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The Gulf War era multiple sclerosis cohort: age and incidence rates by race, sex and service

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We characterize here a new nationwide incident cohort of multiple sclerosis from the US military-veteran population. This cohort provides an update to the only other US nationwide incidence study of multiple sclerosis performed during the 1970s. Medical records and data from the Department of Defense and Department of Veterans Affairs for cases of multiple sclerosis who served in the military between 1990, the start of the Gulf War era, and 2007 and who were service-connected for this disorder by the Department of Veterans Affairs from 1990 on, were reviewed. A total of 2691 patients were confirmed as having multiple sclerosis: 2288 definite, 190 possible, 207 clinically isolated syndrome and six neuromyelitis optica. Overall racial categories were White, Black and other, which included all Hispanics. There were 1278 White males and 556 females; 360 Black males and 296 females; and 200 others, 153 (77%) of whom were Hispanic. Mean age at onset of 30.7 years did not differ significantly by race or sex. Age at onset was 17–50 years in 99%, the same age range as 99% of the military. Average annual age specific (age 17–50 years) incidence rates per 100 000 for the entire series were 9.6 with 95% confidence interval of 9.3–10.0. Rates for Blacks were highest at 12.1 with confidence interval 11.2–13.1, Whites were 9.3 (interval 8.9–9.8) and others 6.9 (interval 6.0–7.9). For 83 Hispanics defined for 2000–07, the rate was 8.2 (interval 6.5–10.1). Much smaller numbers gave rates of 3.3 for Asian/Pacific Islanders and 3.1 for native Americans. Rates by sex for Whites were 7.3 and 25.8 male and female, respectively, for Blacks 8.4 and 26.3, and for Hispanics 6.6 and 17.0. Rates by service were high for Air Force (10.9) and Army (10.6), medium for Navy (9.1) and Coast Guard (7.9), and low for Marines (5.3). Relative risk of multiple sclerosis was 3.39 female:male and 1.27 Black:White. These new findings indicate that females of all races now have incidence rates for multiple sclerosis some three times those of their male counterparts and that among these groups, Blacks have the highest and others (probably including Hispanics) the lowest incidence rates regardless of sex or service. The low rate for Marines is unexplained. This Gulf War era multiple sclerosis cohort provides a unique resource for further study.

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Abbreviations: VAMC = Veterans Affairs Medical Centre

Introduction

Multiple sclerosis is the most common progressive neurological disorder of young adults affecting >1.2 million persons worldwide (Dean, 1994). Pathologically, it is characterized by inflammation and degeneration of both myelin and axons in the CNS (Trapp *et al.*, 1998). Despite decades of intensive research, no specific cause for the disorder has been identified. Epidemiological studies have provided critical data on disease morbidity, risk factors and time trends to help focus hypotheses and provide opportunities for new study.

Population-based prevalence and incidence studies are vital to understanding the disease burden within a country or region. In recent years, there have been relatively few multiple sclerosis studies within the USA (Baum and Rothschild, 1981; Anderson *et al.*, 1992; Hernan *et al.*, 1999; Noonan *et al.*, 2002, 2009; Mayr *et al.*, 2003; Neuberger *et al.*, 2004). Most of these studies have been regionally based and are not reflective of the demographic diversity of the US population. The only prior US nationwide incidence and prevalence study, sponsored by the National Institutes of Health, was carried out between 1970 and 1976 (Baum and Rothschild, 1981). The prevalence rate on 1 January 1976 was 58 per 100 000, and the average annual incidence rate between 1970 and 1975 was 4.2 per 100 000. More recent studies of prevalence in this country have reported rates between 43 and 177 per 100 000 (Anderson *et al.*, 1992; Mayr *et al.*, 2003; Noonan *et al.*, 2009). Overall, multiple sclerosis incidence rates and to a greater extent prevalence rates have increased over the past four decades in the USA. A notable demographic trend, found for most countries throughout the world, has been the increase in multiple sclerosis incidence and prevalence rates for females (Baum and Rothschild, 1981; Hernan *et al.*, 1999; Mayr *et al.*, 2003, Noonan *et al.*, 2009).

