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Association of Agricultural, Occupational, and Military Inhalants With Autoantibodies and Disease Features in US Veterans With Rheumatoid Arthritis

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Abstract

Objective.—To determine the association of inhalant exposures with rheumatoid arthritis (RA)–related autoantibodies and severity in US veterans.

Methods.—Participants in the Veterans Affairs Rheumatoid Arthritis (VARA) registry were mailed surveys assessing occupational, agricultural, and military inhalant exposures. Demographic characteristics, disease activity, functional status, and extraarticular features were obtained from the VARA registry, while HLA–DRB1 shared epitope (SE) status, anti–cyclic citrullinated peptide (anti-CCP) antibodies, and rheumatoid factor (RF) were measured using banked DNA/serum from enrollment. Associations between inhalant exposures and RA-related factors (autoantibodies,

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ebel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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severity, and extraarticular features) were assessed using multivariable linear and logistic regression models adjusted for age, sex, race, and tobacco use and stratified by SE status. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

Results.—Questionnaires were returned by 797 of 1,566 participants (50.9%). Survey respondents were older, more often White or male, and less frequently smokers, and had lower disease activity compared to nonrespondents. Anti-CCP positivity was more common among veterans exposed to burn pits (OR 1.66 [95% CI 1.02, 2.69]) and military waste disposal (OR 1.74 [95% CI 1.04, 2.93]) independent of other factors. Among participants who were positive for SE alleles, burn pit exposure (OR 5.69 [95% CI 2.73, 11.87]) and military waste disposal exposure (OR 5.05 [95% CI 2.42, 10.54]) were numerically more strongly associated with anti-CCP positivity. Several inhalant exposures were associated with the presence of chronic lung disease, but not with the presence of RF or the level of disease activity.

Conclusion.—Military burn pit exposure and military waste disposal exposure were independently associated with the presence of anti-CCP antibodies in RA patients. These findings are consistent with emerging evidence that various inhalant exposures influence autoantibody expression and RA risk.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects 0.5–1% of adults in developed countries. Complex interactions between genetic factors and environmental exposures trigger immune responses that lead to the production of rheumatoid factor (RF) and/or anti–citrullinated protein antibodies (ACPAs) in 60–80% of RA patients (1). Although studies have suggested that ACPAs may be pathogenic in RA, additional studies are needed to better characterize their role in RA (2–4). Moreover, the presence of these autoantibodies is associated with extraarticular features such as interstitial lung disease (ILD) and subcutaneous nodules in RA (5,6).

Cigarette smoke is the strongest environmental risk factor for RA identified to date and is also associated with RA disease severity (7,8). Previous studies have shown a substantial gene–environment interaction between smoking and the presence of shared epitope (SE) alleles (9). The combination of smoking and the HLA–DRB1 SE alleles, the major genetic risk factor for RA, resulted in a 21-fold increased risk of ACPA-positive RA when compared to nonsmokers negative for SE (9,10). While the mechanisms linking cigarette smoking with RA are not fully understood, smoking appears to induce citrullination within the lungs (11). It is unclear whether the production of citrullinated peptides is a direct effect of smoking or is a consequence of airway inflammation resulting from smoking (12). Regardless, smoking appears to contribute to the generation of RA autoantibodies within the lungs (10,13).

Despite emerging evidence of the role of the lungs in RA pathogenesis, there have been few studies investigating the association of RA and inhalant exposures other than smoking. In a Swedish case–control study, men with RA were more than twice as likely as controls to have a farming occupation, and crops/forage exposures were associated with an increased risk of RA in men (14). In the Agricultural Health Study, a cohort study of licensed pesticide applicators in Iowa and North Carolina, several pesticide exposures were independently

associated with RA risk among men (15) and women (16). Findings from this cohort also identified associations of non-pesticide agricultural exposures and RA risk (17). Several other occupations associated with potential noxious inhalant exposures, including bricklayers and concrete workers, material handling operators, and electrical and electronics workers, have shown an increased risk of ACPA-positive RA in men (18). Silica and asbestos exposure, specifically, have been associated with the risk of developing RA (19–21). Furthermore, an elevated risk of incident autoimmune disease has been demonstrated among rescue workers with prolonged exposure to the vast quantities of dust, smoke, and toxins as a result of the World Trade Center disaster (22).

