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ORIGINAL PAPER

Spinal pain and major depression in a military cohort: bias analysis of dependent misclassification in electronic medical records

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Abstract

Background Spinal pain and major depression are prevalent conditions in adult populations and are particularly impactful in the military. However, the temporal relationship between these two conditions remains poorly understood.

Methods Using data extracted from electronic medical records, we assessed the association between incident diagnoses of spinal pain and major depression in a cohort of 48,007 Canadian Armed Forces personnel followed from January 2017 to August 2018. We used multivariate Poisson regression to measure the association between the period prevalence of these two conditions. We used probabilistic bias modelling to correct our estimates for misclassification of spinal pain and major depression.

Results After correcting for misclassification with probabilistic bias modelling, subjects newly diagnosed with spinal pain during the study period were 1.41 times (95% interval 1.25, 1.59) more likely also to be diagnosed with incident major depression, and personnel newly diagnosed with major depression were 1.28 times (95% interval 1.17, 1.39) more likely also to be diagnosed with spinal pain, compared to undiagnosed counterparts of the same age and sex. Without bias corrections, we would have overestimated the magnitude of the association between major depression and spinal pain by a factor of approximately 2.0.

Conclusion Our results highlight a moderate and bi-directional association between two of the most prevalent disorders in military populations. Our results also highlight the importance of correcting for misclassification in electronic medical record data research.

Keywords Military · Depression · Back pain · Neck pain · Bias analysis

Introduction

Major depression is a leading cause of worldwide morbidity [1] and is at least twice as prevalent in military personnel compared to civilians [2–5]. Major depression is associated with an increased risk of suicidal behaviours [6], poor job performance [7], and premature career termination [8].

Spinal pain is another prevalent problem in military organizations. In the U.S. military, back problems are the most common reason for clinical encounters [9] and are a leading cause for medical evacuations out of theatres of operations [10]. In the Canadian military, 23% of personnel report currently suffering from medically diagnosed back problems [11]. Moreover, spinal pain during military service is associated with pain episodes later in life [12].

Major depression and spinal pain are comorbid illnesses [13]. The strong association between depression and pain can be explained by different mechanisms [14]. Depressed mood and the emotional experience of pain are modulated by nociceptive pathways that involve many of the same brain regions and neurotransmitters [14]. Depressed patients experience disruptions in pain perception [15], which could increase their risk of spinal pain onset. Twin [16, 17] and family [18] studies have suggested that depression and pain may also share common genetic risk factors. Other authors have proposed psychosocial mechanisms, whereby debilitating pain leads to social isolation, diminished enjoyment of

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life, and a loss of social roles, ultimately causing the onset of major depression [14].

Longitudinal data are needed to better understand the temporal relationships between major depression and spinal pain in active military personnel. Such data can help inform screening policies, health resource allocation, and multidisciplinary collaborations to reduce the morbidity burden of these two important public health issues.

This study investigated the co-occurrence of incident major depression and spinal pain diagnoses over 20 months in Canadian Armed Forces personnel, using electronic medical record data. We used probabilistic bias analysis to account for important sources of misclassification that are inherent to electronic medical record data.

Methods

Study design

We conducted a 20 month retrospective study of Canadian Armed Forces (CAF) personnel who were free of major depression and spinal pain at baseline. We used electronic medical record data to identify new diagnoses of major depression and spinal pain.

Sample population

Using CAF administrative databases, we identified all individuals who were in the CAF Regular Force on January 1st, 2017, whether they were serving in Canada or abroad ($n = 65{,}981$). To study the co-occurrence of new major depression and spinal pain diagnoses over the study period, we required all study subjects to have neither condition at baseline. We therefore excluded all individuals who had diagnoses of major depression or spinal pain in the 12 months preceding the study start date ($n = 13{,}273$). We also excluded individuals who had not served in the CAF Regular Force for at least 12 consecutive months before the study start date ($n = 4{,}701$). Our final sample consisted of 48,007 subjects.

Measures

We used data extracted from CAF electronic medical records to identify all incident diagnoses of major depression and spinal pain in study subjects from January 1, 2017, to August 31, 2018. Methods used to define incident cases of major depression [19] and spinal pain [20] have been described in additional detail elsewhere.