The military population of the USA has provided a rich resource for epidemiological studies on multiple sclerosis (Kurtzke, 2008). These studies date back to World War I when Davenport (1922) presented the first nationwide distribution in draftees rejected for multiple sclerosis and have progressed to the next generation, those who served in World War II and the Korean Conflict (Kurtzke *et al.*, 1979), and then to a third cohort of those who served in the Vietnam War and later up to 1994 (Wallin *et al.*, 2004). Most of these works utilized a case-control methodology to examine risk factors for multiple sclerosis onset, progression and death.

On 2 August 1990, Iraq invaded and occupied the State of Kuwait. On the same date, the United Nations Security Council passed Resolution 660 demanding immediate withdrawal. On 7 August, the US military were sent to Saudi Arabia as defence against threatened invasion. After further resolutions by the Security Council, on 16 January 1991 a state of war was declared by the United Nations and by the USA on 12 January. Further resolutions took place as new threats arose over the next 20 years. The entire period, from 1990 to the present, has been known as the Gulf War era.

We introduce here a newly assembled population of military veterans with multiple sclerosis and active duty military service in this era. Overall demographics of this cohort are presented along with average annual incidence rates by race, sex and service.

Materials and methods

The Gulf War era multiple sclerosis cohort was assembled similarly to the World War II–Korean Conflict series and the Vietnam and later series (Kurtzke *et al.*, 1979; Wallin *et al.*, 2004). With the assistance of Veterans Benefits Administration, Department of Veterans Affairs databases and Department of Defense data, we identified all veterans who had applied and were evaluated for a service-connection for multiple sclerosis by the Department of Veterans Affairs, and who had active duty service between 1990 and 2007. We also identified individuals who had applied for service connection for a clinically isolated syndrome, including optic neuritis and transverse myelitis. A decision for service connection for multiple sclerosis requires definitive evidence of clinical signs upon examination attributable to multiple sclerosis during or within 7 years after military service. The decision was made without regard to rank, race, sex or financial status. A review of past medical records and examination by a healthcare provider experienced in neurological disease were required to be provided to the Rating Board for every decision as to service connection for neurological disorders.

The compensation and pension file contains initial and ongoing demographic and medical data for all service-connected veterans. With supervision by the study neurologists, all cases were reviewed by trained abstractors and relevant demographic, clinical and environmental exposure variables were recorded. The variables for each case were reviewed, and the diagnosis was confirmed by one of the study neurologists (M.W. and J.K.). Cases with multiple sclerosis or clinically isolated syndrome met the 2005 McDonald criteria for diagnosis (Polman *et al.*, 2005). Cases with neuromyelitis optica were required to meet standardized clinical criteria of Wingerchuk *et al.* (2006). For this study, we included diagnoses of multiple sclerosis, possible multiple sclerosis, clinically isolated syndrome and neuromyelitis optica as cases of multiple sclerosis. The oldest neurological examination after first onset symptoms was coded and scored according to the Kurtzke Disability Status Scale (Kurtzke, 1970). The most recent neurological examination in the veteran's record was also scored with the Disability Status Scale.

Data analysis

All demographic and clinical variables for the cases were obtained from the study database. Denominators for incidence rates came from Department of Defense databases. Active duty population data were obtained for each year 1990–2000 and 2001–10 from the Defense Medical Epidemiological Database (Armed Forces Health Surveillance Centre, 2011). Annual population numbers were available by service, sex and major racial groups: White, Black, and other. Data for Coast Guard were available only by sex (Defense Medical Surveillance System, 1990–2000, 2001–2010; Research Directorate, 2000, 2007; Department of Defense Demographics, 2004). From 2000, Hispanics,

Asian/Pacific Islanders, and American Indian/Alaska Natives (Native American) personnel were identified (Department of Defense Demographics, 2004). Summing each year's active duty forces for the 18 years studied provided total person-years and the denominator for the years 1990–2007. The numerator, all cases, then gave an incidence rate per 100 000 person-years, which is equivalent to an average annual incidence rate per 100 000 population. It is this more commonly used rate that we have employed. Confidence intervals (CI) for the rates were calculated using the Poisson distribution. Standard univariate and multivariate statistical analyses were performed using SPSS (version 17).

