) and our outcomes of interest. However, the frequency of use was low (<1% for any of the pyrethroids evaluated), limiting our ability to detect associations. In our prior analysis in men, pyrethrin use was associated with both allergic and non-allergic wheeze.[7] Permethrin exposure has also been associated with wheeze among children.[27]

Glyphosate was the most used pesticide among these women and is commonly used in the USA.[3 28] Glyphosate use was

Table 4 Current farming practices and ORs and 95% 95% CIs of allergic and non-allergic wheeze among 20 164 women enrolled in the Agricultural Health Study (2005–2010)

Farming practice	Days used/year	No wheeze (N=16 890) n	%	Allergic wheeze (N=1495) n	%	OR	95% CI	Non-allergic wheeze (N=1779) n	%	OR	95% CI
Till or disc the soil with farm machinery	Never	13 770	81.7	1250	83.8			1424	80.2		
	<10 days per year	1721	10.2	138	9.2	0.99	0.81 to 1.21	198	11.1	1.2	1.02 to 1.41
	10–30 days per year	1091	6.5	85	5.7	1.01	0.79 to 1.3	117	6.6	1.12	0.91 to 1.37
	>30 days per year	272	1.6	19	1.3	0.78	0.47 to 1.3	37	2.1	1.33	0.93 to 1.89
Harvest crops with farm machinery	Never	13 750	81.5	1232	82.5			1423	80		
	<10 days per year	1094	6.5	99	6.6	1.13	0.9 to 1.43	132	7.4	1.26	1.04 to 1.53
	10–30 days per year	1376	8.2	118	7.9	1.17	0.94 to 1.45	142	8	1.1	0.92 to 1.33
	>30 days per year	649	3.8	45	3	0.82	0.59 to 1.15	81	4.6	1.29	1.01 to 1.65
Operate diesel-powered tractors	Never	11 991	71.1	1075	71.9			1213	68.2		
	<10 days per year	1717	10.2	154	10.3	1.18	0.97 to 1.43	201	11.3	1.29	1.09 to 1.51
	10–30 days per year	1786	10.6	147	9.8	1.09	0.89 to 1.33	213	12	1.31	1.12 to 1.54
	31–90 days per year	982	5.8	80	5.4	1.19	0.92 to 1.54	105	5.9	1.23	0.92 to 1.54
	>90 days per year	389	2.3	39	2.6	1.27	0.88 to 1.83	47	2.6	1.31	0.95 to 1.79
Natural fertiliser applied to farm	Never	15 919	94.4	1376	92.2			1633	91.9		
	<10 days per year	608	3.6	69	4.6	1.31	0.99 to 1.73	96	5.4	1.57	1.25 to 1.97
	10–30 days per year	239	1.4	39	2.6	2.25	1.55 to 3.28	33	1.9	1.49	1.02 to 2.16
	>30 days per year	106	0.6	8	0.5	0.9	0.41 to 1.96	14	0.8	1.35	0.76 to 2.4
Handling mouldy hay or straw	Never	15 030	89.1	1240	83			1513	85.2		
	Less than once a month	1382	8.2	181	12.1	1.6	1.33 to 1.92	188	10.6	1.43	1.22 to 1.69
	Monthly	239	1.4	37	2.5	1.71	1.15 to 2.53	38	2.1	1.59	1.12 to 2.27
	Weekly or daily	223	1.3	36	2.4	1.88	1.26 to 2.8	37	2.1	1.69	1.18 to 2.42
Harvest crops by hand	Never	15 894	94.2	1356	90.8			1659	93.3		
	<10 days per year	398	2.4	45	3	1.14	0.81 to 1.62	37	2.1	0.89	0.63 to 1.27
	10–30 days per year	352	2.1	60	4	1.45	1.05 to 1.99	50	2.8	1.29	0.95 to 1.77
	>30 days per year	233	1.4	33	2.2	1.33	0.89 to 2	32	1.8	1.21	0.83 to 1.78
Clean grain bins	Never	15 334	90.9	1398	93.5			1588	89.4		
	Less than once a month	1396	8.3	84	5.6	0.91	0.71 to 1.16	169	9.5	1.34	1.13 to 1.6
	Monthly	112	0.7	8	0.5	0.96	0.44 to 2.1	12	0.7	1.13	0.61 to 2.07
	Weekly or daily	31	0.2	5	0.3	2.07	0.74 to 5.78	8	0.5	2.6	1.17 to 5.77

