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Farming Tasks and the Development of Rheumatoid Arthritis in the Agricultural Health Study

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Abstract

Objectives: Farming has been associated with rheumatoid arthritis (RA). Some studies have evaluated the effects of pesticides, but other agricultural exposures may also affect immune response.

Methods: We investigated non-pesticide agricultural exposures in relation to RA in licensed pesticide applicators (N=27175, mostly male farmers) and their spouses (N=22231) in the Agricultural Health Study (AHS) cohort (1993–97) who completed at least one follow-up survey through 2015. Incident RA cases (N=229 applicators and 249 spouses) were identified based on self-report confirmed by use of disease modifying anti-rheumatic drugs or medical records. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated by Cox proportional hazard models adjusting for applicator status, state, smoking, education, and specific pesticide use, allowing estimates to vary by median age when hazards assumptions were not met.

Results: Overall RA was associated with regularly applying chemical fertilizers (OR=1.50; 95%CI 1.11 to 2.02), using non-gasoline solvents (OR=1.40; 95%CI 1.09 to 1.80), and painting (OR=1.26; 95%CI 1.00 to 1.59). In older applicators (>62 years), RA was associated with driving combines (HR=2.46; 95%CI 1.05 to 5.78) and milking cows (HR=2.56; 95%CI 1.01 to 6.53). In younger participants (≤62 years), RA was inversely associated with raising animals as well as crops (HR=0.68; 95%CI 0.51 to 0.89 versus crops only). Associations with specific crops varied by age: some (e.g., hay) were inversely associated with RA in younger participants, while others (e.g., alfalfa) were associated with RA in older participants.

Conclusion: These findings suggest several agricultural tasks and exposures may contribute to development of RA.

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Rheumatoid Arthritis (RA) is the most common systemic autoimmune disease, affecting 1–3% of adults in the U.S. population (1, 2). As with other complex diseases, RA arises from a combination of genetic factors and environmental exposures (3). Established environmental risk factors include cigarette smoking and occupational silica exposure (1, 4–7). Farming occupation has been associated with RA across a range of study populations and designs (8–14). While pesticides are one possible explanation, agricultural settings confer a variety of other possible immune-modulating exposures that may be associated with RA, such inorganic dusts and endotoxins, and UV radiation (15–17). Limited evidence suggests RA may be associated with crop but not livestock farming (8, 18), though findings are inconsistent (12, 19). Given the low frequency of farming occupation in the general population, few studies have looked at specific agricultural exposures, though one case-control study showed non-statistically significant associations of RA with exposure to crops/forage and fertilizers in men (12).

The Agricultural Health Study (AHS) is a prospective cohort study of licensed pesticide applicators, mostly farmers, and their spouses. We previously described associations of incident RA with specific pesticides in male farmers and female spouses in the AHS (13, 20). In the female spouses, associations with RA were also seen for several regular tasks, including applying chemical fertilizers, painting and use of solvents for cleaning (13). Here we extend this research to investigate the relationship of field work and farm tasks with developing RA during up to 20 years cohort follow-up, in a larger sample of incident cases, including new cases from the most recent follow-up) and cases identified in males and in farmers.

METHODS

Study population

The AHS has been previously described (21, 22). Between 1993 and 1997 (Phase 1), 52,394 private pesticide applicators (mostly male farmers) enrolled when they sought to obtain or renew their licenses to apply restricted-use pesticides in North Carolina (NC) and Iowa (IA). Applicators who completed a questionnaire at enrollment were given another questionnaire to complete at home ("take home"), returned by 44%, and an invitation and questionnaire for their spouses to enroll (23). Questionnaires (http://aghealth.nih.gov/collaboration/questionnaires.html) collected information on demographics, health and medical history, and exposures. Participants were asked to update information in three follow-up surveys [Phase 2 (1999–2003), Phase 3 (2005–2010), and Phase 4 (2013–2015)]. The study was approved by the relevant institutional review boards.