This study was approved by the Institutional Review Boards at the Veterans Affairs Medical Centre (VAMC), Washington, DC, and the VAMC, Seattle, WA.

Results

The case cohort

After our case reviews, we identified a total of 3499 military veterans, who had active duty service during the Gulf War era from 1990 to 2007 and who had applied for service-connection for multiple sclerosis or clinically isolated syndrome. We determined that 561 (19.1%) did not have multiple sclerosis, and 247 (7.1%) had a diagnosis of multiple sclerosis before 1990. The remaining 2691 comprise our cohort, with the distribution of specific diagnoses by sex presented in Table 1.

Mean calendar year of entry into active duty was 1987.5 [standard deviation (SD) 8.3] and of onset of symptoms 1996.2 (SD 6.0); data for single years are available in Supplementary Table 1. Supplementary Table 2 shows the details for age at entry into active duty and at onset. Mean age at service entry was 22.0 years (SD 4.8). Median age of symptom onset was 30.0 years with a mean of 30.7 (SD 7.6). Ninety-two per cent were aged 20–44 at onset, and 99% aged 17–50. Supplementary Table 3 shows mean ages at onset and diagnosis for each specific race and sex. There was no significant difference in age of onset among the sex/race groups ($P = 0.091$). The mean age at diagnosis of 33.3 years (SD 7.9) was also similar among the groups. Interval between onset and diagnosis averaged 2.6 years.

The demographic breakdown of cases with multiple sclerosis by sex and race within the four Department of Defense services as well as the Coast Guard, currently part of the Department of Homeland Security, is listed in Table 2. The Army had the greatest number of cases with multiple sclerosis and the Coast Guard by far the fewest. The Air Force had the highest proportion of White females (26%); otherwise, there was little evidence of differences among the services by sex or race.

The mean age of all service members increased slightly from 27.7 years in 1990 to 28.3 years in 2007 (Defense Medical Surveillance System, 1990–2000, 2001–2010; Research Directorate, 2000, 2007). Overall, 99% of the military were aged 17–50 years. The proportion of females has grown more notably over this same period. In 1990, 11.5% of Active Duty Officers and 10.9% of Active Duty enlisted members were female, compared with 15.2% and 14.2%, respectively, for 2007. Within the Department of Defense, the Air Force had the highest percentage of females followed by the Navy, Army and Marines.

Table 1 Composition of Gulf War era series after case review and adjudication

Diagnosis	Male	Female	Total
Total	1779	912	2691
Multiple sclerosis	1511 (66.0)[a]	777 (34.0)	2288
Possible multiple sclerosis	114 (60.0)	76 (40.0)	190
Optic neuritis	79 (68.1)	37 (31.9)	116
Transverse myelitis	63 (81.8)	14 (18.2)	77
Other clinically isolated syndrome[b]	10 (71.4)	4 (28.6)	14
NMO[c]	2 (33.3)	4 (66.7)	6

a Data presented as frequency (%).
b Other clinically isolated syndrome: motor, sensory, brainstem, cerebellar or mixed syndrome.
c NMO = neuromyelitis optica or possible neuromyelitis optica.

Table 2 Gulf War era total series by race, sex and military service at time of multiple sclerosis diagnosis

Sex/race group	Total (*n*)	Army	Navy	Marine Corps	Air Force	Coast Guard
White males	1279	433	339	96	377	34
White females	556	173	154	20	200	9
Black males	360	155	79	30	94	2
Black females	296	169	58	7	59	3
Hispanic males	110	48	29	9	21	3
Hispanic females	43	16	10	4	11	2
Asian/Pacific islander males	14	4	7	3	0	0
Asian/Pacific islander females	12	1	6	0	5	0
Native American/Alaska Native males	4	2	1	1	0	0
Native American/Alaska Native females	3	2	0	0	1	0
Other race males	12	2	5	0	5	0
Other race females	2	0	1	0	1	0
Total	2691	1005	689	170	774	53

Other race = unknown or unable to identify race.