Two types of data signals were used to identify incident cases of major depression: (a) International Classification of Disease (ICD-10) or diagnostic statistical manual of mental disorders (DSM-5) diagnostic codes for major depression recorded by healthcare providers in CAF primary care or specialty mental health clinics, and (b) depressive symptoms selected from a standardized list of clinical impressions, and recorded in CAF clinics within six months of a major depression diagnostic code. The first data signal related to depression recorded during the study period was interpreted as an incident diagnosis. We also manually reviewed the medical charts of patients receiving most of their care from civilian mental health specialists [19]. We thereby identified 116 additional incident major depression diagnoses in patients treated in non-CAF mental health clinics and therefore had incomplete data in their CAF electronic medical records.

Consistent with previous studies [21], we defined spinal pain as pain originating from the cervical, thoracic, or lumbar spine. We identified incident cases of spinal pain using over 150 related ICD-10 codes [22] recorded in CAF primary care clinics. For our study, the first diagnostic code related to spinal pain recorded in a patient's medical chart during the study period was interpreted as an incident diagnosis.

We extracted the age, sex, and employment history of all study subjects from CAF administrative databases. We censored subjects from analyses on their retirement date from the CAF Regular Force, because new diagnoses of spinal pain or major depression would not be recorded in the CAF electronic medical records of retired members.

Statistical models

We used multivariate poisson regression models with robust error variance to compare the period prevalence of new major depression diagnoses in subjects with vs without incident diagnoses of spinal pain during the study period, and vice-versa. All diagnoses and person-years of military service accrued between January 1, 2017 and August 31, 2018 were included. All models were adjusted for sex and age group, and included the log of person-years of observation contributed by each subject as an offset.

Bias analysis

The models described above were at risk of bias, in part because electronic medical record data have several limitations [23]. For example, diagnostic codes can only be recorded during medical encounters, but not all individuals seek care for their symptoms of major depression [24] or spinal pain [25]. Diagnostic codes are also not recorded in the electronic medical record of every care-seeking patient. For example, diagnostic codes are rarely generated in CAF physiotherapy clinics, because CAF physiotherapists tend to scan hand-written notes into the electronic medical record

of spinal pain patients [20]. Finally, military personnel are more likely to seek care for their depressive symptoms if they are experiencing comorbid physical pain [26]. These limitations could create a spurious association between spinal pain and major depression through misclassification. We therefore used probabilistic bias analysis methods [27] to correct for misclassification as defined below.

We simulated 50,000 datasets hypothetically free of misclassification. Because the precise extent of misclassification in our sample was unknown, we relied on available evidence to derive probability distributions for each bias parameter. These reflected a range of plausible values and quantified the uncertainty of each bias parameter.

Misclassification of spinal pain

Based on previous evidence, we assumed that the risk of major depression misclassification depended on the unbiased values of spinal pain [26]. As recommended under such conditions [28], we corrected spinal pain misclassification first, and then used bias-corrected spinal pain status to inform the correction of major depression misclassification.

Based on the results of an internal validation study [20], we sampled a positive predictive value (PPV) from a normal distribution with mean = 0.905 and standard error = 0.025. Similarly, we sampled a negative predictive value (NPV) from a normal distribution with mean = 0.881 and standard error = 0.014. To reflect the interdependence between PPV and NPV, we imposed a correlation coefficient $r = 0.5$ between the randomly sampled values of these two parameters. On the rare occasions where one of the sampled values was > 1.0, the value was replaced with 0.999. We assigned a bias-corrected care-seeking status for each patient with a diagnostic code for spinal pain during the study period using a single Bernouilli trial with $p = \text{PPV}$. We assigned a bias-corrected care-seeking status for each subject with no diagnostic code for spinal pain during the study period using a single Bernouilli trial with $p = 1 - \text{NPV}$.

