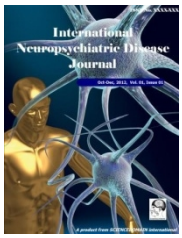

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Ambient Sulphur Dioxide and Emergency Department Visits for Migraine and Depression

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MS, IC, and BHR designed the study. Author MS performed the statistical analysis, and MS wrote the first draft of the manuscript. Authors MS, BHR and IC managed the analyses of the study. Author MW managed the literature review and contributed to writing the manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Depression and migraine are linked especially among women. Little previous research has focused on the potential association between ambient sulphur dioxide (SO_2) exposure and emergency department (ED) visits for migraine, headache, depression, and anxiety.
Study Design: Case-crossover design, in which case and control is the same person, was used as study design for daily recorded diagnosed ED visits. Ambient sulphur dioxide was considered as an exposure.
Place and Duration of Study: ED data from five hospitals in Edmonton, Canada. The data were considered for the period: April 1, 1992 – March 31, 2002 (10 years).
Methodology: ED visits from Edmonton for the four health conditions were analyzed separately using case-crossover methodology. A conditional logistic regression was applied to implement a time-stratified case-crossover technique. The models were constructed for a single (one) air pollutant. Weather factors (temperature and humidity)

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were adjusted using natural splines. Odds ratios (ORs) and their 95% confidence intervals (CI) were estimated for an increase in an interquartile range of SO_2 (IQR = 2.3 ppb).

Results: For females, statistically significant positive associations were observed between SO_2 exposure and ED visits for migraine and depression (OR = 1.02, 95% CI: 1.01-1.03; OR = 1.04, 95% CI: 1.01-1.07, respectively). A positive association was observed for female ED visits for headache and anxiety. For males, ED visits for migraine were associated with ambient sulphur dioxide exposure (OR = 1.04, 95% CI: 1.00-1.08, for patients of age 20 to 60 years).

Conclusion: A known link between migraine and depression has its mapping in responses to ambient air pollution. These results provide additional evidence to indicate that ED visits for depressive disorder and migraine may be associated with exposure to ambient sulphur dioxide.

Keywords: Air pollution; anxiety; depression; exposure; headache; migraine; sulphur dioxide; urban.

1. INTRODUCTION

In this work we consider four health conditions presenting to emergency departments (ED; migraine, headache, depression, and anxiety) and the link to an important marker of air quality. Here the term headache is used to refer to non migraine headache. There is research to indicate that migraine and headache represent a type of “benign” headache which may be associated with various comorbid psychiatric disorders [1-10], including an increase in suicide risk [2]. Migraine represents a highly prevalent health disorder with many associated risks and costs; recent research has estimated prevalence to be approximately 6.1% in males and 15.2% in females [3]. The relatively high prevalence of migraine headaches is a public health concern, as migraine can cause significant losses of productivity and an overall decrease in patient and family quality of life [3,5].

The research linking migraine and other headache disorders to psychiatric comorbidities, such as anxiety and mood disorders, is robust [1-10]; however, there is ongoing debate regarding the causality between and the coexistence of the two distinct entities. A recent review of large-scale population-based research has found migraine sufferers to be between 2.2 and 4.0 times as likely to report having comorbid depression [5]. The prevalence of depression in those suffering from migraine has been estimated to be 17.6%, compared to 7.4% in the general population [8]. Additionally, the relationship between migraine and major depression appears to be bidirectional; migraine has been found to increase the risk for depression and depression has been found to increase the risk for migraine [9]. The psychiatric comorbidities associated with migraine are not limited to depression; migraine headaches have also been significantly associated with anxiety, such as generalized anxiety, panic or phobia disorders [3]. The strong associations between migraine and comorbid mood or anxiety disorders is an critical clinical and public health issue; having both disorders is associated with decreased quality of life, restricted activities, increased disability and increased health service utilization [3].

Much research has examined the impact of the ambient environment on various health conditions, including migraine headaches and psychiatric disorders. In Chile, severe headaches that required hospitalization were increased on days with higher air pollution; of these severe headaches, migraine was the condition most consistently associated with air

pollutants [11]. Short-term ambient air pollution exposure has been significantly associated with ED visits for migraine, headache [12-14], depression [15-17], and suicide attempts in Canada [18]. The link between air pollution and ED visits for the listed conditions raises important public health concerns; additional research is need to further elucidate the relationship between ambient sulphur dioxide (SO_2) exposure and migraine, headache, depression, and anxiety.

