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Original Contribution

Childhood Residential and Agricultural Pesticide Exposures in Relation to Adult-Onset Rheumatoid Arthritis in Women

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Farming and pesticide exposure may influence risk of rheumatoid arthritis (RA); the role of early-life pesticide exposure is unknown. The Sister Study includes a US national cohort of women aged 35–74 years (enrolled 2004–2009); we examined childhood pesticide exposure in women in this cohort with adult-onset RA. Cases ($n = 424$) were compared with 48,919 noncases. Data included pesticide use at the longest childhood residence through age 14 years, farm residence of at least 12 months with agricultural pesticide exposure through age 18 years, and maternal farm experience. Odds ratios and 95% confidence intervals were adjusted for age, race or ethnicity, education, smoking, and childhood socioeconomic factors. Cases with RA reported more frequent and direct (personal) residential pesticide use in childhood (for infrequent/indirect pesticide use, odds ratio (OR) = 1.1; for frequent/direct use, OR = 1.8; P for trend = 0.013). Compared with women without residential farm history, odds of having RA increased for those reporting a childhood-only farm residence with personal exposure to pesticides used on crops (OR = 1.8, 95% confidence interval: 1.1, 2.9) or livestock (OR = 2.0, 95% confidence interval: 1.2, 3.3). Our findings suggest adult-onset RA may be related to childhood exposure to residential and agricultural pesticides, and support further investigations of lifetime pesticide use in RA.

autoimmune diseases; early life; insecticides; pesticides; women's health

Abbreviations: aOR, age-adjusted odds ratio; DDT, dichlorodiphenyltrichloroethane; DMARD, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis.

Established environmental risk factors for rheumatoid arthritis (RA) include smoking and occupational exposure to crystalline silica dust (1). Agricultural occupation also has been associated consistently with higher rates of RA, but whether this is because of pesticides or other exposures is not known (2–9). Evidence on the relationship between RA and pesticides is limited and typically focused on adult occupational exposures, with a lack of data on household pesticide use and exposures across the lifespan. In a prior study of postmenopausal women, a reported history of personal use of insecticides was associated with risk of RA and a related systemic autoimmune disease, systemic lupus erythematosus, especially in those who ever lived or worked on a farm (10). Women who live on a farm may have more exposure to pesticides and also may be more likely to have grown up on a farm.

Early-life and childhood exposures to nutritional factors, infections, and chemicals can have long-term effects on the developing immune system, thus influencing risk of chronic immune-mediated disease in adulthood (11–13). In the case of pesticides, prenatal or early-life exposures have been associated with a range of human health effects, including respiratory function, infections, and cancer (14–17). In an agricultural setting, children may experience carry-home pesticide exposure, direct (i.e., personal) exposure during field work or when mixing or applying pesticides, and environmental exposure due to broadcast pesticide spray from trucks or planes (18, 19), in addition to residential pesticide exposure similar to those in nonfarm settings (20).

Little is known about the role of childhood pesticide exposure in the development of RA. Using data from a large national cohort of women in the United States, we previously identified childhood socioeconomic, perinatal, and other early-life factors associated with prevalent RA diagnosed in adulthood (21). In the present study, we examined the occurrence of residential and

agricultural pesticide exposure in childhood in relation to RA in the same women.

METHODS

Sample

The study sample was derived from a volunteer cohort of 50,884 women (aged 35–74 years at enrollment; 84% non-Hispanic white, 9% black, 8% Hispanic/other) enrolled 2004–2009 in the Sister Study, a national study of environmental factors and health in the United States (22). The Sister Study was approved by the institutional review board of the National Institute of Environmental Health Sciences of the National Institutes of Health. Participants provided written informed consent. The sample included 424 women (0.8%) with probable RA (based on self-reported, physician-diagnosed RA), aged 16 years or older, identified at enrollment and confirmed by the use of disease-modifying antirheumatic drugs (DMARDs) or steroids for RA and bilateral joint swelling for 6 or more weeks (21). The comparison group ($n = 48{,}919$ noncase patients) excluded all other women who received an RA diagnosis when they were younger than 16 years or whose diagnosis was unsubstantiated by RA-specific medication use and symptoms. Women who took DMARDs for RA but who did not report bilateral joint swelling were considered as possible clinical case patients for sensitivity analyses ($n = 166$; the total number of probable or possible case patients was 590).