Based on the results of a population-based survey of CAF personnel [25], we assumed that 1.5% of subjects who had not sought care for spinal pain had actually experienced activity-limiting spinal pain during the study period. We therefore sampled a probability of unreported spinal pain, ψ, from a normal distribution with mean = 0.015 and standard error = 0.010. We assigned a bias-corrected spinal pain status for each subject who had not sought care for spinal pain in the past year using a single Bernouilli trial with $p = \psi$.

Misclassification of major depression

Based on the results of an internal survey [24], we assumed that the probability of care-seeking and subsequent diagnosis among all CAF Regular Force personnel with major depression followed a normal distribution with mean = 0.747 and standard error = 0.042. We randomly selected a diagnosis probability, θ, from this normal distribution. We then divided the observed number of diagnosed cases, nd, by the sampled diagnosis probability, θ, to estimate the total number of incident cases, nt, and the number of undiagnosed cases, nu, as follows:

$$\text{nt} = \frac{\text{nd}}{\theta} \tag{1}$$

$$\text{nu} = \text{nt} - \text{nd} \tag{2}$$

The number of undiagnosed cases of incident major depression, nu, was the sum of undiagnosed cases among patients with (nu_{pain}) and without (nu_{no}) spinal pain.

$$\text{nu}_{\text{pain}} = \text{nu} - \text{nu}_{\text{no}} \tag{3}$$

We also assumed that misclassification of outcome was differential across categories of exposure. More specifically, we assumed that patients with major depression had higher odds of diagnosis if they had comorbid spinal pain. Based on published data from a survey of U.S. military personnel [26] and unpublished results from a survey of CAF personnel [25], we assumed that the odds of diagnosis were 10–50% higher in depressed subjects with vs without spinal pain. We randomly sampled an odds ratio, *OR*, from a uniform distribution bounded by 1.1 and 1.5. We then entered the observed number of diagnosed cases in subjects with (nd_{pain}) and without (nd_{no}) spinal pain in equation [4], and solved for the number of undiagnosed cases among patients with (nu_{pain}) and without (nu_{no}) spinal pain.

$$\frac{\text{nd}_{\text{pain}}}{\text{nu}_{\text{pain}}} = \text{OR} \times \frac{\text{nd}_{\text{no}}}{\text{nu}_{\text{no}}} \tag{4}$$

We then reclassified depression status in nu_{pain} subjects randomly selected among those with bias-corrected spinal pain but no incident diagnosis of depression, and nu_{no} subjects among those without bias-corrected spinal pain and no incident diagnosis of depression.

Bias analysis

We refitted our poisson regression models on the bias-corrected data to obtain bias-adjusted regression coefficients comparing the period prevalence of spinal pain in patients with vs without major depression, and the period prevalence of major depression in patients with vs without spinal pain. We reintroduced random error estimated from the original data. To obtain stable confidence limits, we repeated the bias-correction steps outlined above 50,000 times; the median of our 50,000 iterations was used as the bias-adjusted point estimate, and the 2.5th and 97.5th

Table 1 Demographic characteristics of study subjects, and number of incident diagnoses of major depression and spinal pain during the study period, January 2017 to August 2018

	Total count at baseline		Incident major depression diagnosis		Incident spinal pain diagnosis	
	N	(Column %)	*n*	(Row %)	*n*	(Row %)
Sex						
Female	6165	(12.8)	455	(7.4)	1579	(25.6)
Male	41,842	(87.2)	1724	(4.1)	7941	(19.0)
Age at baseline						
17–29 years	17,536	(36.5)	601	(3.4)	2717	(15.5)
30–39 years	16,753	(34.9)	870	(5.2)	3453	(20.6)
40–49 years	9750	(20.3)	539	(5.5)	2393	(24.5)
50–60 years	3968	(8.3)	169	(4.3)	957	(24.1)
Total	48,007	(100)	2179	(4.5)	9520	(19.8)

Table 2 Number of study subjects with an incident diagnosis of major depression and spinal pain at any point during the study period, January 2017 to August 2018

Incident spinal pain diagnosis	Incident major depression diagnosis		
	Yes	No	Total
Yes	707	8813	9520
No	1472	37,015	38,487
Total	2179	45,828	48,007

