Research Article

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# Farm Characteristics, Allergy Symptoms, and Risk of Non-Hodgkin Lymphoid Neoplasms in the Agricultural Health Study

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## Abstract

**Background:** Because of unique exposures, studies among farmers may yield insights into the relationship between allergies and non-Hodgkin lymphoid (NHL) neoplasms. We evaluated farm characteristics, allergic symptoms and conditions, and risk of NHL including specific subtypes in the Agricultural Health Study, a prospective cohort of farmers and spouses from North Carolina and Iowa.

**Methods:** We identified 710 incident cases of NHL (including chronic lymphocytic leukemia and multiple myeloma) among 82,370 participants with baseline data on crop and animal exposures, including 454 cases among 52,850 participants with baseline data on recent allergy symptoms (rhinitis) and living on a farm during childhood. HR and 95% confidence intervals (CI) were calculated using multivariable-adjusted proportional hazards models.

**Results:** We observed reduced risks of NHL among farmers and spouses with rhinitis at baseline (HR, 0.63; 95% CI, 0.51–0.79), related to growing soybeans (HR, 0.80; 95% CI, 0.67–0.96), and among farmers who handled stored grains or hay (HR, 0.66; 95% CI, 0.52–0.82). Growing up on a farm was associated with increased NHL risk (HR, 1.51; 95% CI, 1.15–1.98). Results did not differ significantly by NHL subtype.

**Conclusions:** Both the reduced risk of NHL among those with allergy symptoms and specific farm exposures in adulthood, and the increased risk among those who grew up on a farm suggest that the host immune response to agricultural allergens may influence NHL development.

**Impact:** This prospective study is, to our knowledge, the first to investigate the relationship between allergy symptoms and NHL risk in farmers; confirmation of these findings in other farming populations is warranted. *Cancer Epidemiol Biomarkers Prev; 24(3); 587–94. ©2015 AACR.*



## Introduction

In recent years, there is growing evidence that the immune response to allergens differs between individuals growing up, living, or working on farms and those in urban areas (1). Farmers and their families are often highly exposed to various allergens including storage mites, proteins from domesticated animals or specific crops (grains, hay, or soybeans), and grass or tree pollens (2), and often at an early age. Multiple studies have demonstrated that living on a farm, particularly during childhood, is associated with a lower prevalence of allergic sensitization and allergic rhinitis that appears to persist into adulthood (1, 3–7), including one such report among female spouses in the Agricultural Health Study (AHS; ref. 8). It has been postulated that early childhood microbial exposures may influence the likelihood of atopic conditions later in life through several possible mechanisms, including persistent effects on T-helper type 1 and type 2 (Th1/Th2) balance, enhanced regulatory T (Treg) activity, and increased production of the anti-inflammatory cytokine IL10 (7, 9, 10).

Conditions and treatments involving severe immune dysregulation (e.g., AIDS, organ transplantation) are strong risk factors for non-Hodgkin lymphoid (NHL) neoplasms, although the role of more subtle immunologic effects in lymphomagenesis is less well understood (11). Having a history of allergic conditions has been associated with a reduced risk of NHL in several large case–control studies (12–14). However, results from prospective general population cohort studies have been inconsistent, with some finding no association between allergies and NHL (13, 15) and others observing an increased risk in certain population subgroups or for specific subtypes of hematologic malignancies (16–18). Notably, a recent cohort study found a reduced risk of lymphoid neoplasms in relation to allergic diseases among those living in rural areas, but not among those in urban areas (18).

We are unaware of any studies that have evaluated the associations between specific farm-related allergen exposures, allergic symptoms or conditions, and risk of NHL. We conducted such an investigation within the AHS, a large prospective cohort that includes farmers and their spouses in Iowa and North Carolina.

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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## Materials and Methods

### Study population

The design of the AHS has been described (19). Briefly, 52,394 private pesticide applicators (farmers) and 32,345 of their spouses were enrolled in Iowa and North Carolina between 1993 and 1997. The farmers were recruited and completed an enrollment questionnaire while attending mandatory certification sessions for applying restricted use pesticides. A subset of farmers completed and mailed in another "take-home" questionnaire designed to solicit more detailed information about certain exposures and health conditions. Spouses enrolled by completing and returning a questionnaire that was sent home with the farmers. For this analysis, we excluded 1,956 participants with a history of cancer at enrollment (1,045 farmers and 911 spouses), 119 participants who were under 18 years of age at enrollment (117 farmers and 2 spouses), and 294 participants living outside Iowa or North Carolina at the time of enrollment (181 farmers and 113 spouses). This left 82,370 participants for the overall analyses and 52,850 participants for the analyses restricted to spouses ($N = 31,319$) and farmers who completed the take-home questionnaire ($N = 21,531$).

The study protocol was approved by the Institutional Review Boards of the NIH (Bethesda, MD) and other relevant institutions.