Data collection

Most data were obtained from a computer-assisted telephone interview, except for a self-administered, take-home questionnaire requesting information about early life and maternal factors; participants were encouraged to contact their mothers for assistance as needed (23, 24). Information on accessing questionnaires is available online (https://www.sisterstudystars.org/).

In a lifetime medical history, women were asked whether they had ever been diagnosed with RA. Women who reported RA were asked their age at diagnosis, whether they had ever experienced bilateral joint swelling of at least 6 weeks, and which medications they had used for RA, including those used currently and those used the longest.

The sources of exposure data are outlined in Appendix 1. Data on residential history included questions on the longest childhood residence up to age 14 years (and also the longest and current adult residence). Participants were asked if the residence was on an active farm or orchard, or had been a farm in the past 20 years, or was within hearing, seeing, or smelling distance of a farm or orchard. Questions asked about regular residential insecticide or pesticide treatments (i.e., for insects, rodents, or other animals considered pests), the frequency of treatments, and whether participants applied the pesticides themselves (never, some, most, or all the time). Those who did not report a farm as their childhood or adult longest residence were also asked if they had ever lived on a farm for 12 months or more, even if just a few months per year over several years. Participants were also asked if they were ever directly in the fog or spray of pesticides; for example, whether as a child had they chased after mosquito fogger trucks. Questions asked about exposures before or after 1975, soon after dichlorodiphenyltrichloroethane (DDT) was banned in the United States (25), and, if exposed, how many times before 1975 and how many times after.

Participants who reported their longest childhood or adult residence had been a farm, or who had lived on a farm at another time for at least12 months, were also asked to complete a residential farm questionnaire. For farm residences of 12 months or longer in childhood (up to age 18 years), women were asked what crops and livestock were raised, whether they worked in the fields or had animal contact, and potential sources of pesticide exposure (e.g., were pesticides used on farm; were they ever in the fields when pesticides were sprayed; did they personally mix, load, apply, or clean equipment used for pesticides; and were pesticides used on animals). On the self-administered take-home questionnaire, women were also asked if their mother had lived or worked on a farm while pregnant with them. Covariate data included birth year, race or ethnicity, pack-years of smoking, level of education, and childhood socioeconomic factors, as previously described (21).

Analyses

Analyses were performed in SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina). Odds ratios and 95% confidence intervals were estimated using logistic regression models adjusted for age. We considered additional model covariates on the basis of prior knowledge and by identifying a minimal adjustment set via a directed acyclic graph and empirically testing the impact of covariates on the change in effect estimates. For most exposures, we saw limited confounding (i.e., change of <10% effect estimate over age-adjusted models) by race or ethnicity (white or nonwhite), having a college degree, the number of pack-years smoking, and a summary score for childhood socioeconomic factors previously associated with RA in this same study sample (21). In the tables, we report age-adjusted and fully adjusted results. Exploratory stratified models were only adjusted for age because of the low frequency of exposed cases.

Whenever possible, we focused our analyses on childhood-only exposures. Most women who applied residential pesticides in childhood also reported adult pesticide use, limiting our ability to conduct analyses of childhood-only residential pesticides. Fewer women lived on a farm as adults than as children, so it was feasible to examine associations of childhood-only agricultural pesticides with RA by excluding those with an adult farm residence. For residential exposures, frequency of use and whether pesticides were personally applied were grouped to assess potential for more exposure (frequent referred to having applied pesticides personally at least monthly; direct referred to having personally applied pesticides some or most of the time). For farm exposures, being in the fields during spraying, personally mixing and/or applying pesticides, and cleaning equipment were grouped as personal exposures. For broadcast sprays, ages at exposure were not specified, so we explored associations for women without any farm history and those with a childhood farm residence. Exposures before 1975 were examined because exposures after 1975 were likely to occur in adulthood only. No meaningful changes were seen in models adjusting for exposures after 1975 and excluding those reporting exposures after 1975. Adult exposures were not specifically examined, because of insufficient information on their timing relative to diagnosis.

Sensitivity analyses used a more inclusive case definition (i.e., any DMARD or steroid use for RA, regardless of bilateral joint symptoms). Models were also run excluding cases diagnosed more than 10 years before enrollment and stratified by median diagnosis age (47 years). We explored associations stratified by birth cohort, encompassing differences in age at exposure and in pesticides used over time. These strata were defined to reflect potential exposure to the organochlorine insecticide DDT, which became available after 1945. Its use peaked in the 1950s and 1960s and was banned in the United States by 1972. No statistical tests for interaction or effect measure modification were conducted.