We propose the use of case-crossover (C-C) design, to investigate the relationship between exposure to ambient air conditions and the number of emergency department (ED) visits for migraine, depression, headache and anxiety in Edmonton, Canada over a period of 10 years. We consider ambient sulphur dioxide pollution and weather factors as an exposure and ED visits for the listed conditions as health outcomes. Weather parameters, temperature and relative humidity, are used as confounders. As these health outcomes are highly linked, we hypothesized that they would have a similar association with exposure to sulfur dioxide.

2. MATERIALS AND METHODS

ED visit data were obtained from Edmonton, Canada, for the period from April 1992 to March, 2002 (10 years, 3,652 days). Edmonton's data were composed of data sets from five different hospitals in the former Capital Health (now referred to as Alberta Health Services (AHS) – Edmonton Zone) region with a population now approaching 1 million people. These 5 EDs are all urban, high-volume ($\geq$ 50,000 visits per year), staffed by full-time dedicated emergency physicians, and involved in emergency medicine teaching through the University of Alberta's Departments of Emergency Medicine and Family Medicine. For most of the study period, there was no dedicated pediatric ED in the city.

The database used contained almost three millions recorded and diagnosed visits for all ages and both sexes. ED visits for the analyzed health outcomes were identified based on a discharge diagnosis (the primary cause) of the conditions using the International Classification for Diseases 9^{th} revision (ICD-9) [19]. They were retrieved usin the following conditions: migraine – 346.90; depression – 311; headache – 784.0; and anxiety – 300. The visits were date-tagged to the day of patient arrival to the ED. These date were used to identify the day of event. Ambient conditions on this day were considered as an exposure.

Air pollution data were obtained from the National Air Pollution Surveillance (NAPS) system, and weather data from Environment Canada's weather archive. We obtained data on different ambient air pollutants. In this study, we used only sulphur dioxide (SO_2). The main reason to restrict our study to one pollutant was that we observed correlations between this pollutant and ED visits for migraine in our previous studies [12-15]. Our main goal in this work was to investigate the similarity of responses to exposure to an air pollutant, sulphur dioxide, for four health conditions.

Daily mean values of pollutant levels as an average of hourly readings (24 values) were used to represent shared exposure of the population in the study (persons served by hospitals in Edmonton). SO_2 was measured using coulometry/ultraviolet fluorescence method and was measured by one fixed monitor in Edmonton. The meteorological variables employed were temperature (dry bulb) and relative humidity. The daily mean as an average of hourly readings (24 measurements) was applied to represent these weather parameters. In the final models, the weather variables were treated as confounders and incorporated in the form of natural splines.

A case-crossover (CC) design was applied in the study [20]. The CC method is an adaptation of the case–control approach. By definition of the case-crossover design, the cases are used as their own controls on a set of predefined control days proximate to the time they became cases. A time-stratified technique to determine controls was widely accepted as it has been shown to produce unbiased conditional logistic regression estimates [21]. In the design, the controls are matched to case periods by day of week for the case period (day), the control periods are determined as other days in the same one calendar month. This strategy was realized in this study, thus 3 or 4 controls are present for each case. Thus, for the case of Monday other Mondays in the same month and year act as controls. Environmental conditions (air pollution, weather) on these Mondays were considered as an exposure for the case and the controls.

The results were generated as odds ratios (OR) and their 95% confidence intervals (CI). The estimated ORs were reported for an increase in the concentration represented as the interquartile range (IQR = 75^{th}- 25^{th} values of percentiles) of the SO_2 level. Temperature and relative humidity were used in form of natural splines with 3 degrees of freedom. For all components in the models, the pollutant and meteorological variables, their values were used in the same day as ED visits (lag 0).

The sequence of 67 overlapping age groups (length of 20 years) was constructed in the following way: the first age group was (0,19), second (1,20), and each next was created from the current one by shifting it by one year. In this sequence, the last one was assumed to be the age group (66, 85). For the elements of this sequence the CC models were constructed separately. The calculations were also executed separately by sex (male, female). In our study, the significance level was set at 0.05.