### Characterization of farm exposures and allergies

Information about farm exposures and allergic symptoms and conditions was ascertained from the enrollment and take-home questionnaires (available from: http://aghealth.nih.gov). On the enrollment questionnaire, farmers were asked about current crops and animals on the farm. We used these data to characterize exposures to common crops (e.g., grains or hay, soybeans) and the type and number of livestock and poultry for both the farmers and their spouses. At enrollment, farmers were asked whether they handled stored grain or hay at least once per year. On the farmer take-home and the spouse questionnaires, participants were asked whether they had symptoms of rhinitis (stuffy, itchy, or runny nose) or viral/infectious conditions that produce nasal symptoms (e.g., cold, flu, sinusitis, or sinus problems) in the past 12 months. Those who reported having rhinitis were asked to specify the number of episodes in the past 12 months and whether symptoms worsened after working with grains and hay. The farmer take-home and spouse questionnaires also included questions about history of atopic conditions (hay fever, eczema) diagnosed by a physician, and whether the participant grew up on a farm (defined as having spent half of their life up to 18 years of age living on a farm). The wording of the questions on rhinitis, atopic conditions, and growing up on a farm is provided in Supplementary Table S1. All participants were asked to provide other information including a history of cancer in first-degree relatives, alcohol consumption, smoking history, and height and weight.

### Cohort follow-up and case ascertainment

Incident cases of NHL were identified through the Iowa and North Carolina state cancer registries and vital status was determined through state mortality registries and the National Death Index. Observation time began at enrollment (the date that the questionnaire was completed) and ended when the participant was diagnosed with any cancer, died, moved out of state, or when follow-up ended (December 31, 2011 in Iowa and December 31, 2010 in North Carolina), whichever came first. NHL and the following B-cell subtypes were defined according to the classifications proposed by the Pathology Working Group of the International Lymphoma Epidemiology Consortium (20): diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and multiple myeloma.

### Statistical analysis

Analyses were conducted for overall NHL risk and risk of specific NHL subtypes as defined above. HRs and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression, with attained age as the underlying time metric. The proportional hazards assumption was met for all analyses ($P > 0.05$). All analyses were performed using a base model adjusting for sex, state of residence (Iowa, North Carolina), race (non-Hispanic white, other/missing), family history of lymphohematopoietic malignancies (no, yes, missing), alcohol consumption (none, <5 drinks/month, ≥5 drinks/month, missing), smoking status (never, former, current, missing), and body mass index (<25 kg/m$^2$, 25–29.9 kg/m$^2$, ≥30 kg/m$^2$, missing). Analyses of rhinitis were further adjusted for viral/infectious conditions that produce nasal symptoms (cold, flu, and sinusitis or sinus problems) and for growing up on a farm. For the main analyses of growing up on a farm, we reported the results without adjustment for rhinitis (because childhood farm exposure could possibly influence NHL risk through its immunomodulatory effects on allergic disease development); however, analyses adjusting for rhinitis were also performed. We assessed trends for ordered categorical variables (coded as 0, 1, 2) using Wald tests. To evaluate multiplicative interaction between the main exposures of interest, we performed Wald tests assessing the joint significance of specific cross-product terms. We also performed the main analyses separately for farmers and spouses and by state of residence (Iowa or North Carolina), and repeated the analyses using a 10-year lag period after enrollment. Analyses of specific NHL subtypes (DLBCL, FL, CLL/SLL, and multiple myeloma) were repeated using polytomous logistic regression models adjusting for the same set of covariates to assess heterogeneity in the risk estimates across subtypes.

All statistical analyses were performed using Stata version 11.0 (StataCorp). Findings were considered statistically significant if two-sided $P$ values were <0.05.

## Results

Baseline characteristics of the overall cohort and the subset of farmers and spouses with information on allergies and childhood farm exposure are reported in Table 1. A total of 710 first primary incident cases of NHL (DLBCL, $N = 162$; FL, $N = 103$; CLL/SLL, $N = 179$; and multiple myeloma, $N = 131$) were observed during 1,205,842 person-years of follow-up in the overall cohort, including 454 cases (DLBCL, $N = 106$; FL, $N = 69$; CLL/SLL, $N = 106$; and multiple myeloma, $N = 86$) during 769,160 person-years of follow-up among the farmer take-home questionnaire respondents and spouses.

Among the farmers and spouses included in this investigation, 81% worked or lived on farms growing grains or hay and 68% on farms growing soybeans; 63% raised livestock and 9% raised poultry; and 75% of farmers reported handling stored grains or hay at least once per year (Table 2). Among the farmer take-home

