Agent Orange Exposure and Risk of Idiopathic Pulmonary Fibrosis Among U.S. Veterans

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At a Glance

What is the current scientific knowledge on this subject?

Observational studies of inhaled particulates and gasses suggest that exposures such as smoking, chronic ambient air pollution, and vocational activities increase the risk of idiopathic pulmonary fibrosis (IPF). However, very little is known about the association between military exposures and IPF.

What does this study add to the field?

In this study, we leveraged the strength of the Veterans Health Administration electronic health record system to evaluate the association between exposure to Agent Orange, an herbicide and chemical defoliant used during the Vietnam War, and IPF. We found that presumptive Agent Orange exposure was associated with a 14% higher risk of developing IPF in an unadjusted analysis and an 8% higher risk of IPF after adjusting for known IPF risk factors. We noted numerically greater risk when limiting the cohort to Veterans who served in the army (highest burden of exposure, surrogate for dose response) and when restricting the cohort to more specific case definitions of IPF.

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ABSTRACT

Rationale: There is limited literature exploring the relationship between military exposures and idiopathic pulmonary fibrosis (IPF).

Objectives: To evaluate whether exposure to Agent Orange is associated with an increased risk of IPF among Veterans.

Methods: We used Veterans Health Administration data to identify patients diagnosed with IPF between 2010 – 2019. We restricted the cohort to male Vietnam Veterans and performed multivariate logistic regression to examine the association between presumptive Agent Orange exposure and IPF. We conducted sensitivity analyses restricting the cohort to army Veterans (highest theoretical burden of exposure) and a more specific case definition of IPF. Fine-Gray competing risk models were used to evaluate age to IPF diagnosis.

Measurements and Main Results: Among 3.6 million male Vietnam Veterans, 948,103 (26%) had presumptive Agent Orange exposure. IPF occurred in 2.2% of Veterans with Agent Orange exposure versus 1.9% without exposure (OR 1.14, 95% CI 1.12 – 1.16, p <0.001). The relationship persisted after adjusting for known IPF risk factors (OR 1.08, 95% CI 1.06 – 1.10, p < 0.001). The attributable risk among exposed was 7% (95% CI 5.3% - 8.7%, p<0.001). Numerically greater risk was observed when restricting the cohort to (1) Vietnam Veterans who served in the army and (2) a more specific definition of IPF. After accounting for the competing risk of death, Veterans with Agent Orange exposure were still more likely to develop IPF.

Conclusions: Presumptive Agent Orange exposure is associated with greater risk of IPF. Future research should validate this association and investigate the biological mechanisms involved.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease associated with high morbidity and mortality (1). In the current conceptual model of IPF, pulmonary parenchymal fibroproliferation develops with age as the lung is exposed to cumulative intrinsic and extrinsic stressors. Over time, this iterative cycle is hypothesized to lead to senescence of the alveolar epithelium and create a microenvironment of abnormal repair, manifesting in diffuse fibrotic lung disease (2).

Observational studies of inhaled particulates and gases suggest that exposures may increase the risk of IPF. Smoking is the most robustly defined of these risk factors (3-6). However, chronic ambient air pollution (7-9), and vocational activities associated with a high probability of dust, fume or gas inhalation (10-16) have also been implicated. These airborne pollutants can trigger alterations in mucosal surfaces, induce oxidative stress, and modify epigenetics, all mechanisms that have been described in the pathogenesis of IPF (2).

The United States (U.S.) Veteran population is demographically primed to develop IPF. Recent literature has suggested that the prevalence of IPF among Veterans may be higher than what has been described in other epidemiologic studies (17, 18). In addition to traditional risk factors of older age and tobacco use, Veterans have unique military exposures that may accelerate the development of pulmonary fibrosis. Agent Orange, a chemical defoliant so named because it was stored in barrels identified by an orange band during the Vietnam War, is an exposure of particular interest to the Veteran Health Administration (VHA) and has been studied extensively by the National Academy of Sciences. Agent Orange refers to a 50:50 formulation of 2,4-dichlorphenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) that was sprayed from 1962 to 1971 to strip the jungle canopy. The component 2,4,5-T also contained the unintended contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD),

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commonly referred to as “dioxin.” The association between dioxin and malignancies such as soft tissue sarcoma, lymphoma, and chronic lymphocytic leukemia have previously been described (19). However, there is limited literature exploring the relationship between Vietnam service, Agent Orange exposure and the subsequent development of IPF. In this study, we used the strength of the Veterans Affairs integrated electronic health record system to evaluate whether presumed exposure to Agent Orange is associated an increased risk of IPF among a national cohort of male U.S. Veterans who served in the Vietnam War.