Exposure to emissions from open-air burn pits, particularly in military settings, has been strongly linked to various lung diseases, including asthma, bronchitis, chronic obstructive pulmonary disease (COPD), and constrictive bronchiolitis, but the effect of this exposure on RA is less known (23–25). Associations between RA and exposure to open-air burn pits have been assessed among Millennium Cohort participants deployed to 3 different campsites in Iraq between 2003 and 2008 (26). In that study, proximity to a burn pit and cumulative days within a 3-mile radius of a burn pit were not consistently associated with newly reported RA, but there was increased RA risk with exposure to burn pits for 132–211 days. Notably, that study was limited by the small number of confirmed RA cases (n = 10 following medical record review), a short follow-up period (mean 1.7 years from exposure to survey completion for those reporting a new diagnosis of RA), and unknown autoantibody status.

Taken together, the studies described above suggest that there may be several inhalant exposures that affect RA risk. However, it remains to be determined how different inhalant exposures influence autoantibody expression and the clinical course of RA. Therefore, our objectives were 1) to evaluate the associations of agricultural, occupational, and military inhalant exposures and RA autoantibody expression in RA patients, stratified by SE status, and 2) to determine the associations between inhalant exposures and RA disease severity and extraarticular disease features. We hypothesized that inhalant exposures would be associated with higher RF and ACPA expression independent of smoking history and that associations of autoantibody concentrations would be enhanced in those with the HLA–DRB1 SE. Additionally, we hypothesized that inhalant exposures would be associated with higher disease activity, poorer functional status, and the presence of extraarticular manifestations.

PATIENTS AND METHODS

Study design and data source.

We performed a nested, cross-sectional study evaluating inhalant exposures within the Veterans Affairs Rheumatoid Arthritis (VARA) registry. Exposure questionnaires were mailed to living participants in the VARA registry, a prospective cohort of US veterans with RA that met the American College of Rheumatology (ACR) 1987 criteria (27). A second survey was mailed if a response was not received within 2 weeks after the initial survey mailing. Upon enrollment in the VARA registry, participants' demographic characteristics and a peripheral blood sample (serum, plasma, or DNA) are collected. Data on disease activity, functional status, and the presence of subcutaneous nodules are collected

longitudinally in the VARA registry as part of routine care. ILD in this cohort is identified through administrative data screening and validation by standardized medical record review (28,29). Participating VARA registry sites for this study were Omaha, NE; Iowa City, IA; Portland, OR; Dallas, TX; Birmingham, AL; Salt Lake City, UT; Washington, DC; Pittsburgh, PA; and Philadelphia, PA. All participants provided informed consent, and this study received institutional review board approval at each site as well as approval from the VARA Scientific Ethics and Advisory Committee.

Inhalant exposure survey.

We administered a survey to assess previous exposures to agricultural, occupational, military, and household inhalants. The questions included in the survey were adapted from the Agricultural Health Study (15), Million Veterans Project (30), and prior studies conducted by members of our multidisciplinary study team (31,32). Questions asked were focused on inhalant exposures related to living/working on a farm, primary occupation, occupational exposures, military exposures, and household exposures. To determine the timeframe and length of exposure, the beginning and ending dates of farm and/or military exposures were collected. Participants also provided a detailed history of tobacco use and alcohol intake as well as the presence of chronic lung disease diagnoses, including COPD, ILD, asthma, farmer's lung disease, and bronchiectasis.

Survey responses to individual exposures were grouped into related exposure categories for primary analysis (e.g., pesticides, herbicides, insecticides, fungicides, and fumigants were grouped together as pesticides). Occupations were grouped into 16 categories modeled after the US Department of Labor Standard Classifications (33). We categorized the duration of farm exposure as follows: no farm exposure, 1–10 years, >10–20 years, and >20 years of exposure. While service period duration data were also collected, the individual exposures were not necessarily continuous (e.g., participants may have been deployed to different locations or performed different roles). Therefore, we did not consider it suitable to assess dose-response associations of military exposures. In order to limit the length and burden of the questionnaire on participants, we did not inquire about specific years for each individual exposure within agricultural, occupational, and military categories. Responses to a history of Agent Orange exposure on the survey were compared to indicators of Agent Orange exposure recorded at Veterans Affairs (VA) enrollment to validate survey results.

Outcome measures.