**Table 1.** Baseline characteristics of study participants[a]

| | Overall cohort | | Participants with information on allergies and childhood farm exposure | | | |
|---|---|---|---|---|---|---|
| | | | Farmers | | Spouses | |
| Characteristic | NHL cases | Non-cases | NHL cases | Non-cases | NHL cases | Non-cases |
| Type of study participant | | | | | | |
| Farmer | 502 (70.7) | 50,549 (61.9) | 246 (100) | 21,285 (100) | | |
| Spouse | 208 (29.3) | 31,111 (38.1) | | | 208 (100) | 31,111 (100) |
| Age at enrollment | | | | | | |
| <40 | 48 (6.8) | 26,178 (32.1) | 10 (4.1) | 5,746 (27.0) | 13 (6.3) | 9,840 (31.6) |
| 40–49 | 132 (18.6) | 22,829 (28.0) | 39 (15.9) | 5,597 (26.3) | 40 (19.2) | 8,969 (28.8) |
| 50–59 | 232 (32.7) | 18,005 (22.1) | 81 (32.9) | 4,930 (23.2) | 74 (35.6) | 7,250 (23.3) |
| 60–69 | 215 (30.3) | 11,251 (13.8) | 79 (32.1) | 3,748 (17.6) | 63 (30.3) | 4,051 (13.0) |
| 70+ | 83 (11.7) | 3,397 (4.2) | 37 (15.0) | 1,264 (5.9) | 18 (8.7) | 1,001 (3.2) |
| Sex | | | | | | |
| Female | 215 (30.3) | 32,227 (39.5) | 5 (2.0) | 525 (2.5) | 205 (98.6) | 30,901 (99.3) |
| Male | 495 (69.7) | 49,433 (60.5) | 241 (98.0) | 20,760 (97.5) | 3 (1.4) | 210 (0.7) |
| State of residence | | | | | | |
| North Carolina | 255 (35.9) | 30,134 (36.9) | 83 (33.7) | 7,502 (35.3) | 61 (29.3) | 10,281 (33.1) |
| Iowa | 455 (64.1) | 51,526 (63.1) | 163 (66.3) | 13,783 (64.8) | 147 (70.7) | 20,830 (67.0) |
| Race | | | | | | |
| White | 691 (97.3) | 77,734 (95.2) | 242 (98.4) | 20,408 (95.9) | 203 (97.6) | 29,728 (95.6) |
| Other/missing | 19 (2.7) | 3,926 (4.8) | 4 (1.6) | 877 (4.1) | 5 (2.4) | 1,383 (4.5) |
| Family history of lymphohematopoietic cancer | | | | | | |
| No | 595 (83.8) | 70,964 (86.9) | 212 (86.2) | 18,453 (86.7) | 173 (83.2) | 27,807 (89.4) |
| Yes | 42 (5.9) | 3,765 (4.6) | 14 (5.7) | 985 (4.6) | 17 (8.2) | 1,666 (5.4) |
| Missing | 73 (10.3) | 6,931 (8.5) | 20 (8.1) | 1,847 (8.7) | 18 (8.7) | 1,638 (5.3) |
| Level of education | | | | | | |
| High school or less | 401 (56.5) | 40,483 (49.6) | 143 (58.1) | 11,599 (54.5) | 91 (43.8) | 12,359 (39.7) |
| Vocational school or some college | 161 (22.7) | 20,000 (24.5) | 57 (23.2) | 4,877 (22.9) | 56 (26.9) | 8,225 (26.4) |
| College graduate | 108 (15.2) | 14,815 (18.1) | 41 (16.7) | 3,810 (17.9) | 35 (16.8) | 6,462 (20.8) |
| Missing | 40 (5.6) | 6,362 (7.8) | 5 (2.0) | 999 (4.7) | 26 (12.5) | 4,065 (13.1) |
| Alcohol consumption | | | | | | |
| None | 304 (42.8) | 29,525 (36.2) | 105 (42.7) | 7,184 (33.8) | 103 (49.5) | 13,468 (43.3) |
| <5 drinks/mo | 186 (26.2) | 24,669 (30.2) | 61 (24.8) | 5,750 (27.0) | 61 (29.3) | 11,830 (38.0) |
| 5+ drinks/mo | 163 (23.0) | 22,308 (27.3) | 67 (27.2) | 7,123 (33.5) | 28 (13.5) | 4,427 (14.2) |
| Missing | 57 (8.0) | 5,158 (6.3) | 13 (5.3) | 1,228 (5.8) | 16 (7.7) | 1,386 (4.5) |
| Smoking status | | | | | | |
| Never | 393 (55.4) | 47,188 (57.8) | 121 (49.2) | 11,195 (52.6) | 145 (69.7) | 21,150 (68.0) |
| Former | 211 (29.7) | 19,903 (24.4) | 93 (37.8) | 6,633 (31.2) | 31 (14.9) | 5,095 (16.4) |
| Current | 70 (9.9) | 10,973 (13.4) | 23 (9.4) | 2,703 (12.7) | 15 (7.2) | 3,092 (9.9) |
| Missing | 36 (5.1) | 3,596 (4.4) | 9 (3.7) | 754 (3.5) | 17 (8.2) | 1,774 (5.7) |
| Body mass index, kg/m$^2$ | | | | | | |
| <25 | 173 (24.4) | 23,230 (28.5) | 56 (22.8) | 5,391 (26.3) | 81 (38.9) | 13,403 (43.1) |
| 25–29.9 | 288 (40.6) | 27,817 (34.1) | 130 (52.9) | 10,174 (49.7) | 74 (35.6) | 8,745 (28.1) |
| 30+ | 114 (16.1) | 13,910 (17.0) | 56 (22.8) | 4,636 (22.6) | 25 (12.0) | 5,091 (16.4) |
| Missing | 135 (19.0) | 16,703 (20.5) | 4 (1.6) | 276 (1.4) | 28 (13.5) | 3,872 (12.5) |
| NHL subtypes | | | | | | |
| DLBCL | 162 (28.2) | | 57 (27.7) | | 49 (30.4) | |
| FL | 103 (17.9) | | 29 (14.1) | | 40 (24.8) | |
| CLL/SLL | 179 (31.1) | | 69 (33.5) | | 37 (23.0) | |
| Multiple myeloma | 131 (22.8) | | 51 (24.8) | | 35 (21.7) | |

[a]Reported as frequencies (column percentages).

questionnaire respondents and the spouses, 73% grew up on a farm (92% of farmers and 60% of spouses) and 65% experienced rhinitis at baseline in the last 12 months (67% of farmers and 63% of spouses; Table 3). The prevalence of rhinitis was modestly lower among those who grew up on a farm (64% vs. 67%, $P < 0.001$), and was significantly higher among the farmers who handled stored grains or hay compared with those who did not (69% vs. 60%, $P < 0.001$; Supplementary Table S2).

