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The Prevalence of Migraine in US Military Beneficiaries with Rheumatoid Arthritis, Systemic Lupus Erythematosus, and Sjögren's Syndrome: a Preliminary Study

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Abstract

Background: A number of studies have explored the association between systemic autoimmune rheumatic diseases (SARD) and headache including migraine. These studies' conclusions frequently stand at odds; an association between migraine and SARD has yet to be clearly demonstrated. Moreover, there has been little inquiry into migraine headache and its relationship to SARD.

Objective: To determine the prevalence of migraine headache, with or without aura, in three of the most common SARD in the military beneficiary population, and compare it to a control population. The author also sought to identify characteristics associated with migraine and SARD, including sex and age.

Methods: Cross-sectional study. All patients were enrolled at the Tripler Army Medical Center (TAMC). Headache data was gathered on a randomized sample of 200 adult patients enrolled from the Rheumatology Clinic who had a diagnosis of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or Sjögren's syndrome (SS). Control headache data was also collected on a randomized sample of 200 patients without SARD from the TAMC Family Medicine Clinic. Data was drawn from the Department of Defense (DoD) healthcare databases at TAMC. Records were reviewed to determine if a diagnosis of headache syndrome or migraine was present. When found, relevant encounters were reviewed to determine probable headache type using the International Classification of Headache Disorders, 2nd Edition (ICHD-II) criteria. A prior history of head injury was also recorded.

Results: SARD TAMC patient records were reviewed in order to segregate a SARD case group (n = 200) and a control group (n = 200). The overall prevalence of migraine and/or probable migraine was 8 percent among cases in the control group versus 12 percent in the SARD group. In a stratified analysis, the prevalence of migraine without aura (MO) in the control group was 6 percent (n = 38) versus 11 percent (n = 44) among the SARD group, which was statistically insignificant. The prevalence of migraine with aura (MA) was 3 percent among the control group (n = 5) and 1 percent (n = 2) in the SARD group. The prevalence of migraine in the RA (10 percent), SLE (15%), and SS (25%) subgroups were not statistically different from the control group (p = 0.522 vs. p = 0.410). The prevalence of MO in RA (9%t) and SLE (13%) were similar to the control group (n = 13 vs n = 6).

The prevalence of MO in SS was 25 percent (n = 12), which was significantly higher than the prevalence (6%) within the control group (n = 200).

Conclusions: Migraine prevalence in the Tripler Army Medical Center military beneficiary population is similar to that of the general U.S. population, with the overall prevalence of MO being higher in the SARD group (11%) and SS subgroup (25%), respectively, than in the control group (6%. This may support increased awareness of migraine headache in patients with SARD, as well as regular screening to identify migraine so that earlier interventions can be made in concert with ongoing SARD treatment. The overarching goal is to improve patient care.

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Introduction

Migraine headache with aura (MA) and migraine without aura (MO) are relatively common in the United States population, with a combined overall prevalence of 11.7 to 22.7 percent [1,2]. Migraine is diagnosed more prevalently in females (17.1% vs 27.6%) than in males (5.6% vs 14.8%) [1,2]. The World Health Organization (WHO) ranks migraine as the 19th most debilitative disease worldwide, and the 12th most debilitative in women (WHO, 2001). *The American Migraine Prevalence and Prevention* (AMPP) was a longitudinal, two-phase, population-based study that assessed the "epidemiology, the burden, and the patterns of treatment for migraine" [1]. To identify the utilization patterns of and need for preventive treatment. According to the AMPP data, migraine headache accounts for 60.7 percent of overall lost productive time (LPT) in employed migrateurs; 76.8 percent of headache-related LPT is due to migraine-related diminished work performance [3]. In the 1990s, it was estimated that migraine sufferers required a total of 12 million days of bed rest [1,4] Missed work days and reduced productivity cost American employers approximately $13 billion per year, nearly $ 8 billion of that cost resulting from missed work days [4]. It is of interest that migraine was found to be under diagnosed and undertreated among U.S. Army Reserve Officer Training Course (US ROTC) cadets, negatively affecting their training [3]. Similarly, individuals who are forced to live with SARDs may also experience similar difficulties that may negatively affect their ability to live and work productive lives. The three most common SARDs are rheumatoid arthritis (RA), Sjögren's Syndrome (SS), and systemic lupus erythematosus (SLE). These conditions fall under the broad category of autoimmune connective tissue diseases (CTD).

SARD occurs when antibodies are produced against self-antigens, causing resultant inflammation and tissue damage that characteristically affect the joints and other somatic structures. Autoantibodies and inflammatory markers of SARD are typically found in the blood (e.g., antinuclear antibody, rheumatoid factor, C-reactive protein, etc.) The basis for diagnosis is the patient's constellation of symptoms, physical examination, and blood test results. Unfortunately, proper diagnosis may take several years, owing to the insidious onset of disease [5-13].

RA, SS, and SLE have been associated with substantially negative outcomes on quality of life (QOL), increased disability, and financial burden [14-16,]. The Arthritis Foundation (2014) estimates that RA affects approximately 1.5 million Americans; females being 3 times more likely to be effected than men. The typical age of onset for adults is between ages 40 and 60 years [17]. RA mainly affects the joints in the extremities, causing an erosive deforming arthritis, and frequently affects major organs [17]. SLE affects approximately 1.5 million Americans, the majority of which are women; onset typically occurs between ages 15 and 44 (childbearing age). Non-Caucasian women are two to three times more likely to develop lupus than Caucasians (LFA, 2014). SLE generally causes joint pain and swelling, coagulopathies, anemia, hair loss, edema, fatigue, and a characteristic butterfly-shaped rash across the cheeks and nose [13]. Sjögren's syndrome (SS) affects as many as four million people in the United States; among that group, 90% are women (SSF, 2014). Onset typically occurs after age 40 [18]. SS may exist by itself, termed primary Sjögren's syndrome, or it may accompany another CTD as Secondary Sjögren's Syndrome, RA or SLE (Dunkin, 2014). SS is commonly associated with sicca complex and may involve non-erosive arthritis, organ inflammation, vasculitis, fatigue, and neuropathy [18]. These three CTDs typically follow a waxing-waning course; however, significant worsening of symptoms or flare-ups may require treatment augmentation. Treatment strategies include proper self-care (diet, exercise, adequate rest, activity planning, etc.) and/or a range of pharmacologic treatments, depending on the type and severity of symptoms [5-813,19].