Case ascertainment

Potential RA cases were first identified based on self-reported doctor diagnosed RA. False-positive self-reported RA is common, but validation studies show that self-reported RA together with disease-modifying antirheumatic drugs (DMARD) use dramatically increases the specificity of RA case ascertainment over self-report alone (24–27). Therefore, we sought additional information to confirm diagnoses as previously described for cases identified through Phase 3 (13, 20). We re-contacted self-reported RA cases to confirm their diagnosis and provide additional information, including the use of DMARDs. A subset of these was also confirmed by physician report or medical records. In the Phase 4 questionnaire, all reported cases were asked about current or past use of DMARDs (20).

Inclusion criteria for cases and non-cases

Criteria for identifying RA cases and non-cases are summarized in Supplemental Figure 1. Of the total enrolled sample (N=84,739), 58,856 participants provided data on RA at enrollment and at least one follow-up survey. Of these, the sample excluded those who were missing age at RA diagnosis or reported a diagnosis before age 16, and those with inconsistent RA reporting, i.e., refuted RA in a later questionnaire. Ultimately 736 cases were identified as probable RA based on DMARDs use and 185 were confirmed by physicians or medical records. Of these 935 probable or physician confirmed cases, 478 were incident and had complete data on base covariates (state, education, and smoking); 48,928 non-cases had complete covariate data.

Exposure assessment

Types of data collected on farming activities are outlined in Supplemental Figure 2. At enrollment, applicators were asked about income producing crops or animals they were currently raising; these data were also used to assign farm characteristics for spouses. All enrolled applicators were asked about activities they performed at least once each year (e.g., repairing engines, veterinary procedures, grinding animal feed). On the "take-home" questionnaire, completed by 53% of applicators in the study sample, participants were asked about regular field work and other farm tasks, including frequency. Spouses were asked about the same the same types of activities, including regular field work in the past growing season and other farm tasks performed at least once a month in summer or winter, but were not asked about frequency.

Statistical analyses

The data available for analyses varied by whether the participant was an applicator or spouse and, for applicators, whether they completed the "take-home" questionnaire (Supplemental Figure 2). Analysis of covariates and crops included all applicators and spouses. We then examined: (1) tasks reported by applicators at enrollment, and (2) combined data from spouses and applicators with equivalent data on regular tasks (at least once per month versus never/less than once per month).

We first assessed the association of RA with age and covariates, estimating odds ratios (OR) and 95% confidence intervals (CI), adjusting for age. For exposures with at least 5 exposed cases, hazard ratios (HR) and 95% confidence intervals (CI) were estimated by Cox proportional hazard models adjusting for state, participant type (applicator or spouse), cigarette smoking pack-years, education. A second set of models also adjusted for pesticides associated with RA (i.e., atrazine, fonofos, chlorimuron ethyl and chlorpyrifos), based on previously reported associations for male applicators (20) and unpublished results in the combined sample. These fully-adjusted models excluded 3729 (7.6%) non-cases and 45 (9.4%) cases with incomplete data on the pesticide covariates, but after adjusting for age, the missingness was not related to RA (OR=0.88; 95%CI 0.65 to 1.20); nine cases were excluded due to missing diagnosis age. Time at risk was accrued until age at diagnosis, death, or last follow-up contact. We assessed the proportional hazards assumption using an interaction term between attained age and covariates. When the assumption was violated (p for proportionality <0.10), we allowed hazards to vary by median attained age in the full sample (i.e., 62 years). Median diagnosis age in cases was 58 years.

Many farm tasks are dependent on the specific crops or livestock raised, and farm work typically involves diverse interrelated tasks. Mutually adjusting for co-dependent exposures may lead to over-adjustment, for example painting and solvent use). Thus, models were not mutually adjusted. Instead we explored two combinations of related tasks with elevated HRs (i.e., painting + solvent use, and planting + chemical fertilizer use). We also ran models stratified by applicator/spouse status and by state, and excluded cases diagnosed the first two years of follow-up to examine the impact of possible early symptoms. We considered differences in RA associations for applicators and spouses for tasks with equivalent data, testing the interactions for the difference in −2 Log Likelihoods for models with and without product terms. Analyses were conducted using AHS data files P1REL0906.00, P2REL201007.00, P3REL1000.00, and AHSREL201304.00 in SAS, version 9.3 (Cary, NC, U.S.).

