

Inorganic Dust Exposure During Military Service as a Predictor of Rheumatoid Arthritis and Other Autoimmune Conditions

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Objective. Rheumatoid arthritis (RA) and other autoimmune (AI) conditions are associated with inorganic dust exposure. Many military activities are likely to entail inorganic dust exposures. We wished to identify associations between prior military dust exposure and RA and other AI conditions.

Methods. We studied persons from a roster of Army, Navy, Air Force, or Marine Corps personnel who had served in Operation Enduring Freedom and Operations Iraqi Freedom and New Dawn. We linked military occupational codes to a job exposure matrix assigning dust exposure likelihood. We used the Veterans Affairs Health Care System (VAHCS) electronic health care records to identify cases of RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), vasculitis, and inflammatory myositis. Generalized estimating equations modeled risk of RA and other AI conditions associated with dust exposure, taking into account military service branch, age at first VAHCS encounter, sex, race/ethnicity, smoking status, and years of military service.

Results. Of 438086 veterans (68% ever-smokers), 44% were classified with likely or somewhat likely dust exposure. Cases included 1139 cases with RA, 467 cases with SLE, and 180 cases with other AI diseases (SSc, vasculitis, or inflammatory myositis). Military dust exposure was associated with increased odds of RA (odds ratio [OR] = 1.10; 95% confidence interval [CI] = 1.003–1.20) and increased odds of SSc, vasculitis, or inflammatory myositis (OR = 1.23; 95% CI = 1.14–1.34) but was protective for SLE (OR = 0.81; 95% CI = 0.76–0.88).

Conclusion. Dust exposure during past military service comprises an occupational and environmental risk factor for RA and other AI diseases. This is potentially relevant for prevention activities.

INTRODUCTION

There is mounting epidemiologic evidence that exposure to inorganic dust is associated with increased risk of rheumatologic and other autoimmune (AI) diseases. The links between dusty environments and rheumatoid arthritis (RA) are evident among miners, especially coal miners, and are strongly implicated in a number of other silica-exposed vocations (1,2). Epidemiological associations have also been shown between silica inhalation and systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) (3,4).

Military service and risk of AI disease have been considered only to a limited degree (5,6). Nonetheless, when considered in the context of its associated vocational and environmental aspects, military service is likely to be associated with excess

exposure to inorganic dusts through a variety of duty assignments. Occupational factors include welding, abrasive blasting, grinding and polishing metals, vehicle and other maintenance work, earth moving and other construction, and explosives detonation (7). In addition, ambient dusty conditions (from duties requiring substantial outdoor time, especially duties that typically disturb soil) can add to the burden of inhaled inorganic dust.

Identifying the presence and magnitude of risk for RA and related AI conditions (eg, SSc and SLE) associated with military service would be directly impactful to the health care of military service personnel and veterans, through both primary prevention and targeted follow-up surveillance. We wished to determine the association between military assignments with likely job-related inorganic dust inhalation and the subsequent development of

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SIGNIFICANCE & INNOVATIONS

- In the first study of this kind, dusty military occupations were associated with increased odds of rheumatoid arthritis.
- These were also associated increased odds of systemic sclerosis, vasculitis, or inflammatory myositis.
- There were no similarly increased odds for systemic lupus erythematosus.
- Military service includes occupations that may carry autoimmune disease risk from dust inhalation.

RA and other AI conditions using an established roster of separated service men and women who served in Operation Enduring Freedom (OEF) or Operations Iraqi Freedom and New Dawn (OIF and OND, respectively) and who subsequently had received care through the Veterans Administration Health Care System (VAHCS).

PATIENTS AND METHODS

Study population. The sampling frame of our study consists of the rosters of OEF and OIF and OND veterans. OEF predominantly includes veterans who served in Afghanistan; the latter two include those who served in Iraq. The roster is a list of veterans who separated from OEF/OIF/OND military service and is provided to the Veterans Affairs (VA) by the Department of Defense Manpower Data Center. This roster has been previously used to link prior military service to disease outcomes through VA medical record linkages (8–11). This study was approved by the San Francisco VA Health Care System and the University of California San Francisco internal review boards (#17-23248); a waiver of informed consent was granted because of the nature of the study.