3. RESULTS

The results were based on the following numbers of ED visits: migraine (all = 56,243; female = 44,133); depression (all = 15,563; female = 9,244); headache (all = 29,138; female = 18,462); anxiety (all = 16,065; female = 10,287). Table 1 presents the numerical results by sex (males, females) for all ages and for one age group [20, 60]. For the time period of our study, the estimated mean value of ambient sulphur dioxide levels in Edmonton were 2.6 ppb (standard deviation 1.8 ppb, Q1=1.3 ppb, and Q3=3.5 ppb). The correlations with other air pollutants were as follows: O3–CO: -0.55, O3–NO2: -0.53, O3–SO2: -0.27, O3–PM10: -0.07, O3–PM2.5: 0.05, CO–NO2: 0.78,CO–SO2: 0.43, CO–PM10: 0.43, CO–PM2.5: 0.32, NO2–SO2: 0.47, NO2–PM2.5: 0.39,NO2–PM10: 0.33, SO2–PM2.5: 0.21, SO2–PM10: 0.22, and PM2.5–PM10: 0.76.

Table 1. Odds ratios (OR) and their 95% confidence limits (95% CI) for an interquartile range (IQR = 2.3 ppb) increase in sulphur dioxide (lag 0)

Age:		All		20-60	
ED visits	**Sex**	**OR**	**95% CI**	**OR**	**95% CI**
Migraine	M	1.02	0.99, 1.05	1.04	1.00, 1.08*
	F	1.02	1.01, 1.03*	1.02	1.01, 1.04*
Depression	M	0.96	0.96, 1.03	1.09	0.98, 1.21
	F	1.04	1.01, 1.07*	1.05	1.02, 1.09*
Headache	M	0.99	0.97, 1.01	1.00	0.97, 1.04
	F	1.02	0.99, 1.04	1.02	0.99, 1.05
Anxiety	M	1.00	0.96, 1.04	0.99	0.95, 1.05
	F	1.00	0.97, 1.03	1.03	0.98, 1.07

**p-value < 0.05. M –males, F –females.*

The results were organized into five figures and one table. Each figure represents estimated values grouped in two parts; results for males (left panel) and results for females (right panel). Fig. 1 shows the frequencies of ED visits for the four considered health conditions. Migraine was the most frequent health condition in this group among female and male patients. Similar numbers of ED visits for depression and anxiety were observed and for both sexes. Moreover, the most frequent patients visiting the EDs for the health outcomes studied were approximately 35 years of age.

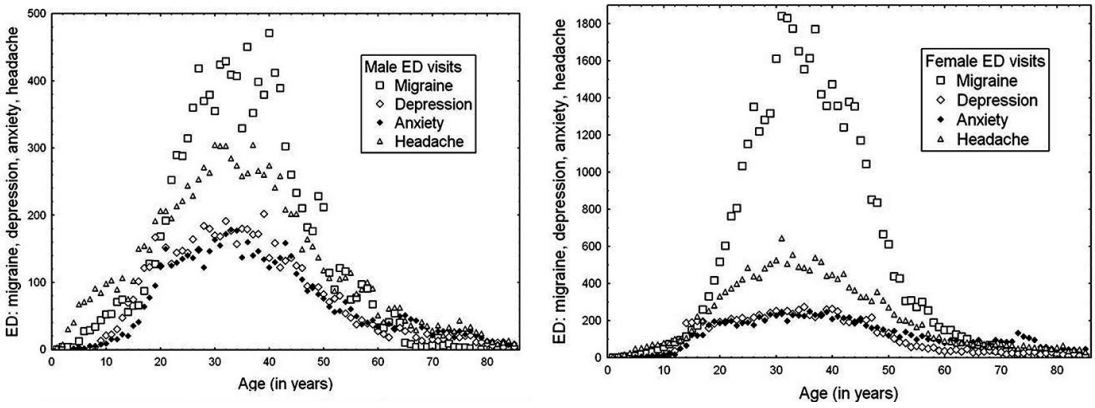

Fig. 1. Frequency of ED visits for migraine, depression, headache and anxiety

Figs. 2 - 5 illustrate the values obtained from the C-C models. The results are composed of 3 values for each considered age group and represent ORs and their 95% CIs, thus 201 (67 x 3) values are shown, for males and females, respectively.

Fig. 2 shows that for female migraine patients the results are positive and statistically significant. Also we observe the positive correlation for males.