Incidence rates of multiple sclerosis

Supplementary Table 4 enumerates the denominator military populations by sex, race and service for the 18-year period under study. Supplementary Table 5 provides average annual incidence rates for each racial group separately by sex and service. These data are summarized in Tables 3 and 4. Table 3 presents average annual incidence rates for multiple sclerosis by race and sex. Table 4 presents the average annual incidence rates for multiple sclerosis by service and sex. The incidence rate for Blacks was the

Table 3 Average annual incidence rates per 100 000 population by sex and major race groups in Gulf War era multiple sclerosis cohort, Department of Defense

Sex/race group	Multiple sclerosis cases total, Department of Defense	Average annual population at risk	Average annual incidence rate per 100 000 (95% CI—Poisson)[a]
Total males	1740	1 321 514	7.31 (6.98–7.67)
Total females	898	202 044	24.69 (23.10–26.36)
Total all groups[b]	2638	1 523 563[c]	9.62 (9.26–9.99)
White males	1245	950 100	7.28 (6.88–7.69)
White females	547	117 846	25.79 (23.67–28.04)
Total whites	1792	1 067 946	9.32 (8.90–9.76)
Black males	358	236 504	8.41 (7.56–9.33)
Black females	293	61 789	26.34 (23.41–29.54)
Total blacks	651	298 293	12.13 (11.21–13.09)
Other race males[d]	137	134 906	5.64 (4.74–6.67)
Other race females[d]	58	22 403	14.38 (10.92–18.62)
Total other race	195	157 309	6.89 (5.95–7.92)
Hispanics 2000–07			
Hispanic males	57	108 083	6.59 (4.99–8.54)
Hispanic females	26	19 072	17.04 (11.13–24.97)
Total Hispanic	83	127 155	8.16 (6.50–10.12)

a Calculated from sum of annual active duty populations, 1990–2007.
b Does not include Department of Homeland Security/US Coast Guard.
c Adjusted for Army White males (Supplementary Table 3).
d Includes Hispanics, Asian/Pacific islanders, American Indian/Alaska Native (Native American) cases and unknown race.

Table 4 Average annual incidence rates per 100 000 population Gulf War era multiple sclerosis cohort by sex and service, Department of Defense and Department of Homeland Security

Sex and service	Multiple sclerosis cases total series	Average population at risk[a]	Average annual incidence rate per 100 000 (95% CI—Poisson)[a]
Total	2691	1 575 146	9.58 (9.22–9.95)
Females	912	207 882	24.63 (23.05–26.28)
Males	1779	1 367 265	7.29 (6.95–7.64)
Army	1005	544 831	10.55 (9.90–11.22)
Females	361	73 541	27.67 (24.90–30.68)
Males	644	471 290	7.83 (7.24–8.46)
Navy	689	414 244	9.11 (8.44–9.81)
Females	229	52 427	24.42 (21.36–27.79)
Males	460	361 817	6.94 (6.32–7.61)
Marine Corps	170	181 463	5.30 (4.53–6.15)
Females	31	10 056	17.89 (12.16–25.39)
Males	139	171 406	4.58 (3.85–5.40)
Air Force	774	396 056	10.87 (10.12–11.67)
Females	277	68 155	22.68 (20.10–25.52)
Males	497	327 901	8.43 (7.70–9.20)
Coast Guard[b]	53	37 268	7.90 (5.92–10.34)
Females	14	3703	21.00 (11.48–35.24)
Males	39	33 564	6.45 (4.59–8.83)

a Number of years at risk defined as range of entry into active duty years surveyed (1990–2007) = 18 years.
b Average active duty population for 1990, 1995, 2000, 2004 and 2007.

highest at 12.1 per 100 000 with 95% CI of 11.2–13.1, and that for Whites was 9.3 per 100 000 (CI 8.9–9.8), and for other races 6.9 per 100 000 (CI 6.0–7.9). Each group then differed significantly from the others. The other group of 200 contained 153 Hispanics (77%), with much smaller numbers of Asians/Pacific Islanders, American Indian/Alaska Natives, multiple and unknown racial groups (*cf*. Table 2).