Data sources. Data fields related to military service such as branch of service (Army, Navy, Air Force, Coast Guard, or Marine Corps), component (National Guard, Reserve, or active duty), rank, dates of deployment, and military occupation codes were obtained from the OEF/OIF/OND roster. The roster does not contain clinical data. We obtained relevant clinical information from the VA Corporate Data Warehouse, which contains data elements extracted from the national VA electronic medical record. These include diagnostic and procedure codes associated with inpatient and outpatient encounters, laboratory results, and pharmacy data. Data were accessed through the VA Informatics and Computing Infrastructure (VINCI) platform. Our study included all clinical data from the time of post-military discharge VA enrollment through September 30, 2018.

Inclusion/exclusion criteria. On the basis of OEF/OIF/OND roster data, we considered veterans from the Army, Navy, Air Force, or Marine Corps ($n = 722352$) as potentially eligible for inclusion, of whom 438086 were included in the final analysis (Figure 1). The bulk of the 288266 excluded fell into several

categories, as follows: 57362 officers or warrant officers (who would likely differ systematically in exposure and other characteristics), 70472 who served for fewer than 2 years (minimal duration of potential exposure), and 78177 with either no in-person encounters in the VA health care system or less than 90 days of VA follow-up. There were also 34639 who were excluded because there was a record of a VA encounter prior to the final military discharge date, which could reflect a reenlistment after previously initiating VA care (thus introducing uncertainty in the timing of exposure). Lastly, we excluded 43492 with missing smoking status from the main analyses.

Definition of RA and related AI diseases. We used ICD9 and ICD10 codes associated with VA encounters to identify veterans with any of the following diseases: RA, SSc, SLE, inflammatory myositis, and vasculitis. For each condition, we required a minimum of two face to face encounters at least 30 days apart with the relevant International Classification of Diseases (ICD) code(s). For RA, we also created a more specific definition, requiring that the ICD codes be associated with two encounters at least 180 days apart, of which at least one encounter was classified as a rheumatology clinic, as well as at least one prescription for a disease-modifying antirheumatic drug (DMARD). These definitions have been previously validated in administrative data-based research (including VA records) on rheumatoid arthritis and related AI diseases (12–16). Patients with RA were categorized according to serologic status, based on positive results from either rheumatoid factor (RF) or cyclic citrullinated peptide (CCP) antibody assays versus negative results of both tests versus unknown results of both tests. We also created the following two combined diagnosis variables: any AI disease except RA and any AI disease except RA and SLE (ie, SSc, inflammatory myositis, or vasculitis).

Although it is possible for an individual to have more than one AI disease diagnosis, for the purposes of this analysis, we chose to hierarchically categorize all patients as only having a single diagnosis (from highest priority to lowest: SSc, vasculitis, inflammatory myositis, SLE, and RA). This hierarchy is based on a previously established diagnostic schema (17).

Exposure assessment. Inorganic dust exposure during service was estimated via military occupation codes (MOCs) contained within the OEF/OIF/OND roster. In these numeric codes (varying by branch of service), the first two characters indicate the general branch of activity, and additional digits provide further detail. We applied a job exposure matrix (JEM) developed for this analysis on the basis of these MOCs. We based this approach on previous experience with JEM exposure assignment in nonmilitary occupations, including JEM exposure in RA risk (18,19). The JEM categorized military duties as likely, somewhat likely, or not likely to involve inorganic dust exposure. The higher level (likely) included occupations such as construction,