RESULTS

Table 1 shows the enrollment characteristics of RA cases and non-cases in the study sample. As previously shown (13, 20), RA was associated with being older, female (OR=1.37; 95%CI 1.14 to 1.64), in NC (OR=1.58; 95%CI 1.32 to 1.90), and greater smoking pack-years (e.g., OR=1.63; 95%CI 1.27 to 2.11 for >18 pack-years versus never smoking).

Table 2 shows associations of crops with RA, adjusting for state, applicator status, education and specific pesticides. In younger participants, RA was inversely associated with raising animals as well as crops (HR=0.68; 95%CI 0.51 to 0.89 versus crops only). This inverse association was primarily seen in younger spouses (HR=0.66; 95%CI 0.46 to 0.95; Supplemental Table 1). Overall RA was also inversely associated with raising hay (overall HR=0.71; 95%CI 0.53 to 0.93), primarily in younger applicators (HR=0.66; 95%CI 0.42 to 0.98), and with raising beef cattle (HR=0.80; 95%CI 0.65 to 0.83). In older participants, RA was associated with growing alfalfa (HR=1.66; 95%CI 1.10 to 2.50) and field corn (HR=1.65; 95%CI 1.05 to 2.61). Inverse associations for RA with combined crop and animal farming were similar by state, but fewer NC farmers raised animals and related-crops (Supplemental Table 2). Given these and other differences in specific crops, subsequent models adjusted for state; we also ran state-stratified analyses to evaluate confounding and possible differences by state.

Table 3 shows associations of RA with between tasks performed at least once per year by applicators. An elevated, non-statistically significant, association was seen for RA with replacing asbestos brakes (HR=1.23; 95%CI 0.86 to 1.75). Most state-stratified estimate were similar (Supplemental Table 3), though RA associations with welding (HR=2.23; 95%CI 0.86 to 5.78) and painting (HR=1.72; 95%CI 0.76 to 3.91) were elevated in older applicators from Iowa.

Table 4 shows associations of RA with regular field work and other farm tasks, overall (spouses and applicators combined) and in applicators only. RA was associated with applying chemical fertilizer (HR=1.50; 95%CI 1.11 to 2.02), and in older applicators, with driving combines/mechanical harvesters (HR=2.46; 95%CI 1.05 to 5.78), milking cows (HR=2.56; 95%CI 1.01 to 6.53) and grinding animal feed (HR=1.90; 95%CI 0.99 to 3.62). Exposure response trends were not seen for most tasks overall, though some individual HRs were elevated for more frequent work (Supplemental Table 4). However, trends differed by age for driving a combine/machine harvesting, with lower risk for more days per year in younger participants, and higher risk for more days driving combines/machine harvesting (Supplemental Table 5). Associations in spouses were like the overall sample (Supplemental Table 6). No consistent differences by state were seen (Supplemental Table 7). Planting and chemical fertilizer use were commonly reported together, and associations were stronger for this combination rather than with fertilizer or planting alone (HR=1.53 both, vs. 1.36 fertilizer only and 1.02 planting only (Supplemental Table 8).

In the combined sample with data on regular farm tasks, associations with RA were seen for using (non-gasoline) solvents to clean (HR=1.40; 95%CI 1.09 to 1.80), and painting (HR=1.26; 95%CI 1.00 to 1.59)(Table 4). Exposure response trends were not seen for most tasks (Supplemental Table 4); however, elevated associations were seen for frequently (weekly) grinding animal feed (HR=1.56; 95%CI 0.96 to 2.54), welding (HR=1.52; 95%CI 0.90 to 2.57), and using solvents to clean (HR=1.83; 95%CI 0.84 to 3.98). Frequent painting was associated with RA in applicators (HR=2.55; 95%CI 1.10 to 5.89), but the overall association of RA with any regular painting was stronger in spouses (HR=1.46; 95%CI 1.07 to 2.01; Supplemental Table 7) than applicators (HR=0.98; 95%CI 0.67 to 1.43)(interaction p=0.055). An association with RA with painting and solvents was most apparent in participants who reported both (HR=1.44; 95%CI 1.09 to 1.90), though elevated HRs were seen for solvents only, overall and in applicators (HR=1.34 and 1.41, respectively; Supplemental Table 8).

