Estimated Incidence of Multiple Sclerosis Among United States Armed Forces Personnel Using the Defense Medical Surveillance System

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ABSTRACT Background: The comprehensive longitudinal medical records of the U.S. Armed Forces provide a valuable tool to study the epidemiology of multiple sclerosis (MS) in persons from a diverse demography. Objectives: This study's objectives were to estimate the frequencies, incidence rates (IRs), trends, and correlates of MS among active component U.S. military members from 2000 to 2009. Methods: An International Classification of Diseases, 9th Revision, code algorithm was used to identify MS cases from the Defense Medical Surveillance System database. IRs were determined by dividing the number of cases of MS by the total person-time of the active component during each year. Results: During the 10-year period, there were 1,827 incident cases of MS with an overall IR of 12.9 per 100,000 person-years (p-yrs). Black non-Hispanics had a higher IR: (18.3 per 100,000 p-yrs) than White non-Hispanics (12.5 per 100,000 p-yrs). The incidence of MS by birth month and geographic home did not show a clear trend of seasonality or latitudinal gradient. Conclusions: This investigation is the first longitudinal study of MS incidence in U.S. Armed Forces personnel. The study demonstrates higher IRs than seen in other populations and reveals a novel pattern of MS incidence by race.

INTRODUCTION

The diagnosis of multiple sclerosis (MS) is particularly significant to the military population on two accounts. First, the cost associated with treatment, potential disability, and possible separation from military service may be substantial. Second, the diagnosis of MS negatively impacts military readiness and worldwide deployability of affected individuals. The military's comprehensive, longitudinal medical records and data accession resources provide a unique opportunity to explore the impact of MS on the U.S. Armed Forces and have the potential to further elucidate its epidemiology.

Risk factors of MS have been previously studied in the U.S. military population using the Physical Evaluation Board's databases and the Department of Defense Serum Repository.[1,2] These studies examined the association of Epstein–Barr virus and serum 25-hydroxyvitamin D levels to MS diagnosis within the military population. Alternatively, epidemiological characteristics of the U.S. veteran population have been studied by Kurtzke et al[3] and Wallin et al.[4] Although these studies have examined risk factors and epidemiological characteristics of military and veteran populations, no study has examined the IR of MS in the active component of the U.S. military. We report the frequencies, IRs, trends, and correlates of MS among active component U.S. military members from 2000 to 2009.

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METHODS

The cohort for this study included all uniformed personnel who served in an active component of the U.S. military during any point in time from January 2000 to December 2009. National Guard and reserve component service members were not included. Incident cases of MS during the study period were determined using medical records of the Defense Medical Surveillance System (DMSS). Although medical encounter data has been available in the DMSS since 1997, for convenience we chose to examine a 10-year period. The DMSS includes all inpatient and ambulatory care provided at a U.S. military treatment facility or purchased through the military health system. Incident cases for this study were defined as (1) an individual with one outpatient encounter of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) 341.xx (demyelinating disease) or ICD-9 340 (MS), followed by one outpatient or inpatient encounter with ICD-9 340; or (2) One inpatient encounter for ICD-9 341.xx, followed by an outpatient encounter with ICD-9 340; or (3) One inpatient encounter for ICD-9 340.

Several additional parameters were established. First, only the primary diagnostic position (dx1) was considered; this is the first provider-assigned diagnostic code in an electronic medical record entry. Second, an individual could only become a case once per lifetime, and if a case was determined to have been a prevalent case (i.e., they had a MS diagnosis before the study period), they were removed from the study. Finally, in those individuals who were defined as MS cases based on two or more medical encounters there was no time limit restriction placed on the period between initial presentation and the case-defining diagnosis.

Demographic data contained in DMSS for these individuals included: age, race, sex, service, rank, birth month, and home-of-record state. Home-of-record state served as a surrogate for birth state in this study, and individuals with a home-of-record state listed as California were divided by zip code into Northern and Southern California for latitude analysis. The time between the initial and case-defining encounter was collected. The total number of inpatient and outpatient medical encounters for MS during the surveillance period for each incident case was also obtained.