Associations with NHL for selected crop and animal exposures are summarized in Table 2. Farmers and spouses on farms growing grains/hay or soybeans had a modestly reduced risk of NHL overall, although only soybeans reached statistical significance (HR, 0.80; 95% CI, 0.67–0.96). We also observed a reduced risk of NHL among those on farms raising ≥50 poultry (HR, 0.61; 95% CI, 0.38–0.96). Among farmers, those who handled stored grains or hay had a statistically significantly reduced risk of NHL compared with those who did not (HR, 0.66; 95% CI, 0.52–0.82). These findings did not differ by NHL subtype ($P_{het} \geq 0.10$; Supplementary Table S3).

As summarized in Table 3, we observed a reduced risk of NHL among those who reported rhinitis at baseline (HR, 0.63; 95% CI, 0.51–0.79), and an increased risk of NHL among those who grew up on a farm (HR, 1.51; 95% CI, 1.15–1.98). These associations remained unchanged after restricting to NHL cases diagnosed at least 10 years after enrollment (rhinitis: HR, 0.57; 95% CI, 0.43–0.75; growing up on a farm: HR, 1.52; 95% CI, 1.01–2.28). After further adjustment for rhinitis, the association between growing up on a farm and risk of NHL was largely unchanged (HR, 1.44; 95% CI, 1.09–1.89). The inverse association between allergy symptoms and NHL risk was stronger among those who reported more frequent episodes of rhinitis in the last 12 months (≥3 episodes: HR, 0.59; 95% CI, 0.46–0.77; $P_{trend} < 0.001$). Having a history of physician-diagnosed hay fever or eczema was also associated with a reduced risk of NHL (HR, 0.61; 95% CI, 0.42–0.87). These findings were generally similar for farmers and spouses, although few farmers were not raised on a farm ($N_{cases} = 14$). Results were consistent for participants in Iowa and North Carolina (Supplementary Table S4), and further adjustment for specific crops and animals and exclusion of records with missing covariate data did not change these results (data not shown). For specific NHL subtypes (Table 4), we observed statistically significant inverse associations with rhinitis for CLL/SLL (HR, 0.62; 95% CI, 0.40–0.97) and multiple myeloma (HR, 0.50; 95% CI, 0.30–0.83) but not for DLBCL (HR, 0.82; 95% CI, 0.51–1.33) or FL (HR, 0.69; 95% CI, 0.39–1.22); differences in risk estimates were not statistically significant ($P_{het} = 0.56$). For growing up on a farm, the risk estimates for specific NHL subtypes ranged from 1.51 to 1.83 ($P_{het} = 0.98$), although none of the subtype-specific findings achieved statistical significance.