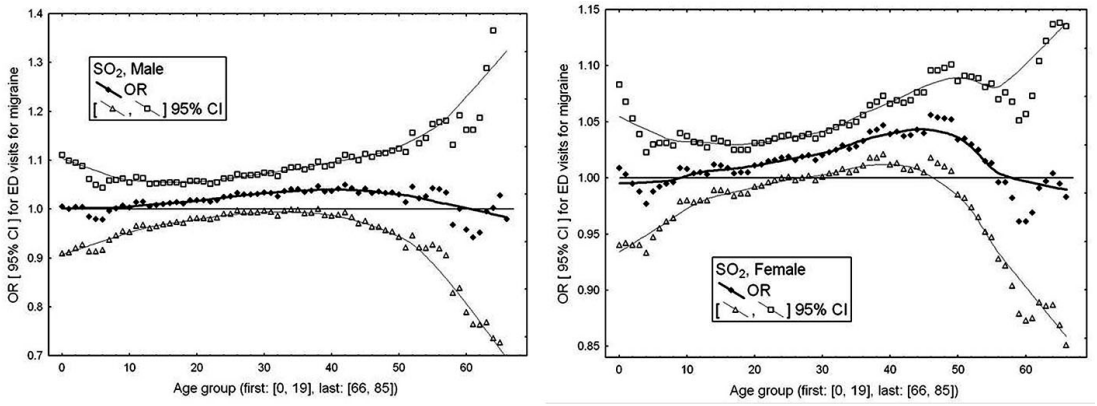

Fig. 2. ORs and their 95% CIs for ED visits for migraine (67 age groups)

Almost for the same age intervals for female, ED visits for depression are correlated with ambient sulphur dioxide (Fig. 3). The significant correlations were estimated for the youngest male patients with a diagnosis of depression.

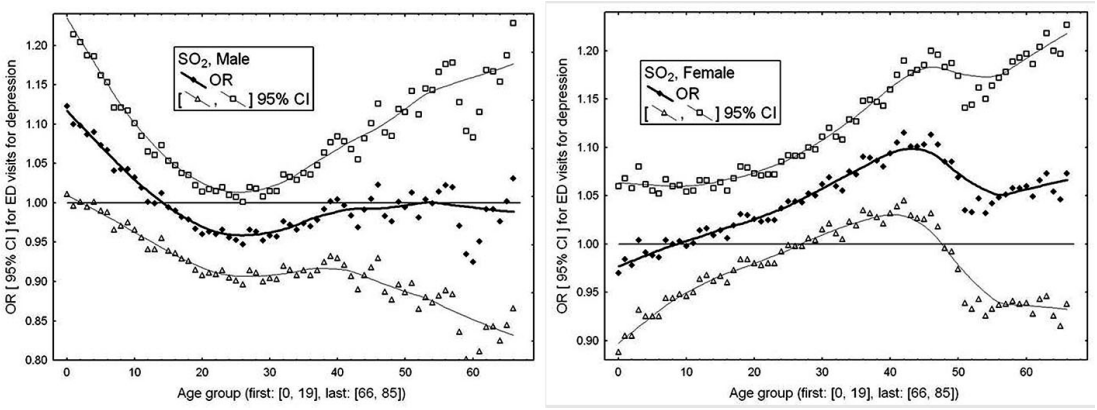

Fig. 3. ORs and their 95% CIs for ED visits for depression (67 age groups)

We observed few significant correlations with air pollution for female ED visits for headache (Fig. 4).