Incidence density rates were determined by dividing the number of cases of MS by the total person-time of the active component population during each year. These rates, referred to here as incidence and IRs, were calculated for separate demographic subgroups of interest. Incidence by birth month and home-of-record state was determined by dividing the number of cases of MS by the total population within each category for this time period. Denominators were calculated in the standard way for epidemiologic study of IRs. All individuals in the surveillance population (active component service members of the U.S. Armed Forces) began contributing person-time at the beginning of the study period (January 2000). Person-time was censored once an individual became an MS case, once they left service or died, or at the end of the study period.

DMSS has a demographic record for all active component service members, which allowed us to calculate the complete time an individual contributed to the denominator. For example, if a service member began service on January 1, 2005 and left service on January 1, 2009 she/he would have contributed 4 years of person-time to the denominator. If that service member was determined to be an incident case of MS on January 1, 2006, they would only have contributed 1 year of person-time to the denominator. All person-time after the service member became a case would have been censored, because they were no longer "at risk" of becoming a case.

RESULTS

Between 2000 and 2009, there were 1,827 incident cases of MS among active component armed forces members, for an overall IR of 12.9 per 100,000 person-years (p-yrs) (Table I). During the 10-year period, the IRs of MS were stable (Fig. 1).

The overall IR was greater among females (*n* = 660; IR: 32.0 per 100,000 p-yrs) than males (*n* = 1,167; IR: 9.6 per 100,000 p-yrs), and this trend was consistent throughout the 10-year surveillance period. The IR increased with age at diagnosis, from 2.1 cases per 100,000 p-yrs in those less than 20 years old to 26.9 per 100,000 p-yrs in those 40 years old or older.

TABLE I. MS: Counts and Rates, Active Component, 2000–2009

Variable	Count	Percentage	Rate per 100,000 person-years	IR Ratio
Total	1,827	100.0	12.9	
Sex				
Males	1,167	64	9.6	-
Female	660	36	32.0	3.3
Age at Diagnosis				
<20	30	2	2.1	0.3
20–24	323	18	6.7	-
25–29	401	22	13.8	2.1
30–34	339	19	16.7	2.5
35–39	390	21	21.9	3.3
40+	344	19	26.9	4.0
Race				
White non-Hispanic	1,124	62	12.5	-
Black non-Hispanic	462	25	18.3	1.5
Hispanic	133	7	9.4	0.8
Other	108	6	8.4	0.7
Service				
Army	571	31	11.5	1.9
Navy	444	24	12.5	2.1
Air Force	639	35	18.3	3.1
Marines	108	6	6.0	-
Coast Guard	65	4	16.8	2.8

Black non-Hispanics had an overall higher IR (*n* = 462; IR: 18.3 per 100,000 p-yrs) than White non-Hispanics (*n* = 1,124; IR: 12.5 per 100,000 p-yrs), Hispanics (*n* = 133; IR: 9.4 per 100,000 p-yrs), and those categorized as "Other" (*n* = 108; IR: 8.4 per 100,000 p-yrs). These higher rates among Blacks were consistent in both males and females throughout the 10-year period (Fig. 2 and Table I).

IRs were higher in the Air Force (*n* = 639; IR: 18.3 per 100,000 p-yrs) than any other service during this time (IRs, Army: 11.5 per 100,000 p-yrs; Navy: 12.5 per 100,000 p-yrs; Marines: 6.0 per 100,000 p-yrs; Coast Guard: 16.8 per 100,000 p-yrs), and these rates were consistently higher throughout all 10 years (Fig. 3 and Table I). The Coast Guard was not included in trend analysis because of low frequency of cases, which led to unstable rates.

The incidence of MS by birth month did not show a clear trend of seasonality among cases and specifically did not indicate increased incidence in spring months (Fig. 4). Incidence by home-of-record state did not show a clear latitudinal gradient from North to South (Fig. 5).