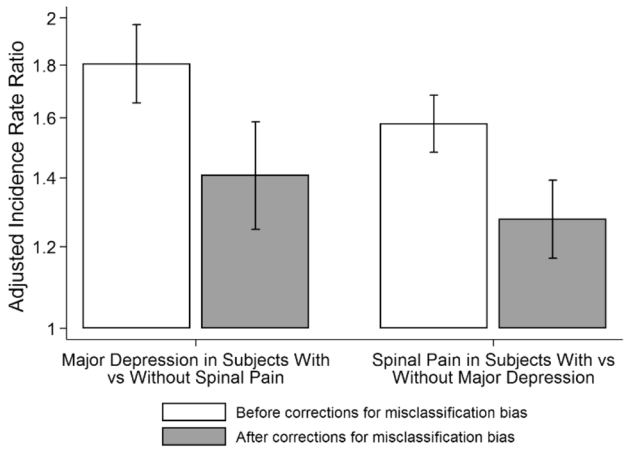

Fig. 1 Ratios comparing the prevalence of new major depression diagnoses in subjects with vs without incident diagnoses of spinal pain during study period, and the prevalence of new spinal pain diagnoses in subjects with vs without incident major depression diagnoses. Multivariate Poisson regression models adjusting for sex and age group were fitted on observed data (white bars), and on data corrected for misclassification of spinal pain and major depression through 50,000 bias analysis iterations (grey bars)

percentiles were used as the lower and upper bounds of its new 95% interval [26]. All analyses were performed using Stata, version 14.0 [29].

Results

Our sample consisted of 48,007 CAF personnel observed over 76,163 person-years of military service. Most study subjects were male, and younger than 40 years (Table 1). By design, no subject had been diagnosed with spinal pain or major depression in the 12 months preceding the study start date.

During the study period, 9520 subjects were diagnosed with spinal pain, and 2179 subjects were diagnosed with major depression (Table 2). After adjusting for age and sex, subjects with diagnoses related to spinal pain at any point during the study had a 1.80-fold (95% CI 1.65, 1.97) higher likelihood of also being diagnosed with major depression, compared to those without a spinal pain diagnosis. Conversely, subjects diagnosed with major depression at any point during the study had a 1.58-fold (95% CI 1.48, 1.68) higher likelihood of also being diagnosed with spinal pain, compared to those without a major depression diagnosis (Fig. 1). After correcting for misclassification of both spinal pain and major depression with bias modelling, these adjusted prevalence ratios decreased to 1.41 (95% interval 1.25, 1.59) and 1.28 (95% interval 1.17, 1.39), respectively (Fig. 1).

Among the 707 subjects diagnosed with both spinal pain and major depression during the study period, the incident spinal pain diagnosis preceded the incident major depression diagnosis in 49.9% of cases, and the incident major depression diagnosis preceded the incident spinal pain diagnosis in 45.3% of cases. The remaining 4.8% of comorbid cases received both diagnoses on the same day.

Discussion

We found that incident diagnoses of major depression and spinal pain were comorbid in a large sample of military personnel. Over 20 months, personnel newly experiencing spinal pain were 80% more likely to be diagnosed with major depression, and personnel newly diagnosed with major depression were 58% more likely to have a diagnosis of spinal pain than counterparts of the same age and sex. After correcting for misclassification in our bias modelling, these associations decreased in magnitude from 80 to 41%, and from 58 to 28%, respectively. Furthermore, we found evidence that these associations were bi-directional.

Our results are consistent with recent studies suggesting a bi-directional relationship between pain and depression in general adult populations in the United States, Sweden, and Taiwan [30–32]. Indeed, approximately half of patients who experienced both outcomes during the study period were diagnosed with spinal pain before major depression; a similar percentage were diagnosed with major depression first and spinal pain second. This symmetry in the timing of incident diagnoses is consistent with models of shared vulnerability to major depression and spinal pain [14, 16]. Some military personnel may already be at high risk for both outcomes; in these individuals, the onset of one outcome may precipitate the onset of the other, but the disorders could conceivably manifest in any order.