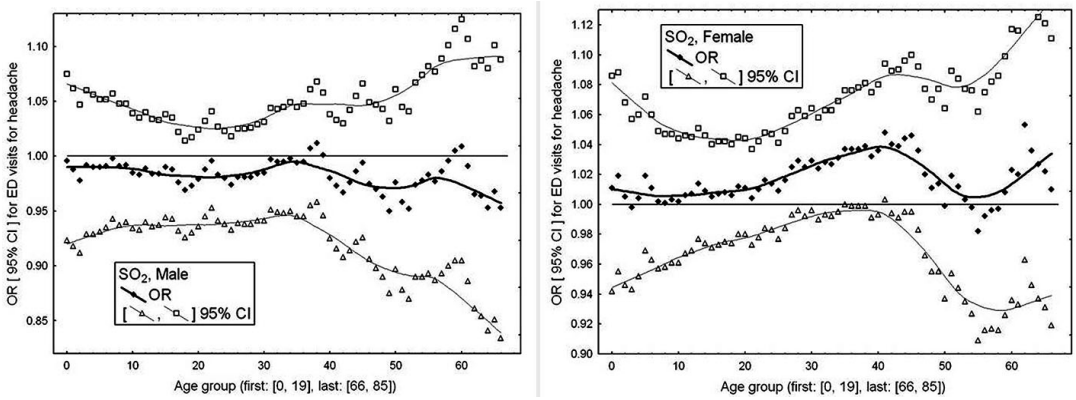

Fig. 4. ORs and their 95% CIs for ED visits for headache (67 age groups)

For anxiety, for both sexes, the correlations with air pollutant (OR ~= 1.00) are not significant (Fig. 5).

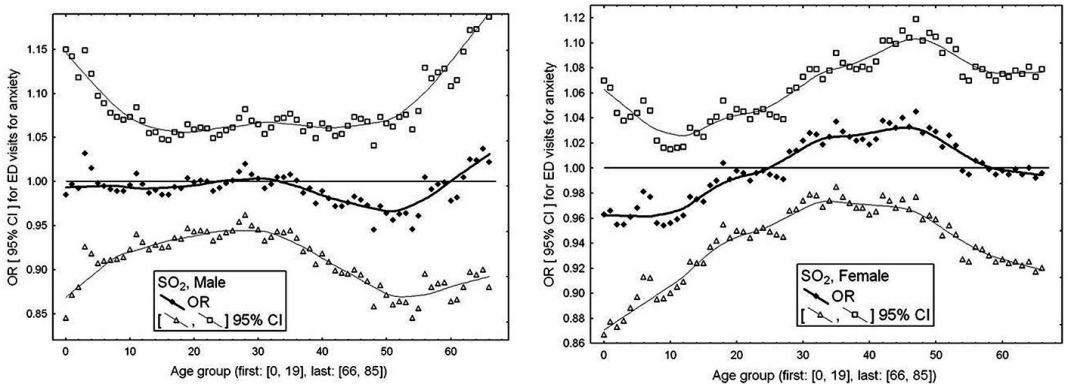

Fig. 5. ORs and their 95% CIs for ED visits for anxiety (67 age groups).

Female ED visits for migraine and depression are positive and statistically significant. For males only OR for male ED visits for migraine is significant, and only for restricted age range.

The results of this study found significant short-term effects of ambient air sulphur dioxide exposures on daily ED visits for migraine and depression for all female patients and for males in the 20-60 years age range. Among female patients, ED visits for depression was stronger for the age interval of 20-60 years than for all ages. The positive correlations were also noted for females with the headache diagnosis. Interestingly, in females, plots of ORs for by age groups for depression and migraine, headache and anxiety demonstrate a very similar trend (Figs. 3-5). It may be that similar environmental conditions affect all of these health conditions; however, further research would be required to validate this assertion. The results of this study are congruent with previous research observing comorbidity between depression and migraine [1-10].

4. DISCUSSION

While much of the evidence detailing the neurological effects of ambient air pollution is derived from animal models, mechanisms linking airborne inflammatory factors to depression and anxiety have been postulated. The ingestion of airborne inflammatory factors, including ambient pollutants, induces inflammatory immune responses in the respiratory system [22,23]; it has also been established that activation of the peripheral immune response produces depressive or anxious behaviour [24-26]. Furthermore, recent research has demonstrated that inflammatory responses in the nasal cavity are capable of increasing cytokine production in the brain [27]. While it is uncertain whether the cytokines directly produce depressive-like behaviour, it is posited that their expression plays a contributing role for the manifestation of depressive-life behaviour [28]. Cytokines activate the hypothalamic-pituitary-adrenal (HPA) axis, the body's main stress response system, and decrease neurogenesis, leading some to propose that depressive and anxious behaviours may result through the direct actions of cytokines on synaptic plasticity [29]. Therefore, while it is uncertain whether the inflammatory responses to pollutants play an etiological role in the development of depression or anxiety, they may exacerbate or contribute to the condition [28]. This pathway provides biological plausibility to the hypothesis that exposure to ambient air pollution may result in neurological changes that may aggravate or manifest as symptoms of depression or anxiety.