Among those with SARD, specifically SLE, SS, and RA, headache is a common complaint (SLE and migraine = 42.5%, RA and migraine 10.0%, [20] SS and headache = 71.8%, SS and TTH = 53.5%, SS and migraine = 26.8%, [21,22]. found the most prevalent neuropsychiatric disorder in SLE and SS to be headache (SLE and migraine = 44%, SS and migraine = 35%; SLE and tension type headache [TTH] = 56%, SS and TTH = 56%).

Several studies have explored the association between SARD and headache. However these studies' conclusions frequently stand at odds as to any significant association between SARD and headache. Gökçay found that patients with primary SS were significantly more likely to have migraine or TTH than healthy controls ($p < .001$), a finding supported by [21,23-25] found that SLE patients did not have migraines statistically more frequent than controls [26]. Found no significant an association between headache or migraine between SLE patients and controls. [9]. supported a positive association of classical migraine (MA) with SLE. Similarly [27] found a higher odds ratio for migraine and RA or SLE when compared to controls. Weder-Cisneros and Téllez-Zenteno (2004) [28] found a higher percentage of headaches in SLE, and Whitelaw, Hugo, Spangenberg, and Rickman (2004) concluded that migraine was more prevalent in SLE patients than in controls. However, the association between migraine and SARD has not been statistically established [29,27,30,44]. Moreover, study formats varied widely, depending on one or more of the following to derive information: questionnaires, phone or in-person interviews, and medical record reviews. In addition, not all studies used *The International Classification of Headache Disorders: 2nd edition*, (2003) [31]. Furthermore, some of these studies were small in scale ($n < 100$) [9,21-23,25,27,28,30-35].

To date, SARD and migraine research among the military population remains largely unexplored, especially considering the more than 1.4 million active service members in the U.S. [36]. TRICARE serves approximately 9.6 million beneficiaries world-wide (active duty and retired), and serves nearly 170,000 beneficiaries in Hawaii. The primary purpose of this study was to investigate associations among migraine headaches (with or without aura) among service members also diagnosed with three common SARDs (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren's syndrome (SS). This preliminary study was designed to ascertain whether this line of research merits further study [36].

It was hypothesized that the prevalence of migraine headache (with and without aura) would be higher in military beneficiaries with SARDs than among control cases without SARDs. The objective of this study was to assess the prevalence of migraine headache, with or without aura, in RA, SLE, and SS in the military beneficiary population. Secondly, risk factors of migraine, including age, gender, and race were examined. Experimental group data was gathered on a randomized sample ($n = 200$) and is adult patients enrolled from the Rheumatology Clinic at *Tripler Army Medical Center* (TAMC). The control group was comprised of military beneficiaries from the TAMC Family Medicine Clinic (FMC). Other headache syndromes were also considered, and will henceforth be referred to as *Headache Other Than Migraine* (OTM).

Methods

The population of interest consists of adult military beneficiaries with the diagnoses of RA, SLE, or SS, in addition to migraine (MA or MO) enrolled at TAMC during the 2013 calendar year. The study protocol was approved by the *Human Use Committee* at Tripler Army Medical Center. Investigators adhered to the policies for protection of human cases as prescribed in 45 Code of Federal Regulation 46. A full waiver of *Health Insurance Portability and Accountability Act* (HIPAA) authorization was granted for the purposes of this study.

This retrospective cohort study utilized medical records available from the *Department of Defense* (DOD) healthcare databases at TAMC, including the *Composite Health Care System* (CHCS), Armed Forces Health Longitudinal Technology Application (AHLTA), and TRICARE® enrollment records, as illustrated in Figure 1. Each patient's diagnosis of RA, SLE, or SS was documented in AHLTA by a board-certified rheumatologist at the TAMC Rheumatology Clinic [36]. The diagnoses of migraine, OTM, and/or prior head trauma were dependent upon AHLTA electronic medical record documentation. The ICHD-II criteria for migraine were applied to AHLTA documentation to diagnose MA, MO, probable MA (PMA), and probable MO (PMO); all headache related diagnoses that failed to meet migraine or probable migraine criteria were classified as OTM. *The Human Information Management Branch*, TAMC *Patient Administration Division*, provided a list of all the visits for the Rheumatology Clinic from the CHCS *Medical Expense and Performance Reporting System* (MEPRS) Code for initial Rheumatology Clinic visits (systematically coded as BAOA), using the International *Classification of Diseases* (ICD), 9th Revision, Clinical Modification (ICD-9-CM) codes to identify patients over the age of 17 years who had diagnoses of RA, SLE, or SS and were seen in the Rheumatology Clinic from 1 January 2013 to 31 December 2013 __ > ? (1989). For the control group, the TAMC TRICARE Operation

Branch Chief provided the total enrollment for the Family Medicine Clinic from 1 January 2013 to 31 December 2013. All patients 17 years of age or younger were deleted from the list, leaving in excess of 10,000 adults.

The TAMC FMC was divided into two 'Home Teams', which were reported as demographically equivalent by the TAMC TRICARE Operation Branch Chief. The composite patient data were separated into the two Family Medicine 'Home Teams'. For ease of analysis, one team was chosen by random to serve as control, and de-identified patient lists were randomized utilizing a random number generator, the resulting control group represented nearly 5000 cases, as well as over 200 SARD patients who had at least one Rheumatology Clinic visits. For each list, the first 200 randomized patients that did not meet the exclusion criteria (i.e., had patient encounters recorded in AHLTA) were included in the AHLTA medical records review, for a total of 400 records. A Master Key was created to assign a unique alphanumeric designation for each individual patient. This Master Key was kept separate from the medical data, and a hard copy was locked in a file cabinet in a secure building. The original CHCS and TRICARE patient lists were encoded according to the alphanumeric code. For the purpose of the records review, TAMC FMC patients who did not have any documented encounters in AHLTA were excluded. The Master Key was used to identify patients for the records review. CHCS and TRICARE patient lists were stored in *Excel* and demographic data were collected, including age, gender, and military service status (active or not active duty). All data were encrypted and password-protected on a DoD common access card (CAC) protected computer. Demographic and diagnostic data were recorded in separate *Excel* spreadsheets; alphanumeric codes were used in place of Personally Identifiable Information (PII) (Sjögren's syndrome (SS) Sjögren's syndrome (SS); all personally identifiable information was physically and digitally destroyed upon the completion of medical records review.

