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Seasonality in Major Depressive Disorder: Effect of Sex and Age

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ABSTRACT

Background: Aside from the concept of seasonal affective disorder, the evidence for a seasonal pattern (SP) of major depressive disorder (MDD) is controversial. Furthermore, the effect of sex and age is still unclear.
Methods: This is a nationwide, registry-based study assessing all inpatient admissions in mental health hospitals due to MDD episodes according to ICD-10 (moderate (F32/33.1), severe (F32/33.2) and severe with psychotic features (F32/33.3)) in Austria across 14 years. Calculations were based on deviations from expected monthly admissions.
Results: The sample comprised 231,824 hospitalisations (36.8% men) for MDD. A significant SP (p=0.001) in moderate and severe depressive episodes in both women and men with decreased admission rates in the summer months and December was detected. In psychotic depression a significant SP was only evidenced in women ($p = 0.002$, men: $p = 0.291$). Patients older than 55 years had a reduced SP compared to those being younger.
Limitations: Only anonymised admission data of inpatient treatments were available. Hospitalization rates cannot fully be equated to the occurrence of MDD.
Conclusions: The current study indicates a seasonal variation in MDD symptoms that may go beyond seasonal affective disorder. Knowledge about the predictability of depressive symptoms in patients should encourage preventive strategies.

1. Background/Introduction

The global prevalence of major depressive disorder (MDD) was estimated to exceed 320 million in 2015, affecting 4.4 percent of the total world population (WHO). In fact, some countries evidenced a significant increase in MDD within the last decade (Steffen et al., 2020). Overall, the disorder is one of the leading causes of years lived with disability, causing a significant disease burden (James et al., 2018). Many affected individuals seem to exhibit changes in various psychosocial areas of functioning, including drive, sleep, or mood, which are influenced by seasonality (Kasper et al., 1989; Monteleone and Maj, 2008). However, between 0.4 and 2.9 percent of the general population suffer from a distinct subtype of MDD that is subject to seasonal variation, which was first described by Rosenthal and colleagues in 1984 as seasonal-affective disorder (SAD) and can nowadays be specifically classified in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (Magnusson and Stefansson, 1993; Mersch et al., 1999a; Muscettola et al., 1995; Pjrek et al., 2016; Rosenthal et al., 1984; Westrin and Lam, 2007; Wirz-Justice et al., 2019).

To date, only a few studies have investigated a potential seasonal pattern (SP) of MDD hospital admissions, whereby the results yielded were contradictory. One recent investigation from Canada failed to demonstrate any seasonal variation for admissions to hospitals for unipolar depression (Pillai et al., 2017). In contrast, earlier studies conducted in Poland (Dominiak et al., 2015) and Norway (Morken et al., 2002) postulated a clear SP of inpatient service utilisation for depression with peaks in the months of spring (March to May) and autumn (September to November). In a recent systematic review, a larger

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number of studies aiming to elucidate seasonal variations in MDD symptoms per se for both in- and outpatients were summarised. Considerable inconsistencies in the evidence for seasonality in MDD symptoms were uncovered, as well as many critical unresolved questions (Overland et al., 2019). Consequently, the authors encouraged the use of registry data to shed light on this important research issue (Overland et al., 2019). Furthermore, the effect of age and sex on the SP of hospitalisations for MDD is still unexplored and needs to be clarified. Being aware of the limited comparability, evidence derived from SAD patient populations point towards an association of younger age with regard to vulnerability to SAD (Magnusson and Stefansson, 1993; Saheer et al., 2013). Further, the ratio of female to male patients in the SAD literature was mostly comparable or even slightly more pronounced compared to non-seasonal depression (Kasper et al., 1989; Oyane et al., 2005; Wirz-Justice et al., 2003). However, recent research showed mixed results. A Swiss longitudinal cohort study found women to be three to five times more affected by SAD (Wirz-Justice et al., 2019), while an Austrian investigation failed to demonstrate any gender differences (Pjrek et al., 2016). In order to narrow the aforementioned empirical gaps, the present study sought to (1.) elaborate a potential seasonal pattern of admissions to hospital due to MDD and (2.) to examine the effect of sex and age in a large sample of psychiatric admissions derived from national health care data over a period of 14 years.