The results of this study are consistent with reports from other research. In one study, the authors investigated air pollution exposure and hospital admission for migraine in Chile [11]. They reported for a 6.20-ppb increase in sulphur dioxide a 17% increase in admission (relative risk (RR) = 1.17; 95% CI: 1.08, 1.26). This RR value was the largest among estimates for the considered air pollutants. It is interesting that in a similar study performed by these authors for epilepsy, they observed an 10% increase in hospitalization (RR = 1.108; 95% CI: 1.021, 1.204) [30]. The impact of air pollution on suicide deaths has also been reported [31-33]. One publication reported an association between air pollution with home doctors' visits for headache [34]. Another study reported a significant correlation between dust and headaches [35]. In another study [36], 50 subjects were studied in relation to headache and exposure to chemicals in the work place. The study distinguished between acute and extensive exposure versus routine and limited. Low level exposure at the work place appeared to cause headaches that stopped soon after cessation of exposure. In contrast a single accidental and intensive exposure caused a new headache syndrome that, in some cases, lasted several months or years [36]. Finally, in another study the relationship between diagnosed depression and occupational pesticide exposure was evaluated. The results suggested that acute high-intensity and cumulative pesticide exposure may contribute to depression among persons working with these products [37]. The study also indicated that chronic pesticide exposure is associated with depression.

While there are limitations associated with this research, they are typical limitations related to this type of research. Due to the use of case-crossover methodology, we are only able to demonstrate the association between an exposure and the frequency of ED visits. While we cannot demonstrate a causal relationship between ambient air pollution and ED visits, the results show a strong and statistically significant association, indicating that ambient SO_2 pollution may represent an important trigger for the acute presentation of migraine, depression and anxiety. We estimated associations with the odds of a daily visit for an individual, not the numbers of daily ED visits in the population. Our study evaluated cross-sectional data and could not examine risk of migraine or depression, and therefore a casual

association could not be established. It is not possible to confirm that air pollution triggers migraine or depression through observational data.

Other limitations include the sample and the impact of potential measurement error in the exposure and outcome variables. While not all headaches, including migraine, and/or depression/anxiety cases present to the ED, it is likely that the cases that do are more severe. Coding errors may have produced random variations in the results; however, we do not believe that these errors biased the reported estimates. Additionally, we used 0- day lag in our models. While other lags may also have been applicable, previous studies have shown that exposure on same day as the case has the strongest effects [13]. The air monitoring stations within Edmonton are relatively sparse; it is likely that the exact location of residence, personal activities prior to the event, and work exposures may influence or vary the exposure to SO_2. Moreover, only one monitoring station exists for SO_2; however, previous research by our group shows that there are strong correlations across the city for other air pollutants when they are compared using all three monitoring stations. Finally, other factors such as diet, exercise, body mass index, smoking status, drug/alcohol use, current treatment, and other unmeasured patient risk factors that may affect ED presentation of these conditions were not examined. However, the case-crossover methodology used in this study, in which each patient serves as his or her own control, reduces or eliminates the confounding effects of the otherwise unmeasured factors associated with living conditions and air pollution exposures. It is important to consider that there is still potential for confounding with time-varying characteristics.

5. CONCLUSION

We have demonstrated that the pattern of responses to exposure to sulphur dioxide among females for four considered health conditions is consistent, even when examining different age groups. The results support the hypothesis that ED visits for depressive disorders, anxiety and headaches (including migraine) are associated with ambient SO_2 concentrations. The large majority of this type of air pollution arises from combustion of fossil fuels (e.g., diesel motor vehicles, petrochemical activities), an exposure that occurs frequently in North America and other developed countries. The public health implications of the associations between ambient air pollution and ED visits for migraine, depression, and anxiety are large due to the common, daily exposure to such pollution. Consequently, efforts to reduce SO_2 emissions may in turn reduce the presentations of these chronic conditions to EDs in the future.

CONSENT

This research used de-identified administrative data obtained from Capital Health (now AHS-Edmonton Zone); informed consent was not required by the ethics committee.

ETHICAL APPROVAL

The University of Alberta Health Research Ethics Board that oversees the research activities of the participating hospitals approved the access to data, and the aggregated data were transferred to Health Canada after personal identifying information was removed. This study was also approved by Health Canada's Research Ethics Board.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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