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Research paper

Season of treatment initiation with antidepressants and suicidal behavior: A population-based cohort study in Sweden

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ABSTRACT

Background: Decreased binding capacity of SERT in the prefrontal cortex has been observed in both suicide victims and suicide attempters. Moreover, some studies have shown that SERT has a seasonal variation with lower binding capacity in the spring and summer, which coincides with a seasonal peak of suicides. Our aim was to explore whether the season of treatment initiation with antidepressants is associated with suicide or suicide attempt and compare it with the underlying suicide seasonality in the general population.
Methods: Using Swedish registers, patients who initiated treatment with an antidepressant were followed up to three months for suicidal behavior. Cox regression analyses were used. Results were compared with the underlying seasonal pattern by calculating standardized mortality ratios (SMRs) for suicides and standardized incidence ratios (SIRs) for suicide attempts.
Results: Patients aged ≥65 years had higher risk for suicide when initiating antidepressant treatment in the summer, and also a higher risk for suicide attempt when initiating treatment in the spring and summer. Young patients (0–24 years) presented a higher risk for suicide attempt when initiating treatment in the autumn. Patients with previous suicide attempt had a seasonal pattern, with a higher risk to carry out a suicide attempt in the summer and autumn. Results from the SMR and SIR calculations numerically support these findings.
Limitations: We used information of filling an antidepressant prescription as a proxy of actual antidepressant treatment. Patients with combination, augmentation therapy or those switching antidepressant during follow-up were excluded. Thus, our results refer to less complicated psychopathology.
Conclusions: Our results indicate an interaction between biological and health care-related factors for the observed seasonal pattern of suicidal behavior in the elderly, whereas psychological and societal factors may be more important for the seasonality observed in the younger patients.

1. Introduction

Antidepressants appear to exert their pharmacological action by enhancing serotonergic neurotransmission. Antidepressants have been exhaustively investigated in randomized clinical trials and in systematic meta-analyses. Such investigations have demonstrated their efficacy for the treatment of depressive and anxiety disorders, but also that they may have the potential adverse effect of triggering suicidal behavior (Jick et al., 2004; Juurlink et al., 2006; Martinez et al., 2005; Olfson et al., 2006; Stone et al., 2009).

Investigations suggesting that antidepressants, and more specifically selective serotonin reuptake inhibitors (SSRIs), trigger suicidal behavior were first reported in the 1990s (Teicher et al., 1990). Studies thereafter reported conflicting results, with some finding no increased risk for suicide, regardless of treatment assignment (Beasley et al., 1991; Hammad et al., 2006; Khan et al., 2000; Storosum et al., 2001), whereas others reported increased risk for suicide attempts and self-harm behaviors (Fergusson et al., 2005; Gunnell et al., 2005; Martinez et al., 2005). Later, a differential risk of antidepressant-induced suicidal behavior across the age spectrum was suggested, with a greater risk at the younger end of the spectrum, a declining risk with aging, and perhaps even a protective effect in elderly depressed patients (Martinez et al., 2005; Olfson et al., 2006; Stone et al., 2009). Several possible mechanisms have been suggested for how antidepressants may trigger suicidality, including the resolving psychomotor retardation in depression, which may activate the patient to commit suicide before any mood

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improvement has occurred (Nutt, 2003), the development of akathisia-like symptoms (Maris, 2002), the short term effects in impulsivity and aggression, as well as the poorly defined although clinically evident jitteriness/anxiety syndrome (Sinclair et al., 2009).

Moreover, a temporal association between antidepressants and suicide may be due to non-response to antidepressant treatment itself. Meanwhile, ecological studies have reported that a higher prescription of SSRIs is associated with lower suicide rates (Gibbons et al., 2005, 2006; Grunebaum et al., 2004; Isacsson and Mathe, 2008; Milane et al., 2006).

Several lines of evidence from postmortem studies of suicide victims, as well as in vivo imaging studies of suicide attempters, suggest that serotonergic neurotransmission is implicated in the suicidal process, possibly through a decreased serotonin transporter (SERT) binding in the prefrontal cortex (Arango et al., 1995; Leyton et al., 2006; Mann et al., 1996). A low concentration of the major serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid is known to be associated with suicidal behavior (Asberg et al., 1986). Suicidal or impulsive aggressive behavior in patients with mood or personality disorders has been associated with a low central serotonergic function in the limbic-hypothalamic brain regions (Coccaro, 1992).