The primary study outcome measures were RA-related autoantibody positivity/concentration and RA disease severity. RA autoantibodies assessed were anti–cyclic citrullinated peptide antibodies (anti-CCPs) and rheumatoid factor (RF). Anti-CCP antibody concentrations were measured using a second-generation enzyme-linked immunosorbent assay, and RF concentrations were measured by nephelometry on banked serum from VARA registry enrollment, as previously described (34,35). RF positivity was defined as ≥15 IU/ml, and anti-CCP positivity was defined as ≥5 units/ml. Based on a previous study, seroconversion from autoantibody positivity to negativity was infrequent, so we would not expect that there would be a meaningful difference in our results if autoantibody measurements were taken proximate to survey administration (36). RA disease severity was assessed by calculating the

mean Disease Activity Score in 28 joints (DAS28) and Multidimensional Health Assessment Questionnaire (MDHAQ) from VARA registry enrollment until the administration of the survey (37,38). Analyses using the disease activity and functional status scores most proximate to survey administration were consistent with the primary approach (data not shown). Secondary outcome measures were chronic lung diseases (both self-reported from survey response and reported from VARA cohort ILD validation methods) and extraarticular manifestations, defined for this study as ILD (by survey response or cohort ILD validation methods as described above) and/or subcutaneous nodules.

SE status.

We used banked cells/DNA from VARA registry enrollment to evaluate for the presence of HLA–DRB1 SE alleles (39). SE alleles were those with *01 and *04 (except *0402, *0403, *0406, *0407, *0414, *0417, *0420) sequences.

Statistical analysis.

We compared patient characteristics between survey respondents and nonrespondents using chi-square tests and independent *t*-tests. Descriptive statistics were evaluated by site to examine for any clustering of survey responses by location, which only occurred for farm-related exposures (data not shown). Associations of inhalant exposures with autoantibody positivity were assessed using multivariable logistic regression models. Inhalant exposures were assessed individually in separate models and were adjusted for potential confounders. Associations with autoantibody concentrations were assessed using ordinary least-squares regression after log-transforming autoantibody concentrations for normality. Covariates in these models were selected a priori and included age, sex, race, and tobacco use.

Regression models evaluating agricultural exposures were clustered by site, based on the results of initial descriptive analyses. Because there was correlation at the site level for agricultural exposures, we accounted for this correlation in our variance–covariance estimation to generate standard errors and 95% CIs by using the vce(cluster) option within Stata. Ordinary least-squares regression was also used to examine the association of inhalant exposure with functional status and disease activity with the same covariates as listed above. To evaluate the associations of specific inhalant exposures in the setting of SE alleles, we assessed combined exposure and SE status referent to those without exposure or SE alleles. Additive gene–environment interactions of specific inhalant exposures with SE were assessed by calculating the relative excess risk due to interaction (RERI) (40). Values >0 are suggestive of an additive interaction. All statistical analyses were performed using Stata version 15. *P* values less than 0.05 (2-tailed) were considered significant.

RESULTS

Of the 1,566 participants, a total of 797 returned the surveys for a response rate of 50.9%. At the time of the VARA registry enrollment, respondents were older (mean 69.5 years), more likely to be White (82.1%) and male (86.7%), but less likely to be current smokers (20.4%), compared to survey nonrespondents (Table 1). The mean ± SD time from VARA registry enrollment to the survey administration was 6.5 ± 4.2 years. Respondents had lower disease

activity (DAS28 score of 3.2 versus 3.6) and better functional status (MDHAQ score of 0.8 versus 0.9) compared to nonrespondents. The frequencies of the different agricultural, occupational, and military exposures are listed in Table 2. Inhalant exposures were common among respondents, with 72.2% reporting occupational dust exposure, 31.1% reporting occupational asbestos exposure, and 25.6% reporting military asbestos exposure. Nearly half of the respondents (44.8%) had lived or worked on a farm. The most frequent occupations included construction, production, and labor; maintenance, repairs, and mechanic; transportation; and farm, fish, and forestry. All military service periods and 99.4% of farm exposure were initiated prior to registry enrollment. Respondents served during the following periods of war: Vietnam (1961–1975; 70.8%), Persian Gulf (1990–1991; 11.5%), Korea (1950–1955; 8.8%), recent conflicts (2001 and after; 6.5%), and World War II (1941–1946; 0.5%).

We evaluated the validity of self-reported exposures in multiple ways. In comparing respondents who indicated self-reported Agent Orange exposure to those with indicators of Agent Orange exposure at time of VA enrollment, we found 84% agreement. We also assessed the military service periods for respondents who self-reported burn pit exposures, using the dates from the VA Open Burn Pit Registry as an indicator of service during traditional open-air burn pit exposure periods (Operation Enduring Freedom [OEF], Operation Iraqi Freedom [OIF], Operation New Dawn, Operations Desert Shield/Desert Storm) (41). We found that 19% of those reporting burn pit exposures served during these periods.

Inhalant exposures, autoantibodies, and disease severity.