It was not possible to search in CHCS for these subgroups (i.e. RA with migraine, etc.); it is unlikely that such search results could be delineated by initial diagnosis of migraine beyond the year 2013. This researcher sought to determine if cases in the control group and cases with RA, SLE, or SS had migraine or headache diagnosed in any encounter recorded in AHLTA. The data sought in these records were demographic, including age, gender, military status, and whether the person had been diagnosed with migraine or other headache syndrome (with or without the diagnosis of the aforementioned conditions (RA, SLE, or SS), as these diagnoses were listed in AHLTA's *Master Problem List.*

The Master Problem List contained diagnoses that were directly derived from patient disposition utilizing ICD-9 codes. When a headache syndrome was found, relevant encounters were reviewed to determine probable headache type, using ICHD-II criteria. A diagnosis of *probable migraine* with or without aura was made, according to ICHD-II, which states, "Attacks and/or headache missing one of the features needed to fulfill all criteria for a disorder coded above" that is "not attributable to another disorder" [4]. Given that few patients with probable migraine were diagnosed, and since there was a possibility of incomplete records, cases with probable migraine were included in their respective migraine group (MA or MO), rather than being placed in a separate group. An annotation was added in the event of a history of head trauma that preceded the headache diagnosis. It was not possible to collect ethnicity or race data on many cases due to the limitations of the employed databases, however, active duty cases included Army, Navy, Marine Corps, Air Force, and Coast Guard service members; therefore significant diversity is assumed. Non-active duty cases included military retirees and their dependents, active duty dependents (spouses, children, adult dependents), and Veterans Affairs beneficiaries.

With a sample size of 200 cases per group and an alpha level of 0.05, the study had 80 percent power to detect a difference of 11 percentage points in the prevalence of migraines between patients with SARD and the control group, assuming a baseline rate of 13 percent in the control group. Due to sample size, a two-tailed Fisher's exact test was used to assess whether there was a statistically significant association between SARD and the prevalence of migraines. In cases where all subgroups contained 10+ cases, a Pearson's chi-square statistic was used for data analysis. Logistic regression was used to estimate the odds ratios (OR) and adjusted for potential risk factors such as age, gender, and active duty status. A confidence level of 0.05 was used for all statistical analyses. Further analyses were performed that controlled for age (< 45 vs. > = 45 years) and gender (female vs. male). The statistical package used to analyze the data was Statistical Analysis Systems (SAS).

Results

Two hundred patient records with ICD-9 codes for RA, SLE, and SS were reviewed. Figure 2 displays the relative composition of the SARD group. Because one ICD-9 code represents the more general sicca syndrome as well as Sjögren's syndrome (aka keratoconjunctivitis sicca) in CHCS, there were two patients with diagnoses of sicca syndrome that did not have symptomology or blood work consistent with the diagnosis of Sjögren's syndrome. These two cases were included in SARD group for data analysis, but were not included in the SARD subgroup analyses. Neither case had a headache syndrome in his/her electronic medical record. The control group consisted of 200 FMC patients with encounters in AHLTA.

Figure 3 summarizes the proportion of cases with migraine or OTM in the control versus SARD group. The data for the prevalence of migraine headache in the control, SARD, and SARD subgroups are summarized in Table 1. The prevalence of migraine headache (MO and MA) was higher in cases with SARD than in controls but the difference was not significant (8% vs. 12%, $p = 0.182$). The prevalence of migraine without aura was significantly higher for SARD cases as compared to the control group (22% vs. 12 %, $\chi^2 = 4.00$, $p = .046$, indicating statistical significance). The prevalence of migraine in the SARD subgroups and control group is graphically represented in Figure 4. The prevalence of MO in cases with RA or SLE did not vary significantly from controls. The prevalence of MO in the SS group was significantly higher than in the control group (25% vs. 6%, $p = .022$). Females with SS also experienced more MO than controls (30% vs. 7%, $p = .039$). However, this is based on a small sample size in the SS group ($n = 12$, SS females = 10). With the exception of MO in the SS group, cases in the SARD, RA, SLE, and SS groups did not experience significantly more MA or OTM headaches than control cases. This holds true when controlling for case gender. The OTM prevalence did not vary significantly among the groups of interest; its greater frequency than migraine was expected, given that OTM was a catchall category. Of note, one 38-year-old female with RA and one 32-year-old female in the control group had both MO and MA. Each case with both MO and MA was counted once for her respective group's overall migraine frequency and prevalence.

Given the small number of cases over the age of 65 years, the prevalence of migraine in TAMC military beneficiaries was calculated using two age groups for the control and SARD groups, respectively, as displayed in Table 2. The two age groups were 18 to 44 years and 45 to 99 years. For 18- to 44-year-olds, prevalence of MO between the SARD and control groups approached statistical signifiance (14% vs. 7%, $p = 0.080$); OTM prevalence was (28% vs. 18%, $p = 0.068$). The prevalence of migraine and MA were not significant among the 18- to 44-year-old group; the 45- to 99-year-old SARD group did not demonstrate significant differences from the control group for migraine, MO, MA, or OTM. Interestingly, the frequency of MA in control cases ($n = 5$) was more than twice that of SARD cases ($n = 2$), all occurring in non-active duty females under the age of 45 years.

Multivariable logistic regression was used to estimate odds ratios (OR) adjusted for potential risk factors such as age, gender, head trauma, and active duty status Table 3. Cases in the 18 to 44 age group were 2.36 times more likely to have migraine headache than cases 45 to 99 years of age (OR = 2.36, $\chi^2 = 5.06$, $p = 0.025$, indicating significance). Odds ratios for migraines were more than 2.00 for women relative to men, and were found to be marginally significant (OR = 2.79, $\chi^2 = 3.40$, $p = 0.065$). For migraine without aura, the odds ratio for 18- to 44-year-olds relative to 45- to 99-year-olds was more than 2.00, and were also found to have been marginally significant (OR = 2.10, $\chi^2 = 3.32$, $p = 0.068$). The remaining logistic regression analyses revealed no differences for migraine (SARD vs. control, active duty vs. non-active duty) and MO (SARD vs. control, active duty vs. non-active duty, and female vs. male).