Moreover, positron emission tomography and single-photon emission computed tomography studies in healthy and depressed individuals have reported that the SERT presents a seasonal variation pattern with increased binding capacity in winter and decreased capacity in the spring (Buchert et al., 2006; Matheson et al., 2015; Praschak-Rieder et al., 2008; Ruhe et al., 2009), although other researchers could not verify this specific finding (Cheng et al., 2011; Koskela et al., 2008). Such a seasonal pattern is suggested to be mainly driven by the short allele of SERT (Kalbitzer et al., 2010). If a seasonal variation of SERT binding capacity really exists, this variation coincides with the seasonal peak of suicide in the spring and early summer that has been reported in many ecological studies from different countries (Christodoulou et al., 2012). We have previously reported an increased seasonal pattern in suicide victims with positive forensic screening for antidepressants in blood at the time of suicide (Makris et al., 2013), which might also suggest a possible synergistic effect of other seasonal factors with antidepressants. Thus our hypothesis was that there would be a clear seasonal pattern in suicidal behavior among patients starting antidepressant treatment, which cannot be fully explained by the underlying seasonal pattern of suicides in the general population.

1.1. Aims of the study

The primary aim of this study was to assess the relationship between season of initiation of antidepressant treatment and the risk of suicide or suicide attempt. As a secondary aim, we examined the seasonal pattern of suicide among antidepressant initiators in relation to the seasonal pattern of suicide in the general population.

2. Methods

2.1. Data sources

Both individual based and aggregated data were obtained from the National Board of Health and Welfare and Statistics Sweden. The Swedish medical registers use a ten-digit national registration number (NRN), a unique personal identifier assigned to all Swedish residents, allowing accurate linkage between registers.

The National Patient Register (NPR) has nearly complete nationwide coverage for discharge diagnoses in both somatic and psychiatric settings in Sweden based on the International Classification of Diseases (ICD), with full coverage of all psychiatric inpatient care since 1987. Outpatient specialist visits, including psychiatric visits from both private and public caregivers, are included since 2001. Each record includes admission and discharge dates, the main discharge diagnosis and secondary diagnoses.

The Cause of Death Register includes all individuals who died either in Sweden or abroad since 1952 and who were registered in Sweden at the time of death. The data are based on death certificates that provide information on date as well as underlying main and secondary causes of death using the ICD codes.

The Swedish Prescribed Drug Register contains individual-level information for all dispensed prescribed drugs in Sweden for the entire Swedish population since July 2005.

Aggregated data on monthly suicides and suicide attempts during the period July 2006 and December 2012 were also obtained from the National Board of Health and Welfare for the calculation of Standardized Mortality Ratios (SMR) and Standardized Incidence Ratios (SIR) in different seasons.

2.2. Inclusion and exclusion criteria

From the Swedish Prescribed Drugs Register, we initially identified 1 027 666 patients who filled a prescription of at least one antidepressant between July 2006 and December 2012. Patients who had filled a prescription of antidepressants (N06A), antipsychotics (N05A) or antiepileptics (N03A), or who had been admitted to a psychiatric department during the year prior to inclusion were excluded. Some 12 532 patients were excluded because they had a prescription of antipsychotics or mood stabilizers at the same time as the prescription of antidepressants. An additional 202 patients were excluded because the date of dispense was after the date of death. Finally, 224 patients were excluded because of invalid information in the prescription register. After exclusions, the total population comprised of 1 014 708 patients. We divided the total population into four groups according to seasons of treatment initiation (autumn: September-November, winter: December-February, spring: March-May and summer: June-August) and followed them up to three months for suicide or suicide attempt. During the three-month follow-up, 411 patients were censored because they moved from Sweden and 99 397 were dispensed afterwards another of the above mentioned drug groups (N03A, N05A, N06A) and were therefore censored at that time.

2.3. Calculation of SMR and SIR

In order to compare with the underlying seasonal pattern in completed and attempted suicides, we calculated the standardized mortality ratios (SMRs) for suicides and the standardized incidence ratios (SIRs) for suicide attempts among those starting an antidepressant treatment. We divided the observed suicides and suicide attempts among those starting on antidepressants in each season in our study population with the expected number, which was calculated by multiplying the age- and sex-specific rates from the general population with the corresponding contributed person-time for each season.

2.4. Exposure measure

Season of treatment initiation with an antidepressant agent.

2.5. Outcome measures

Suicide or suicide attempt (ICD-10 codes: X60-X84, Y10-Y34) during the three-month follow-up.

2.6. Follow-up

For patients who began treatment in a specific season, we assigned an exposure of that season and followed them for up to three months until outcome, loss-to-follow-up, or end of season, whichever occurred first.