Sensitivity analyses showed minor impact of excluding cases diagnosed during the first two years follow-up (n=51 cases; not shown).

DISCUSSION

Our results indicate that a variety of agricultural tasks may be associated with developing RA. Including new data on applicators and increasing the number of incident cases, we confirmed our previously reported associations in female spouses between RA and the use of chemical fertilizers, cleaning with solvents, and painting. New results included associations with RA that varied by age; for example, raising animals or hay in younger participants and driving combines in older applicators. Together, these findings provide evidence of several potential etiologic exposures, other than pesticides, arising from various aspects of fieldwork, animal care, and equipment and facility maintenance, that may contribute to the development of RA.

The association of chemical fertilizers with RA in the present study corroborates our earlier findings in female spouses (13). A previous case-control study also reported an association with fertilizers and RA in men, but did not specify the type of fertilizer (12). Chemical fertilizers are concentrated formulations of common ingredients, including nitrogen, phosphorus and potassium compounds, and sometimes other micronutrients, which are typically applied during field preparation and at different times during the early crop growth. We did not have information on the type of chemical fertilizer reported at enrollment. The first follow-up questionnaire (Phase 2, 1999–2003) provided more detailed data on chemical fertilizers in applicators: the most common types reported were regular/complete fertilizer, anhydrous ammonia, and liquid nitrogen. Our sample size was too small to support a more complex analysis of RA and fertilizer use characteristics reported in Phase 2 by applicators only.

Fertilizers are well-known as sources of nitrates and can be respiratory irritants, but immune effects are not well known. A previous commentary suggested that the association of RA with chemical fertilizers may be due to heavy metal contamination during the mining of phosphates (28, 29). However, levels of cadmium and other metals in commercial fertilizers are highly variable (30), and organic manures used as natural fertilizers may also be a source of heavy metals (31). We did not see an overall association of RA with use of manure. Fertilizers may also be combined with pesticides for some applications, or common equipment may be contaminated (32); unrecognized exposures due to contamination may be a concern, especially absence of protective gear. Chemical fertilizer use was related to the use of more pesticides in spouses (23), but specific pesticides did not confound the observed association of RA with chemical fertilizers. Fertilizer use may coincide with other exposures during field work, such as planting and tilling, which were modestly associated with RA in applicators. In applicators, chemical fertilizers and planting were reported by most (83%), with too few unexposed to be able to evaluate their joint effects on RA risk.

The observed associations of RA with solvents and painting confirm results from our previous analysis of RA in female spouses (13). Organic solvents have been related to other types of autoimmune diseases, but evidence is limited for RA (33). The overall association of RA with painting was more apparent in spouses than applicators, through an elevated hazard was associated with frequent painting in applicators. Solvent use and painting may include exposures to volatile organic compounds (also found in cigarette smoke), and solvents can have irritating respiratory effects as well as neurologic and immunologic effects (34). Solvents are used to clean hands, prepare for painting, and to degrease and lubricate engines. Painting may include other types of exposures. In addition to oil-based paints, epoxies or resin-based aluminum paints may be used for reflectivity on grain bins and silos. In addition to solvents, sandblasting may be used to clean surfaces prior to painting, leading to likely exposure to silica dust.

Respirable exposure to crystalline silica (quartz) dust, a widespread occupational hazard, is an established risk factor for RA and other systemic autoimmune diseases (15). Asbestos, amorphous silica, is another mineral dust that has been associated with RA (12, 35), and in applicators replacing asbestos brakes was modestly associated with RA. The percent quartz in some NC soils is high, and some tasks may result in elevated silica exposure (36, 37). But we noted no evidence of RA associations with crops we thought might be related to higher silica exposure (i.e., peanuts and tobacco in North Carolina). More detailed data are needed to assess agricultural and occupational silica exposure (36, 38), and analyses also will need to consider smoking as a susceptibility factor, requiring a larger sample size of male cases, who were more likely to smoke.