RESULTS

Case patients with RA reported more smoking, were older, more likely to be nonwhite, and less likely to have a college degree compared with noncase patients (Table 1). Regular pesticide use at the longest childhood residence was reported by nearly 1 in 4 women (i.e., 27% of case patients with RA and 24% of noncase patients), and slightly less than half of the sample reported regular adult residential use (49% of case patients; 44% of noncase patients). Similar proportions of case patients and noncase patients reported a farm as their longest childhood residence (15% and 16%, respectively) or adult residence (7% and 8%, respectively).

Case patients were somewhat more likely than noncase patients to report a rural (age-adjusted odds ratio (aOR) = 1.3, 95% CI: 0.95, 1.7) or urban (aOR = 1.2, 95% CI: 0.93, 1.6) residence in childhood compared with a residence in the suburbs (Table 2). RA was not associated with a long-term childhood residence on an active or former farm or living near a farm or orchard, nor with using well water at the childhood residence. Pesticides use at the longest childhood residence was associated with RA (aOR = 1.3, 95% CI: 1.0, 1.6), with stronger associations for more frequent use (at least monthly), both for indirect (i.e., others applied the pesticide; aOR = 1.8, 95% CI: 1.2, 2.7) and direct use (i.e., personally applied the pesticide; aOR = 2.5, 95% CI: 1.3, 4.9; P for trend = 0.0001 for indirect/infrequent use, indirect/frequent, direct/infrequent, and direct/frequent use compared with no use). Full covariate adjustment attenuated the estimated odds ratios (e.g., frequent and direct use, multivariable-adjusted OR = 1.8, 95% CI: 0.82, 3.9), but the overall trend remained significant (P for trend = 0.013). In the absence of adult residential pesticide use, indirect childhood-only exposure was not associated with RA (multivariable-adjusted OR = 0.87, 95% CI: 0.54, 1.4; not shown), and the RA association with direct exposure was only somewhat elevated (multivariable-adjusted OR = 1.3, 95% CI: 0.41, 4.2). For those reporting adult residential pesticide exposure, RA was associated with indirect (multivariable-adjusted OR = 1.4, 95% CI: 0.95, 1.9) and direct (aOR = 1.8, 95% CI: 1.6, 3.3) residential pesticide exposure in childhood.

Maternal farm residence was not associated with RA (Table 3). Compared with women without a residential farm history, a childhood-only farm history (i.e., a farm residence of at least 12 months before age 18 years but no adult farm residence) was associated with RA (aOR = 1.3, 95% CI: 1.0, 1.7). The odds of having RA were increased for women reporting a childhood farm residence where pesticides were used on crops (aOR = 1.4, 95% CI: 0.99, 2.1) and for those reporting personal exposure to pesticides used on crops (e.g., exposed in the field, or personally mixed or applied; aOR = 1.9, 95% CI: 1.2, 3.1). RA was also associated with personal contact with pesticide-treated

Table 1. Characteristics of Case and Noncase Patients With Rheumatoid Arthritis, Sister Study, United States, 2004–2009

Characteristic	Case Patients With RA (n = 424)		Noncase Patients (n = 48,919)	
	No.	%	No.	%
Age at enrollment, years[a]	57.9 (8.2)		55.1 (9.0)	
Pack-years of smoking[a,b]	17.4 (16.1)		14.6 (15.3)	
Birth year				
1928–1945	163	38	14,051	29
1946–1955	177	42	19,211	39
1956–1965	73	17	13,014	27
After 1965	11	3	2,643	5
Never smoker	184	43	26,451	54
College degree	170	40	23,770	49
Nonwhite or Hispanic race or ethnicity	82	19	7,764	16
No. of childhood socioeconomic factors[c]				
0	113	28	17,300	37
1	124	31	15,858	24
2	126	31	10,389	22
3–4	42	11	3,404	8
Age at home of longest residence[d]				
Childhood (age ≤14 years)	102	27	10,340	24
Adulthood (age ≥18 years)	207	49	21,548	44
Home of longest residence was a farm[e]				
Childhood (age ≤14 years)	65	15	6,822	16
Adulthood (age ≥18 years)	36	8	3,451	7
Other farm residence ≥12 months	41	10	3,489	7

Abbreviation: RA, rheumatoid arthritis.

[a] Values are expressed as mean (standard deviation).

[b] Missing data on pack-years of smoking for 19 case patients (4%) and 1,387 noncase patients (3%).