'Never' category was used as the reference group.
Models were adjusted for state, categorised age, body mass index, current diagnosis of asthma and smoking (never/past/current).

associated with both allergic and non-allergic wheeze; but, among the most frequent users, the associations were stronger with allergic wheeze, indicating that glyphosate may play a role in airway reactivity or inflammation. Animal studies have suggested potential mechanisms for 'glyphosate-induced[29]' occupational lung disease, specifically lung inflammation. In murine

Table 5 Animals currently raised on farm and ORs and 95% 95% CIs of allergic and non-allergic wheeze among 20 164 women enrolled in the Agricultural Health Study, 2005–2010

Type of animal	No wheeze (N=16 890) n	%	Allergic wheeze (N=1495) n	%	OR	95% CI	Non-allergic wheeze (N=1779) n	%	OR	95% CI
Any livestock	4163	24.6	387	25.9	1.27	1.1 to 1.45	478	26.9	1.26	1.12 to 1.41
Any cattle	3219	19.1	304	20.3	1.27	1.09 to 1.47	362	20.3	1.2	1.05 to 1.36
Beef cattle	2954	17.5	271	18.1	1.2	1.03 to 1.4	316	17.8	1.11	0.97 to 1.27
Dairy cattle	380	2.2	46	3.1	1.45	1.03 to 2.05	66	3.7	1.79	1.36 to 2.35
Hogs	1490	8.8	128	8.6	1.21	0.98 to 1.49	180	10.1	1.33	1.12 to 1.58
Horses	319	1.9	39	2.6	1.2	0.82 to 1.75	33	1.9	0.95	0.66 to 1.37
Sheep	412	2.4	52	3.5	1.38	0.99 to 1.92	42	2.4	1	0.72 to 1.38
Any poultry	720	4.3	83	5.6	1.25	0.97 to 1.63	82	4.6	1.13	0.89 to 1.43
Poultry (broilers)	499	3	49	3.3	1.2	0.87 to 1.66	50	2.8	1.03	0.77 to 1.4
Poultry (layers)	315	1.9	48	3.2	1.58	1.12 to 2.24	45	2.5	1.38	1 to 1.91

Participants reported not currently raising a specific animal group/species were used as the reference group.
Models adjusted for state, categorised age, body mass index, current diagnosis of asthma and smoking (never/past/current).

models, exposure to environmental air samples can increase eosinophil and neutrophil counts, mast cell degranulation and production of cytokines interleukin 33 (IL-33), thymic stromal lymphopoietin or TSLP, IL-13 and IL-5, involved in immunological response to environmental exposures.[29]

Our study demonstrated important associations of wheeze with farming activities. First, it is important to note that farming practices carried out by women in the AHS were less frequent than past research has demonstrated among men.[30] Despite the lower frequency of engagement in farming activities by women, we observed that harvesting crops, handling mouldy hay or straw and cleaning grain bins were each associated with both types of wheeze, with stronger associations observed with non-allergic wheeze. Further, we found that exposure to working with any type of cattle was also associated with both allergic and non-allergic wheeze. Prior research has suggested that farming activities can contribute to allergic sensitisation and adverse respiratory outcomes due to exposure to airborne allergens of multiple origins (eg, fungi and animals) in farm workers.[31] Since the late 1990s, multiple respiratory conditions, including rhinitis, asthma and hypersensitivity pneumonia, have been associated with working in animal confinement environments. Prior research demonstrates that among adults, exposure to large animal farming is a strong risk factor toward the development of occupational asthma and related diseases, including an increased prevalence of rhinitis[32 33] and non-IgE-mediated occupational asthma.[34 35] As farms are complex environments, the agents responsible for respiratory diseases are not completely understood, but it is increasingly appreciated that exposures due to farming activities can include endotoxins, peptidoglycans and respirable dust particles. Advances in understanding the chronic inflammatory adaptation response in humans and animal modelling should provide the tools to implement strategies to ultimately prevent and/or reduce respiratory disease burden in exposed workers.