Compared with growing crops alone, raising animals in addition to crops was inversely associated with RA in younger participants, especially spouses. Inverse associations were also seen for raising hay in younger participants, and with beef cattle, overall. By contrast, in older applicators, we saw increased associations for other animal-related tasks, such as milking cows and grinding feed. Silage is a type of animal feed often made of fermented alfalfa hay and sometimes other crops; and alfalfa and field corn were positively associated with RA in older participants. A previous study suggested RA in men was associated with handling forage (12). Together, these results suggest a possible role for organic dust exposures in developing RA, with differential effects depending on the timing of exposure, extending our previous findings in female spouses suggesting early life plus adult livestock exposure may be protective for RA (13). Most applicators had a childhood farm residence, so the positive associations of RA with animal-associated tasks in older participants are notable. Respiratory exposure to organic dusts can influence the immune system through constituents such as endotoxin or peptidoglycans in Gram-positive bacteria (39). The lung is a site of mucosal events thought to contribute to the development of RA (40), and smokers may be more susceptibility to the effects of organic dusts on RA risk. In a controlled laboratory setting, smokers exposed to lipopolysaccharide had acute pulmonary inflammation and alveolar epithelial injury (41), suggesting mechanisms by which organic dusts might contribute to lung-associated pathology in the development of RA.

As with all observational studies, ours has strengths and limitations. Strengths included detailed and prospective data on a diverse range of tasks and exposures other than pesticides. The low incidence of RA was a limiting factor, however, and only half of the applicators provided data on regular tasks. For most tasks there was insufficient sample size or heterogeneity to address questions of exposure-response, multiple exposures, or interactions. Many tasks are often sporadic, and fewer participants reported frequent regular tasks. For example, in the enrollment questionnaire, 67% of applicators reporting painting at least once per year, which was not associated with RA, while in the “take-home” questionnaire 4% of applicators reported frequent painting, which was associated with RA. False-positive associations are possible given the number of comparisons made; however, we did not adjust for multiple comparisons, given the exploratory nature of the research, and instead present results in the context of existing knowledge, highlighting the patterns or novelty of observed associations.

The AHS cohort is a unique group of licensed pesticide applicators and their spouses who share an agricultural background. Results may not be generalizable to other populations. Our study sample was limited to participants remaining in the cohort after administrative censoring and loss to follow-up due to mortality and non-response. In prior examples of smoking-associated cancers in AHS, loss to follow-up was impactful only when both factors were very strong predictors of disease risk and follow-up (e.g., smoking and lung cancer) (42). In this example, loss to follow-up in AHS was related to age (younger and older) and being from North Carolina, but weighting for these and other factors had marginal ability to correct biased estimates, and personal pesticide use and raising animals were not strongly related to loss to follow-up (42). We confirmed known associations of RA with age and smoking in this sample. Our models adjusted for these and other covariates, and we ruled out confounding by specific pesticides (13, 20). Other factors may be related to field work and other farm tasks; but we are not aware of any of sufficient strength to confound the observed results. We adjusted for state, which is related to different crops; but state-stratified models did not suggest over-adjustment. RA was not associated with baseline days per year of field work in female spouses (11), but lifetime use of multiple pesticides (14+) was associated with RA in older male applicators (18). We did not adjust for the total number of pesticides, as this may reflect greater cumulative exposure to other farm tasks. Our data were limited to crops and task in the most recent year or growing season at enrollment. We lacked data on the duration and types of farming tasks over the lifespan. For several tasks, increased associations were seen in older applicators, which may reflect cumulative exposures.