The time interval between the initial presentation and the case-defining encounter was between 0 and 90 days for 54% (*n* = 983) of the cases, and 23% were diagnosed by a time interval ≥365 days (Fig. 6). There were 18,536 medical encounters for MS following initial presentation among cases during this 10-year period;18,289 were outpatient encounters and 247 were inpatient encounters. The majority of cases (*n* = 1,650) were defined by the first case definition: an individual with one outpatient encounter of ICD-9 341.xx or ICD-9 340, followed by one outpatient or inpatient encounter

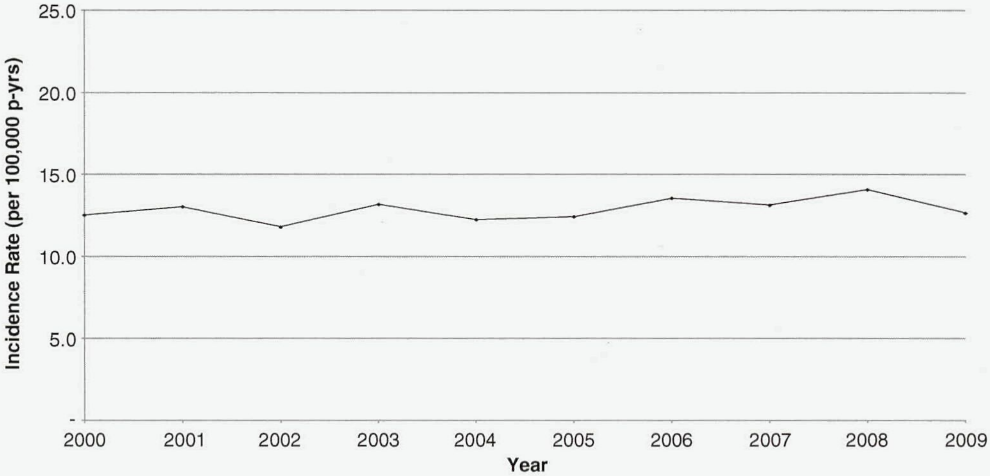

FIGURE 1. MS overall IRs active component 2000–2009.

with ICD-9 340 (Table II). A third of all cases (n = 604) had previously deployed to support Operation Iraqi Freedom or Operation Enduring Freedom.

DISCUSSION

Incidence of MS varies by geographic location and latitude. Hirtz et al[5] performed a systematic review of worldwide MS incidence and found the median estimate of the annual incidence was 4.2 per 100,000 p-yrs (range 0.8–12.0). The only incidence study cited from North America (Minnesota) used data from 1985 through 2000, and reported 7.5 cases per 100,000 population per year.[6] This higher IR may be indicative of Minnesota's latitude. The paucity of MS incidence studies in the United States may reflect the limited number of comprehensive, longitudinal databases available to characterize the disease in this way.

Our study was ideally suited to contribute to the incidence data of MS because of the unique characteristics of the DMSS database. DMSS integrates data from sources worldwide to continuously track the military and medical experiences of service members throughout their military careers. As a longitudinal relational database currently containing data relevant to more than 12 million individuals since 1990, DMSS enables calculations of rates.[7] This study demonstrated stable IRs of MS diagnoses from 2000 to 2009 among active component members. These rates (cumulative IR = 12.9 per 100,000 p-yrs) are much higher than the reported median IR worldwide (4.2 per 100,000 p-yrs) and higher than those found in the other North American study.[5] Our cases of MS represent individuals from all 50 states as well as U.S. territories and foreign countries.