**Table 2.** Crop and animal exposures at enrollment and risk of NHL neoplasms among farmers and spouses in the AHS[a]

| | Overall | | | Farmers | | | Spouses | | |
|---|---|---|---|---|---|---|---|---|---|
| **Exposure** | **Cases** | **Non-cases** | **HR (95% CI)** | **Cases** | **Non-cases** | **HR (95% CI)** | **Cases** | **Non-cases** | **HR (95% CI)** |
| *Crops grown* | | | | | | | | | |
| Grains or hay[b] | | | | | | | | | |
| No | 148 (21.1) | 15,571 (19.2) | 1.00 (Ref.) | 112 (22.3) | 10,390 (20.6) | 1.00 (Ref.) | 36 (17.9) | 5,181 (17.0) | 1.00 (Ref.) |
| Yes | 555 (79.0) | 65,415 (80.8) | 0.84 (0.68–1.04) | 390 (77.7) | 40,159 (79.5) | 0.83 (0.65–1.08) | 165 (82.1) | 25,256 (83.0) | 0.80 (0.52–1.22) |
| Soybeans | | | | | | | | | |
| No | 248 (35.3) | 25,656 (31.7) | 1.00 (Ref.) | 184 (36.7) | 16,683 (33.0) | 1.00 (Ref.) | 64 (31.8) | 8,973 (29.5) | 1.00 (Ref.) |
| Yes | 455 (64.7) | 55,330 (68.3) | 0.80 (0.67–0.96) | 318 (63.4) | 33,866 (67.0) | 0.80 (0.65–0.99) | 137 (68.2) | 21,464 (70.5) | 0.78 (0.56–1.10) |
| *Animals raised* | | | | | | | | | |
| Livestock[c] | | | | | | | | | |
| No | 274 (39.0) | 29,855 (36.9) | 1.00 (Ref.) | 204 (40.6) | 19,307 (38.2) | 1.00 (Ref.) | 70 (34.8) | 10,548 (34.7) | 1.00 (Ref.) |
| Yes[d] | 429 (61.0) | 51,131 (63.1) | 0.87 (0.74–1.02) | 298 (59.4) | 31,242 (61.8) | 0.85 (0.70–1.03) | 131 (65.2) | 19,889 (65.3) | 0.91 (0.67–1.24) |
| <500 | 242 (35.3) | 29,796 (37.6) | 0.85 (0.71–1.01) | 165 (33.8) | 18,393 (37.2) | 0.79 (0.64–0.98) | 77 (39.1) | 11,403 (38.2) | 0.94 (0.68–1.31) |
| ≥500 | 162 (23.7) | 18,816 (23.7) | 0.87 (0.71–1.08) | 113 (23.2) | 11,222 (22.7) | 0.88 (0.68–1.13) | 49 (24.9) | 7,594 (25.4) | 0.85 (0.57–1.26) |
| | | | $P_{trend} = 0.17$ | | | $P_{trend} = 0.21$ | | | $P_{trend} = 0.43$ |
| Poultry[e] | | | | | | | | | |
| No | 644 (91.6) | 73,781 (91.1) | 1.00 (Ref.) | 456 (90.8) | 46,084 (91.2) | 1.00 (Ref.) | 188 (93.5) | 27,697 (91.0) | 1.00 (Ref.) |
| Yes[d] | 59 (8.4) | 7,205 (8.9) | 0.93 (0.71–1.21) | 46 (9.2) | 4,465 (8.8) | 1.02 (0.75–1.38) | 13 (6.5) | 2,740 (9.0) | 0.69 (0.39–1.21) |
| <50 | 36 (5.1) | 3,334 (4.1) | 1.22 (0.87–1.71) | 27 (5.4) | 2,061 (4.1) | 1.29 (0.88–1.91) | 9 (4.5) | 1,273 (4.2) | 1.01 (0.52–1.97) |
| ≥50 | 19 (2.7) | 3,552 (4.4) | 0.61 (0.38–0.96) | 16 (3.2) | 2,184 (4.3) | 0.72 (0.44–1.19) | 3 (1.5) | 1,368 (4.5) | 0.32 (0.10–1.00) |
| | | | $P_{trend} = 0.14$ | | | $P_{trend} = 0.53$ | | | $P_{trend} = 0.07$ |
| *Handling stored grain or hay*[f] | | | | | | | | | |
| Handled stored grain or hay at least once per year | | | | | | | | | |
| No | | | | 149 (29.7) | 12,462 (24.7) | 1.00 (Ref.) | | | |
| Yes | | | | 353 (70.3) | 38,087 (75.4) | 0.66 (0.52–0.82) | | | |
| Combined variable for growing and handling stored grains/hay | | | | | | | | | |
| Neither | | | | 83 (16.5) | 7,055 (14.0) | 1.00 (Ref.) | | | |
| Growing grains/hay | | | | 66 (13.2) | 5,407 (10.7) | 0.95 (0.67–1.34) | | | |
| Handling stored grains/hay | | | | 29 (5.8) | 3,335 (6.6) | 0.65 (0.42–1.01) | | | |
| Both | | | | 324 (64.5) | 34,752 (68.8) | 0.64 (0.47–0.86) | | | |

[a]Age as underlying time metric in all analyses, with adjustment for sex, state of residence, race, family history of lymphohematopoietic cancer, alcohol consumption, smoking status, and BMI. The reported frequencies may not sum to the total number of study subjects due to missing data.
[b]Includes the following crops: corn, oats, wheat, sorghum, other small grains, hay, or alfalfa.
[c]Includes dairy cattle, beef cattle, hogs/swine, sheep, and other farm animals.
[d]Frequencies for number of livestock or poultry do not sum to the total in this category due to missing data for some participants.
[e]Includes poultry or poultry for eggs.
[f]Restricted to farmers only.

In Table 5, we observed stronger inverse associations with overall NHL risk among those who had allergy symptoms and did not grow up on a farm (HR, 0.47; 95% CI, 0.33–0.69) and among those whose allergy symptoms worsened after working with grains or hay (HR, 0.58; 95% CI, 0.43–0.78; $P_{\text{trend}} < 0.001$). In joint analyses with crop and animal exposures, the reduction in NHL risk was generally greatest among those who had rhinitis in combination with specific farm exposures, although tests of interaction with these exposures were not statistically significant ($P_{\text{interaction}} \geq 0.14$).

## Discussion

Numerous studies have demonstrated that farm exposures, particularly during early childhood, may be associated with a reduction in allergic disease development (1, 3–8). However, whether such exposures or their resulting allergy-related immunomodulatory effects influence NHL development remains poorly understood, and the relationship between allergies or exposure to allergens in the agricultural environment and risk of NHL among individuals growing up, living, and/or working on farms needs further evaluation. This is, to our knowledge, the first prospective study to investigate allergic symptoms and conditions and risk of NHL in an adult farming population. We found that future risk of NHL was decreased among individuals reporting allergy symptoms at baseline, in particular for CLL/SLL and multiple myeloma; these findings support the hypothesis that altered immunologic response to allergens may play a role in the etiology of lymphoid malignancies (11). We also observed an increased risk of NHL among those who grew up on a farm, which is consistent with one prior report on hematologic cancer mortality in New Zealand (21). Given that early life farm exposures have been linked to a reduced burden of allergic disease that persists into adulthood, we speculate that the allergy-suppressive immunomodulatory effects of early life farm exposures might underlie this association with NHL risk. In support of this, we note that individuals who had allergy symptoms and did not grow up on a farm had the lowest risk of developing NHL.