Farmers (and often spouses) need to perform work on the farm, regardless of health, though health problems may lead to reduction in physically demanding tasks. New onset inflammatory arthritis typically progresses to diagnosed disease within a few months; but in some individuals RA symptoms may come on gradually and could lead to changes in farming tasks or reporting bias. Sensitivity analyses showed minor impact of excluding cases diagnosed in the first two years of follow-up. Some misclassification of RA is likely. Because self-reported RA is notoriously non-specific, we limited our analyses to cases confirmed by reported use of DMARDs or physicians/medical records. This definition is specific for clinical RA, but may not identify cases in populations less likely to use DMARDs, e.g., older males (43, 44). If factors related to DMARD use were also related to farming tasks and exposures, we may have missed some associations. Our results may not be generalizable to all RA cases in this population. Growing evidence suggests RA is a syndrome comprising different phenotypes with underlying pathogenesis and risk factors dependent on whether patients express specific autoantibodies (e.g., anti-citrullinated protein antibodies). We did not have these data, as cases were unable to accurately report antibody status.

In sum, our study provides novel evidence that multiple types of agricultural tasks and exposures other than pesticides contribute to risk of RA in farmers. Further research with a larger number of cases is warranted to better understand the role of individual exposures and dose-response for associations with fertilizers, solvents, inorganic and organic dusts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

What is already known about this subject?

Previous research has shown an association of farming occupation with RA, but little is known regarding the role of non-pesticide agricultural exposures.

What are the new findings?

In the Agricultural Health Study cohort, we saw elevated risk of RA in participants associated with reported use of solvents and chemical fertilizers in farmers and their spouses after accounting for key covariates and pesticide use.

How might this impact on policy or clinical practice in the foreseeable future?

These findings highlight the potential role of diverse occupational exposures in risk of developing rheumatoid arthritis in agricultural settings, supporting the collection of occupational histories from patients in clinical settings and epidemiologic research.

Table 1 –

Characteristics of incident RA cases and non-cases in licensed private pesticide applicators and spouses, Agricultural Health Study

At enrollment	Non-cases N=48928 N (%)	Incident RA N=478 N (%)	OR (95%CI)[1]
Age			
< 40	14995 (31)	93 (19)	Reference
40–49	14721 (30)	144 (30)	1.58 (1.21 to 2.05)
50–59	11495 (22)	156 (33)	2.19 (1.69 to 2.83)
60+	7717 (16)	85 (18)	1.78 (1.32 to 2.39)
Participant type			
Applicator	26946 (55)	229 (48)	Reference
Spouse	21982 (45)	249 (52)	1.34 (1.12 to 1.61)
Sex[2]			
Male	26246 (54)	220 (46)	Reference
Female	22682(46)	258 (54)	1.37 (1.14 to 1.64)
State			
IA	33782 (69)	273 (57)	Reference
NC	15146 (31)	205 (43)	1.58 (1.32 to 1.90)
Race/Ethnicity			
White	47691 (98)	461 (96)	Reference
Other	1195 (2.)	17 (4)	1.41 (0.86 to 2.29)
Education			
<= High School	24095 (49)	267 (56)	Reference
> High School	24833 (51)	211 (44)	0.85 (0.70 to 1.02)
Smoking status			
Never Smoked	32051 (66)	273 (57)	Reference
Past Smoker	11287 (23)	120 (25)	1.14 (0.92 to 1.42)
Current Smoker	5516 (11)	85 (18)	1.86 (1.46 to 2.38)
Pack-years cigarettes			
None	32051 (65)	273 (57)	Reference
<5 pack-years	5969 (12)	47 (10)	0.93 (0.68 to 1.27)
5–18 pack-years	5675 (12)	77 (16)	1.54 (1.20 to 1.99)
> 18 pack-years	5233 (11)	81 (17)	1.63 (1.27 to 2.11)

[1] Odds Ratios (OR) and 95% Confidence Intervals (CI), adjusting all other covariates by age.

[2] Of the males, 112 non-cases and no cases were spouses; of the females, 812 non-cases and 9 cases were applicators.

Table 2.