We were able to calculate incidence rates directly for Hispanics and the other named races for the period 2000–7, when denominator data became available: the 83 Hispanic cases had a rate of 8.2 per 100 000, with 95% CI of 6.5–10.1, somewhat higher than the total for others of 6.9 (CI 6.0–7.9). Asian/Pacific Islanders with 15 cases had a rate of 3.3 (CI 1.9–5.5) and the five American Indian/Alaska natives gave a rate of 3.1 (CI 1.0–7.3). However, direct comparison with the prior racial groups is conjectural since they were not drawn from the entirety of the same populations. Each 'other' racial group, however, still showed rates significantly lower than those for Blacks and Whites, except that the comparison between Hispanics and Whites did not attain statistical significance. For each of the three main racial groups, rates for females were three times those of males.

The highest incidence rates for multiple sclerosis among the military services were those for the Army at 10.6 per 100 000 (CI 9.9–11.2) and the Air Force at 10.9 (CI 10.1–11.7), as seen in Table 4. Rates for the Navy and the small number (53) from the Coast Guard were lower at 9.1 (CI 8.4–9.8) and 7.9 (CI 5.9–10.3), respectively. Significantly below all other services was the Marine Corps with an incidence of 5.3 per 100 000 (CI 4.5–6.2). For each service, including the Marines, the same 3:1 female:male ratio was found.

Time trends

Longitudinal trends in risk for multiple sclerosis in our three separate military-veteran cohorts across a 60-year period are displayed in Table 5 for the major sex/race groups. Risk was calculated as relative risk ratios for the World War II–Korean Conflict series (Kurtzke *et al.*, 1979) and Vietnam and later series (Wallin *et al.*, 2004) as opposed to risk ratios from the incidence rates of the current series. Compared to White males as the reference, there has been a steady rise in risk for multiple sclerosis among Black males, other race males, White females and Black females. There were no other race females in the World War II–Korean Conflict series, and their rates in the Vietnam and later cohort were unstable, with just nine cases and six controls. Their relative risk ratio in the Gulf War era series is 1.98 (CI 1.5–2.6). In all of these series, Hispanics were part of the other group.

For the major groups, the relative risk ratio was 3.39 (CI 3.13–3.67) for females versus males. The relative risk ratio for Blacks versus Whites was 1.27 (CI 1.16–1.39). For others versus Whites, it was 0.72 (CI 0.62–0.83), and for Blacks versus others, the relative risk ratio was 1.76 (CI 1.49–2.05).

Discussion

The Gulf War era multiple sclerosis cohort is a large, demographically diverse cohort reflecting the contemporary military population. Our findings that Blacks have a higher incidence rate of multiple sclerosis than Whites and that both are higher than other races are novel. Three-quarters of the 'other' race group were Hispanic, and we suspect that they too have rates lower than Whites, even though the difference for the subset available did not attain statistical significance. Note that these are age-specific rates for persons aged 17–50. Within the 'other' group, we also identified small numbers of American Indian/Alaska Native and Asian/Pacific Islanders with multiple sclerosis rates of 3 per 100 000 each. A consistent finding within each major racial group is the high multiple sclerosis rate for females at triple that for males. These results were already suggested by our 'Vietnam and later' multiple sclerosis cohort (Wallin *et al.*, 2004).

Incidence is the best measure of disease morbidity as it is not influenced by survival time. Within North America and Western Europe, annual incidence rates for multiple sclerosis have generally been increasing over the past 50 years with recent overall rates of 3–10 per 100 000 (Koch-Henriksen and Sorensen, 2010). This trend has also been seen, but at lower levels, in the Middle East and Asia (Houzen *et al.*, 2008; Elhami *et al.*, 2011). Our incidence rates for the Gulf War era multiple sclerosis cohort are limited to active duty military comprising predominantly young adults, which is, however, the major at-risk population for this disease. Ninety-nine per cent of our cases were aged 17–50 at onset, the same age range as 99% of our military population at risk.

Table 5 Risk of multiple sclerosis versus white males by race and sex groups

Group	World War II and Korean Conflict adjusted case-control ratios[a]	Vietnam and later adjusted case-control ratios[b]	Gulf War era relative risk (95% CI)
White males	1.00*	1.00*	1.00*
Black males	0.44	0.67	1.16 (1.03–1.30)
Other males	0.22	0.30	0.77 (0.65–0.92)
White females	1.79	2.99	3.54 (3.20–3.91)
Black females	1.28	2.86	3.62 (3.18–4.11)
Other females		(3.51)[c]	1.98 (1.52–2.58)

a Data from Kurtzke *et al.* (1979).
b Data from Wallin *et al.* (2004).
c Unreliable; rate based on 9/6 multiple sclerosis/controls.
*Reference.