METHODS

The University of California San Francisco and the San Francisco Veterans Affairs (VA) Healthcare System Institutional Review Boards approved this study.

Data Source and Patient Identification

We extracted the electronic health record data of Veterans who were enrolled in the VHA and had at least one inpatient or outpatient encounter at a VHA facility or a non-VHA facility paid for by VHA between 2010 and 2019 (Figure 1). We identified all patients who had an International Classification of Disease (ICD) diagnosis code for IPF (ICD-9-CM code 515, 516.3, 516.31 or ICD-10-CM code J84.111, J84.112, J84.89, J84.9, J84.10, J84.17) recorded between January 1, 2010 and December 31, 2019. Patients were considered to have IPF if they did not have any other diagnosis code for an alternative interstitial lung disease after the first diagnosis code for IPF as has been defined in other large electronic health record-based studies (20-23). We restricted the analytic cohort to male Vietnam Veterans (there were very few females with Agent Orange exposure) who were born between 1910 and 1957 to ensure that patients would have been between the ages of 18 and 65 years old during the Vietnam War and excluded those who died before the study start date (1/1/10). Over 95% of patients were between the age of 55 and 74 years old at the study start date, consistent with that the majority of the cohort

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being in their 20s and 30s during Vietnam service. We chose to study the incidence of IPF between 2010 - 2019 rather than immediately post-Vietnam to allow sufficient time lapse from exposure to disease as it is known that IPF develops as the lung ages, and to ensure consistency in the case definition of IPF per society guidelines.

Covariates including age, race, ethnicity, rural vs. urban residence, military service branch, and smoking history were obtained from electronic heath records. The VA defines rurality using the U.S. Department of Agriculture's Rural-Urban Commuting Area (RUCA) system (24). RUCA codes classify U.S. census tracts using measures of population density, urbanization and daily commuting. All Veterans were categorized into rural vs. urban residence based on home address at time of IPF diagnosis. A positive smoking history was defined as an ICD-9 or ICD-10 diagnosis code for tobacco use disorder during the study period but prior to IPF diagnosis. We also included a positive tobacco use assessment from the health factor database as indicative of smoking history. Patients were dichotomized into ever-smokers and never-smokers with unknown smoking history defaulting to the classification of never-smokers.

Presumptive Agent Orange exposure was identified by the "Agent Orange Flag," which is determined by a Veteran's military discharge paperwork. Veterans marked as having a Vietnam Campaign Medal, signifying military service with "boots on the ground" in Vietnam and thus at risk for Agent Orange exposure, received the Agent Orange Flag on their military discharge paperwork. Because of widespread spraying and unpredictability of wind dispersal patterns, it is not possible to quantify the exact extent of exposure for an individual Veteran.

Statistical Analysis

We examined characteristics of Vietnam Veterans with and without presumptive Agent Orange exposure using t-test for continuous variables and x^2 for categorical variables. We calculated adjusted odds ratios using regression standardization via parametric g-computation

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(25) from the model that included potential confounders (age, race, ethnicity, smoking history, rurality) that have been associated with IPF and were associated with Agent Orange in the bivariate analyses. We included rurality in our multivariable model based on prior literature suggesting an association between rural residence and pulmonary fibrosis in the Veteran population (17). Within the VA Healthcare System, rurality also correlates with socioeconomic status (SES) as rural Veterans often have lower education and income than urban Veterans (26). In addition, rurality captures potential exposures such as agriculture and farming that have also been postulated to be associated with IPF.

We allowed for an interaction between age*Agent Orange and smoking*Agent Orange as data from other disease processes such as asbestosis and lung cancer have noted compounding risk among patients with both tobacco use and occupational exposures (27). Due to interactions noted between Agent Orange*age and Agent Orange*smoking, we reported the odds of IPF among those with and without presumptive Agent Orange exposure by age and smoking in a subgroup analysis.