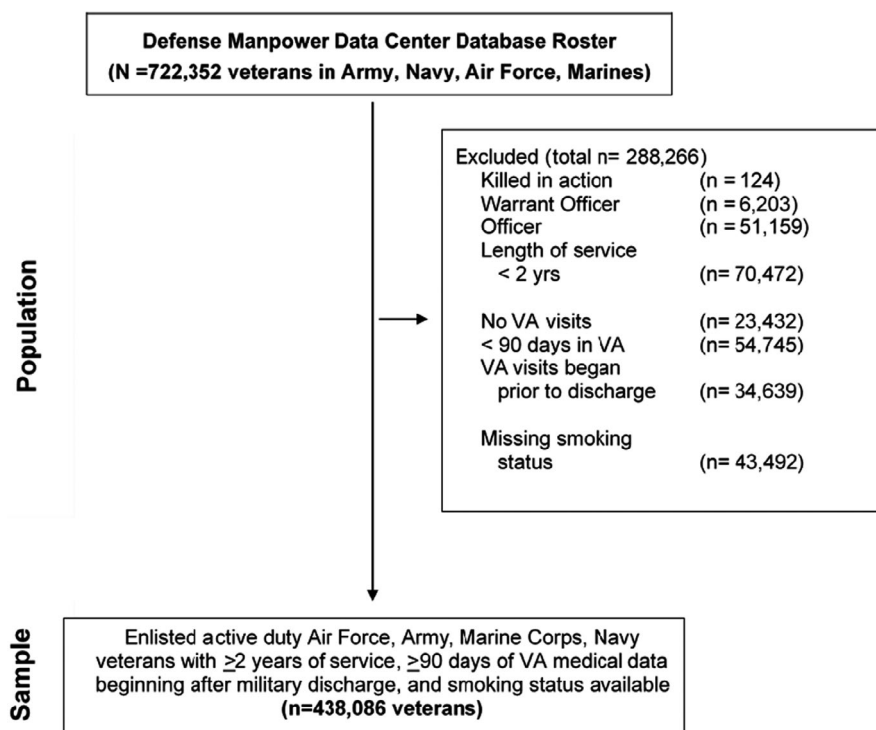


Figure 1. Study inclusion and exclusion criteria. VA, Veterans Affairs.

vehicle repair, firefighting, explosives disposal, and utilities repair/installation. The moderate level (somewhat likely) included examples such as electricians, electronics repair workers, telecom technicians, and motor vehicle operators. This JEM schema did not characterize likelihood of exposure to other dusts (such as from organic materials), gases, fumes, or vapors, although occupational categories such as construction involve a range of potential inhaled exposures. All supervisors of either moderate- or higher-level occupations were assigned intermediate-level exposure. As a sensitivity analysis, we downgraded the exposure level of supervisors of moderate-level occupations to the negligible exposure; the results did not differ from those of the main analysis and are not presented here.

Smoking status. We assigned smoking status (defined dichotomously as ever-smoker: yes or no) using Health Factor data in the VA electronic medical record. These data are collected by VA providers in response to automated clinical reminders. Using Health Factor data in this way has been validated in comparison to patient questionnaire (20). For veterans not identified as ever-smokers on this basis, additional information leading to ever-smoker classification was based on any of the following being present in the medical record: a consult request for smoking cessation clinic, an encounter with a smoking cessation clinic, or a prescription for a nicotine replacement product and/or varenicline. As noted previously, indeterminate smoking status was a study exclusion criterion.

Other covariates. Demographic variables, including date of birth, sex, and race/ethnicity were obtained from the OEF/OIF/OND roster. If race was listed as “missing” or “other,” we substituted race/ethnicity data from the VA electronic medical record, using an algorithm to classify race/ethnicity that was employed in our previous work (21). This method resulted in classification of all but 2.6% of the sample, who were classified as “other” for these analyses. We used ICD9 and ICD10 codes associated with VA encounters 30 days or more apart to identify veterans with comorbid post-traumatic stress disorder (PTSD) to include in an additional analysis, given that this diagnosis has been associated with RA (11).

Statistical analysis. We used generalized estimating equations (GEEs) to model the risk of RA and other AI conditions (separately) associated with inorganic dust exposure as measured by the JEM as a dichotomous variable (negligible versus intermediate/higher level). All models controlled for age at first VA encounter, race/ethnicity, sex, and smoking status. The GEE models accounted for correlation within members of the same branch of service.