In regards to cases with a prior history of head trauma of any type documented prior to documentation of headache, there were seven such cases whose demographics and headache type(s) are summarized in Table 4. The amount of time between the occurrence of head injury and subsequent headache diagnosis was not limited. Two control and four SARD cases had headache diagnoses that succeeded mild to severe head trauma. One SARD case did not have documented head trauma, but did have a history of seizure. A 30-year-old active duty control male developed MA. A 39-year-old active duty SARD male developed MO and OTM. A 35-year-old non-active duty SARD female developed PMO. The remainder of head injury cases had OTM. This author cautions that these observations do not imply causal inference.

Figure 5 displays the age frequency distribution for the control and SARD groups, respectively. Table 5 summarizes secondary analyses that included age, sex, and active duty status. Age comparisons were based on 2 by 4 contingency tables, in which the adult age ranges were divided into four categories, 18-24, 25-44, 45-64, and 65+ years. When compared to the control group, the SARD group was older, and was comprised of more female cases (85% vs. 61%), and less likely to be active duty (16% vs. 38%). The majority of the SARD group consisted of patients with RA (n = 140). When compared to the control group, the RA group was significantly older and was comprised of more females than males (82% vs. 61%), and had fewer active duty service members (18% vs. 38%).

The SLE group's mean age (n = 39 years) was similar to the control population (n = 41) and comprised of significantly higher female cases (91% vs. 61%), as well as fewer active duty military service members (16% vs. 38%). The SS subgroup's mean age was greater than the control group (51 years vs. 41 years) and was found to be marginally significant, (p = .052); however, no notable differences were found in the proportion of females to males or military active duty service cases when compared to controls Table 5.

Discussion

This study provides new information about the prevalence of migraine headache in the U.S. military beneficiary population and its SARD subset. The author found that 8 percent of military beneficiaries in the control group (seen at TAMC FMC during 2013) had a past diagnosis of migraine headache, while the prevalence of migraine in the SARD group was 12 percent. Migraine prevalence in the control group was lower than the combined overall prevalence range of larger studies, while the SARD group fell within the range of existing studies in the literature [1,37,38]. The prevalence of migraine without aura was nearly double in the SARD group (11% vs. 6%), however, this finding did not reach significance after controlling for age. Conversely, 3 percent of control cases had migraine with aura versus 1 percent of SARD cases. It may be significant that all cases were female.

This data and study are consistent with other studies that found MO to be much more prevalent than MA in the U.S. population, with one study reporting the prevalence of MA as 5.3 percent in women and 1.9 percent in men in a given year [2,5,33]. Five control cases representing 3 percent and 2 SARD cases representing 1 percent showed documentation of MA. Furthermore, it should be noted that all cases were female; additionally, one case in each group showed documentation of both MO and MA.

Concerning prevalence of migraine when associated with age, this study found significantly higher in 18- to 44-year-olds than 45- to 99-year-olds. The younger age group was twice as likely to suffer migraine as the older group (χ^2 = 5.06, OR = 2.36, P = .025). The control migraneur age distribution favored a younger population when compared to the findings of the American Migraine Study II ([AMS-II] [1] and American Migraine Prevalence and Prevention Study ([AMPP] [1]. This was not unexpected because the bulk of TRICARE enrollees are active duty sponsors and family members, who tend to be younger than the general U.S. population. The majority of SARD cases had a diagnosis of RA, and it should be noted that there was a slight age difference in this group when compared to the controls (51 years vs 41 years). It is noted that the SARD migraine age distribution was similar to the AMS-II and AMPP study [1].

Despite randomization, the control cases were 61percent female; of the SARD group, 85 percent were female. These findings are reflective of the gender predominance of the general diagnostic characteristics of SARD. More females than males suffered from migraine headaches in both groups (Control: 10% female vs. 5% male; SARD: 14% female vs. 3% male); gender was found to be significant, as females were 2.5 times more likely to have migraine (MO or MA) than males (x^2 = 3.40, p = .065), this finding marginally significant. Other studies have shown similar gender predominance [18,22,28,41] Concerning gender among cases with MO, no association was found to (p = .128).

The composition of the SARD group is not reflective of the current U.S. population, given that it was drawn from a concentrated sample (military rheumatology clinic). It is probable that the severity of symptoms and specific treatments for particular SARD presentations dictate whether a patient is seen by such a specialty clinic. SLE (.02% to .07%, cited in Pons-Estel., *et al*. 2010) [39] is much less common than SS or RA , and RA (.5% to 1.0%, cited in Silman and Pearson, 2002) [40], and somewhat more common than SS (.09% to

.72% per American-European consensus group criteria [AECG], as cited in Patel and Shahane, 2014) [41]. The prevalence of migraine in the cases with RA or SLE did not differ significantly from control cases (Migraine: *RA* = 16%, SLE = 7%, Control = 16%; MO: RA = 6%, SLE = 6%, Control = 12%; MA: RA = 2%, SLE = 0%, Control = 5%), regardless of migraine type. These findings are in disagreement with some of the findings from a Danish twin study [27] the study by Le, Tfelt-Hansen., *et al*. found an increased comorbidity of SLE or RA in patients with migraine (Migraine with SLE = 0.4%, OR = 2.83, p < .001; Migraine with RA = 1.5%, OR 2.09, p < .001; 2010). Other studies from the UK (Glanz., *et al*. 2001) also found an association between SLE and migraine; moreover, a recent study in the United States (Glanz., *et al*. 2001) also found higher prevalence of migraine in patients with SLE. However, this study was based on a questionnaire that was voluntarily completed and returned by patients with SLE (Glanz., *et al*. 2001) [32]. However, findings by this researcher do not completely reflect results of the prospective- Comparative study by Katsiari., *et al*. 2011) [30] that found no difference in migraine prevalence between SLE and matched healthy controls in a Greek population.