The high incidence of MS in our study may reflect the imprecision of an ICD-9-based case definition. It may also represent an increased risk for MS among active component members of the armed forces. The U.S. military is composed of mostly young and middle aged adults, whereas general populations include all age groups including the very young and very old, who are at much less risk of incident clinical

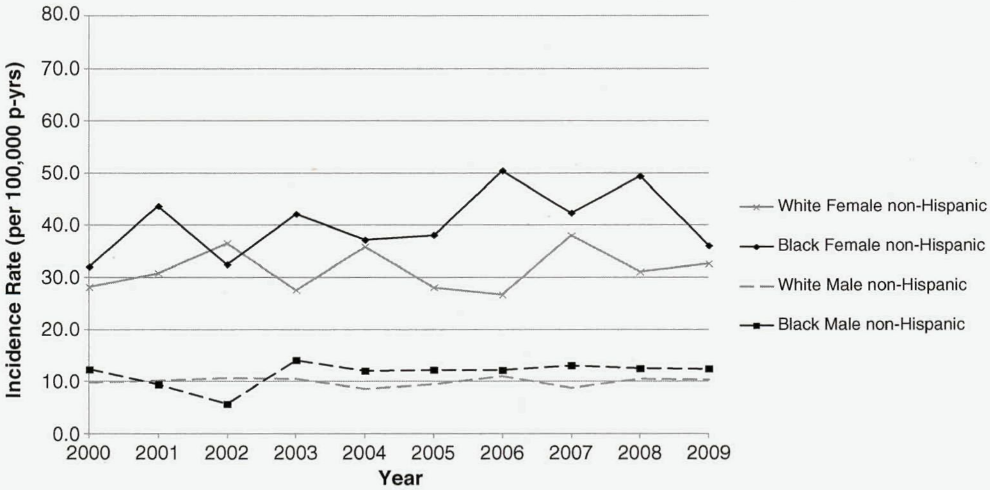

FIGURE 2. MS IRs by sex and race (Black and White), active component 2000–2009.

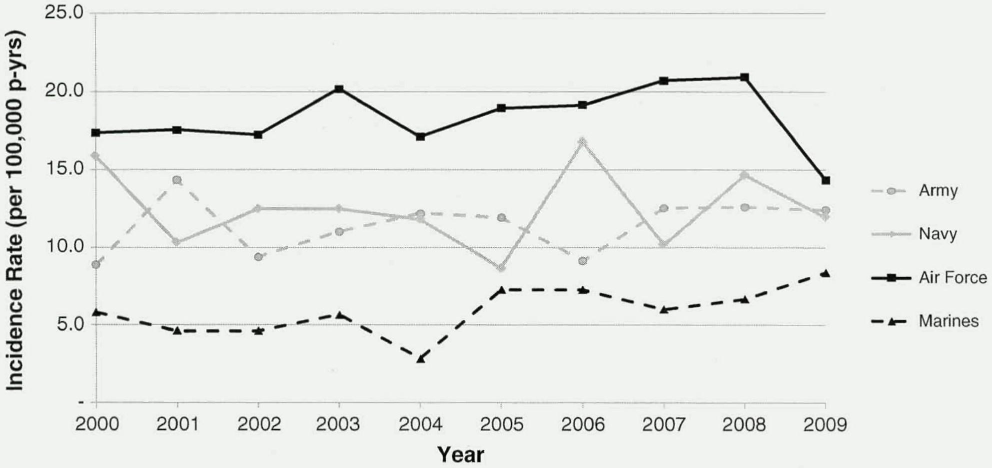

FIGURE 3. MS IRs by Service, active component 2000–2009.

presentation of MS. Additionally, access to health care is very high in the military; this increased access to care may account for these increased rates. The factor(s) that may elevate this risk and lead to increased rates of MS is a subject for further study.

The IR of MS remained stable over the 10-year period. This is of interest since previous studies have suggested severe stressful life events may increase the risk of MS, but the evidence has not been consistent.[8,9] This risk is generally thought to become evident years or decades later. Our study has stable and consistent data collection for 2 years before the onset of large-scale troop deployments to Afghanistan and Iraq, and the following 8 years of sustained combat operations with associated environmental, physical, and mental stresses. When viewed over the past decade, these stressors did not appear to influence the complex neurological etiology of MS. It is certainly possible that enough time has not elapsed to observe an increase in MS incidence in this population, and we will continue to follow IRs over the coming decade.