To further explore the role of smoking in these analyses, we re-estimated the main study model including a dust-smoking interaction term and separately re-estimated the model including patients with unknown smoking status (as a separate category). To explore the potential role of PTSD comorbidity on dust exposure risk in RA, we added PTSD as an independent predictor variable to the main study model.

We further modeled risk stratification separately among seropositive RA and seronegative RA. In a sensitivity analysis, we examined the effects of assigning all patients with unknown serologic status first as seropositive and then as seronegative. In another sensitivity analysis, we used a more specific definition of RA that included prescription of a DMARD.

We also carried out a series of stratified analyses. Because of the potential interrelationship of disease onset and length of military service, the data were partitioned at 2 to 4 years, 4 to 8 years, and more than 8 years of service, roughly equivalent to the 25th, 50th, and 75th percentiles of the study population. We remodeled the risk of SLE stratified by sex, given the extreme sex imbalance in that disease and likely sex differences in exposures.

To reduce misclassification bias, models of each condition studied excluded those diagnosed with any of the other conditions, such that the comparison group always consisted of individuals with none of the AI diagnoses of interest. In analyses based on RA serologic status, we also excluded persons with positive serology who did not meet the study definition of RA. All analyses were conducted in SAS version 9.4.

RESULTS

Among 438 086 veterans included in this analysis, 88% were men and 63% white, non-Hispanic (Table 1). Average age at first VAHCS encounter after military discharge was 30.4 years, ranging from 19 years to 66 years. Nearly half of the veterans had served in the Army. The median length of service for the entire sample was 4.3 years (interquartile range = 3.2-8.2 years). Approximately two-thirds were ever-smokers. The majority of those studied (56%) were classified as having low or no likelihood of inorganic dust exposure through their military occupation. The proportions with moderate or high dust exposure employments were similar (22.2% and 21.6 %, respectively). The median duration of care through the VA was 6.8 years (interquartile range = 4.7-9.5 years).

Using the primary definition of RA, which was based on ICD-linked encounters alone, we identified 1139 cases of RA (26 cases per 10 000), of whom 461 (40%) were known to be positive for either RF or anti-CCP (171 [15%] had unknown serologic status). Using the more specific definition of RA, which included a longer observation period and a DMARD prescription, the number with RA was reduced to 660 (15 per 10 000), of whom 359 (54%) were seropositive, 271 (41%) were seronegative, and 30 (5%) had unknown serologic status. SLE was the next most common rheumatologic condition (467 cases, including 298 among women); other AI diseases (SSc, vasculitis, or inflammatory myositis) were present in the medical records of 180.

In multivariable general estimating modeling (Table 2), moderate- and higher-level dust in military employment was associated with 10% increased odds of RA (odds ratio [OR] = 1.10; 95% confidence interval [CI] = 1.003-1.20). Several of the

Table 1. Subject characteristics among 438 086 military veterans included in the analysis

Characteristic	Frequency
Sex, male, n (%)	385 516 (88.0)
Age at first VA encounter, mean \pm SD (range), years	30.4 \pm 7.3 (19-66)
Race/ethnicity, n (%)	
White	276 481 (63.1)
Black	84 576 (19.3)
Hispanic	51 815 (11.8)
Asian/Pacific Islander	13 782 (3.1)
Other	11 432 (2.6)
Years of military service, median (IQR)	4.3 (3.2-8.2)
Service branch, n (%)	
Army	213 182 (48.7)
Air Force	53 848 (12.3)
Marine	90 469 (20.7)
Navy	80 587 (18.4)
Education level, n (%)	
Less than HS	3359 (0.8)
HS diploma	397 629 (90.8)
Post-secondary education	37 098 (8.5)
Smoking status, n (%)	
Ever	296 796 (67.7)
Never	141 290 (32.3)
Dust exposure in military occupation, n (%)	
Low/no exposure	246 200 (56.2)
Any exposure	191 886 (43.8)
Moderate exposure	97 320 (22.2)
High exposure	94 566 (21.6)
Years of VA observation, median (IQR)	6.8 (4.7-9.5)
Number of encounters, median (IQR)	21 (9-49)
Diagnoses of autoimmune disease, n (%)	
Rheumatoid arthritis, sensitive definition	1139 (0.26)
Rheumatoid arthritis, specific definition	660 (0.15)
Systemic lupus erythematosus	467 (0.11)
Other autoimmune diseases	180 (0.04)
Vasculitis	76 (0.02)
Inflammatory myositis	55 (0.01)
Systemic sclerosis	49 (0.01)