2. Methods

2.1. Design

We conducted a registry-based nationwide study in Austria for psychiatric admissions in the period 2003 to 2016. Data was provided in anonymised form by the national statistics agency, Statistics Austria. They collect data annually from the Austrian health system and provide data access for scientific research.

2.2. Sample

The current study examined data from all patients who were admitted to psychiatric adult or child and adolescent departments with a diagnosis of depressive disorder (ICD-10: F32/F33) as the main reason for inpatient treatment. Age groups were given by the national statistics agency in 5-year intervals.

The dataset contained the following variables: depressive disorder (sub-)diagnoses (ICD-10 F32/3.0-3, and F32/3.8-9), sex, length of hospital stay in days, calendar week of admission, medical specialty and type of treatment care (acute vs. rehabilitation) of the treating department. For further calculations, depression sub-diagnoses were grouped into moderate depressive (ICD-10 F32/33.1), severe depressive (F32/33.2) and severe depressive episodes with psychotic features (F32/33.3). To improve the diagnostic specificity and representativeness of acute inpatient psychiatric care, patients were excluded from the study in a first step if they were admitted to non-psychiatric departments or rehabilitation clinics (n=150,119), in a second step if they were younger than 15 years of age (n= 3,227), third if they had been hospitalised for more than one year (n=29) and finally if they had been diagnosed with mild (F32/33.0, n=8,526) or unspecified depressive episodes (ICD-10: F32/3,8-9, n=15,155 or had been in remission (ICD-10: F33.4, n=1401). Thus, a total of 178,457 were excluded from the initial 410,281 inpatient treatments.

2.3. Statistical methods

Data management and analysis were done in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The SP was calculated on a monthly basis and described by the difference in the number of admissions observed within a month from the expected numbers, based on the annual numbers divided by the length of the month. The effect of seasonality was tested using chi-squared tests. In order to minimise alpha errors through a large number of statistical tests, only descriptive methods were used to assess the effect of age. According to previous publications assessing SPs in bipolar disorder (Yang et al. 2013 and Fellinger et al. 2019), age groups were determined and divided into 15 to <35, 35 to <55 and 55+ years. The overall level of significance was set at 5%. The level of significance for individual p-values was set at 5%/10 = 0.5% in order to adjust for multiple testing based on 10 tests.

3. Results

The data set comprised 231,824 admissions of patients with depression, n = 113,197 (48.8%) for moderate depressive episodes (ICD-10 F32/33.1), n = 91,777 (39.6%) for severe depressive episodes (F32/33.2) and n = 26,850 (11.6%) for severe depressive episodes with psychotic features (F32/33.3). Women comprised 63.2% (n = 146,439) of all admissions. The mean age at admission was 49.5 years (SD 17.1) in women and 46.8 years (SD 15.7) in men. On average patients were admitted for 18.1 days (moderate: 15.4, severe: 19.8 and severe episodes with psychosis 23.6 days).

Psychiatric admissions due to an episode of MDD showed a significant seasonal pattern (p=0.001) independent of severity and sex (Suppl. Table 1). While the SP was comparable in moderate and severe depressive episodes, it was less pronounced in severe depressive episodes with psychotic symptoms (Fig. 1). With regard to the duration of admissions, a seasonal variation comparable to the inpatient admission rate was observed in all groups (Suppl. Figure 1) and the individually assessed ICD-10 subgroups (Suppl. Figure 2) respectively.

Sex and Seasonality

Seasonality was significant in women and men at the adjusted significance level of 0.5% in all depressive subtypes, except in men with major depressive episodes with psychotic features (moderate and severe depressive subtypes in women and men: p<0.0001, severe depressive subtype with psychotic features in women: p=0.002, and in men: p=0.291; Suppl. Table 1). The distinct seasonal variation was observed in men and women for both moderate and severe depressive episodes with the lowest inpatient admission rate in the summer and a maximum in the winter months (January to March), with the exception of a sudden low in December. In major depressive episodes with psychotic features, there was no clear SP, except for a decline in admissions for women in December (see Fig. 2–4). Comparing SPs between men and women within the depressive subtypes, no significant difference could be observed (moderate: p=0.174, severe: p=0.067, severe with psychotic features: p=0.062).