Females had a much higher incidence of MS compared to males in our study. Hirtz et al[5] found an incidence twice as high among females compared to males, whereas we found an incidence 3.3 times higher among females. This increased risk among females compared to males is a characteristic commonly seen in other autoimmune diseases. The peak age of onset has previously been regarded as being between 20 and 30 years, whereas we found an increased incidence in the 35 and older category. This is consistent, though, with more recent literature, where the age at diagnosis appears to be in the mid to late 30s. A recent study in Iceland reported a mean age at diagnosis of 36.3 years, and an analysis from the North American Research Committee on Multiple Sclerosis reported an MS diagnosis from 34.5 to 37.4 years, depending on racial/ethnic groupings.[10,11]

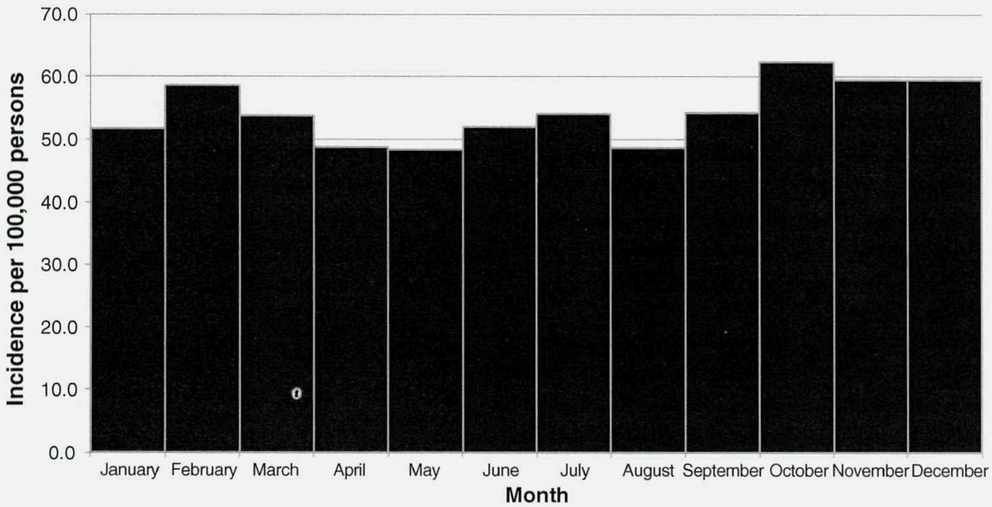

FIGURE 4. MS IRs by birth month, active component 2000–2009.