Abbreviation: HS, high school; IQR, interquartile range; VA, Veterans Affairs.

For sensitive and specific definitions of rheumatoid arthritis, see Methods.

covariates included in the model also were statistically associated with RA (Table 2), most notably, age at first VA encounter (OR = 1.07; 95% CI = 1.05-1.08), female sex (OR = 3.03; 95% CI = 2.82-3.25), ever smoking (OR = 1.25; 95% CI = 1.10-1.41), and Hispanic ethnicity (OR = 1.26; 95% CI = 1.05-1.52). A smoking \times dust exposure term added to this model was not consistent with an interaction ($P = 0.64$). In a sensitivity analysis in which persons with unknown smoking status ($n = 42 492$) were added back into the study population, there was no substantive change in the estimated odds for RA associated with moderate to high dust exposure (OR = 1.09; 95% CI = 1.002-1.19). We further retested the main model, adding PTSD as a covariate. This had minimal impact on the previously estimated OR for RA associated with moderate to higher-level dust exposure (OR 1.11; 95% CI 1.02-1.21).

Table 2. Risk of RA associated with dust exposure in military occupations, with and without adjustment for covariates

Risk Factors	Odds (Risk) of RA	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Dust exposure (any versus none)	1.02 (0.87-1.19)	1.10 (1.003-1.20)
Age at first VA encounter, years	1.06 (1.04-1.09)	1.07 (1.05-1.08)
Female sex	2.80 (2.44-3.21)	3.03 (2.82-3.25)
Race (versus white)		
White, non-Hispanic (reference)	1.0 (---)	1.0 (---)
American Indian	1.68 (0.98-2.87)	1.39 (0.74-2.61)
Asian	1.23 (0.81-1.87)	0.95 (0.66-1.39)
Black	1.50 (1.12-2.01)	1.09 (0.94-1.27)
Hispanic	1.26 (0.92-1.72)	1.26 (1.05-1.52)
Hawaiian/Pacific Islander	1.91 (1.22-2.97)	1.54 (0.92-2.58)
Other	1.16 (0.99-1.35)	0.97 (0.65-1.45)
Ever-smoker (versus never-smoker)	0.95 (0.80-1.12)	1.25 (1.10-1.41)
Years of service	1.06 (1.04-1.09)	1.00 (0.99-1.02)

Abbreviation: OR, odds ratio; RA, rheumatoid arthritis; VA, Veterans Affairs.

All estimates from general estimating equation models accounting for military service branch. Adjusted general estimating equation model includes all variables shown.

In further multivariable modeling that included two separate variables for moderate and high dust exposure (compared with no/low exposure), the ORs were 1.06 (95% CI = 0.97-1.15) for moderate exposure and 1.14 (95% CI = 1.01-1.28) for high exposure (see Supplemental Table S1).