3.2. Age and Seasonality

In the two patient groups with moderate and severe depressive episodes (ICD-10: F32/3.1 and F32/3.2), the seasonal variation up to the age of 55 years was similar and markedly more pronounced than in patients over 55 years of age. Furthermore, while the lowest admission rate for those up to 55 years of age was in July or August, those aged 55 and above had the lowest rates in December (Suppl. Fig. 3 and 4). In severe depressive episodes with psychotic features (ICD-10: F32/3.3), the effects of age were not clearly evident (Suppl. Fig. 5).

4. Discussion

To our best knowledge, the current study analyzing over 230,000 admissions across a period of 14-years in Austria represents the most extensive investigation of seasonality for major depressive disorder (MDD) to date. First, our results revealed a seasonal pattern (SP) in patients with moderate and severe depressive episodes, which was

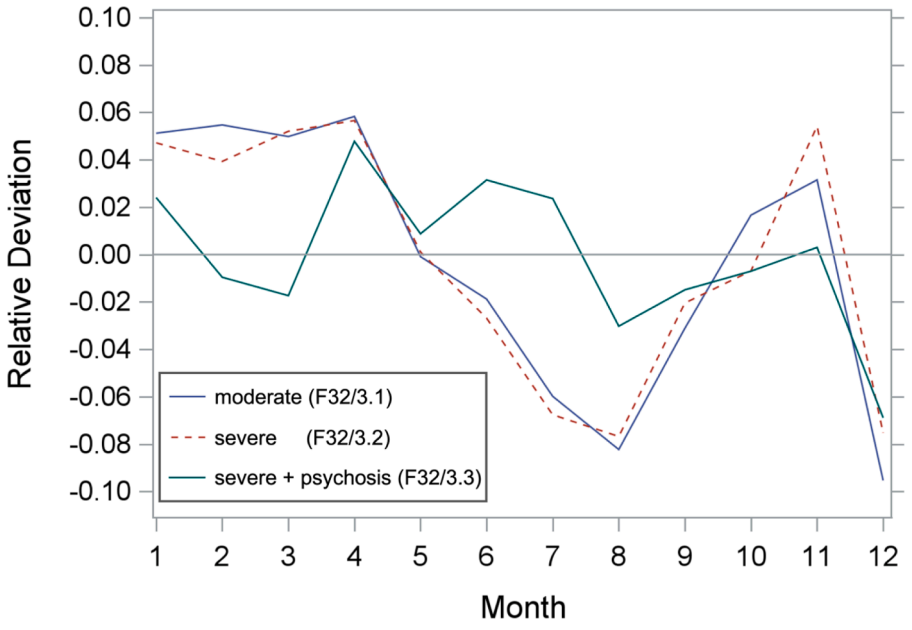

Figure 1. Seasonal variations of depressive subtypes according to ICD-10: moderate (F32/33.1), severe (F32/33.2) and severe depressive episodes with psychotic features (F32/33.3)

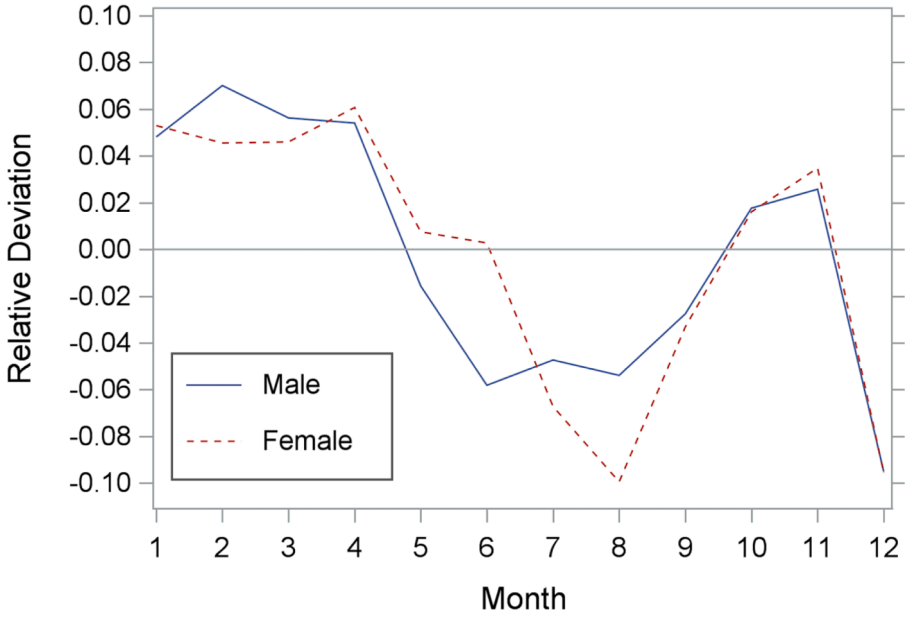

Figure 2. Seasonal variation of moderate depressive episodes (ICD-10 F32/33.1) shown as relative deviations in male and female.