Attributable fraction of IPF among exposed (AF_e) was calculated using the formula $AF_e = (I_e - I_u) / I_e$ where I_e is the incidence in exposed group and I_u is the incidence in the unexposed group to estimate the percent of IPF cases among exposed that could plausibly be attributed to Agent Orange.

Fine-Gray competing risk models examined time to IPF onset with age as the time scale and accounting for death as a competing risk. Time to event was calculated from age at beginning of study period (1/1/10) until the age of IPF diagnosis, death, or end of study period (12/31/19) by assuming independent left truncation (28). We summarized age specific risk using the sub distribution hazard ratio (sHR) with associated 95% confidence interval.

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We conducted four additional sensitivity analyses. In the first, we required a computed tomographic (CT) scan of the thorax or a lung biopsy before the last IPF diagnosis code. Of note, Veterans have several options for healthcare coverage, including dual enrollment through both VA and non-VA (Medicare, Medicaid or employer sponsored) health insurance plans. For dual users, if the CT scans were completed outside the VA, these patients may not have been captured in this narrower cohort. In the second sensitivity analysis, we restricted the cohort to Vietnam Veterans who served in the army as a surrogate measure of dose response. For this analysis, we excluded Veterans who had served in the navy, air force, marines and coast guard during the Vietnam War. In the third sensitivity analysis, we restricted IPF diagnosis to patients with ICD codes 516.3, 516.31 or ICD-10-CM code J84.111, J84.112 and no subsequent codes for an alternative ILD, because these codes have been shown to have improved specificity (albeit reduced sensitivity) for IPF. In the final sensitivity analysis, we restricted the cohort to both army Veterans and the most specific ICD codes. All analyses were conducted using StataCorp Analysis Software version 16.1.

RESULTS

Among approximately 3.6 million male Vietnam Veterans who received care through the VHA between 2010 and 2019, 948,103 (26%) had an “Agent Orange Flag,” signifying presumptive dioxin exposure. The median age at the beginning of the study period among Veterans with Agent Orange exposure was 62.7 years old (Table 1). Veterans with Agent Orange exposure were more likely to be White (80% vs. 71%), non-Hispanic or Latino (88% vs. 83%), live in rural areas (39% vs. 37%) and have served in the Army (58% vs. 50%).

A total of 71,495 cases of IPF among male Vietnam Veterans were identified over the 10-year study period. IPF occurred in 2.2% of the male Vietnam Veterans exposed to Agent Orange versus 1.9% without presumptive Agent Orange exposure (unadjusted OR 1.14, 95% CI

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1.12 – 1.16, p <0.001) (Table 2). The relationship held true after adjusting for known IPF risk factors including age, race, ethnicity, smoking, and rural residence and accounting for the interaction between Agent Orange*age (p = 0.008) and Agent Orange*smoking (p = 0.026). The odds of IPF among Vietnam Veterans with presumptive Agent Orange exposure was 8% higher than those with no exposure (adjusted OR 1.08, 95% CI 1.06 – 1.10, p < 0.001). The attributable fraction of IPF among Veterans with presumptive Agent Orange exposure was 7% (95% CI 5.3% - 8.7%, p<0.001). Similar results were observed when restricting the IPF cohort to Veterans who had a CT scan within the VA Healthcare System before their last IPF diagnosis (univariate OR 1.12, 95% CI 1.10 – 1.15, p < 0.001; multivariate OR 1.06, 95% CI 1.03 – 1.08).

There were differential effects among Veterans with presumptive Agent Orange exposure by age and smoking with a higher point estimate of risk among the youngest age quartile (OR 1.15, 95% CI 1.11 – 1.20, p < 0.001) and among never-smokers exposed to Agent Orange (OR 1.13, 95% CI 1.08 – 1.18, p < 0.001) (Table 3).