Our rates for all cases were 9.6 per 100 000, with all females at 24.7 per 100 000 and all males at 7.3 per 100 000 being among the highest reported. Baum and Rothschild (1981) published a maximal incidence rate of 10.5 per 100 000 for individuals aged 30–39 in their US study from the 1970s. The highest age-specific incidence rates for the all female Nurses' Health Study and Nurses' Health Study II, which spanned 1976 to 1994, was 18.9 per 100 000 person-years for the 40–44-year-old group (Hernan *et al.*, 1999). In Western Europe, incidence rates for persons aged 20–49 in Denmark for 1991–2000 were 17.5 for females and 8.0 for males (Koch-Henriksen, 1999; Koch-Henriksen and Sorensen, 2010), our incidence rates for Whites aged 17–50 were 25.8 and 7.3 per 100 000, for females and males, respectively, for 1990–2007. Regarding the clinical features of multiple sclerosis within the Veterans Affairs healthcare system in general, we have recently shown that the clinical characteristics of Veterans Affairs users to be similar to other large population-based multiple sclerosis cohorts (Culpepper, 2008); those for the Gulf War era multiple sclerosis cohort will be presented in a later paper.

This is the first study to evaluate the incidence of confirmed multiple sclerosis cases in a multi-ethnic cohort. In support of our findings by race, sex and service, we point to a recent report by Deussing (2011). Using administrative data for active duty personnel for 2000–9, he reported multiple sclerosis incidence rates in Blacks (18.3 per 100 000 person–years) 1.5 times those in Whites (12.5 per 100 000). Rates for Hispanics and all other races were 9.4 and 8.4 per 100 000, respectively. Similar to our data, the incidence was 3.3 times higher in females and within service branches was highest in the Air Force at 18.3 and lowest in the Marine Corps at 6.0. Since the cases of multiple sclerosis were defined exclusively by diagnostic codes and not adjudicated, these rates are likely to be inflated. For example, we found that only about half of patients with an International Statistical Classification of Diseases and Related Health Problems (ICD-9) code for multiple sclerosis within the medical record system of academically affiliated VAMCs actually had a correct multiple sclerosis diagnosis after rigorous adjudication using the McDonald criteria (Culpepper *et al.*, 2006). A recent US community-based prevalence study for multiple sclerosis in three regions revealed prevalence rates of Whites to be greater than for Blacks and Hispanics, but the differences were not significant (Noonan *et al.*, 2009).

Potential explanations for the high multiple sclerosis incidence rates for blacks are important to explore. Based on our prior work with military cohorts cited above (Table 5), these changes have manifested themselves fairly recently, over the past two to three generations. Just as with the almost universal increasing rates in females, this type of change implicates a major role for environmental risk or aetiological factors. As such, it would be reasonable to consider smoking, vitamin D deficiency and viral infections as possible risk factors for multiple sclerosis onset based on their support from the literature (Ebers, 2008). Alternatively, there may be unique environmental exposures within the military that increase ones risk for multiple sclerosis above that of the general population. Potential factors that have some plausibility include vaccinations (Kerrison *et al.*, 2002), infectious diseases among troops (Hyams *et al.*, 1995), airborne exposures (Riise *et al.*, 2002), and the military experience itself, particularly for those stationed in theatres of combat operations.

Since smoking rates across all racial groups and both sexes have dramatically decreased over the past 30 years (MMWR, 2011), it is difficult to propose smoking as an explanation for our findings. Differential levels of vitamin D or sun exposure within Blacks or other dark-skinned racial groups may be playing a role and deserves further study. Assessment of vitamin D status in the critical period prior to first symptom onset is vital in determining the impact of this variable on susceptibility. A relevant study utilizing presymptom onset serum in a military cohort showed a significant correlation between low serum 25-0H vitamin D and multiple sclerosis in whites but not in Blacks or Hispanics (Munger *et al.*, 2006). Additionally, geographic latitude during adolescence appears to be playing less of a role in determining multiple sclerosis risk within the USA. In our 'Vietnam and later' cohort, there was a clear decrease in the north–south gradient found for the World War II cohort, and, with small numbers, Alaska seemed to be a low risk state (Wallin *et al.*, 2009). Finally, changes in infection rates with the Epstein–Barr virus or other viruses may be responsible for these alterations in multiple sclerosis risk and should be evaluated (Owens *et al.*, 2011).