considerably less apparent in those suffering from depressive episodes with psychotic features. Second, it could be shown that both sexes were equally affected by SP of their MDD episodes, with the exception of men with psychotic depression, who showed no seasonal variation. The third novel finding was a reduced SP in patients with MDD older than 55 compared to younger individuals.

Overall, our findings largely strengthen the existing evidence for a SP in hospitalisations for MDD (Dominiak et al., 2015; Morken et al., 2002) and are, hence, in contrast to a recent investigation from Canada that failed to show any seasonal variation (Pillai et al., 2017). In our study the lowest admissions rates were clearly evidenced during the summer season (June to August) and in line with similar studies from Poland and Norway, admission rates peaked in spring (March to April) and autumn (September to November) respectively (Dominiak et al., 2015; Morken et al., 2002). However, contrary to our expectations, the rate of inpatient admissions was decreased in December for all patients regardless of the MDD subtype, sex and age. The effect might be best explained as a result of the public holidays and religious festivals in December. Decreased inpatient service utilization due to reduced help seeking behaviour in holiday periods was repeatedly described in the literature (Aviv et al., 2011; Davies et al., 2000; Hillard et al., 1981). Interestingly, the length of stay in hospital showed a seasonal variation similar to the admission rates and underlines the increased need for inpatient care due to increased symptoms of MDD at specific times of the year.

Regarding the severity of symptoms, we found a similarly expressed seasonal variation of admissions in patients with moderate and severe depressive episodes. This is in contrast to a recent study that found only mild depressive symptoms to be subject to seasonal changes (Lukmanji

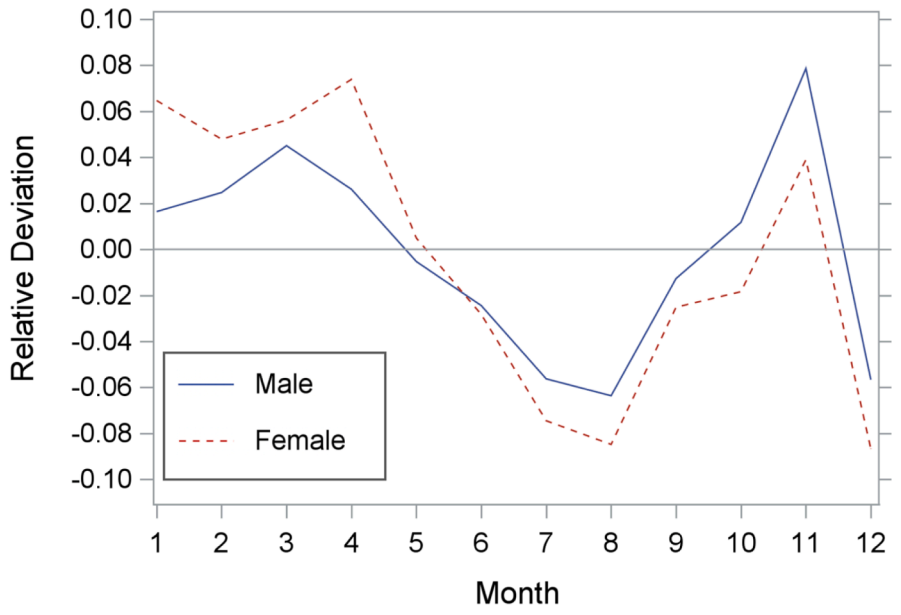

Figure 3. Seasonal variation of severe depressive episodes (ICD-10 F32/33.2) shown as relative deviations in male and female.