Incident RA in relation to crops and livestock at enrollment

	Overall sample (applicators and spouses) [1]		
Raised for income	**RA cases N=427 N (%)**	**HR[2] (95%CI)**	**P-value**
Crops only, ≤62	103 (37)	Reference	
>62	54 (36)	Reference	
Animals only, ≤62	5 (1)	0.83 (0.34 to 2.04)	0.69
>62	2 (0)	NC	---
Both, ≤62	148 (35)	0.68 (0.51 to 0.89)	0.005
>62	80 (19)	1.08 (0.75 to 1.55)	0.67
Neither, ≤62	23 (5)	1.16 (0.73 to 1.85)	0.53
>62	12 (3)	0.82 (0.43 to 1.56)	0.54
Crops[3]			
Alfalfa, ≤62	66 (15)	1.08 (0.80 to 1.49)	0.57
>62	39 (9)	1.66 (1.10 to 2.50)	0.015
Field corn, ≤62	203 (48)	0.92 (0.65 to 1.30)	0.64
>62	112 (26)	1.65 (1.05 to 2.61)	0.031
Hay, ≤62	72 (17)	0.71 (0.53 to 0.93)	0.014
>62	56 (13)	1.37 (0.97 to 1.92)	0.074
Oats	96 (22)	1.06 (0.31 to 1.35)	0.64
Soybeans	289 (68)	0.98 (0.77 to 1.25)	0.86
Sweet corn	45 (11)	1.25 (0.91 to 1.72)	0.18
Wheat	50 (12)	0.91 (0.66 to 1.26)	0.56
Livestock[2]			
Beef cattle	143 (33)	0.80 (0.65 to 0.83)	0.034
Hogs, ≤62	91 (21)	0.80 (0.60 to 1.06)	0.12
>62	37 (9)	1.06 (0.70 to 1.59)	0.79

[1] Numbers shown are for overall sample with complete data on pesticide covariates and diagnosis age, including all enrolled applicators (196 cases and 24357 non-cases) and spouses (231 cases and 20842 non-cases).

[2] Hazard ratios (HR) and 95% confidence intervals (CI) estimated by Cox proportional hazards model adjusting for state, participant type (applicator/spouse), smoking pack-years, education, and specific pesticides. Hazard ratios allowed to vary by the median age (i.e., 62 years) when proportional hazards assumption was not met (p≤0.10).

[3] Common crops or livestock (with at least 10% cases exposed)

Table 3.

Incident RA in relation to farm tasks reported by applicators at enrollment

Tasks (at least once per year)	RA cases N=196 N (%)	HR (95%CI)[1]
Veterinary services	97 (49)	0.83 (0.62 to 1.14)
Butcher animals	29 (15)	0.99 (0.66 to 1.50)
Work in swine areas	52 (26)	0.99 (0.70 to 1.41)
Work in poultry areas	5 (3)	0.64 (0.26 to 1.56)
Load/unload silage	43 (22)	1.15 (0.80 to 1.66)
Grind animal feed	92 (47)	1.12 (0.81 to 1.54)
Handle stored grain	133 (68)	0.96 (0.65 to 1.40)
Handle stored hay	108 (55)	0.93 (0.69 to 1.25)
Repair engines	92 (47)	1.10 (0.82 to 1.46)
Replace asbestos brakes	40 (20)	1.23 (0.86 to 1.75)
Weld	135 (69)	0.95 (0.68 to 1.23)
Paint	136 (69)	1.04 (0.80 to 1.43)
Repair pesticide equipment	131 (67)	0.95 (0.69 to 1.31)

[1]Results shown for enrolled applicators with complete data on pesticide covariates and diagnosis age (196 cases and 24357 non-cases).

[2]Hazard ratios (HR) and 95% confidence intervals (CI) estimated by cox proportional hazards model adjusting for state, participant type (applicator/spouse), smoking pack-years, education, and pesticides. Hazard ratios allowed to vary by the median age (i.e., 62 years) when proportional hazards assumption was not met (p≤0.10).

Table 4.