When patients were disaggregated according to serologic status (Table 3), dust exposure was a statistically significant risk factor for seronegative RA (OR = 1.25; 95% CI = 1.14-1.36) but not seropositive RA (OR = 1.02; 95% CI = 0.85-1.21). Because 15% of patients with RA were missing serologic status, we examined the effect of assigning all those with unknown status first to seropositive and then to seronegative statuses. When the unknown cases were assigned to be seronegative, the OR for seronegative RA associated with dust exposure was reduced to 1.15 (95% CI = 1.09-1.21), consistent with misclassification of some of the unknown cases. The dust-associated risk estimates for RA were similar when the latter was defined by more specific

DMARD-based criterion (OR = 1.12; 95% CI 1.06-1.20). Similarly, the risk estimates for seronegative (OR = 1.23; 95% CI = 1.07-1.41) and seropositive RA (OR = 1.06; 95% CI = 0.88-1.24) followed the same pattern as they did for the more sensitive RA definition (see Supplemental Table S2).

In the models stratified by years of service (Table 4), RA was most strongly associated with dust exposure in those with 4 years to 8 years of service (OR = 1.4; 95% CI = 1.3-1.6); there was no statistical association among those with either fewer or more years of service. In contrast to RA, dust exposure was statistically protective for SLE (OR = 0.81; 95% CI = 0.76-0.88), with this statistically significant protective association being present in those with 2 years to 4 years and 4 years to 8 years of service but not in the those with more than 8 years of service. The point estimate was even larger among women, with dust being statistically protective up to 8 years. In men, dust was not statistically protective. Disaggregating SSc, vasculitis, and inflammatory myositis (thus excluding SLE and RA) showed that these three conditions as a group were statistically associated with dust exposure in the full sample (OR = 1.23; 95% CI = 1.14-1.34) and among the stratum of veterans with more than 8 years of service (OR = 1.57; 95% CI = 1.52-1.62).

DISCUSSION

In this large sample of veterans of the Afghanistan and Iraqi wars, we observed 10% elevated odds of RA associated with military service more likely to involve exposure to inorganic dust. The odds were higher for seronegative RA (a 25% elevation), whereas there was no statistical increase observed for seropositive RA. For those with moderate length of service (4-8 years; roughly one-third of those studied), the excess odds of RA increased to 40%, although this did not carry through to those with longer service. In contrast, there was no such relationship to SLE, the second most common AI disease we studied. For SSc, myositis, and vasculitis, however, likely exposure to inorganic dust was associated with 23% increased odds, and service for more than 8 years was associated with 57% increased odds.

The specific question of exposure to inorganic dusts through military service in relation to prospective risk of RA and

Table 3. Risk of RA by seropositive and seronegative status associated with dust exposure intensity from military occupations

Dust Exposure	Any RA		Seropositive RA		Seronegative RA	
	Percentage With Condition	Adjusted OR (CI)	Percentage With Condition	Adjusted OR (CI)	Percentage With Condition	Adjusted OR (CI)
All	0.260	NA	0.106	NA	0.117	NA
No/low exposure	0.258	1.0 (reference)	0.109	1.0 (reference)	0.108	1.0 (reference)
Moderate/high exposure	0.264	1.10 (1.003-1.20)	0.102	1.01 (0.86-1.20)	0.128	1.25 (1.14-1.36)

Abbreviation: CI, confidence interval; NA, not applicable; OR, odds ratio; RA, rheumatoid arthritis.

All model estimates from generalized estimating equations accounting for military branch and controlling for age at first Veterans Affairs encounter, sex, race/ethnicity (seven categories), smoking status, and years of military service.

Models of serologic status also exclude 171 patients with unknown serostatus, 2416 seropositive patients without RA, and patients with the opposite serostatus (507 seronegative excluded from seropositive model; 451 seropositive excluded from seronegative model).