Three of 12 cases with SS met ICHD-II criteria for migraine, specifically MO; in the MO subset, cases with SS had a significantly higher prevalence of MO according to gender (p = .039). It should be noted that these findings are in agreement with a Taiwan registry-based study (2.6%, p < .001, Kang., *et al*. 2010) [23] as well as a similar British questionnaire-based study (46%, p = .05, Pal., *et al.* 1989), [34] which found that the prevalence of migraine in patients with primary Sjögren's Syndrome was significantly higher when compared to controls. The Ka., *et al*. 2010) [32] study relied on ICD-9 codes, while the Pal., *et al*. 1989 [34] study utilized questions that included three typical migraine symptoms including: "(a) some warning before the headache; (b) associated nausea or vomiting; (c) pain on one side of the head only." (p. 313).

There were a number of limiting factors for this study: documentation of migraine was restricted to the time each case was enrolled in TRICARE. These ranged from a low of several months to several decades, and could not account for diagnoses made prior to enrollment, after disenrollment, or outside of the TRICARE in a managed care setting. Documentation was not always complete; therefore, this researcher depended on the healthcare providers' observations as recorded in AHLTA. One caveat is the possibility that different healthcare providers may report headaches/symptoms differently for active duty service members than for other military beneficiaries, perceiving that such a diagnosis of migraine headache may negatively affect a service member's career. Additionally, self-reporting of symptomology and severity necessarily depend upon the perceptions of the cases themselves. It is also relatively common for some patients do not seek medical attention for headaches, and may have no way of knowing if they are having migraine headaches. There may also be differences in symptom presentation for treatment between dependents, active duty service members, retirees, or veteran affairs beneficiaries that are beyond the scope of this study. It is not possible to ascertain whether those with SARD are more likely or less likely to seek care for migraine, as they are more regularly followed than controls. Furthermore, the TAMC FMC control group, which consisted predominantly of active duty personnel and their dependents, was selected on the basis that they represent a generally healthy population when compared to the TAMC Internal Medicine Clinic population that consisted of predominantly military service retirees and their dependents. It should be noted that the SARD group was closer in age to the TAMC Internal Medicine Clinic population. Cases diagnosed/suspected to have SLE and/or SS comprised a low percentage of the SARD group, which was comprised of cases with RA diagnosis or symptomology Given the results of this study, a sample of size of 500 patients would have been required for each group to detect a difference between prevalence rates of 6 percent and 11 percent.

A search of the current literature revealed several discordant conclusions among studies. Possible explanations include application of different diagnostic criteria for migraine headache and/or different data collection methodology, as not all studies employed the ICHD-I or ICHD-II criteria for migraine headache. Patient headache questionnaires are contingent on self-report and voluntary participation, which may attract more headache sufferers than non-sufferers to complete the questionnaire. Patient interviews, although voluntary, give a trained healthcare provider the opportunity to evaluate the patient in person, which may help diagnostically, despite the potential for leading the patient to a migraine diagnosis. Finally, medical record reviews may be susceptible to reporting and perception as previously discussed under limiting factors [46-49].

Conclusions

The prevalence of migraine headache in the Hawaii military beneficiary population is similar to that of the general U.S. population (Control = 8%; U.S. AMPP study = 12%) [1]. However, the results of this study cannot be generalized to the U.S. military population, given the demographical limitations of this study and the paucity of migraine research within the military population. Despite the higher percentage of SARD patients when compared to controls experiencing migraine headaches, these findings were not significant with the following exceptions: the overall prevalence of migraine without aura was higher in the SARD group than in the control group (11% vs 6%); the prevalence of migraine without aura was higher in cases with SS than in controls (25% vs 6%), which included the mixed gender group and the female-only (30% vs 7%) groups. Overall, 18- to 44-year-old patients were twice as likely to have a history of migraine as 45- to 99-year-olds ($\chi^2 = 5.06$, $P = .025$, OR = 2.79). More females than males had migraines ($\chi^2 = 3.40$, $P = .065$, OR = 2.79), but this fell short of statistical significance. Very few cases in either the control or SARD group had migraine with aura (Control n = 5 [3%], SARD *n* = 2 [1%]). Given the results of this study indicating the prevalence of migraine headache in military beneficiaries with SARD, further examination is warranted, particularly among cases where the diagnoses of Sjögren's Syndrome was made. A carefully designed, case-control study utilizing de-identified data may provide a more robust statistical examination of associations among these diagnoses and/or conditions. Future studies may further elucidate unknowns concerning demographics, including military sponsor rank, race/ethnicity, as well as migraine morbidity, comorbidities, quality of life impact, and migraine treatments, including possible drug interactions with common SARD-related treatments. This proposed large-scale study may increase awareness of migraine headache symptomology in patients with SARD, as well as suggesting the incorporation of regular screening to better identify migraine so that upstream interventions can be made along with treatment for SARD .

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Human Use

The application for full waiver of HIPAA authorization was approved by the TAMC Investigational Review Board/Human Use Committee, as this study involved no more than a minimal risk to the privacy of individuals.

Key

SARD	Systemic autoimmune rheumatic disease
MO	Migraine without aura
MA	Migraine with aura
OTM	Headache other than migraine
PM	Probable migraine
PMO	Probable migraine without aura
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
C	Control group
S	SARD group
TAMC	Tripler Army Medical Center, Hawaii

PRMC	Pacific Region Medical Command
DOD	Department of Defense
CHCS	Composite Health Care System
AHLTA	Armed Forces Health Longitudinal Technology Application
ICHD-II	International Classification of Headache Disorders: 2nd edition, 2003
MEPRS	Medical Expense Performance Reporting System
BAOA	Rheumatology Clinic, initial visit
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification

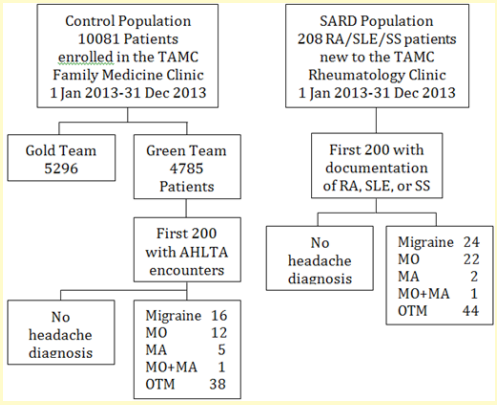

Figure 1: *Schematic summary of retrospective chart review.*

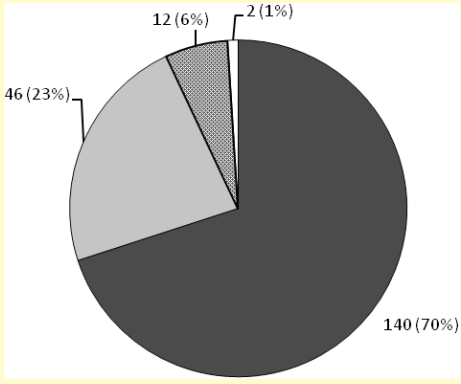

Figure 2: *Composition of SARD group.*

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sjögren's syndrome
- Sicca syndrome (No Sjögren's diagnosis; excluded from SARD subgroup analysis

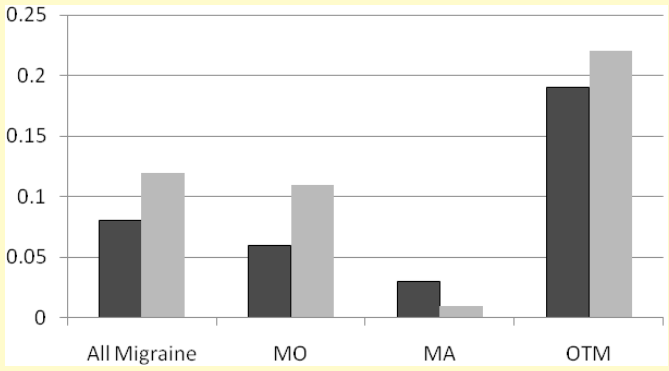

Figure 3: *Proportion of subjects with migraine or headache other than migraine.*

Control
SARD

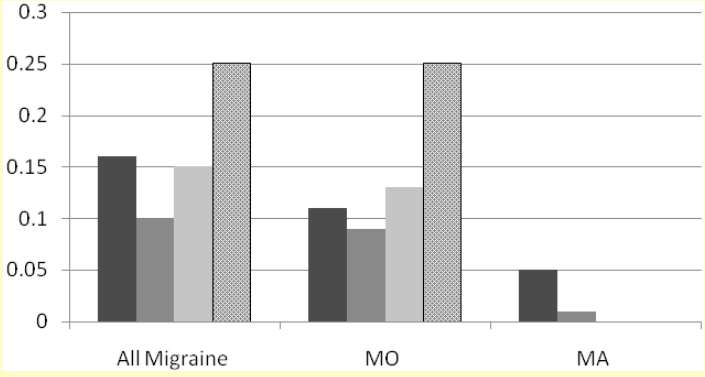

Figure 4: *Prevalence of migraine in control, RA, SLE, and SS groups*

Control
Rheumatoid arthritis
Systemic lupus erythematosus
Sjögren's syndrome

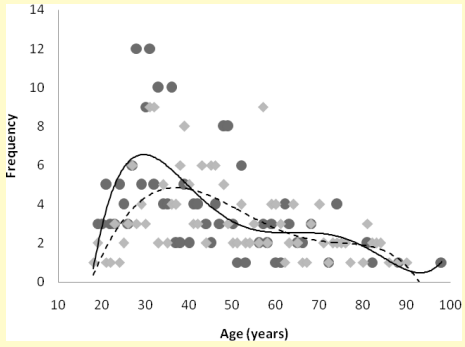

Figure 5: *Age frequency distribution in control and SARD populations.*

	Control (n = 200)		SARD (n = 200)			RA (n = 140)			SLE (n = 46)			SS (n = 12)		
	N	**(%)**	**N**	**(%)**	**P-value**	**N**	**(%)**	**P-value**	**N**	**(%)**	**P-value**	**N**	**(%)**	**P-value**
All														
Migraine or PM	16	(8)	24	(12)	0.182† $\chi^2 = 1.78$	14	(10)	0.522† $\chi^2 = .410$	7	(15)	0.130† $\chi^2 = 2.30$	3	(25)	0.080
MO or PMO	12	(6)	22	(11)	0.046† $\chi^2 = 4.00$	13	(9)	0.180† $\chi^2 = 1.80$	6	(13)	0.100	3	(25)	0.022
MA	5	(3)	2	(1)	0.449	2	(1)	0.704	0	(0)	0.587	0	(0)	1.000
OTM	38	(19)	44	(22)	0.505† $\chi^2 = 0.45$	31	(22)	0.516† $\chi^2 = .422$	10	(22)	0.719† $\chi^2 = .130$	3	(25)	0.708
Female	(n = 21)		(n = 69)			(n = 115)			(n = 42)			(n = 10)		
Migraine or PM	12	(10)	23	(14)	0.341† $\chi^2 = 0.91$	13	(11)	0.730† $\chi^2 = .120$	7	(17)	0.268	3	(30)	0.089
MO or PMO	8	(7)	21	(12)	0.116	12	(10)	0.292† $\chi^2 = 1.11$	6	(14)	0.196	3	(30)	0.039
MA	5	(4)	2	(1)	0.133	2	(2)	0.447	0	(0)	0.329	0	(0)	1.000
OTM	22	(19)	41	(24)	0.247† $\chi^2 = 1.34$	29	(25)	0.212† $\chi^2 = 1.56$	9	(21)	0.820	3	30	0.409
Male	(n = 79)		(n = 31)			(n = 25)			(n = 4)			(n = 2)		
Migraine or PM	4	(5)	1	(3)	1.000	1	(4)	1.000	0	(0)	1.000	0	(0)	1.000
MO or PMO	3	(4)	1	(3)	1.000	1	(4)	1.000	0	(0)	1.000	0	(0)	1.000
MA	0	(0)	0	(0)	-	0	(0)	-	0	(0)	-	0	(0)	1.000
OTM	16	(21)	3	(10)	0.264	2	(8)	0.228	1	25	1.000	0	(0)	1.000

Table 1: *Prevalence of Migraine and Other Headache Types in U.S. Military Beneficiaries at TAMC with Rheumatoid Arthritis, Systemic Lupus Erythematosus, and Sjögren's Syndrome.*

**P-values are based on the two-sided Fisher's exact test comparing each group separately vs. the controls.*

†When all subgroups had 10 or more subjects, the P-values were based on the chi-square test.