In a sensitivity analysis (Table 4) restricting the cohort only to Veterans who served in the army as a surrogate measure for dose response, the odds of IPF was 15% higher among army Veterans with presumptive Agent Orange exposure (unadjusted OR 1.15, 95% CI 1.13 – 1.18, p <0.001) and 13% higher among army Veterans with presumptive Agent Orange exposure after controlling for other IPF risk factors (adjusted OR 1.13, 95% CI 1.09 – 1.17, p < 0.001). The odds of IPF was 10% higher among non-army Veterans (navy, air force, marines, coast guard) with presumptive Agent Orange exposure (unadjusted OR 1.10, 95% CI 1.09 – 1.13, p < 0.001) and 5% higher among non-army Veterans with presumptive Agent Orange exposure after controlling for other IPF risk factors (adjusted OR 1.05, 95% CI 1.01 – 1.09).

In a second sensitivity analysis restricting IPF diagnosis to more specific ICD codes, the odds of IPF was 17% higher among Veterans with presumptive Agent Orange exposure

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(unadjusted OR 1.17, 95% CI 1.12 – 1.23, p < 0.001) and 11% higher among Veterans with presumptive Agent Orange exposure after controlling for other known IPF risk factors (adjusted OR 1.11, 95% 1.05 – 1.17, p < 0.001).

In a final sensitivity analysis restricting the cohort to Army Veterans with more specific ICD diagnosis codes, the odds of IPF was 23% higher among Veterans with presumptive Agent Orange exposure (unadjusted OR 1.23, 95% CI 1.16 – 1.31, p < 0.001) and 17% higher among Veterans with Agent Orange exposure after adjusting for other IPF risk factors (adjusted OR 1.17, 95% CI 1.09 – 1.25, p < 0.001).

There were 810,808 (22%) deaths without IPF diagnosis during the study period. After accounting for competing risk of death, Veterans with presumptive Agent Orange exposure were still more likely to develop IPF (unadjusted sHR 1.13, 95% CI 1.10 – 1.15, p <0.001). Difference in percent cumulative incidence of IPF diagnosis over the 10-year study period in those with and without Agent Orange exposure using age as the time scaler is shown in Figure 2.

DISCUSSION

Among a national cohort of 3.6 million male Vietnam Veterans, presumptive exposure to Agent Orange was associated with a 14% higher risk of developing IPF in an unadjusted analysis and an 8% higher risk of IPF after adjusting for age, race, ethnicity, smoking history, and rural residence. Numerically higher odds were estimated when limiting the cohort to Veterans who served in the army (highest theoretical burden of Agent Orange exposure and surrogate measure for dose response) and when restricting the cohort to a more specific case definition of IPF. This study is the first to examine the impact of presumptive Agent Orange exposure on the subsequent development of IPF and contributes to a growing body of literature implicating the interplay between genetics and exposures in IPF pathogenesis.

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Smoking is among the most robustly defined risk factors associated with IPF (3-6) with epidemiological studies demonstrating a greater than two-fold increase in risk of IPF among ever-smokers (10, 20, 29-31). Recent literature has suggested that other environmental and occupational exposures such as ambient air pollution (7-9) and activities associated with exposure to vapors, gasses, dusts and fumes (10-15) may increase the risk of IPF as well. Recognizing the need to review this emerging evidence, the American Thoracic Society and European Respiratory Society published a joint statement examining the impact of occupational exposures on the burden of nonmalignant respiratory diseases (16). The pooled population attributable fraction of workplace exposure on IPF was 26% for vapors, gasses, dusts and fumes, with variability across exposure subtype. However, this literature has largely excluded the systematic evaluation of military exposures, an important vocational risk factor particularly relevant to Veterans.

The impact of military exposures on health is an area of concern for the VA. Prior literature examining the epidemiology of IPF among the Veteran population has noted higher incidence and prevalence rates compared to registry-based studies. This may in part be due to underlying demographics of the source population such as older age and tobacco use as well as vocational exposures unique to the Veteran population (17, 18). Agent Orange in particular has gained attention as an exposure of interest due to a combination of toxicology data documenting the harmful effects of dioxin and epidemiologic studies of disease among patients with occupational or environmental dioxin exposures. Although no longer used commercially in the U.S., dioxin is a highly persistent chemical pollutant that accumulates in fatty tissues. Once absorbed, the elimination half-life is estimated to be 7 to 11 years (32), which suggests lingering health implications even after an initial inhalational insult (33). U.S. Public Law 102-3, the Agent Orange Act of 1991, has directed the National Academy of Sciences to regularly review new scientific evidence describing the association between dioxin and health outcomes of Veterans