The associations of selected inhalant exposures and autoantibody positivity are shown in Figures 1A and B. After adjusting for age, sex, race, and tobacco use, military burn pit and military waste disposal exposures were both associated with higher odds of anti-CCP positivity (OR 1.66 [95% CI 1.02, 2.69] for military burn pit exposure; OR 1.74 [95% CI 1.04, 2.93] for military waste disposal exposure). In these models, tobacco use was strongly associated with anti-CCP positivity (in the burn pit model, OR 1.78 [95% CI 1.19, 2.66] for former tobacco use and OR 3.48 [95% CI 1.88, 6.44] for current tobacco use). Military burn pits and waste disposal were also independently associated with higher anti-CCP concentrations (for burn pit exposure, log-transformed β 0.41 [95% CI 0.03, 0.80]; for waste disposal exposure, log-transformed β 0.20 [95% CI −0.20, −0.61]). Notably, military burn pit and waste disposal exposures were frequently reported together (85% agreement; $P =$ 0.07 by McNemar's test). Sensitivity analyses were performed for military burn pit and military waste disposal exposure associations with anti-CCP positivity, adjusted for smoking pack-years, and the results were consistent with those of the primary analyses (OR 1.73 [95% CI 1.05, 2.86] for burn pit exposure and OR 1.89 [95% CI 1.10, 3.25] for waste disposal exposure). Other inhalant exposures were not associated with anti-CCP positivity or concentration. Agricultural, occupational, and military inhalant exposures were not associated with RF positivity or concentration.

Several inhalant exposures, including occupational dust, occupational pesticides, occupational asbestos, military asbestos, and military burn pits, were independently

associated with the presence of chronic lung disease (Figure 1C). None of the inhalant exposures were significantly associated with the presence of extraarticular manifestations of ILD or subcutaneous nodules (Figure 1D). Inhalant exposures were not significantly associated with mean disease activity scores or functional status throughout registry follow-up (Table 3). Similarly, duration of farm exposure was not associated with anti-CCP antibody positivity, RF positivity, chronic lung disease, extraarticular manifestations, or RA disease severity by disease activity or functional status (data not shown).

Interaction between inhalant exposures, SE status, and antibody positivity.

Recognizing the gene–environment interaction between smoking and SE alleles for seropositive RA, we evaluated the associations of military burn pit and/or military waste disposal exposure and anti-CCP antibodies in combination with SE alleles. Participants with burn pit exposure and SE alleles had an OR of 5.69 (95% CI 2.73, 11.87) for anti-CCP positivity compared to those who were SE negative and not exposed to burn pits. This association was stronger than for either risk factor in isolation (OR 2.86 [95% CI 1.92, 4.26] for SE alone and OR 1.28 [95% CI 0.58, 2.86] for burn pit exposure alone) (Figure 2A). Similar findings were observed for associations of military waste disposal and SE with anti-CCP positivity, as participants with military waste disposal exposure and SE alleles had an OR of 5.05 (95% CI 2.42, 10.54) for anti-CCP positivity, which was a stronger association than for either risk factor alone (OR 3.18 [95% CI 2.13, 4.73] for SE alone and OR 2.19 [95% CI 0.92, 5.21] for waste disposal exposure alone) (Figure 2B). We performed additional sensitivity analyses assessing the associations of military burn pit exposure and waste disposal exposure with anti-CCP antibody positivity, adjusted for SE. While the point estimate for the association of military burn pit exposure with anti-CCP antibody positivity did not change, the 95% CI did span 1 (OR 1.66 [95% CI 0.98, 2.80]). Analyses of waste disposal exposure were not meaningfully changed (OR 1.82 [95% CI 1.04, 3.17]). The estimated RERI between military burn pit exposure and SE alleles was 2.55 (95% CI −1.45, −6.54), which did not reach statistical significance. There was no evidence of an additive interaction between military waste disposal exposure and SE (RERI 0.69 [95% CI −3.21, −4.58]).

DISCUSSION

We found that multiple occupational and military-related inhalant exposures were associated with the presence of chronic lung diseases, but no associations between agricultural or occupational inhalant exposures and RA autoantibodies or disease severity were found. However, military burn pit exposure and military waste disposal exposure were specifically associated with anti-CCP positivity independent of tobacco use. Furthermore, this association was most notable among those with HLA–DRB1 SE alleles, which is similar to the gene–environment interaction between SE and tobacco use for autoantibody expression in other studies (9,42). Our findings suggest that other inhalant exposures, particularly military-related burn pit exposure and military waste disposal exposure, may influence autoantibody expression and, thus, confer risk for RA development. Although we did not find a statistically significant additive interaction between military burn pit exposure and SE, this gene–environment interaction may have been underpowered. The estimated RERI was

considerably greater than 1, the threshold defined for an additive interaction, and should be evaluated in future studies. Due to the simultaneous examination of several exposures, some of our findings may have been due to chance. However, we observed consistent associations of military burn pit exposure and waste disposal exposure with anti-CCP positivity and anti-CCP concentration despite adjustment for multiple covariates and several sensitivity analyses.