[c] Score of 4 factors previously associated with RA in the sample: highest childhood household educational level is high school or less, low/poor relative household income, young maternal age (<20 years), food insecurity (21); missing data for 19 case patients (4%) and 1,968 noncase patients (4%); percentages do not add to 100 because of rounding.

[d] Missing childhood residence data for 43 case patients (10%) and 5,053 noncase patients (10%). Childhood residential pesticide use and adult residential pesticide use are not mutually exclusive.

[e] Missing childhood farm residence on 47 case patients (11%) and 5,065 noncase patients (10%). Responses for childhood farm residence and adult farm residence are not mutually exclusive. Those who reported neither were asked about other residential farm experience of 12 months or longer.

Table 2. Childhood Residential Factors, Potential Pesticide Exposures, and Association With Rheumatoid Arthritis, Sister Study, United States, 2004–2009

Longest Residence to Age 14 Years	Case Patients With RA (n = 424)		Noncase Patients (n = 48,919)		Age Adjusted		Fully Adjusted[a]	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Residential area[b]								
Urban	106	25	10,921	23	1.2	0.93, 1.6	1.2	0.89, 1.6
Suburban/other	98	23	13,488	28	1.0	Referent	1.0	Referent
Small town	107	25	12,467	26	1.1	0.84, 1.5	1.1	0.81, 1.5
Rural	111	26	11,190	23	1.3	0.95, 1.7	1.2	0.91, 1.6
Near or on a farm or orchard[c]								
Not a farm/not near a farm	242	64	28,112	64	1.0	Referent	1.0	Referent
Near a farm	53	14	6,024	14	1.0	0.77, 1.4	1.1	0.82, 1.5
Used to be a farm	21	6	2,908	7	0.87	0.55, 1.4	0.96	0.60, 1.5
On an active farm	65	17	6,822	16	1.0	0.76, 1.3	1.0	0.75, 1.4
Source of drinking water[d]								
City/town water supply	295	71	35,637	75	1.0	Referent	1.0	Referent
Private/community well, other	123	29	11,972	25	1.2	0.96, 1.5	1.2	0.92, 1.4
Residential pesticide use[e]								
Never	275	73	33,515	76	1.0	Referent	1.0	Referent
Ever	102	27	10,340	24	1.3	1.0, 1.6	1.2	0.92, 1.6
Frequency								
Less than monthly	62	17	7,401	17	1.1	0.85, 1.5	1.1	0.85, 1.5
Monthly	27	7	1,765	4	2.1	1.4, 3.1	1.6	1.0, 2.6
At least weekly	9	2	662	2	1.7	0.88, 3.4	1.4	0.69, 2.9
Personally applied								
Never	84	22	9,176	21	1.2	0.95, 1.6	1.2	0.91, 1.5
Some of the time	10	3	971	2	1.4	0.72, 2.6	1.1	0.53, 2.2
Most or all the time	8	2	171	0	6.1	3.0, 12.6	4.7	2.2, 10.0
Combined exposure level[f]								
Indirect and infrequent	53	13	6,746	14	1.1	0.78, 1.4	1.1	0.80, 1.5
Indirect and frequent	27	6	1,947	4	1.8	1.2, 2.7	1.5	0.97, 2.4
Direct and infrequent	9	2	647	1	1.9	0.95, 3.6	1.6	0.83, 3.9
Direct and frequent	9	2	476	1	2.5	1.3, 4.9	1.8	0.82, 3.9
P for trend					0.0001		0.013	

Abbreviations: CI, confidence interval; OR, odds ratios; RA, rheumatoid arthritis.

[a] Models were adjusted for age, race or ethnicity, college education, pack-years of smoking, and childhood socioeconomic status score (numbers are reduced because of missing covariate data for 37 case patients and 3,232 noncase patients).

[b] Numbers do not add to the total number of cases because of missing data for 2 case patients (0.5%) and 853 noncase patients (2%). Percentages do not add to 100 because of rounding.

[c] Numbers do not add to the total number of cases because of missing data on childhood farm residence for 43 case patients (10%) and 5,053 noncase patients (10%). Percentages are based on nonmissing data and do not add to 100 because of rounding.

[d] Numbers do not add to the total number of cases because of missing data for 6 case patients (1%) and 1,310 noncase patients (3%). Percentages are based on nonmissing data.