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(30). The committee categorizes health outcomes related to Agent Orange exposure into four groups based on the strength of epidemiologic literature and biological plausibility of the association: (1) sufficient evidence of an association, (2) limited or suggestive evidence of an association, (3) inadequate or insufficient evidence to determine an association or (4) limited or suggestive evidence of *no* association. To date, soft tissue sarcomas, lymphomas, and chronic lymphocytic leukemia have the strongest tier one level associations while most non-malignant respiratory conditions have had inadequate evidence to determine association (19). Our study adds to the literature and may support a future change in the categorization of IPF.

There is limited data examining the direct causal relationship between dioxin exposure in animal models and subsequent development of pulmonary fibrosis. However, several potential mechanisms through which dioxin may cause fibrosis have been proposed. Current literature examining the impact of dioxin exposure in animal models suggests that dioxin is immunotoxic (34) and has broad effects on gene expression (35, 36). Dioxin binds to and activates the aryl hydrocarbon receptor (Ahr), an important modulator of adaptative immune response and thus may contribute to pulmonary fibrosis through its chronic effects on lung inflammation (37). Toxicology studies have demonstrated that dioxin induces migration of pulmonary fibroblast through the AhR-axis (38) and that dioxin exposure is associated with portal fibrosis and cholangiofibrosis in rats (39). Ahr activation has also been shown to act on lung epithelial cells to alter mucin expression. Given the known association between a mucin gene polymorphism associated with mucous over-secretion and pulmonary fibrosis, direct effects on the airway epithelium could also be important. Further exploration of these mechanisms of actions and studies that evaluate whether dioxin exposure in animals *causes* pulmonary fibrosis are needed to support the biological plausibility of the epidemiologic association found in this study.

Our study has a number of limitations. First, we used an ICD code-based algorithm to identify cases of IPF, which have not been individually case validated. Accurate identification of

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IPF cases using billing code-based algorithms depend on the characteristics of the underlying source population. Prior case validation studies of EHR cohorts have reported positive predictive values ranging from 44% to 83% depending on the demographics of the population and the specificity of the algorithm used (23, 40). We hypothesize that given the underlying demographics of the Veteran population (older age, male sex, high prevalence of tobacco use), the pre-test probability of IPF is higher than cohorts with younger, more heterogenous populations. We thus started with a broader more sensitive case definition of IPF and subsequently conducted sensitivity analysis with more specific IPF case definitions to ensure consistency of results. Reassuringly, the conclusions remained internally consistent and were in fact numerically greater when utilizing more specific ICD codes for IPF. Second, we used an Agent Orange Flag, which is derived from military discharge paperwork, as indicative of dioxin exposure. Patients receive an Agent Orange Flag if they served with “boots on the ground” in Vietnam. Although it would be informative to allow differentiation among Veterans with Agent Orange flags over a gradient of exposure likelihood, for example, by deployment to areas of highest defoliant use, this data is not currently available in the electronic health record. We thus conducted a sensitivity analysis restricting the cohort to army Veterans as a surrogate for dose response as they were most likely to have greater time with boots on the ground. While the above limitations likely introduce some level of false positives into our case definition and exposure determination, we would expect such systematic classification error (i.e., including minimally exposed Veterans in the exposure category) to bias results toward the null. That an association was still observed, therefore, is notable. Third, we accounted for the competing risk of death via Fine-Grey modeling. This model accounts for survival bias during the study period (2010 – 2019) but not prior to study entry. Analysis of cases prior to 2010 was beyond the scope of this study. Fourth, although limited animal studies demonstrate that dioxin induces migration of pulmonary fibroblasts and is associated with fibrogenesis in the liver, studies examining whether dioxin exposure in animals *causes* pulmonary fibrosis are needed. Lastly, although we