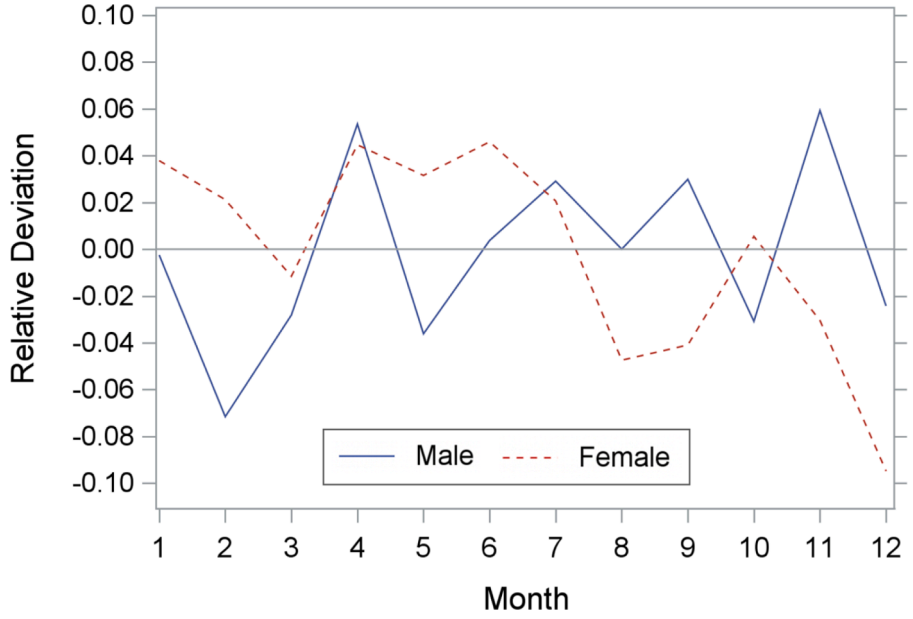

Figure 4. Seasonal variation of severe depressive episodes with psychotic features (ICD-10 F32/33.3) shown as relative deviations in male and female.

et al., 2019). Furthermore, it has been estimated that the extent of subsyndromal SAD in the general population is greater than SAD as such (Melrose, 2015). In depressive episodes with psychotic features, a notable exception of a clear SP was observed in our study, which was even more pronounced in male patients. Interestingly, a previous report found an association of psychotic symptoms with barometric pressure rather than preceding exposure to sunlight as a marker for seasonal variation (Radua et al., 2010). According to recent studies, patients suffering from MDD with psychotic features have to be considered more severely ill, with a higher disease burden and functional impairment. However, this cannot be ascribed to depressive symptoms and therefore differs significantly from patients with non-psychotic MDD (Costa et al., 2020). Evidence for a higher probability of a family history of schizophrenia or psychotic bipolar disorder in patients with psychotic depression suggests genetic proximity to the spectrum of psychotic disorders (Buoli et al., 2013; Musliner et al., 2020), which may be an explanatory model for the much less distinct susceptibility to seasonal variation. The known SP of hospitalizations for schizophrenia follows a course with peaks in January and June, which in part does not correspond to the pattern typical for affective disorders (Hinterbuchinger et al., 2020). Concerning depression severity and SP, our findings indicate that moderate and severe depressive episodes are associated with a distinct seasonal variation that has to be appraised as novel.

A further aspect in need of clarification was the impact of sex on the presence of a seasonal variation of MDD symptoms. Despite some recent evidence of lacking gender disparity in SAD (Pjrek et al., 2016), the most evidence points towards a discrepancy in favour of female patients (Magnusson, 2000) with a considerable magnitude of up to a five-fold higher prevalence in a recently published report (Wirz-Justice et al., 2019). The few studies devoted to seasonality of MDD hospitalizations hardly covered this aspect. Our results reveal a significant SP of hospital admissions for both male and female patients with moderate and severe

depressive episodes and to a lesser extent also for female patients with psychotic depression. For male MDD patients exhibiting psychotic features, no SP was observed. However, in our study, there was no significant difference between men and women per depressive subtype in terms of seasonal fluctuations. Accordingly, we suppose that both sexes are subject to a seasonal variation of their MDD symptoms, whereby women could be more likely affected by or prone to the dimensional seasonality trait that specifies SAD.