While a prior study did not find that deployment within a 3-mile radius of a documented burn pit was associated with the development of RA (26), several differences between that study and ours may explain the contradictory findings. The prior study evaluated RA risk among veterans who served during a single service period and was limited by the small number of confirmed RA cases (n = 10), short duration of follow-up (average of 1.7 years), and unknown autoantibody or SE status. In contrast, our study was conducted only among RA subjects who met ACR classification criteria, was focused on autoantibodies and disease outcomes, used standardized assays for RA autoantibodies and SE testing, and included veterans from several service periods.

Supporting the validity of our findings, several inhalant exposures were associated with chronic lung diseases, which is consistent with prior studies (43,44), and tobacco use was strongly associated with anti-CCP positivity (9,10). The independent association of burn pit exposure with chronic lung disease and anti-CCP, but not RF, suggests the possibility that this inhalant exposure may induce the generation of citrullinated proteins and inflammatory responses within the lungs, analogous to the pathophysiologic process being identified to accompany cigarette smoking (11,12). Ultimately, future research is needed to investigate these potential mechanisms.

Besides burn pit exposure and waste disposal exposure, we did not find other inhalant exposures associated with anti-CCP positivity or concentration. An association of particulate fine matter with anti-CCP and RF was previously observed in this cohort (45). In the present study, most survey respondents reported several inhalant exposures (e.g., 72% with dust exposure, 77% with tobacco exposure, and 59% with pesticide exposure), which may result in an underestimation of the associations of specific exposures and anti-CCP positivity. Other studies evaluating the risk of RA in pesticide applicators have shown increased risk of RA, but these individuals likely had higher cumulative doses of pesticide exposure compared to our study respondents who were not all pesticide applicators by occupation (15,16). Specific time periods and dose of individual exposures were not collected in our study in order to avoid survey burden; however, military service periods and farm exposures were almost universally initiated prior to registry enrollment and time of autoantibody measurement. Future studies could provide additional insight into the links between other exposures and RA-related autoimmunity. We also did not find exposures to be associated with disease activity and functional status. The exception was for Agent Orange, which was associated with higher MDHAQ scores but not disease activity. The small magnitude of this association, the cross-sectional design, and potential for residual confounding from comorbid conditions related to Agent Orange (e.g., diabetes mellitus, select cancers) (46) do not support a causal interpretation of this finding.

One limitation of our questionnaire is that to encourage completion and a high response rate, it did not collect extensive data on the specific site of deployment, proximity to burn pits, or duration of self-reported burn pit exposure. When those with self-reported burn pit exposure from our study were compared to those eligible to participate in the VA's Airborne Hazards and Open Burn Pit Registry (41) based on the service period reported (e.g., Gulf war, OEF/OIF), we found that only 19% of survey respondents served during service periods characterized by classic open-air burn pits on military bases. However, there was significant overlap between military burn pit exposure and military waste disposal exposure in our study (85% concor dance). Thus, this discrepancy in burn pit exposure as reported by patients in our study may not represent what is traditionally classified as open-air burn pit exposures in that respective registry, but rather various means of disposing of trash and other waste products through incineration. When the validity of other self-reported exposures was assessed by comparing respondents who indicated self-reported Agent Orange exposure to those with indicators of Agent Orange exposure at the time of VA enrollment, we found 84% agreement. While military service periods and farm exposures nearly universally occurred prior to registry enrollment (and study outcome assessment), the timing of individual exposures was not collected, and some exposures may have occurred after RA onset.

Our study was also limited by the cross-sectional design among a homogenous veteran population, all of whom had an established diagnosis of RA. Our study did not include a non-RA comparator group because this population was not available. However, our findings from a large study of RA patients demonstrated how unique inhalant exposures are associated with autoantibody expression and serves as a crucial foundation which can be built on by future, large, prospective studies that include non-RA subjects.

While there is emerging evidence that the lungs play an important role in development of RA and may be the site of autoantibody generation (13), the cross-sectional design of our study prohibited us from evaluating whether the association of inhalant exposures and chronic lung disease may subsequently drive autoantibody production. Longitudinal study designs will be needed to further investigate this hypothesis. Finally, because of the male predominance of the cohort, we were unable to evaluate associations of inhalants and disease features among men and women separately. This may be important since prior studies have suggested that occupational exposures may be more closely associated with RA risk among men (14,19,47).