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adjusted for known IPF risk factors, observational data can never completely rule out the possibility of confounding. It is possible that the association noted in this study is due to an upstream risk factor or a co-exposure. For example, although Agent Orange was the primary herbicide used during the Vietnam War, an arsenic-based herbicide, Agent Blue, was also used in South Vietnam. Although chronic arsenic exposure has not been linked epidemiologically with IPF, it has been associated with respiratory conditions in humans and fibrosis in animal models (41, 42). For the above reasons, further exploration of the relationship between military service during Vietnam, Agent Orange, and IPF is warranted before definitive conclusions can be drawn. Further studies that investigate the association between Agent Orange exposure and IPF among the resident civilian and military populations of Vietnam could also lend important insight on the impact of dioxin exposure in IPF pathogenesis.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, our findings suggest that Vietnam Veterans with presumptive Agent Orange exposure are at higher risk for IPF. Additional work is needed to evaluate whether this association between Agent Orange and fibrosis is also seen in other forms of interstitial lung disease. Future studies that further refine the methodology for case and exposure identification and examine the potential biological mechanisms involved are needed and will help facilitate better understanding of pulmonary fibrosis among the U.S. Veteran population.

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Figure 1. Cohort Identification.

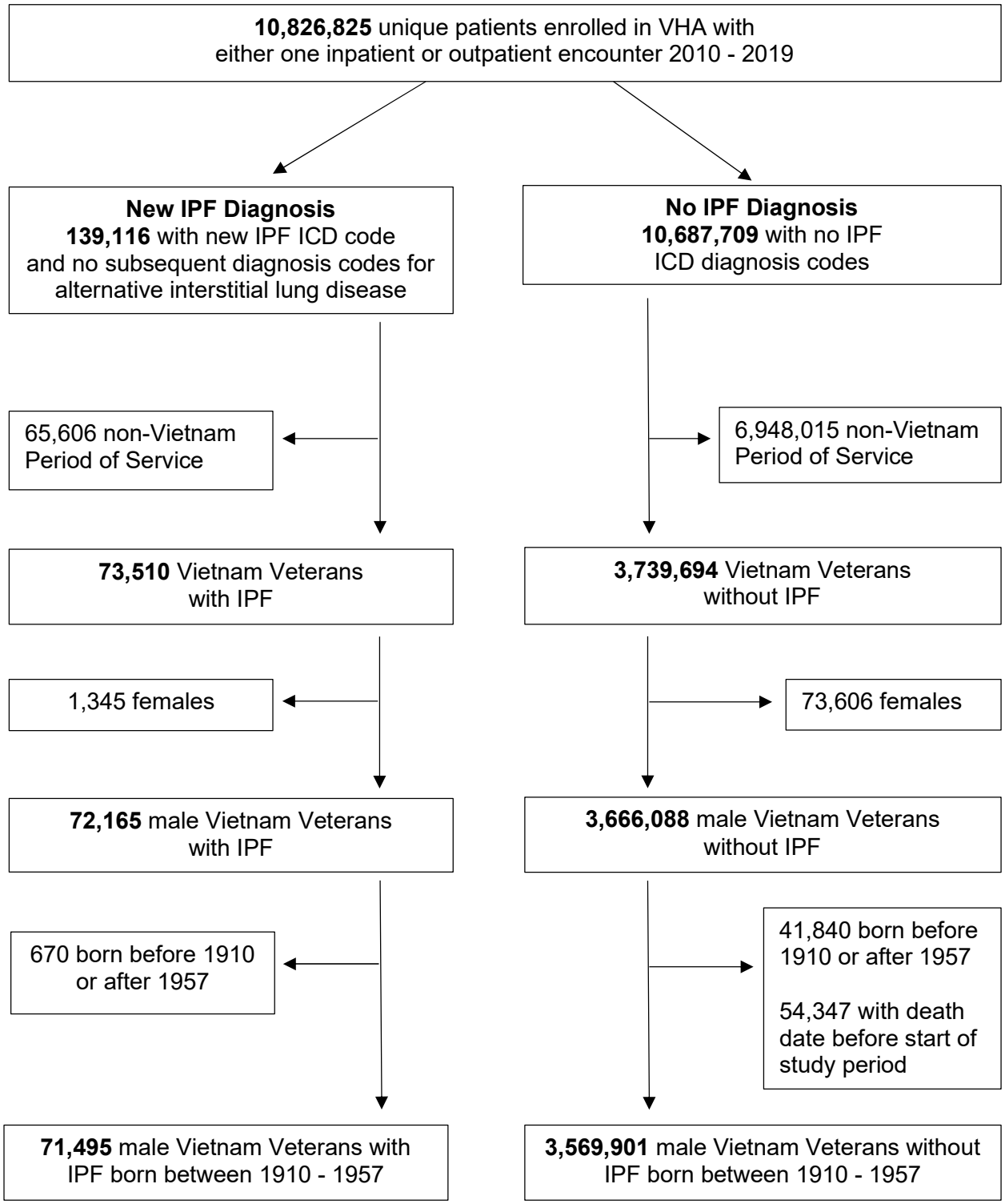

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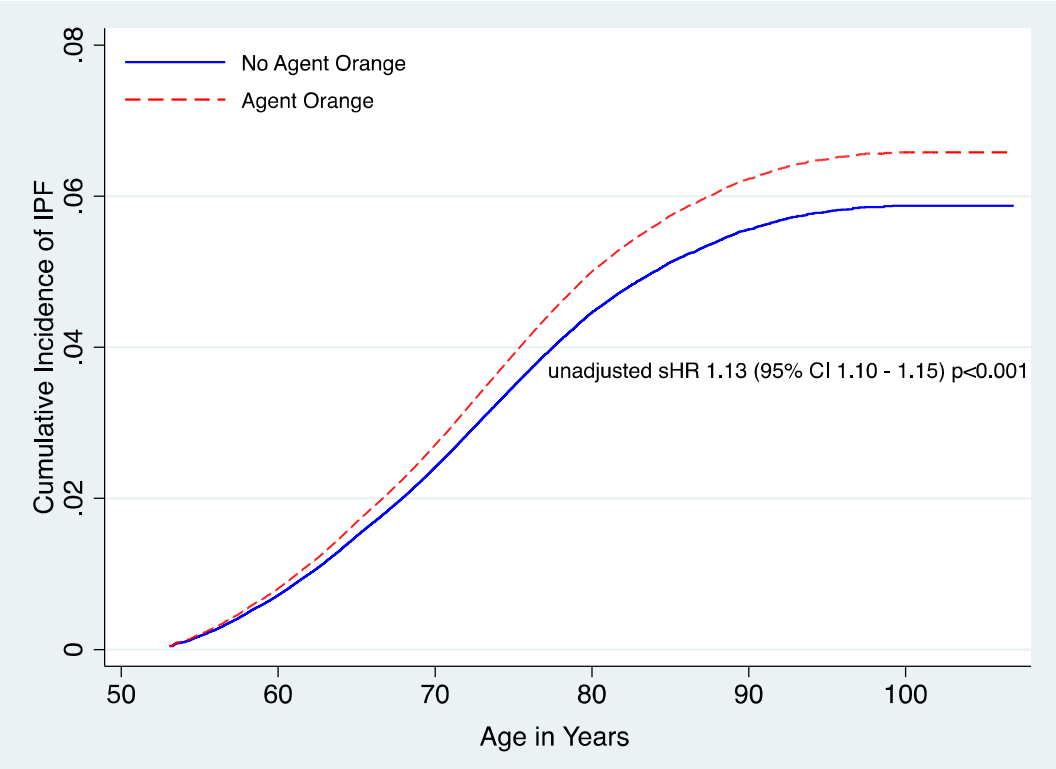
Figure 2. Cumulative Incidence of Idiopathic Pulmonary Fibrosis in Veterans With and Without Agent Orange Exposure.



Time to event was calculated using age as the time scaler from beginning of study period (January 1, 2010) until the date of IPF diagnosis, death, or the end of study period (December 31, 2019) assuming independent left truncation.