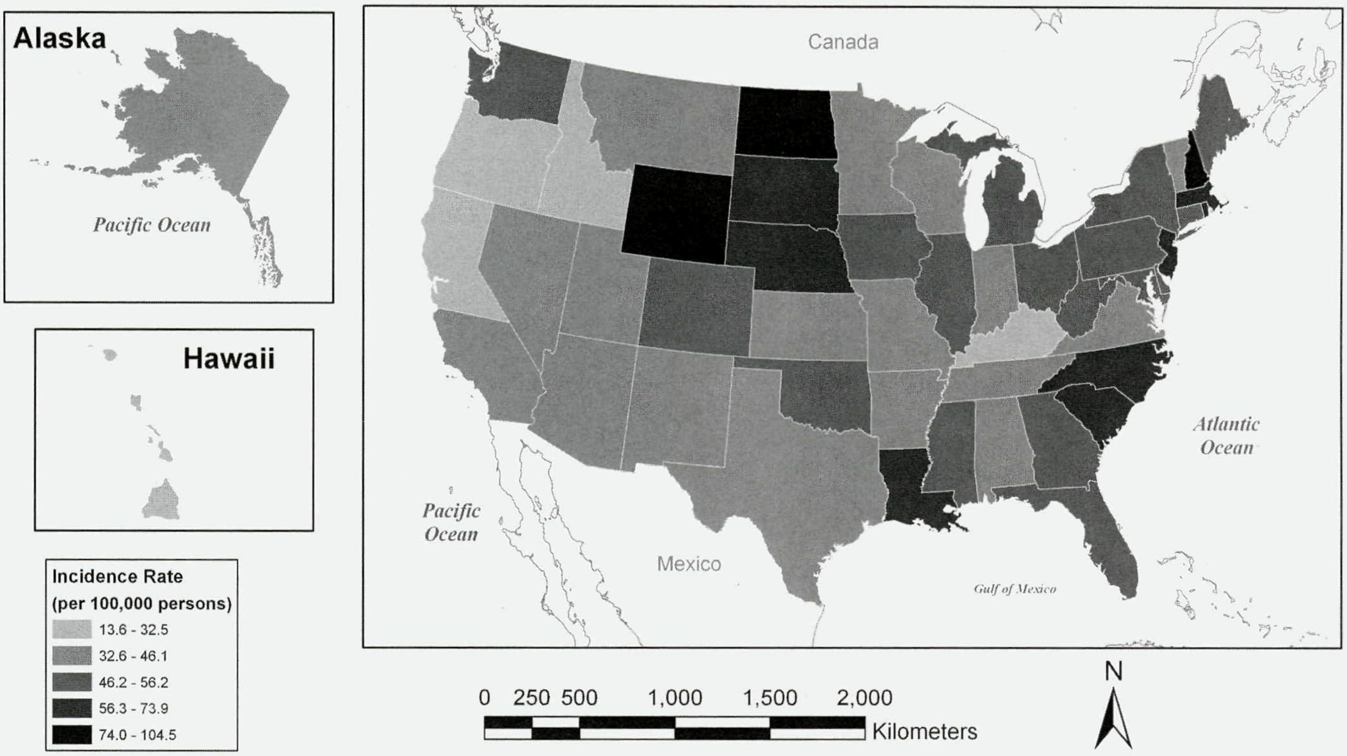

FIGURE 5. MS IRs by state, active component 2000–2009.

IRs of MS diagnoses among blacks, and specifically black females, were higher than their white counterparts (incidence risk ratio = 1.5). This relationship in an adult population has not been previously seen in literature and has only recently been described in children.[12] The novelty of this finding is perplexing. Do these results represent an unidentified risk factor in our population among black females, or are these results representative of actual risk not previously appreciated in the general U.S. population? The active component of the armed forces represents a diverse racial composition. This population has high access to free health care irrespective of race or socioeconomic background. This combination of robust racial representation and increased access to care may reveal a racial group at increased risk unrecognized in previous studies.

Service specific rates observed in our study may reflect differences in demographic characteristics. For instance, there may be more females in the Air Force than the other services, or perhaps the age stratifications differ between the services and contribute to these IRs. Another possible explanation for service specific rates is differences in diagnostic practices between services. Multiple regression analysis in future studies is required to further evaluate these findings.

The latitude gradient observed in MS has frequently been correlated with a proxy such as vitamin-D.[2,13] This study used home-of-record state and birth month as surrogates for latitude and possible early childhood or in utero vitamin D

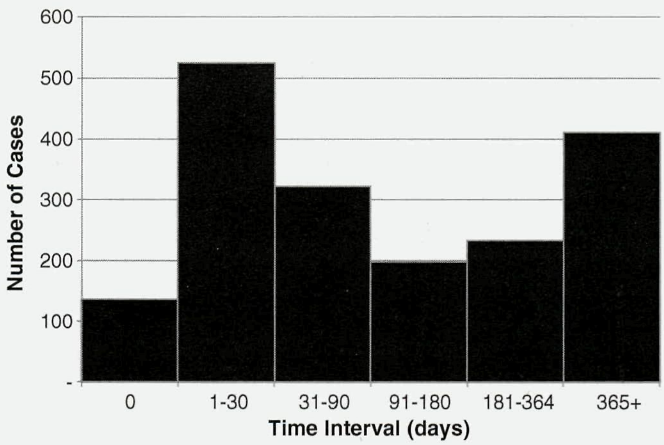

FIGURE 6. Time interval between initial diagnosis and case definition diagnosis, among cases.