Table 4. Risk of RA and other AI diseases associated with dust exposure in military occupations from generalized estimating equations accounting for military branch, with and without stratification by years of service

Models	Cases/Total	Full Sample		2-4 Years of Service		>4-8 Years of Service		>8 Years of Service	
		Adjusted OR (CI) for Dust Exposure		Cases/Total	Adjusted OR (CI) for Dust Exposure	Cases/Total	Adjusted OR (CI) for Dust Exposure	Cases/Total	Adjusted OR (CI) for Dust Exposure
RA	1139/437 439	1.10 (1.003-1.2)		298/196 077	1.00 (0.68-1.48)	278/129 286	1.41 (1.27-1.56)	563/112 076	0.97 (0.83-1.12)
SLE and other AI diseases	647/436 947	0.92 (0.86-0.99)		246/196 025	0.87 (0.79-0.96)	166/129 174	0.77 (0.56-1.06)	235/111 748	1.13 (1.04-1.23)
SLE only	467/436 767	0.81 (0.76-0.88)		165/195 944	0.80 (0.75-0.86)	135/129 143	0.63 (0.44-0.91)	167/111 680	0.98 (0.85-1.13)
SLE, women	298/52 570	0.68 (0.65-0.71)		100/22 217	0.67 (0.54-0.83)	94/17 338	0.54 (0.32-0.91)	104/12 741	0.78 (0.48-1.28)
SLE, men	169/384 471	1.05 (0.81-1.36)		65/173 727	1.02 (0.70-1.49)	41/111 805	0.76 (0.57-1.01)	63/98 876	1.29 (0.93-1.80)
SSc, myositis, and vasculitis only	180/436 480	1.23 (1.14-1.34)		81/195 860	0.98 (0.80-1.20)	31/129 039	1.49 (0.83-2.50)	68/111 581	1.57 (1.52-1.62)

Abbreviation: AI, autoimmune; CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

All models are generalized estimating equations accounting for military branch, with and without stratification by years of service.

Full sample models control for age at first Veterans Affairs encounter, sex, race/ethnicity (seven categories), smoking status, and years of service.

Stratified models control for age at first Veterans Affairs encounter, race/ethnicity (white versus all others), sex, and smoking status.

Other AI diseases include SLE, SSc, myositis, and vasculitis.

Models of RA omit patients with other autoimmune diseases.

Models of other AI disease omit patients with RA.

Models of SLE omit patients with other AI diseases.

other AI conditions has not been addressed previously, although several studies have considered these conditions in relation to military service. For example, an analysis of Millennium Cohort data investigated factors associated with self-reported RA and SLE, including broad military job categories, without identifying any consistent association (22). Occupational duties and dust were not included in that analysis. Another Millennium Cohort Study analyzed RA and SLE in relation to burn pits, which might be relevant to particulate inhalation (23). In that study, there was no significant relationship to exposure, but there were also few self-reported cases confirmed by medical records. A more recent analysis using the VA Rheumatoid Arthritis Registry also investigated self-reported burn pit exposure and waste disposal, observing an increased risk in relation to anti-CCP positivity among persons with disease (5). Dust exposure in military occupations also was not considered in that analysis. Investigations exploiting the OEF/OIF/OND roster have provided insights into chronic conditions (8–11). Of note, one analysis using that cohort did study AI disease risk in association with PTSD, although military occupation was not considered (11). A more recent Millennium Cohort Study also has observed an association between PTSD and AI disease (6). There is no basis, however, to posit a role of dust exposure as an unmeasured confounder in such a relationship.

None of these prior studies of rheumatologic disease outcomes employed a JEM to assign risk linked to military duties. Even in studies of other health conditions linked to military service, this approach is used rarely. An early study of brain tumor risk among Air Force personnel marks one notable exception (24). The general concept of exploiting MOS codes as a surrogate for exposures was explored by Gadermann et al in 2014 (25). More recently, a 2019 investigation went farther by linking specific MOS codes to a set of specific inhalational exposures, essentially a JEM approach (26). Ours is the first application of an MOS-linked JEM in the study of RA and other AI conditions.

A number of challenges beyond exposure assessment limit the study of health outcomes in military cohorts generally. Epidemiological investigations that compare those with military service records with others typically face a “healthy soldier effect,” in which all-cause and specific mortality rates are reduced for a number of chronic diseases, but this effect appears to erode over time among veterans from multiple armed forces (27–29). Follow-up in VAHCS treatment is able to take advantage of this erosion to reveal elevated risk (28).