In conclusion, we found burn pit and military waste exposure to be specifically associated with anti-CCP positivity in a well-characterized cohort of veterans with RA, particularly in those positive for HLA–DRB1 SE. These findings support emerging evidence that various inhalant exposures may contribute to the generation of RA autoantibodies such as ACPAs. Prospective cohort studies comprehensively evaluating the impact of inhalant exposures, including military burn pits and waste disposal, and the impact of genetic factors on RA risk are needed.

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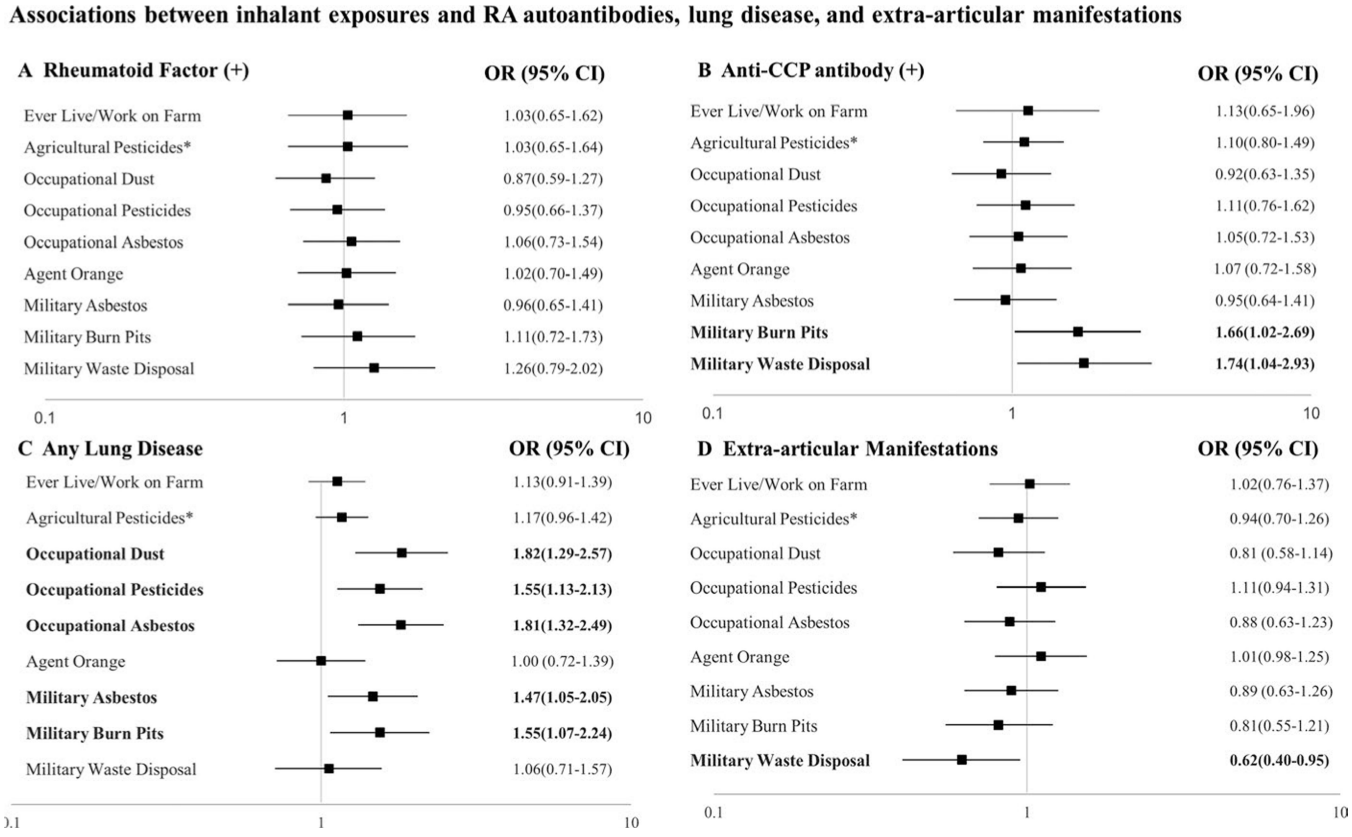
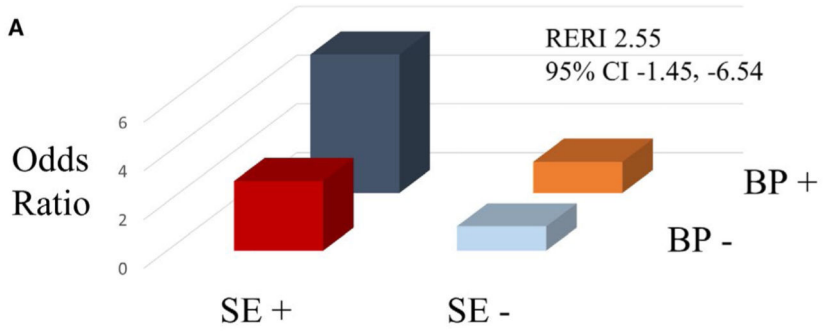
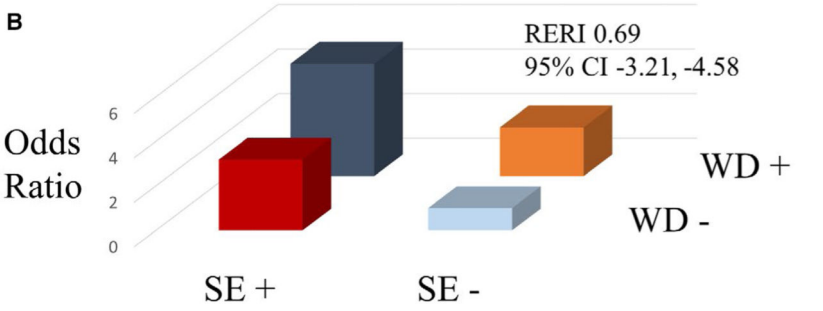