Genetic susceptibility for multiple sclerosis is largely tied to the human leukocyte antigen DRB1 loci in majority White populations. Within Blacks with multiple sclerosis, the major histocompatability complex (MHC) appears to be less critical as a determinant of disease risk. In this regard, a recent study confirmed two MHC class II single nucleotide polymorphisms that were associated with multiple sclerosis in Blacks (McElroy *et al.*, 2010). The interplay between MHC alleles via epistasis within racial groups could be a factor but has not been extensively studied (Ramagopalan and Ebers, 2009).

Strengths and limitations of this study should be noted. Our case ascertainment strategy to identify all new cases with multiple sclerosis could be questioned. We would argue that the use of service-connected cases provided us with essentially all new cases of multiple sclerosis within the military during the period of interest. Until recently, a diagnosis of multiple sclerosis was grounds for automatic medical discharge. But, in our cohort, there were a small number of persons who had continued on active duty after its diagnosis, a point also noted by Deussing (2011). Unlike the private healthcare system in the USA, the Department of Defense healthcare system is free to all service members and has open access to specialists. We did not include cases of multiple sclerosis that had their first diagnosis outside the window of Gulf War era military service, which is another limitation. So there may be individuals with onset of multiple sclerosis after discharge from the military that were missed because they had not applied for service-connection or were past the 7-year presumptive period. The incentives for service-connection are great, however. In addition to receiving monthly disability income, having a service-connection for an illness like multiple sclerosis assures free access to the Veterans Affairs healthcare system after discharge from the military for extensive medical care, medical equipment and social services. The Veterans Affairs Multiple Sclerosis Centres of Excellence, launched in 2003, have improved the outreach, diagnostic expertise and clinical care for veterans with this disorder and

broadened awareness of the service-connected benefits for multiple sclerosis (Wallin, 2010).

The primary limitation of this study, and of our previous studies on military-veteran populations, however, is that the cases in all of these were limited to members of the active duty military, and extrapolation beyond this unique subset can well be questioned. And indeed it has been. In a paper written to address this specific point, Kurtzke (1978, p. 59) wrote 'The age distribution of veterans, however, resembles that of no general population known to man'. In that work, he compared the distribution of multiple sclerosis for the 4097 white male Veterans of World War II in the reported series by state of residence at entry into service, versus that of their 3943 pre-illness, matched controls (as described in the publication of the next year; Kurtzke *et al*., 1979) with the distribution of the same 4097 cases versus the 1940 census population of some 20 million White males aged 15–34 by state of residence; both distributions included the District of Columbia and California divided in two: north and south. The two distributions were virtually identical. Spearman coefficient of correlation (r_s) was 0.950; $t_{48} = 21.120$ ($P = 0.001$; $t_{48} = 3.515$).

In summary, the newly defined Gulf War era multiple sclerosis cohort is demographically diverse and reflects both the military and perhaps the USA population. Multiple sclerosis incidence rates for Blacks were higher than Whites, and rates for Hispanics were lower than either. Female rates across all racial groups and military services were some three times those of males. We plan further studies of this cohort to assess risk factors for multiple sclerosis onset and progression. One major line of investigation will be the impact of the military experience on the presence or severity of this disease. Rates were higher for the 'boots on the ground' Army and Air Force, and lower for the naval services. This explanation does not seem at all likely to answer why Marines had much lower rates—perhaps half as high, as their military peers of the other services. This finding is possibly the most unexpected, yet still valid, finding of the study so far. Environmental risk factors as well as genetic susceptibility in minority populations should also be explored to better understand these observations.

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Supplementary material

Supplementary material is available at *Brain* online.

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