Reduced risks of NHL were also observed for some farming exposures in adulthood, particularly for handling stored grains or hay, an activity that is likely to involve substantial exposure to allergens and other microbial products (2, 22). Growing soybeans and raising ≥50 poultry were also associated with reduced NHL risk. In a previous report among male farmers in the AHS (23), raising poultry was associated with an increased risk of NHL ($N = 23$ exposed cases), although there was not increased risk with larger flock sizes. An older definition of NHL that did not include multiple myeloma or most CLL/SLL cases was used in the previous investigation; when we repeated our analyses using the same definition, risk was modestly elevated among male poultry farmers, although no longer statistically significant with additional years of follow-up ($N = 33$ exposed cases, HR, 1.3; 95% CI, 0.9–1.9).

There is some evidence of a protective effect of occupational allergen exposures (estimated by job-exposure matrices) in case–control studies of lymphoma, although these studies were not focused specifically on allergens in the farm environment. Two studies reported a reduced risk of lymphoma among those with occupational allergen exposures (24, 25), although a previous investigation in Spain found no association (26). These studies did not assess the relationship between allergy symptoms and lymphoma.

A number of large case–control studies have reported inverse associations between atopic conditions and NHL (11–14), and levels of specific immunoglobulin classes (including IgE) are reduced among patients with NHL (27). Findings from cohort studies in the general population have been inconsistent, although the definitions of allergies and NHL/subtypes varied between studies (13, 15–18). In a nested case–control study within the Finnish Maternity Cohort (13), risk of NHL was reduced in relation to specific IgE seropositivity in samples collected shortly before NHL diagnosis but not in samples collected ≥10 years before diagnosis. A history of physician-diagnosed allergic conditions (including asthma, hay fever, and other allergies) was not associated with risk of NHL in the Multiethnic Cohort (16), and there was no evidence of increased mortality from NHL or multiple myeloma among

**Table 3.** Allergy symptoms at enrollment, growing up on a farm, and risk of NHL neoplasms among farmers and spouses in the AHS[a]

| | Overall | | | Farmers | | | Spouses | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases | Non-cases | HR (95% CI) | Cases | Non-cases | HR (95% CI) | Cases | Non-cases | HR (95% CI) |
| Rhinitis in the last 12 mo[b] | | | | | | | | | |
| No | 198 (46.8) | 17,442 (34.9) | 1.00 (Ref.) | 104 (44.6) | 6,705 (32.7) | 1.00 (Ref.) | 94 (49.5) | 10,737 (36.5) | 1.00 (Ref.) |
| Yes | 225 (53.2) | 32,496 (65.1) | 0.63 (0.51–0.79) | 129 (55.4) | 13,774 (67.3) | 0.70 (0.51–0.95) | 96 (50.5) | 18,722 (63.6) | 0.58 (0.42–0.80) |
| Number of rhinitis episodes in the last 12 mo[b] | | | | | | | | | |
| None | 198 (47.1) | 17,442 (35.4) | 1.00 (Ref.) | 104 (44.8) | 6,705 (33.2) | 1.00 (Ref.) | 94 (50.0) | 10,737 (37.0) | 1.00 (Ref.) |
| 1–2 | 101 (24.1) | 13,227 (26.9) | 0.69 (0.53–0.90) | 55 (23.7) | 5,504 (27.3) | 0.73 (0.50–1.05) | 46 (24.5) | 7,723 (26.6) | 0.68 (0.46–0.99) |
| ≥3 | 121 (28.8) | 18,564 (37.7) | 0.59 (0.46–0.77) | 73 (31.5) | 7,980 (39.5) | 0.68 (0.48–0.97) | 48 (25.5) | 10,584 (36.4) | 0.51 (0.34–0.76) |
| | | | $P_{\text{trend}} < 0.001$ | | | $P_{\text{trend}} = 0.04$ | | | $P_{\text{trend}} = 0.001$ |
| Allergy history and rhinitis symptoms[b] | | | | | | | | | |
| Neither | 191 (45.7) | 16,365 (33.1) | 1.00 (Ref.) | 103 (44.2) | 6,314 (31.2) | 1.00 (Ref.) | 88 (47.6) | 10,051 (34.5) | 1.00 (Ref.) |
| Symptoms only | 185 (44.3) | 26,695 (54.0) | 0.62 (0.49–0.78) | 113 (48.5) | 11,583 (57.2) | 0.68 (0.50–0.93) | 72 (38.9) | 15,112 (51.8) | 0.55 (0.39–0.78) |
| History of atopy[c] | 42 (10.1) | 6,360 (12.9) | 0.61 (0.42–0.87) | 17 (7.3) | 2,354 (11.6) | 0.51 (0.30–0.87) | 25 (13.5) | 4,006 (13.7) | 0.73 (0.45–1.18) |
| | | | $P_{\text{trend}} < 0.001$ | | | $P_{\text{trend}} = 0.004$ | | | $P_{\text{trend}} = 0.03$ |
| Grew up on a farm[d] | | | | | | | | | |
| No | 69 (15.9) | 13,615 (26.7) | 1.00 (Ref.) | 14 (5.8) | 1,739 (8.3) | 1.00 (Ref.) | 55 (28.8) | 11,876 (39.7) | 1.00 (Ref.) |
| Yes | 364 (84.1) | 37,399 (73.3) | 1.51 (1.15–1.98) | 228 (94.2) | 19,351 (91.8) | 1.39 (0.80–2.39) | 136 (71.2) | 18,048 (60.3) | 1.52 (1.11–2.09) |

[a]The reported frequencies may not sum to the total number of study subjects due to missing data.