Figure 1.

Associations between exposures and rheumatoid arthritis (RA) autoantibodies, extraarticular manifestations, and lung diseases. Forest plots of odds ratios (ORs) were generated with 95% confidence intervals (95% CIs) and were adjusted for age, sex, race, and smoking status. * The category “agricultural pesticides” included pesticides, herbicides, insecticides, fungicides, and fumigants. **A**, Associations between inhalants and rheumatoid factor positivity. **B**, Associations between inhalants and anti–cyclic citrullinated peptide (anti-CCP) antibody positivity. **C**, Associations between inhalants and chronic lung disease. Presence of chronic lung disease (chronic obstructive pulmonary disease, interstitial lung disease [ILD], asthma, farmer’s lung disease, and bronchiectasis) was obtained by survey responses and Veterans Affairs Rheumatoid Arthritis (VARA) cohort ILD validation methods. **D**, Associations between inhalants and extraarticular manifestations, which included ILD and/or subcutaneous nodules. Presence of ILD was obtained by survey response or VARA cohort ILD validation methods.



Exposure	Anti-CCP + / Total	Odds ratio (95% CI) for anti-CCP +
Neither SE or Burn Pit	110/187 (58.8)	Referent
SE Alone	316/394 (80.2)	2.86 (1.92-4.26)
Burn Pit Alone	21/32 (65.6)	1.28 (0.58-2.86)
SE & Burn Pit	83/93 (89.3)	5.69 (2.73-11.87)
Odds ratios were adjusted for age, sex, race, and tobacco use		



Exposure	Anti-CCP + / Total	Odds ratio (95% CI) for anti-CCP +
Neither SE or Waste Disposal	107/187 (57.2)	Referent
SE Alone	329/407 (80.8)	3.18 (2.13-4.73)
Waste Disposal Alone	24/32 (75.0)	2.19 (0.92-5.21)
SE & Waste Disposal	70/80 (87.5)	5.05 (2.42-10.54)
Odds ratios were adjusted for age, sex, race, and tobacco use		

Figure 2.

Association of the combination of shared epitope (SE) status and military burn pit (BP) exposure and of the combination of SE status and military waste disposal (WD) exposure with anti–citrullinated protein antibody positivity. Results from analyses of anti–cyclic citrullinated peptide (anti-CCP) positivity in relation to SE status in combination with military burn pit exposure (**A**) or military waste disposal exposure (**B**) are shown. The combination of military burn pit exposure or military waste disposal exposure and the SE allele had a stronger association with anti-CCP positivity than that for either risk factor in

isolation. Additive gene–environment interactions of specific inhalant exposures with SE were assessed by calculating the relative excess risk due to interaction (RERI) (40). Values >0 are suggestive of an additive interaction. 95% CI = 95% confidence interval.

Table 1.