Evaluating the impact of pesticide exposure on human health is challenging and requires a large study population with detailed information on personal pesticide use and farming activities. An important strength of the AHS is that it addresses these challenges, providing unique data for studying the effects of specific pesticides and farming-specific agricultural exposures. Self-reported pesticide use in the AHS is accurate and reliable.[36] The potential for measurement error is important to acknowledge. During their interview, women provided information on pesticide use since their last interview and on respiratory outcomes in the past year. Therefore, for some women, 'current' pesticide exposure may have occurred up to 5 years before the outcome was assessed. This exposure–outcome temporal gap would differ among women, and that heterogeneity may have made it less likely to see an association with pesticides. Our study does have some limitations. Due to the low prevalence of pesticide use among women in our study, we were unable to consider severity or frequency of wheezing episodes. Because our analysis is cross-sectional, we cannot be sure if pesticide use preceded wheeze. Nor can we be sure of the closeness or ordering in time among each woman's specific exposures. We did not undertake analysis of mixtures as analysis of potential combinations of agents is particularly challenging in our sample—partly because of the temporal issue already mentioned and partly because few women reported exposure to multiple specific pesticides (most spouses did not regularly engage in pesticide application).

The pesticides that we studied do not appear to be correlated with each other (online supplemental table 6) or with farming activities (online supplemental table 7). Nevertheless, to minimise potential for confounding from correlated pesticides, we conducted sensitivity analyses and adjusted for the most used pesticide, glyphosate. We cannot rule out that these observed associations may be related to other ingredients included in the pesticide formulation; we cannot disentangle these associations due to the lack of publicly available data on these ingredients. The associations may also be influenced by other unidentified environmental factors or measured exposures not accounted for in our models. For example, protective factors may play a role in the associations with poor respiratory outcomes such as wheeze. We were able to evaluate the role of living on a farm (online supplemental table 8), however, did not observe differences in estimates. Finally, the CIs that we report are not adjusted for multiple comparisons in accordance with common epidemiologic practice.[37 38] These authors have argued against adjusting for multiple comparisons with preference for data presentation consistent with Hill[39] criteria, where study design, analytical approach and consistency of the evidence over time or across study populations are given priority.

This work represents the most comprehensive analysis of specific pesticide use as a risk factor for allergic and non-allergic wheeze among women to date. Although women in the AHS reported very limited use of pesticides, 4 of the 15 pesticides evaluated were associated with either allergic or non-allergic wheeze. While this analysis was limited to female farmers who, most likely, have more commonly applied pesticides compared with the general population, the chemicals that they use are not exclusively agricultural. Our analysis included commonly used residential pesticides, such as glyphosate, 2,4-D, permethrin and carbaryl, which underscores the significance of our findings and relevance to pesticide users in both residential and commercial settings. Future research studies should evaluate potential biological mechanisms of these chemicals and evaluate ways to minimise risk of exposure.

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Contributors JAH, DPS, LEBF, SJL and PKH designed the data collection instruments and collected the data. JYI and AM conducted the statistical analyses. JYI drafted the manuscript. JYI, AM, DMU, DPS, LEBF, SJL, PKH and JAH reviewed and provided critical comments on the draft manuscript. All authors reviewed and approved the final manuscript. JAH is the guarantor of this work.

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