The impact of age regarding the vulnerability to seasonal changes or the prevalence of SAD, respectively, could be outlined in many but not all studies covering this topic (Magnusson, 2000). Our findings clearly support recent publications that found younger individuals to be more susceptible (Lukmanji et al., 2019; Lukmanji et al., 2020) and older patients (> 65 years) to be less influenced by season as a moderator to their depressive symptoms (Holloway and Evans, 2014). Compared to the aforementioned publications, our study had the considerable advantage that the cohort covers the entire age spectrum and thus the possibility to discriminate certain age groups more precisely.

Generally spoken, our findings may corroborate the hypothesis of a seasonal variation of MDD symptoms that may go even beyond the concept of SAD. Consequently, the present results may be in line with authors stating that SAD may not be considered a unique diagnostic entity (Melrose, 2015) but might rather be a subtype of MDD found in patients with exceptional vulnerability of their symptoms to season. The dual vulnerability model postulated 20 years ago suggests that patients suffering from SAD and non-seasonal depression experience a shared vulnerability for depression, whereby only individuals with SAD are vulnerable to seasonal factors like the photoperiod (Lam et al., 2001). According to our findings, MDD symptoms, in general, might be subject to a considerable variation influenced by the season, SAD patients located at a very end of a continuum may, however, experience a maximum expression of seasonal variation with a specific presentation of their symptoms and a high likelihood for recurrence (Melrose, 2015).

4.1. Strengths and Limitations

The greatest strength of our investigation is the large sample size and the long observation period, allowing a robust response to our research question. In addition, the appropriateness of using administrative data-derived mental health diagnoses for severe mental disorders, including MDD, derived from administrative data has recently been described in the literature (Davis et al., 2016; Nesvag et al., 2017). Another strength is the differentiated investigation of the severity of the depression and the corresponding gender and age influences as well as the adjustment for the number of statistical tests used. In analogy with previous publications (Fugger et al., 2020), the terms gender and sex were both used in order to cover biologically based (sex) as well as societal/culturally based (gender) aspects (Clayton and Tannenbaum, 2016). However, our findings have to be carefully interpreted in light of the following limitations. First, the possibility of a misclassification or selection bias of severely ill patients cannot be ruled out in registry-based data. Consequently, our findings may not apply to patients who are not identified by healthcare inpatient treatment. Second, the number of hospital admissions as a proxy for the incidence of a mood disorder may be influenced by confounding factors like the number of available empty beds or the possibility of home care by relatives for instance. Third, the onset of a major depressive episode and the inpatient admission date may differ, which could have distorted the results. Fourth, the effect of latitude on seasonality, albeit small (Mersch et al., 1999b), has to be taken into account. Therefore, the seasonality pattern observed in our investigation might only be valid for Austria and geographical regions situated around the same latitude. Finally, future studies should focus on patient-related data in order to be able to assess additional influencing factors such as comorbidity, psychopharmacological or psychotherapeutic treatment.

5. Conclusion

The observed SP of hospitalisations for major depression in both sexes enriches the existing body of evidence pointing towards a seasonal variation of depressive symptoms. Older individuals and patients exhibiting psychotic symptoms, especially men, appeared to be less affected. Thus, on the one hand, our results further underscore the importance of the concept of SAD, but on the other hand, we hypothesise that many MDD patients who do not fully meet the diagnostic criteria of SAD may nonetheless be subject to seasonal fluctuations of their symptoms. The predictability of seasonal changes in MDD represents an important indicator for prevention measures. A promising strategy might be the timely utilization of bright light therapy, which has been shown to be efficacious in seasonal as well as non-seasonal depressive disorders (Al-Karawi and Jubair, 2016; Pjrek et al., 2020) as well as the application of antidepressants or the implementation of psychotherapeutic approaches (Nussbaumer-Streit et al., 2017).

Abbreviations

ICD-10 – International Classification of Diseases, tenth edition
MDD – Major Depressive Disorder n – Number
SD – Standard Deviation
SP – Seasonal Pattern
Suppl. Fig. – Supplementary Figure

Declarations

Ethics approval and consent to participate
Not applicable.
Consent for publication
Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The authors had permission to use the anonymised database by the national statistics agency, Statistics Austria.

Competing interest

All authors declare that no competing interests exist.

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Authors' contributions

MJF and GF contributed to designing the study, statistical analyses, and writing the report, including the first draft of the manuscript. TW undertook the statistical analysis. TW, BH, NP, DK, AG, SV and BV contributed to designing the study and critically reviewing the paper. All authors have read and approved the final manuscript.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.09.051.

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