[e] Numbers do not add to the total number of cases because of missing data on childhood residential pesticide use for 47 case patients (11%) and 5,064 noncase patients (10%), on frequency for an additional 4 case patients (1%) and 512 noncase patients (1%), and on personal use for an additional 22 noncase patients (0%). Percentages are based on nonmissing data.

[f] Direct refers to having applied pesticide personally some or most of the time; indirect refers to others having applied pesticide; frequent refers to having applied pesticide at least monthly; infrequent refers to having applied pesticide less often than monthly.

Table 3. Rheumatoid Arthritis Association With Maternal Farm Experience, Childhood Farm Residence, and Pesticide Use, Sister Study, United States, 2004–2009

Residential Farm Experience	Case Patients With RA		Noncase Patients		Age Adjusted		Fully Adjusted[a]	
	No.	%	No.	%	OR	95% CI	OR	95% CI
Mother lived or worked on farm while pregnant[b]	407		46,918					
No	320	79	38,483	82	1.0	Referent	1.0	Referent
Yes	87	21	8,435	18	1.1	0.88, 1.4	1.0	0.79, 1.3
Lifetime farm residence[c]	414		47,192					
No farm residence, child or adult	292	74	36,255	80	1.0	Referent	1.0	Referent
Childhood only	84	21	7,036	15	1.3	1.0, 1.7	1.3	0.98, 1.6
Any adult	38	9	3,910	7	1.1	0.81, 1.6	1.1	0.75, 1.6
Childhood-only farm residence[d]								
Pesticides use on crops								
No pesticides used	30	8	3,000	7	1.0	0.71, 1.5	0.97	0.67, 1.4
Used, no personal exposures	30	8	2,370	5	1.4	0.99, 2.1	1.4	0.97, 2.1
Used, with personal exposures	20	5	1,235	3	1.9	1.2, 3.1	1.8	1.1, 2.9
Livestock contact, pesticide use								
No livestock contact	24	6	2,094	5	1.2	0.82, 1.9	1.2	0.74, 1.8
Contact, but no pesticides used	35	9	3,314	8	1.1	0.77, 1.6	1.1	0.74, 1.5
Contact, and pesticides used	20	5	1,066	2	2.1	1.3, 3.3	2.0	1.2, 3.3
Use on livestock and/or crops[e]								
No livestock (crops only)								
No pesticides used	14	4	1,236	3	1.2	0.68, 2.0	1.1	0.62, 1.9
Pesticides used on crops	15	4	1,044	2	1.7	1.0, 2.8	1.7	0.96, 2.9
Yes, livestock:								
No pesticides used	13	3	1,745	4	0.79	0.45, 1.4	0.78	0.44, 1.4
Pesticides on crops only	22	6	1,769	4	1.4	0.92, 2.2	1.4	0.88, 2.2
Pesticides on crops and animals	20	5	1,066	2	2.0	1.3, 3.3	2.0	1.2, 3.2

Abbreviations: CI, confidence intervals; OR, odds ratios; RA, rheumatoid arthritis.

[a] Models were adjusted for age, race or ethnicity, college education, pack-years of smoking, and childhood socioeconomic status score (numbers are reduced because of missing covariate data on 37 case patients and 3,232 noncase patients).

[b] Missing data on maternal farm residence for 17 case patients (4%) and 2,001 noncase patients (4%). Percentages are based on nonmissing data.

[c] Missing responses on 10 case patients (2%) and 1,727 noncase patients (3%) who were eligible but did not complete the farm module. Percentages are based on nonmissing data.

[d] Excludes those with adult farm residence. Numbers do not always add to total with childhood-only farm residence because of missing values: pesticide use on crops missing for 4 case patients (1%) and 431 noncase patients (1%), livestock contact/pesticide use missing for 5 case patients (1%) and 560 noncase patients (1%). Percentages are based on nonmissing data. Questions about pesticides used on livestock were asked only of women with livestock contact. "No use" included 3% of case patients and noncase patients who reported "don't know," and 6% of case patients and 7% of noncase patients who reported no pesticides were applied to animals.

[e] Includes those with crops only under "no livestock" and livestock only under "livestock," assuming no livestock contact was equivalent to no pesticide use. Missing responses were assigned to unexposed, no pesticide use categories.

livestock (aOR = 2.1, 95% CI: 1.3, 2.7). Compared with women who had no farm history, in those who did, RA was associated with exposure to crop pesticides in the absence of livestock contact (aOR = 1.7, 95% CI: 1.0, 2.8) and with exposure to both crop and livestock pesticides (aOR = 2.0, 95% CI: 1.3, 3.3).