	C 18-44 (n = 130)	S 18-44 (n = 97)		C 45-99 (n = 70)	S 45-99 (n = 103)	
	N (%)	N (%)	P-value	N (%)	N (%)	P-value
Migraine*	13 (10)	16 (16)	0.169 χ^2 = 1.89	3 (4)	8 (8)	.529
MO*	9 (7)	14 (14)	0.080	3 (4)	8 (8)	.529
MA	5 (3)	2 (2)	0.702	0 (0)	0 (0)	-
OTM	23 (18)	27 (28)	0.068 χ^2 = 3.32	15 (21)	17 (17)	0.413 χ^2 = .67

Table 2: *Prevalence of Migraine in U.S. Military Beneficiaries in PRMC, Controlling for Age.*

**Probable migraine headache is included.*

†When all subgroups had 10 or more subjects, the chi square probability was used for analysis.

Variable	Wald χ^2	P-value	Odds Ratio	95% CI
Migraine (overall)				
SARD vs. Control	1.24	.266	1.49	0.74-3.01
Active Duty (Yes vs. No)	0.04	.843	1.10	0.45-2.69
Age (18-44 vs. 45-99)	5.06	.025	2.36	1.12-4.97
Female vs. Male	3.40	.065	2.79	0.94-8.34
Migraine without aura				
SARD vs. Control	3.03	.082	2.01	0.92-4.44
Active Duty (Yes vs. No)	0.02	.885	1.08	0.40-2.91
Age (18-44 vs. > = 45)	3.32	.068	2.10	0.95-4.65
Female vs. Male	2.32	.128	5.55	0.76-8.52

Table 3: *Adjusted Odds Ratios for Migraine (overall) and Migraine Without Aura Based on Logistic Regression Analyses.*

	Age	Sex	Active Duty	Headache type	SARD diagnosis
Control *					
C95	30	Male	Yes	MA	No
C123	22	Male	Yes	OTM	No
SARD*					
S67	39	Male	Yes	MO, OTM	RA
S85**	35	Female	No	Probable MO	SLE
S111	73	Female	No	OTM	RA
S119	45	Female	No	OTM	RA
S135	34	Male	Yes	OTM	RA

Table 4: *Subjects with Headache Diagnosis and Prior History of Head Trauma.*
**Subject numbers were randomly assigned. The key linking subject numbers to personally identifiable information was destroyed.*
***Subject had no formal diagnosis of head trauma but had a history of seizure.*

	Control		SARD			RA			SLE			SS		
	N	(%)	N	(%)	P-value	N	(%)	P-value	N	(%)	P-value	N	(%)	P-value
Age (years)														
18-24	24	(12)	10	(5)	< 0.001	5	(4)	< 0.001	4	(9)	0.688	0	(0)	.105
25-44	106	(53)	87	(44)		54	(39)		28	(61)		4	(33)	
45-64	54	(27)	67	(34)		51	(18)		12	(26)		7	(58)	
65+	16	(8)	36	(18)		33	(24)		2	(4)		1	(8)	
Mean age (std)	41	(15)	48	(17)	< 0.001	51	(18)	< 0.001	39	(12)	0.363	51	(14)	0.022
Median	36		45											
Gender														
Female	121	(61)	169	(85)	< 0.001 $\chi^2 = 28.89$	115	(82)	< 0.001 $\chi^2 = 18.17$	42	(91)	< 0.001	10	(83)	0.137
Male	79	(40)	31	(16)		25	(18)		4	(9)		2	(17)	
Active duty military														
Yes	75	(38)	32	(16)	< 0.001 $\chi^2 = 23.59$	25	(18)	< 0.001 $\chi^2 = 15.30$	4*	(9)	< 0.001	2*	(17)	0.218
No	125	(63)	168	(84)		115	(82)		42	(91)		10	(83)	

Table 5: *Age, Sex, and Military Status of Control, SARD, and SARD Subgroup Populations.*
**P-values are based on the two-sided Fisher's exact test comparing each group separately vs. the controls when subgroups n < 10.*