Demographic and clinical characteristics of the survey respondents and nonrespondents [*]

	Respondents (n = 797)	Nonrespondents (n = 769)	$P^{\dagger}$
Age, mean ± SD years	69.5 ± 9.7	68.2 ± 11.5	0.02
Sex, male	689 (86.7)	653 (85.1)	0.39
White	651 (82.1)	532 (69.4)	<0.001
High school education or above	666 (92.1)	612 (90.3)	0.22
BMI, mean ± SD kg/m^2	29.4 ± 5.9	28.9 ± 5.9	0.14
Smoking status			<0.001
Current smoker	157 (20.4)	223 (30.2)	
Former smoker	435 (56.6)	343 (46.4)	
Never smoked	176 (22.9)	173 (23.4)	
Anti-CCP positivity	782 (77.0)	490 (78.9)	0.42
RF positivity	481 (76.5)	489 (78.9)	0.31
Shared epitope allele positivity	495 (68.9)	432 (63.1)	0.02
RA disease duration, mean ± SD years	17.0 ± 11.0	17.5 ± 10.9	0.35
DAS28 score, mean ± SD	3.2 ± 1.1	3.6 ± 1.1	<0.001
MDHAQ score, mean ± SD	0.8 ± 0.5	0.9 ± 0.5	<0.001
Subcutaneous nodules	149 (18.7)	137 (17.82)	0.65
ILD[‡]	48 (6.0)	53 (6.9)	0.48

[*] Except where indicated otherwise, values are the number (%) at the time of Veterans Affairs Rheumatoid Arthritis (VARA) registry enrollment except for age and RA duration, which are from time of survey administration. BMI = body mass index; anti-CCP = anti–cyclic citrullinated peptide; RF = rheumatoid factor; RA = rheumatoid arthritis; DAS28 = Disease Activity Score in 28 joints; MDHAQ = Multidimensional Health Assessment Questionnaire; ILD = interstitial lung disease.

[†] By chi-square or independent *t*-test.

[‡] Determined by VARA cohort screening methods.

Table 2.

Frequency of agricultural, occupational, and military exposures

Exposure	No. (%)
Agricultural exposures	
Ever lived/worked on farm	357 (44.8)
Duration on farm	
0–10 years	126 (38.1)
10–20 years	94 (26.3)
>20 years	97 (27.2)
Agricultural pesticides*	210 (58.8)
Swine confinements	102 (28.6)
Occupational exposures	
Total dust†	575 (72.2)
Gasoline	426 (53.5)
Adhesives	359 (45.0)
Metal grinding	331 (41.5)
Asbestos	248 (31.1)
Pesticides	241 (30.3)
Organic solvents	153 (19.2)
Occupations‡	
Construction, production, and labor	128 (16.1)
Maintenance, repairs, and mechanic	112 (14.1)
Transportation	74 (9.3)
Farm, fish, and forestry	67 (8.4)
Military exposures	
Gasoline	357 (44.8)
Asbestos	204 (25.6)
Agent Orange	232 (29.1)
Burn pits	148 (18.6)
Waste disposal	128 (16.0)
Industrial solvents	105 (13.2)
Air pollution	80 (10.5)

*Includes pesticides, herbicides, insecticides, fungicides, and fumigants.

†Includes wood, sand, coal, grain, fumes, stored hay, stored grain, silage, grain dust, and other dust.

‡Most frequent occupations.

Table 3.

Associations between inhalant exposures, disease activity, and functional status*

Exposure	Mean MDHAQ, β (95% CI)	Mean DAS28, β (95% CI)
Ever lived/worked on farm	0.05 (−0.06, 0.16)	−0.05 (−0.28, 0.18)
Agricultural pesticides†	0.01 (−0.02, 0.04)	−0.02 (−0.13, 0.08)
Occupational dust	0.02 (−0.07, 0.11)	0.04 (−0.12, 0.21)
Occupational pesticides	0.004 (−0.08, 0.09)	0.11 (−0.06, 0.28)
Occupational asbestos	0.01 (−0.07, 0.10)	0.10 (−0.07, 0.27)
Agent Orange	0.09 (0.01, 0.18)‡	0.08 (−0.09, 0.26)
Military asbestos	0.04 (−0.05, 0.13)	0.13 (−0.04, 0.31)
Military burn pits	0.06 (−0.04, 0.16)	0.09 (−0.11, 0.28)
Military waste disposal	0.04 (−0.06, 0.14)	0.04 (−0.17, 0.25)

*Beta coefficients were generated with 95% confidence interval (95% CI) and were adjusted for age, sex, race, and tobacco use. Functional status and disease activity were measured as mean values during Veterans Affairs Rheumatoid Arthritis registry follow-up. MDHAQ = Multidimensional Health Assessment Questionnaire; DAS28 = Disease Activity Score in 28 joints.

†Includes pesticides, herbicides, insecticides, fungicides, and fumigants.

‡$P = 0.03$.