Incident RA in relation to regular field work and tasks at enrollment, overall and in applicators only

	Overall[1]			Applicators only[2]		
	RA Cases N=351 N (%)	HR (95% CI)[3]	P-value	RA Cases N=120 N (%)	HR (95% CI)[3]	P-value
Field work						
Till soil (cultivate, disc, plow)	163 (47)	1.02 (0.75 to 1.37)	0.92	111 (95)	1.32 (0.57 to 3.05)	0.52
Plant	183 (53)	1.23 (0.83 to 1.62)	0.14	110 (94)	1.31 (0.61 to 2.35)	0.49
Use natural fertilizer (manure)	105 (31)	1.04 (0.78 to 1.37)	0.79	70 (61)	1.09 (0.72 to 1.63)	0.69
Use chemical fertilizer	145 (42)	1.50 (1.11 to 2.02)	0.009	100 (85)	1.25 (0.66 to 1.88)	0.41
Drive combines, ≤62 years	116 (34)	1.03 (0.73 to 1.45)	0.86	47 (73)	0.59 (0.31 to 1.17)	0.13
>62 years				43 (84)	2.46 (1.05 to 5.78)	0.039
Handpick crops	114 (33)	1.17 (0.92 to 1.50)	0.21	46 (40)	1.21 (0.79 to 1.89)	0.37
Other tasks and exposures						
Milk cows, ≤62 years	6 (2)	0.59 (0.26 to 1.33)	0.20	2 (2)	NA	---
>62 years	6 (2)	1.83 (0.80 to 4.21)	0.15	5 (4)	2.56 (1.01 to 6.53)	0.049
Vet procedures, ≤62 years	66 (19)	0.92 (0.68 to 1.25)	0.61	22 (18)	0.71 (0.40 to 1.25)	0.23
>62 years				20 (17)	1.51 (0.82 to 2.79)	0.19
Grind feed, ≤62 years	63 (19)	1.14 (0.82 to 1.59)	0.43	26 (22)	1.00 (0.56 to 1.78)	0.43
>62 years				23 (19)	1.90 (0.99 to 3.62)	0.053
Drive trucks	158 (50)	0.94 (0.74to 1.19)	0.59	75 (36)	0.86 (0.64 to 1.15)	0.30
Diesel tractor, ≤62 years	106 (31)	0.78 (0.55 to 1.11)	0.17	83 (72)	1.02 (0.67 to 1.58)	0.91
>62 years	71 (20)	1.26 (0.78 to 2.04)	0.35			
Gasoline tractor	135 (44)	0.91 (0.70 to 1.17)	0.44	75 (64)	0.78 (0.53 to 1.16)	0.22
Welding	83 (25)	1.15 (0.78 to 1.69)	0.47	80 (63)	1.38 (0.90 to 2.11)	0.13
Repairing engines	59 (18)	1.19 (0.84 to 1.69)	0.32	56 (48)	1.29 (0.89 to 1.88)	0.18
Grind metal	87 (26)	1.11 (0.75 to 1.64)	0.62	81 (70)	1.12 (0.73 to 1.70)	0.61
Use gasoline to clean	83 (25)	1.06 (0.80 to 1.39)	0.70	47 (40)	1.03 (0.70 to 1.51)	0.89
Use other solvents to clean	91 (27)	**1.40 (1.09 to 1.80)**	0.009	34 (29)	1.26 (0.84 to 1.89)	0.26
Painting[4]	132 (39)	**1.26 (1.00 to 1.59)**	0.048	46 (39)	0.98 (0.67 to 1.43)	0.98

[1] Results shown for combined sample of applicators who completed the "take home" questionnaire (120 cases and 13436 non-cases) and enrolled spouses (231 cases and 20842 non-cases)

[2] Data from the applicator "take-home" questionnaire only.

[3] Hazard model adjusted for state, participant type (applicator/spouse), smoking pack-years, education, and pesticides; not applicable (NA) for less than 5 exposed cases. Hazard ratios allowed to vary by the median age (i.e., 62 years) when proportional hazards assumption was not met ($p \leq 0.10$).

[4] Interaction by sex, $p=0.055$, HR=1.42 in spouses (95%CI 1.07 to 1.89).