TABLE II. Total Counts per Case Definition

Case Definition	Total
Case Definition 1: One Outpatient Encounter for ICD-341 or 340, Followed by One Outpatient or Inpatient Encounter for ICD-340	1,650
Case Definition 2: One Inpatient Encounter for ICD-341, Followed by One Outpatient Encounter With ICD-340	41
Case Definition 3: One Inpatient Encounter for ICD-340	136

exposure. We did not find a pattern of correlation between cases of MS and home-of-record state or birth month. This could be as a result of a number of factors. Though a previous study using Veterans Affairs data showed a strong correlation between measures of effect for birth state and state of entry into the service, we recognize that home-of-record state may not be an accurate proxy for birth state.[4] Another possibility is that over the past half century the association between latitude of birth and subsequent MS diagnosis has gradually weakened because of changes within society. It has recently been suggested that this association is weakening, or perhaps altogether erroneous.[4,14]

The bimodal distribution of time interval between initial presentation and the case-defining encounter is likely as a result of several factors. The high access to care in this population enables individuals who may have a provisional diagnosis of MS to be followed-up within a short time interval. This characteristic is also likely reflected in the overall frequency of inpatient and outpatient encounters observed. On the other hand, the natural history of MS is often indolent, and exacerbations of symptoms may have intervals of several months to years. This characteristic might contribute to the later, lower mode in the distribution.

This study's findings should be interpreted with consideration of certain limitations. The cases in this study were determined exclusively with ICD-9 code diagnoses, which reflected a case definition based on healthcare provider-assigned diagnostic codes entered into the electronic medical record of service members. Similarly, Diaz et al[15] used a diagnostic code-based case definition of MS to obtain IRs in Chile. Our algorithmic case definition was attributable to the nature of the DMSS data; its reliability in identifying actual cases of MS is unknown. However, the VA Center of Excellence on MS used a similar algorithmic methodology to identify MS cases in the Veterans Health Affairs database to populate their MS surveillance registry.[16] Thus, a statistical algorithm was applied to an administrative database to ascertain cases. This process produces an estimate of actual cases of MS.

Our case definition required either an inpatient diagnosis of MS or at least two outpatient diagnoses of MS or an outpatient or inpatient diagnosis of demyelinating disease followed by one outpatient or inpatient diagnosis of MS. This flexibility increased the likelihood of our definition capturing "true" cases of MS, though limitations remained. MS is a clinical diagnosis with no single confirmatory lab or radiologic test, and it often requires several months to make a diagnosis. Ideally, a neurologist specialized in evaluating and treating MS should make the diagnosis. As a result, a detailed chart review with accurate application of clinical criteria is the only standardized way to define a case of MS. An adjudication of our cases through this type of process in future studies may reveal an overestimated incidence of MS. Such an analysis was beyond the scope of this initial descriptive epidemiologic study.

This study was also limited because our data was part of a passively collected electronic health database. As a result, there may be missed cases. The high access to health care mitigates this limitation, but it cannot be entirely eliminated. The Healthy Worker/Warrior Effect also should be considered; this effect would potentially result in lower rates of MS in the military population compared to the general population. Additionally, our study cannot be generalized beyond the active component of the armed forces population during this time period.

CONCLUSIONS

In summary, this study provides the first evaluation of MS incidence among U.S. Armed Forces. Constructed from a robust and consistent data collection system, this study demonstrates a stable incidence of MS before and during sustained combat operations and foreign deployments, where significant physical and emotional stress has been placed on individuals serving in the U.S. Armed Forces. This study describes higher rates of MS than generally seen in other populations and reveals a novel pattern of MS by race. Further studies are being developed that rely on data collection directly from military neurology clinics, reducing potential misclassification and providing opportunities to explore diagnostic and treatment research questions.

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