Bibliography

1. Lipton RB., *et al*. "Migraine prevalence, disease burden, and the need for preventive therapy". *Neurology* 68.5 (2007): 343-349.
2. Lipton RB., *et al*. "Migraine in the United States - Epidemiology and patterns of health care use". *Neurology* 58.6 (2002): 885-894.
3. Helseth EK and Erickson JC. "The prevalence and impact of migraine on US military officer trainees". *Headache* 48.6 (2008): 883-889.
4. Hu XH., *et al*. "Burden of migraine in the United States - Disability and economic costs". *Archives of Internal Medicine* 159.8 (1999): 813-818.
5. Baer A. "Diagnosis and classification of Sjögren's syndrome". *Retrieved January* 7 (2014).
6. Baer A. "Treatment of dry mouth and other non-ocular sicca symptoms in Sjögren's syndrome". *Retrieved January* 7 (2014).
7. Fox R and Creamer P. "Treatment of systemic and extraglandular manifestations of Sjögren's syndrome". *Retrieved January* 7 (2014).
8. Fox R and Moschella S. "Clinical manifestations of Sjogren's syndrome: extraglandular disease".
9. Isenberg DA., *et al.* "A Study of Migraine in Systemic Lupus-Erythematosus". *Annals of the Rheumatic Diseases* 41.1 (1982): 30-32.
10. Lupus Foundation of America. "What is lupus?" *Retrieved January* 6 (2014).
11. Sjögren's Syndrome Foundation, Inc. "About Sjogren's". *Retrieved January* 6 (2014).
12. Venables P and Maini R. "Clinical manifestations of rheumatoid arthritis".
13. Wallace D. "Overview of the management and prognosis of systemic lupus erythematosus in adults" (2014).
14. Burton W., *et al*. "Systematic review of studies of productivity loss due to rheumatoid arthritis". *Occupational Medicine-Oxford* 56.1 (2006): 18-27.
15. Narayanan S., *et al*. "Economic Burden of Systemic Lupus Erythematosus Flares and Comorbidities in a Commercially Insured Population in the United States". *Journal of Occupational and Environmental Medicine* 55.11(2013): 1262-1270.
16. Meijer JM., *et al*. "Health-related quality of life, employment and disability in patients with Sjogren's syndrome". *Rheumatology* 48.9 (2009): 1077-1082.
17. Arthritis Foundation. "What is Rheumatoid Arthritis?" *Retrieved January* 6 (2014).
18. Dunkin M. "What is Sjogren's Syndrome? Retrieved
19. Schur PH and Moreland LW. "General principles of managements of rheumatoid arthritis in adults". *Retrieved January* 7 (2014).
20. Appenzeller S and Costallat LTL. "Clinical implications of migraine in systemic lupus erythematosus: relation to cumulative organ damage". *Cephalalgia* 24.12 (2004) 1024-1030.
21. Tjensvoll AB., *et al*. "Migraine is frequent in patients with systemic lupus erythematosus: A case-control study". *Cephalalgia* 31.4 (2011): 401-408.
22. Harboe E., *et al*. "Neuropsychiatric syndromes in patients with systemic lupus erythematosus and primary Sjogren syndrome: a comparative population-based study". *Annals of the Rheumatic Diseases* 68.10 (2009): 1541-1546.
23. Kang JH and Lin HC. "Comorbidities in Patients with Primary Sjogren's Syndrome: A Registry-based Case-control Study". *Journal of Rheumatology* 37.6 (2010): 1188-1194.
24. Pal B., *et al*. "A Study of Headaches and Migraine in Sjögren's Syndrome and Other Rheumatic Disorders". *Annals of the Rheumatic Diseases* 48.4 (1989): 312-316.
25. Hanly JG., et al. "Headache in Systemic Lupus Erythematosus Results From a Prospective, International Inception Cohort Study". *Arthritis and Rheumatism* 65.11 (2013): 2887-2897.
26. Katsiari CG., *et al*. "Headache in Systemic Lupus Erythematosus vs Multiple Sclerosis: A Prospective Comparative Study". *Headache* 51.9 (2011): 1398-1407.
27. Le H., *et al*. "Comorbidity of migraine with somatic diseases in a large population based study". *Journal of Headache and Pain* 11 (2011): S7-S7.
28. Weder-Cisneros ND., *et al*. "Prevalence and factors associated with headache in patients with systemic lupus erythematosus". *Cephalalgia* 24.12 (2004): 1031-1044.

29. Gokcay F., *et al*. "Headache in primary Sjogren's syndrome: a prevalence study". *Acta Neurologica Scandinavica* 118.3 (2008): 189-192.
30. Katsiari CG., *et al*. "Headache in Systemic Lupus Erythematosus vs Multiple Sclerosis: A Prospective Comparative Study". *Headache* 51.9 (2011): 1398-1407.
31. Breslau N., *et al*. "Migraine Headaches and Suicide Attempt". *Headache* 52.5 (2012): 723-731.
32. Glanz BI., *et al*. "Prevalence of migraine in patients with systemic lupus erythematosus". *Headache* 41.3 (2001): 285-289.
33. Gokcay F., *et al*. "Headache in primary Sjogren's syndrome: a prevalence study". *Acta Neurologica Scandinavica* 118.3 (2008): 189-192.
34. Pal B., *et al*. "A Study of Headaches and Migraine in Sjögren's Syndrome and Other Rheumatic Disorders". *Annals of the Rheumatic Diseases* 48.4 (1989): 312-316.
35. Whitelaw DA., *et al*. "Headaches in patients with systemic lupus erythematosus: a comparative study". *Lupus* 13.7 (2004): 501-505.
36. TRICARE®. "About TRICARE. Number of Beneficiaries". *Retrieved January* 14 (2014).
37. Kalaydjian A and Merikangas K. "Physical and mental comorbidity of headache in a nationally representative sample of US adults". Psychosomatic Medicine 70.7 (2008): 773-780.
38. National Center for Health Statistics. "National Interview Health Survey (2011) with Special Feature on Socioeconomic Status and Health". Hyattsville, MD: Public Health Service (2012).
39. Pons-Estel GJ., *et al*. "Understanding the Epidemiology and Progression of Systemic Lupus Erythematosus". *Seminars in Arthritis and Rheumatism* 39.4 (2010): 257-268.
40. Silman AJ and Pearson JE. "Epidemiology and genetics of rheumatoid arthritis". *Arthritis research* 4 Suppl 3 S265-272.
41. Patel R and Shahane A. "The epidemiology of Sjogren's syndrome". *Clinical epidemiology* 6 (1989): 247-255.
42. ICD-9-CM. "Official authorized addendum for the International Classification of Diseases, Ninth Revision, Clinical Modification. Volumes 1, 2, and 3. Effective for discharge October 1, 1988. National Center for Health Statistics and the Health Care Financing Administration". *Journal (American Medical Record Association)* 59.8 (1988): 1-34.
43. ICD-9-CM. "Official authorized addendum for the International Classification of Diseases, Ninth Revision, Clinical Modification. Volumes 1, 2, and 3. Effective for discharge October 1, 1988. National Center for Health Statistics and the Health Care Financing Administration". *Journal (American Medical Record Association)* 59.8 (1988): 1-34.
44. Pons-Estel., *et al*. "Understanding the Epidemiology and Progression of Systemic Lupus Erythematosus". *Seminars in Arthritis and Rheumatism* 39.4 (2010): 257-268.
45. Queiroz LP., *et al*. "Characteristics of migraine visual aura". *Headache* 37.3 (1997): 137-141.
46. Sjögren's Syndrome Foundation, Inc. "About Sjogren's". *Retrieved January* 6 (2014).
47. US Department of Health and Human Services, P. H. S., Health Care Financing Administration. (1989). The International Classification of Diseases: 9th Revision, Clinical Modification: ICD-9-CM.
48. Victor., *et al*. "Migraine prevalence by age and sex in the United States: A life-span study". *Cephalalgia* 30.9 (2010): 1065-1072.
49. World Health Organization. "The World Health Report 2001: Mental health: new understanding, new hope". *World Health Organization* (2001).

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