Table 4 shows exposure to broadcast pesticides sprayed from trucks or airplanes before 1975 in relation to RA, stratified by farm history. In women without a lifetime residential farm history of at least 12 months, RA associations were inverse to null for reporting at or below (aOR = 0.53, 95% CI: 0.30, 0.95) and above (aOR = 1.0, 95% CI: 0.66, 1.7) the median number of exposure episodes ($n = 6$ in noncase patients) versus none. For women with a childhood farm history, RA was positively associated with broadcast pesticide exposures before 1975 (aOR = 2.3, 95% CI: 1.3, 4.1, above the median vs. none).

Sensitivity analyses (not shown) revealed no major differences in our primary findings when possible cases were included (i.e., all case patients who used DMARDs), excluding cases diagnosed more than 10 years before interview, or stratified by median diagnosis age (47 years). Childhood residential

Table 4. Rheumatoid Arthritis Association With Broadcast Pesticides Sprayed From Trucks or Airplanes Before 1975, Sister Study, United States, 2004–2009

Times Exposed to Broadcast Sprays[a]	No Lifetime Farm Residence						Child-Only Farm Residence					
	Case Patients With RA ($n = 284$)		Noncase Patients ($n = 35,761$)		Age Adjusted		Case Patients With RA ($n = 84$)		Noncase Patients ($n = 7,036$)		Age Adjusted	
	No.	%	No.	%	OR	95% CI	No.	%	No.	%	OR	95% CI
None	252	89	30,371	85	1.0	Referent	66	79	5,740	84	1.0	Referent
No more than the median	12	4	3,042	8	0.53	0.30, 0.95	2	2	546	8	NC[b]	
More than the median	20	7	2,358	7	1.0	0.66, 1.7	15	18	580	8	2.3	1.3, 4.1

Abbreviations: CI, confidence intervals; NC, not calculated; OR, odds ratio; RA, rheumatoid arthritis.

[a] Median split based on distribution in noncase patients with 6 episodes before 1975. There were missing data on 10 noncase patients (0%) with no lifetime farm residence and on 1 case patient (1%) and 170 noncase patients (2%) with childhood-only farm residence.

[b] Not calculated because there were fewer than 3 exposed cases.

pesticide use was more common in the younger birth cohorts (e.g., those born after 1955; 35% of case patients and 28% of noncase patients) versus those born before 1946 (20% of case patients and 16% of noncase patients). In women who reported adult residential pesticides, RA was associated with direct exposure to childhood residential pesticides in women born 1946–1955 and those born after 1955 (aORs = 3.2 and 3.6, respectively), and with indirect childhood exposure in women born 1946–1955 (aOR = 1.8; Web Table 1, available at https://academic.oup.com/aje). Having a childhood farm residence was, by contrast, more common in the older birth cohorts (e.g., those born before 1946: 28% of case patients and 25% of noncase patients) versus after those born after 1955 (19% of case patients and 12% of noncase patients). Adjusting for maternal farm experience in pregnancy, the association of RA with childhood agricultural pesticide exposure was seen in women born before 1946 and in the years 1946–1955 (compared with women with no farm lifetime history, aORs = 1.8 and 2.0, respectively,; Web Table 2). In these models, maternal farm experience was associated with RA only for those born after 1955 (aOR = 2.0).

DISCUSSION

Previous studies have shown that using insecticides during adulthood and having an agricultural occupation are associated with RA (2–9). Results of the present study suggest childhood pesticide exposure may also be related to adult-onset RA; this is supported by dose-related increases in associations across multiple measures of residential and agricultural pesticide use. Taken together, these findings support the need for investigation of lifetime pesticide exposure and risk of RA.

To our knowledge, ours is the first study to specifically examine childhood pesticide exposure in relation to RA. Strengths of this study include the analyses of multiple types of exposure data and detail on farm-related exposure to pesticides. The observed pesticide associations with RA are consistent with our findings for a related disease, systemic lupus erythematosus, in the same cohort (26). Our results also showed internal consistency for associations of RA with agricultural pesticide and broadcast spray exposures in those with a childhood-farm history. Although the lack of an association with the longest childhood farm residence seems somewhat inconsistent with these findings, most women (75%–80%) with a long-term residence on or near a farm in childhood did not report personal exposures to agricultural pesticides (data not shown). Furthermore, long-term farm residence extended only to age 14 years, whereas residential farm history extended to age 18 years; older teenagers may have greater potential for high levels of pesticide exposure on par with adult occupational exposures. Although we attempted to focus on childhood-only exposures, direct exposure to childhood residential pesticides was uncommon in women lacking adult exposure, so we could not estimate independent associations of RA for childhood-only residential pesticides.