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Table 1. Characteristics of U.S. Vietnam Era Male Veterans by Agent Orange Exposure

	No Agent Orange Flag (N = 2,693,293)	**Agent Orange Flag** (N = 948,103)
Idiopathic Pulmonary Fibrosis	51,086 (1.9%)	20,409 (2.2%)
Demographics		
Median Age (IQR)	62.9 (59.5 – 66.9)	62.7 (61.0 – 64.8)
Race (Column %)		
White	1,922,947 (71%)	762,049 (80%)
Black or African American	333,894 (12%)	85,772 (9%)
Asian/Native Hawaiian or Pacific Islander/American Indian	49,599 (2%)	17,707 (2%)
Unknown	386,853 (14%)	82,575 (9%)
Ethnicity (Column %)		
Hispanic or Latino	101,550 (4%)	36,761 (4%)
Not Hispanic or Latino	2,226,246 (83%)	836,539 (88%)
Unknown	365,497 (14%)	74,803 (8%)
Rurality		
Rural	989,166 (37%)	371,684 (39%)
Unknown	120,926 (4%)	27,771 (3%)
Tobacco Use	1,656,838 (62%)	588,190 (62%)
Military Service		
Army	1,338,519 (50%)	554,398 (58%)
Navy	558,554 (21%)	153,891 (16%)
Air Force	487,227 (18%)	105,045 (11%)
Marine	265,104 (10%)	131,193 (14%)
Coast Guard	25,599 (1%)	2,130 (0.2%)
Other	18,290 (0.7%)	1,446 (0.2%)

Age calculated at beginning of study (1/1/10). P-values were calculated with t-test for continuous variables and chi-square test for categorical variables. All p-values were <0.001.

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Table 2. Odds of Idiopathic Pulmonary Fibrosis Among Male Vietnam Veterans with Agent Orange Exposure vs. No Agent Orange Exposure

	Odds Ratio (95% CI)	p-value
Overall Unadjusted	1.14 (1.12 – 1.16)	<0.001
Overall Adjusted	1.08 (1.06 – 1.10)	<0.001

Adjusted multivariable regression controlled for known IPF risk factors (age at beginning of study, race, ethnicity, smoking history, rurality) and interactions between Agent Orange*age and Agent Orange*smoking.

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Table 3. Odds of Idiopathic Pulmonary Fibrosis Among Male Vietnam Veterans with Agent Orange Exposure vs. No Agent Orange Exposure by Subgroup

	Odds Ratio (95% CI)	p-value
Subgroups (Adjusted)		
Age at Beginning of Study Period		
Quartile 1: 53 – 60.1 years old	1.15 (1.11 – 1.20)	<0.001
Quartile 2: 60.1 – 62.8 years old	1.08 (1.04 – 1.11)	<0.001
Quartile 3: 62.8 – 66.3 years old	1.06 (1.03 – 1.10)	<0.001
Quartile 4: 66.3 – 100 years old	1.02 (0.97 – 1.06)	0.482
Tobacco Use		
Smoker	1.07 (1.05 – 1.09)	<0.001
Non-Smoker	1.13 (1.08 – 1.18)	<0.001

Due to non-linearity of variable age, age at beginning of study period (1/1/2010) was subcategorized into equal quartiles. Adjusted multivariable regression controlled for IPF risk factors (age, race, ethnicity, smoking history and rurality) and accounted for interactions between Agent Orange*age and Agent Orange*smoking in the model. The subgroup analysis compares risk of IPF among Veterans with Agent Orange exposure vs. no Agent Orange exposure (reference group) for each interaction subgroup while holding other variables constant.

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Table 4. Odds of Idiopathic Pulmonary Fibrosis Among Male Vietnam Veterans with Agent Orange Exposure vs. No Agent Orange Exposure (Sensitivity Analysis)

	N		Odds Ratio (95% CI)	p-value
Restricted to Army	IPF: 38,326	No-IPF: 1,854,591	Unadjusted 1.15 (1.13 – 1.18) Adjusted 1.13 (1.09 – 1.17)	<0.001 <0.001
Restricted to Most Specific IPF ICD Codes	IPF: 8,818	No-IPF: 3,569,901	Unadjusted 1.17 (1.12 – 1.23) Adjusted 1.11 (1.05 – 1.17)	<0.001 <0.001
Restricted to Army + Most Specific IPF ICD Codes	IPF: 4,620	No-IPF: 1,854,591	Unadjusted 1.23 (1.16 – 1.31) Adjusted 1.17 (1.09 – 1.25)	<0.001 <0.001

Adjusted multivariable regression controlled for age, race, ethnicity, smoking history, and rurality and accounted for interactions between Agent Orange*age and Agent Orange*smoking in the model.

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