[b]Age as underlying time metric, with adjustment for sex, state of residence, race, family history of lymphohematopoietic cancer, alcohol consumption, smoking status, BMI, viral/infectious conditions (common cold, sinusitis, and influenza), and growing up on a farm.

[c]Defined as reporting a history of doctor-diagnosed hay fever or eczema, with or without allergy symptoms.

[d]Age as underlying time metric, with adjustment for sex, state of residence, race, family history of lymphohematopoietic cancer, alcohol consumption, smoking status, and BMI.

**Table 4.** Rhinitis at enrollment, growing up on a farm, and risk of non-Hodgkin lymphoma subtypes[a]

| | DLBCL | | FL | | CLL/SLL | | MM | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases | HR (95% CI) | Cases | HR (95% CI) | Cases | HR (95% CI) | Cases | HR (95% CI) | $P_{het}$[b] |
| Rhinitis in the last 12 mo[c] | | | | | | | | | |
| No | 41 | 1.00 (Ref.) | 29 | 1.00 (Ref.) | 50 | 1.00 (Ref.) | 39 | 1.00 (Ref) | |
| Yes | 50 | 0.82 (0.51–1.33) | 35 | 0.69 (0.39–1.22) | 53 | 0.62 (0.40–0.97) | 43 | 0.50 (0.30–0.83) | 0.56 |
| Grew up on a farm[d] | | | | | | | | | |
| No | 14 | 1.00 (Ref.) | 12 | 1.00 (Ref.) | 13 | 1.00 (Ref.) | 11 | 1.00 (Ref) | |
| Yes | 85 | 1.69 (0.93–3.07) | 52 | 1.51 (0.77–2.93) | 90 | 1.67 (0.90–3.10) | 72 | 1.83 (0.94–3.56) | 0.98 |

Abbreviation: MM, multiple myeloma.

[a]Case frequencies do not sum to the total number of NHL cases due to missing exposure data and the exclusion of T-cell and some types of B-cell malignancies from the subtype-specific analyses.

[b]Tests of heterogeneity across subtypes were performed using polytomous logistic regression models adjusted for the same set of covariates that were included in the main analyses.

[c]Age as underlying time metric in all analyses, with adjustment for sex, state of residence, race (except for the CLL/SLL analyses), family history of lymphohematopoietic cancer, alcohol consumption, smoking status, BMI, viral/infectious conditions (common cold, sinusitis, and influenza), and growing up on a farm.

[d]Age as underlying time metric in all analyses, with adjustment for sex, state of residence, race (except for the CLL/SLL analyses), family history of lymphohematopoietic cancer, alcohol consumption, smoking status, and BMI.

those with a history of physician-diagnosed hay fever in the Cancer Prevention Study II (15). In the Vitamins and Lifestyle cohort (17), self-reported plant, tree, or pollen allergies at baseline were associated with increased future risk of mature B-cell neoplasms (excluding CLL/SLL and multiple myeloma). Consistent with our findings, a recent report from the Iowa Women's Health Study found that self-reported allergic diseases were associated with a reduced risk of lymphoid neoplasms among those living in rural areas; no association was observed among residents in urban areas (18).

The mechanisms through which allergies and growing up on a farm may influence NHL risk remain unclear. It is possible that in our study population, the presence of allergy-related symptoms may possibly reflect an activated immune response that might promote immune surveillance and a heightened response to tumor-specific antigens (28). Alternately, as has been suggested previously (13), it is possible that suppression of the allergic response may be a prodromal effect of as-yet undiagnosed NHL. The fact that the inverse association between allergy symptoms and NHL persisted after restricting to NHL cases diagnosed 10 or more years after ascertainment of rhinitis suggests reverse causation is unlikely to explain our findings. However, we cannot exclude the possibility of prodromal effects very early in the disease process for slowly progressing tumors.

The farming background of the AHS participants provides a unique opportunity to investigate the relationships between specific allergen-related exposures, allergies, and risk of NHL. Other strengths include a prospective design; the large number of participants with detailed baseline information on crop and animal exposures, allergic symptoms and conditions, and potential confounding factors; and the identification of incident NHL cases through linkage with state cancer registries. This study also has limitations. We used self-reported information to characterize current crop and animal exposures and allergy symptoms in the last 12 months at the time of enrollment. These data may not reflect the lifetime history of these exposures and symptoms, and may be subject to error. Because of the prospective design of our study, we would expect any exposure misclassification to generally be nondifferential between NHL cases and non-cases, which would likely result in attenuated risk estimates. The misclassification of crop and animal exposures among spouses might be greater than among the farmers because this information was obtained from the farmer enrollment questionnaire, which would make it more difficult to detect an association among spouses. Although it is unknown whether spouses had direct crop/animal contact, they were presumably exposed to allergens through living on the farm because of opportunities for indirect exposure. We evaluated the results separately for farmers and spouses, and findings were generally similar (Table 2).