We saw some attenuation in RA associations with frequent and direct childhood pesticide use after adjusting for race or ethnicity, education, smoking, and childhood socioeconomic factors. We cannot rule out confounding by unmeasured factors; treatment for household pests may reflect other household conditions or use of chemical products for cleaning. Associations with agricultural pesticides were robust to covariate adjustment. However, children who work on a farm may experience other early-life and/or prolonged immune-modifying exposures to animals, organic dusts, and sunlight. Pesticide use and exposure to different active ingredients may vary by geographic region (27–29), but we did not adjust for geographic location, because prior analyses showed no independent associations of RA with region in this same study sample (21).

Our findings are subject to other sources of potential bias. Ascertainment of clinical RA on the basis of DMARD use is specific compared with medical records review (30). Our case definition also included those taking steroids for RA, with increased specificity based on symptoms of bilateral joint involvement, which may have favored more severe disease and could bias results if early-life pesticide exposure was related to disease severity. Sensitivity analyses including case patients regardless of bilateral joint symptoms did not change observed associations. Case patients were volunteers in a larger cohort study and, thus, were healthy enough to participate. Compared with the general population, patients with RA have increased morbidity and death rates, which could influence results if childhood

pesticide exposures decreased either survivorship and cohort participation.

Case patients who attributed their disease to pesticide exposures could be more likely to report pesticide use; planned analyses of incident cases as they arise in the cohort will provide an opportunity to reduce the possible influence of recall bias. However, the original study was focused on risk factors for breast cancer, so hypotheses linking pesticides to RA were not likely to be considered by participants as they completed their questionnaires. Biased recall seems less likely to account for associations with agricultural residence and farm work, both of which are relatively objective life experiences. The possibility that adult pesticide use may influence recall of childhood use is more of a concern but may be difficult to distinguish from inextricably linked lifetime behaviors.

Nondifferential misclassification of residential pesticide exposure in childhood is also likely owing to recall errors; nearly 10% of participants reported they did not know if their childhood residences were treated with pesticides. Similar proportions of case and noncase patients were missing data for this reason and were excluded from analyses. For rare exposures, false-positive misclassification errors may have more influence on observed results than false-negative errors. For farm-related pesticide exposure, we considered "don't know" responses to be unexposed, under the assumption of greater awareness of pesticide use for those living in agricultural settings. This assumption is consistent with findings of a validation substudy in which 1,000 mothers of participants provided data on early-life factors (A.A.D., unpublished data, 2016) (22). The findings showed a positive predictive value of greater than 90% for pesticides used on crops versus 56% for residential pesticides.

Research on specific pesticides and RA in women has been limited. An earlier study reported that adult exposure to insecticide was a risk factor for RA in postmenopausal women, but the study elicited no additional information on the types or timing of exposure (10). In the current study, the questionnaire referred only to "insecticides or pesticides …used to treat insects, rodents, or other pests." Mechanisms leading to the development of RA are not fully understood but are thought to involve immune dysregulation leading to production of specific autoantibodies and increased inflammatory cytokines, the convergence of which results in clinical symptoms and damage (31). Although no experimental models of RA have been used to study the role of pesticide exposure, general toxicology studies suggest a diverse range of immunological effects through which early-life pesticide exposures may contribute to later-life immune dysregulation and inflammation in RA (32, 33).

The most specific prior evidence on insecticides and RA in humans pertains to organochlorines, including DDT, which have known immune-modulating effects and have been associated with lymphomas and autoimmunity in experimental and human studies (34–36). Most research on prenatal and early-life DDT exposure has focused on outcomes such as obesity, neurodevelopment, and breast cancer (37–39). However, shared mechanisms may provide links to RA; for example, endocrine disruption, inflammation, and stress response (40–42). In a US population sample (1999–2001), organochlorine levels were elevated in women with self-reported RA (43). Early research in the Agricultural Health Study cohort showed no association of RA in women reporting use of DDT, but the study included only 135 cases (mostly prevalent) (44). Subsequent analyses in the Agricultural Health Study showed lifetime DDT use was associated with incident RA, primarily in women who had grown up on a farm (45). Women with a childhood-farm history may have had earlier, longer, or more frequent pesticide exposures.