Shared immunological citrullinated targets have been described in the lungs and synovial tissue of patients with RA, which would imply that dust might be more likely to be associated with anti-CCP seropositive RA (30). Consistent with this, a population-based case-referent investigation of RA in Sweden (the Epidemiological Investigation of Rheumatoid Arthritis [EIRA] study) observed a strong association between RA and self-reported occupational exposure to silica, restricted to those with seropositive disease (RF in one analysis and anti-CCP in another),

whereas silica was not a risk factor for seronegative RA (31,32). A preferential relationship of occupational exposure to seropositive disease, however, has not been consistently reported. Further follow-up from EIRA, for example, found that, among male bricklayers and concrete workers and among electronics workers, risk was similarly elevated for seropositive and seronegative disease (ORs = seropositive, 2.9 [brick/concrete], 2.4 [electronics]; seronegative, 2.2 [brick/concrete], 2.6 [electronics]) (33). Another analysis, combining EIRA with additional Swedish national registry cases, estimated a silica exposure OR in men of 1.4 for seropositive disease versus 1.3 for seronegative disease (34). In a separate cohort study, also from Sweden, the estimated risks of seropositive and seronegative disease associated with silica and other inorganic dust were all similar (relative risks ranging from 1.27 to 1.46) (19). The number of persons with unknown serologic status in this analysis is a limitation that may arise from VA patients who have received specialty care in the community with testing that was not performed at a VA laboratory and whose results thus were not warehoused in the VINCI system. To the extent that such patients, when they report negative testing, are more likely to be retested at the VA, this could lead to systematic bias in missingness of data, yielding a case mix with a higher proportion of seronegative persons than would otherwise be observed.

Other potential limitations of our study should be kept in view. We could only study OEF/OIF/OND veterans who chose to receive their care through the VA system. Although our identification of cases used an approach validated in electronic medical record–based research, we did not carry out sample chart review and data extraction. The anticipated associations we observed between RA and its known risk factors, notably cigarette smoking and sex, support the validity of our case identification methods. Our JEM approach does not employ supporting industrial hygiene data and is likely prone to misclassification of exposure, although there is no reason to presume that this is systematic in any direction. Random exposure misclassification should bias toward the null and would not account for the associations we did observe. Moreover, as opposed to self-reported exposure, which dominates military occupational epidemiology, the JEM approach is free of recall bias, an advantage underscored in a 2020 review of exposure assessment in the epidemiologic study of chronic disease in military populations (35). The JEM that we applied considered likely inorganic dust exposure but did not address other inhalants, such as work-related organic dusts. Animal and textile dusts, for example, were associated with RA risk (seropositive and seronegative) in a recent study (36). Endotoxin (a key component of organic dusts) has been shown to potentiate silica-induced lung injury in an experimental model (37). We did not assess combined inorganic and organic dust exposure in terms of RA risk. Our failure to observe a monotonic association between RA and duration of military service could reflect a “healthy worker survivor effect,” which is well-recognized in occupational studies (38). In contradistinction, the exposure-associated risk of SSc, myositis, and

vasculitis was strongest among those with the longest service. Because the roster does not contain health condition information, we are precluded from taking earlier disease or symptom onset into account. Only 12% of our cohort was female, and, moreover, work exposures even within JEM categories likely differed systematically by sex. This complicates the interpretation of AI diseases for which sex is a powerful risk factor and may account for the statistically significant protective effect of exposure for SLE among women (but not men).

In conclusion, our study is notable for being the first large-scale investigation exploring dusty exposures in past military service as a risk factor for the future diagnosis of RA and other AI conditions. Although the excess odds we identified were modest, the large numbers of persons exposed suggests that the absolute number of theoretically attributable and potentially preventable cases of disease, especially RA, is not trivial.

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. Blanc 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.

Study conception and design. Schmajuk, Trupin, Blanc.

Acquisition of data. Ying, Trupin, Blanc.

Analysis and interpretation of data. Ying, Schmajuk, Trupin, Blanc.

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