Implications

The U.S. Preventive Task Force currently recommends depression screening in primary care settings for all adult patients [33]. The Canadian military conducts mental health screening for all personnel reporting to primary care clinics for mandatory health exams, but such exams only occur once every five years for individuals in certain occupational groups. Currently, patients reporting to primary care clinics for specific physical complaints are not systematically screened for mental health symptoms. The close relationship between spinal pain and major depression incidence reported herein suggests that, in theory, mental health screening in CAF primary care clinics could improve major depression case detection among spinal pain patients. However, depression screening has associated costs [34], and its benefits are context-dependent [35]. Future research is warranted to measure the benefits of major depression screening in spinal pain patients in a military context.

Our results should also encourage increased collaboration between primary care clinicians, mental health specialists, and pain specialists in treating adults with major depression or spinal pain. The two conditions are prevalent, comorbid, and their respective onsets tend to cluster in time. Integrated healthcare systems offer an opportunity for the multidisciplinary management of these two disorders. Other authors have also recommended engaging mental health specialists to treat spinal pain patients [36]. Cognitive behavioural therapy—a first-line psychotherapy for major depression [37] is an effective treatment for spinal pain [38]. Additionally, effective treatment of major depression can improve spinal pain outcomes and vice-versa [39].

Finally, our results highlight the importance of correcting for misclassification bias in epidemiological studies relying on electronic medical record data to measure disease status. The adjusted prevalence ratios measuring the association between major depression and spinal pain decreased substantially after bias modelling. Insofar as our bias parameters were correctly specified, part of the association between major depression and spinal pain observed in electronic medical record data was due to misclassification. If we had failed to correct for misclassification, our biased results would have overestimated the need for clinical and preventive resources specifically targeted to major depression and spinal pain.

Limitations

Our study had noteworthy limitations. First, we operationalized major depression and spinal pain as two dichotomous outcomes. However, symptoms of major depression and spinal pain range in severity [40, 41], and previous studies have found that symptom severity is an important effect modifier in the association between chronic pain and depression [42, 43]. We reported moderate associations between our dichotomous variables, but there may be stronger associations between severe depression and severe spinal pain. We could not assess these associations because of difficulties in measuring symptom severity with our data. Second, we did not measure musculoskeletal pain originating from body regions other than the spine. Our results can therefore not provide a comprehensive overview of pain and depression comorbidity. However, chronic pain and major depression are complex disorders, with hundreds of contributing factors [44, 45]. Developing comprehensive models of pain and depression was beyond the scope of this study. Our objective was simply to measure the association between two of the most impactful health conditions in military personnel, which did not require accounting for non-spinal pain. Third, we did not account for care-seeking delays. We assumed that care-seeking patients sought care for major depression or spinal pain immediately after symptom onset. However,

military personnel who seek care for depression sometimes only do so years after the onset of their depressive symptoms [46]. It is, therefore, possible that patients met clinical criteria for major depression before the onset of new pain episodes but sought mental healthcare for their depressive symptoms only once their spinal pain had been diagnosed. This limits the temporal interpretation of our findings but does not limit their relevance for screening efforts and clinical programmes. Our results show that diagnosis of one of these conditions is often followed by the diagnosis of the other. Ensuring that mental health resources are available to patients first presenting with spinal pain and that pain management resources are available to patients first presenting with major depression could be beneficial regardless of the actual timing of symptom onset. Fourth, our bias modelling did not guarantee the complete elimination of bias. We could have inadvertently increased – rather than reduced—misclassification bias if our bias parameters were incorrectly specified [47]. As recommended [48], we mitigated this risk by specifying our bias parameters using results from internal studies and by specifying wide probability distributions for each bias parameter.

Conclusion

In conclusion, we have completed one of the largest studies to date of the incidence of major depression and spinal pain in a military population. Our results could inform future screening efforts, prevention programs, and multidisciplinary collaborations. Our results also highlight the importance of correcting for misclassification bias in electronic medical record data research.

Author contributions All authors contributed to the study's conception and design. RAH and FLT performed data collection. Data analysis was performed by FLT. The first draft of the manuscript was written by FLT, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflicts of interest None declared.

Ethical approval This study was approved by the CAF Deputy Surgeon General and the University of Ottawa Office of Research Ethics and Integrity.

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