Widespread DDT use began after World War II and peaked in the 1950s–1960s before being banned in in the early 1970s (25). Middle-aged and older women in our study may have been exposed to DDT in childhood and as adults, whereas younger women would have been born during or immediately after the era of peak DDT use. Exploratory analyses suggested RA associations with direct or frequent childhood residential exposures were limited to women born after 1945, though most also used pesticides as adults and so may have been exposed to a greater number and different types of pesticides over a longer time. Stratified analyses of childhood-only farm pesticide exposures did not show differences by birth cohort, but maternal farm experience during pregnancy was independently associated with RA for women born after 1955.

For women without a farm residence, our findings did not show an association of RA with broadcast pesticide exposure before 1975. This question lacked direct information on the ages of exposure, but all case patients were born before 1975 and would have had potential childhood DDT exposure. An inverse association of RA was seen for infrequent broadcast spray exposure; it was slightly stronger in women born in the years 1945–1965 (OR = 0.41, 95% CI: 0.19, 0.88), who were most likely to have childhood exposure during a time of peak DDT use. Although nonmonotonic or low-dose effects of DDT or other endocrine disruptors have been proposed (46, 47), we are unaware of studies on immune effects. Among women with a childhood-only farm residence, the positive association with frequent broadcast spray exposures could reflect higher concentrations of agricultural pesticides or other correlated farm exposures. These observations should be interpreted with caution; our ability to make inferences to specific pesticides is limited, especially based on self-reported data recalled from decades earlier. Multiple comparisons were made in stratified analyses that increase the possibility of associations arising due to chance.

In conclusion, our findings provide initial support for an association between childhood pesticide exposure and risk of RA. Replication is needed in other study populations. Further research should include incident cases, consider adult exposures, and attempt to investigate the role of specific pesticides.

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(Appendix follows)

APPENDIX 1

Questionnaire data on residential histories, farm history, and pesticide use were collected by computer-assisted telephone interview, except for the early-life information collected by self-administered questionnaire. Information on study questionnaires and access to full documentation are available online (48).

1. Residential questionnaire: longest childhood to age 14 years
   a. Was residence rural, urban, suburban, or small town?
   b. What was main source of drinking water (i.e., bottled water, community well, city/town water, private well, rain water/cistern, river, lake, or pond water)?
   c. Was residence regularly treated with insecticides or pesticides, by you or someone else, for insects, rodents, or other pests?
      i. If yes, how often were pest control chemicals applied (i.e., daily, weekly, monthly, every 2 or 3 months, once or twice a year, less than yearly)?
      ii. If yes, when they were applied, how often did you personally apply them (i.e., all of the time, most of the time, about half of the time, some of the time, never)?
   d. Residence was located:
      i. On a farm or orchard? (If yes, administer residential farm questionnaire.)
      ii. Near a farm or orchard (i.e., within seeing, smelling, or hearing distance)?
      iii. Used to be to be a farm or orchard (i.e., in the past 20 years)?
2. Residential questionnaire: current adult and longest adult residence (if not current)
   a. Was residence ever treated regularly with insecticides or pesticides, either by you or someone else, to control insects, rodents, or other pests?
   b. Was residence on a farm or orchard? (If yes, administer residential farm questionnaire.)
3. Residential questionnaire: other questions
   a. At any other time, did you ever live on a farm at least 12 months? (If yes, administer residential farm questionnaire.)
   b. Were you ever directly in the fog or spray of pesticides (e.g., when a truck or airplane sprayed for mosquitos)?
      i. If yes, was this before or after 1975, or both?
      ii. If yes, how many times before 1975 and after 1975?
4. Residential farm questionnaire (administered if current or longest adult residence or childhood residence was a farm, or if participant reported having lived on a farm at any other time for at least 12 months)
   a. Did you live on a farm 12 or more months at any time from birth until age 18 years?
      i. If yes, up to age 18 years, what crops were raised (list provided)?
         a. Were pesticides used on crops?
         b. Were you ever in field when pesticides were applied?
         c. Did you personally mix, load, or apply pesticides, or clean pesticide mixing or application equipment?
   b. If yes, were livestock raised on this farm?
      i. Did you feed, clean, herd, milk, shear, slaughter, or have other contact with livestock?
         a. If yes, were pesticides used on livestock or buildings?
5. Early-life questionnaire
   a. Did your mother live on a farm while pregnant with you?
   b. Did your mother work on a farm while pregnant with you?