The lack of clinical measures of atopy and our reliance on self-report of allergic symptoms are potential limitations of our study. However, a previous investigation in a subset of male farmers in the AHS observed a lower prevalence of atopy (based on total IgE in serum) compared with demographically similar participants in the National Health and Nutrition Examination Survey (29). Previous studies in the general population (30, 31) have characterized self-reported allergic symptoms using nonstandardized questions and varying definitions. Although IgE measurements were not available for our analyses of NHL risk, we note that stronger associations with NHL were observed among those who reported more frequent episodes of symptoms in the last 12 months at baseline, and all analyses were adjusted for viral/infectious conditions that produce nasal symptoms. Although some (but not all) previous studies assessed NHL risk in relation to self-report of physician-diagnosed allergic diseases, many individuals with allergic symptoms may not receive a diagnosis of allergies because symptoms can be managed without medical professional intervention. Thus, self-report of allergic symptoms may provide a more complete assessment of allergies than medical records (30).

Finally, we note that there were a relatively small number of cases of specific NHL subtypes. Although the differences in risk estimates across NHL subtypes were not statistically significant, we did observe suggestive evidence of NHL subtype specificity in some analyses that may warrant further evaluation in future studies.

In summary, our findings of inverse associations with NHL for allergy symptoms and certain farming activities (e.g., handling stored grains/hay) and a positive association with growing up on a farm suggest that the host immune response to allergen exposures in the farm environment may influence risk of NHL. Confirmation of these findings in other prospective cohorts of farming populations is warranted. In particular, it will be important to characterize risk of NHL and NHL subtypes in relation to specific allergic hypersensitivities and immune responses, to evaluate specific farm-related allergen exposures, and to determine the relevance of the timing of these exposures

**Table 5.** Risk of NHL neoplasms in relation to the joint effects of rhinitis in the last 12 months with growing up on a farm and exposure to crops, stored grains and hay, and animals at enrollment[a]

| Exposure #1 | Exposure #2 | Cases | HR (95% CI) |
|---|---|---|---|
| Rhinitis | Grew up on a farm | | |
| No | Yes | 171 | 1.00 (Ref.) |
| No | No | 27 | 0.59 (0.39–0.90) |
| Yes | Yes | 181 | 0.60 (0.48–0.77) |
| Yes | No | 42 | 0.47 (0.33–0.69) |
| | | | $P_{int} = 0.3$ |
| Rhinitis | Worse after handling grain or hay | | |
| No | | 198 | 1.00 (Ref.) |
| Yes | No | 148 | 0.66 (0.52–0.84) |
| Yes | Yes | 77 | 0.58 (0.43–0.78) |
| | | | $P_{trend} < 0.001$ |
| Rhinitis | Growing grains or hay | | |
| No | No | 40 | 1.00 (Ref.) |
| No | Yes | 155 | 0.74 (0.50–1.10) |
| Yes | No | 31 | 0.45 (0.28–0.75) |
| Yes | Yes | 191 | 0.50 (0.34–0.75) |
| | | | $P_{int} = 0.14$ |
| Rhinitis | Handling stored grains or hay[b] | | |
| No | No | 30 | 1.00 (Ref.) |
| No | Yes | 74 | 0.76 (0.48–1.23) |
| Yes | No | 34 | 0.87 (0.51–1.48) |
| Yes | Yes | 95 | 0.50 (0.31–0.82) |
| | | | $P_{int} = 0.3$ |
| Rhinitis | Growing soybeans | | |
| No | No | 61 | 1.00 (Ref.) |
| No | Yes | 134 | 0.89 (0.64–1.24) |
| Yes | No | 65 | 0.64 (0.44–0.93) |
| Yes | Yes | 157 | 0.56 (0.40–0.79) |
| | | | $P_{int} = 0.9$ |
| Rhinitis | Raised livestock | | |
| No | No | 83 | 1.00 (Ref.) |
| No | Yes | 112 | 0.76 (0.57–1.03) |
| Yes | No | 73 | 0.54 (0.38–0.76) |
| Yes | Yes | 149 | 0.53 (0.39–0.72) |
| | | | $P_{int} = 0.2$ |
| Rhinitis | Raised poultry | | |
| No | No | 184 | 1.00 (Ref.) |
| No | Yes | 11 | 0.68 (0.37–1.24) |
| Yes | No | 200 | 0.61 (0.48–0.77) |
| Yes | Yes | 22 | 0.66 (0.42–1.05) |
| | | | $P_{int} = 0.2$ |

[a]Age as underlying time metric in all analyses, with adjustment for sex, state of residence, race, family history of lymphohematopoietic cancer, alcohol consumption, smoking status, BMI, viral/infectious conditions (common cold, sinusitis, influenza), and growing up on a farm (except for the joint analysis with allergy symptoms). Case frequencies may not sum to the total number of NHL cases due to missing data.
[b]Restricted to farmers only for this joint analysis.

during the life course and the resultant host immune response in the etiology of NHL.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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**Conception and design:** J.N. Hofmann, A. Blair, M.C. Alavanja, L.E. Beane Freeman
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**Other (responsible for developing the concept and design of the Agricultural Health Study and managing data collection since the inception of the study, and also worked with the lead author of this paper on reviewing data analysis and providing scientific editing of this submitted paper):** M.C. Alavanja

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