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2.7. Statistical analyses

Cox regression analyses were performed to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). To determine the significance of variables we performed two likelihood ratio tests (LRTs). The first was made to identify whether season had an association with the outcome of suicide or suicide attempt within various strata. This analysis was achieved (using a stratified dataset relevant to the analysis at hand) by comparing the full model (e.g., covariates included were confounders plus three dummy variables representing spring, summer and autumn) to the full model excluding the dummy variables representing the seasons (this is the p-value in the figures). The second LRT was performed to identify whether the association of season with the outcome of suicide or suicide attempt was modified by a variable of interest. This analysis was achieved (in the full dataset) by comparing the full model (e.g., covariates included were confounders plus three dummy variables representing spring, summer and autumn and the variable of interest) to the full model that included interaction terms between the seasonality dummy variables and the variable of interest. When the variable of interest comprised a single variable (e.g., sex had only one dummy variable for being male), three additional interaction variables were added to the model for simultaneous testing. When the variable of interest was comprised of two variables (e.g., age had two dummy variables, 25–64 and ≥65), six additional interaction variables were added to the model for simultaneous testing (note, this is the interaction p-value). We proceeded to further stratified analyses in i.e. age groups when the p-value of the interaction term was < 0.15. Results with p-values lower or equal to 0.05 were considered as statistically significant, while those with p-values greater than 0.05 and lower or equal than 0.10 as borderline significant.

2.8. Covariates

We adjusted the hazard ratios for the following covariates: calendar year, age, sex, setting of prescription and previous suicide attempt.

2.9. Sensitivity analysis

The seasonal pattern of antidepressants prescriptions showed a stable pattern during the study period, with a lower number of prescriptions in July (Fig. 1). This observation led us to perform a sensitivity analysis that excluded July. We subsequently repeated the same exposure assignment as before, but with some additions. Patients whose follow-up time began before 1 July and continued on or beyond 1 July were censored on 30 June. Patients whose follow-up time began during July and continued beyond July had their entire July exposure time removed from the analyses (i.e. their exposure was followed from 1 August). Patients whose follow-up existed only within July were removed from the analyses.

Table 1
Descriptive data of the cohort population.

Variable of interest		N	%
		1014708	100.0
Sex	Men	373421	36.8
	Women	641287	63.2
Age (years)	0–24	114183	11.3
	25–64	614353	60.5
	≥65	286172	28.2
Outcome	Suicide	383	
	Suicide attempt	2164	
Prescription Setting	Primary care	707415	69.7
	Somatic	130365	12.8
	Psychiatry	175452	17.3
	Missing	1476	0.2
Antidepressants	TCA (N06AA)	129635	12.8
	SSRI (N06AB)	669621	66.0
	Other (N06AF, AG, AX)	215452	21.2
Psychiatric diagnoses in the patient register (diagnoses from primary care are not included)*	Mental and behavioral disorders due to psychoactive substance use (F10–19)	10470	1.0
	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20–29)	865	0.1
	Mood [affective] disorders (F30–39)	62799	6.2
	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40–48)	48877	4.8
	Eating disorders (F50)	3649	0.4
	Specific personality disorders (F60)	2595	0.3
	Self-harm (X60-X84, Y10-Y34)	14987	1.5
	Others (remaining codes between F00-F99)	5363	0.5

* The percentages of the psychiatric diagnoses do not sum up to 17.3%, (which is the percentage of people receiving their prescription from the psychiatric setting and thus having a registered diagnosis in the patient register) due to psychiatric comorbidity; an individual may have more than one diagnosis.

2.10. Ethics

The study was approved by the research ethics committee in Stockholm, Sweden.
(Dnr 2011/1358-31/3 and 2013/1775-32).

3. Results

Our total study population consisted of 1 014 708 patients (37% were males) (Table 1). During the three-month follow-up, 383 patients

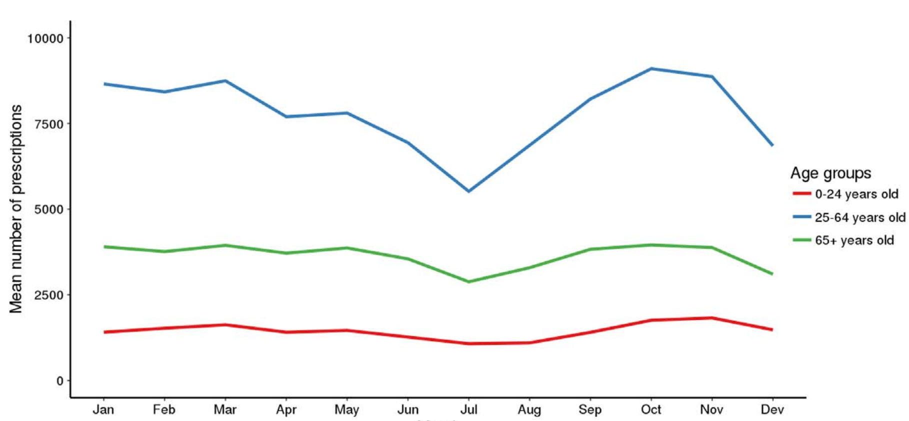

Fig. 1. Mean number of filled antidepressant prescriptions by month in three age groups (0–24, 25–64 and ≥65) during July 2006 and December 2012.

died by suicide and 2164 attempted suicide. The mean time from the initiation of treatment to completed suicide was 20 days for men and 27 days for women; for suicide attempt, the mean time was 30 days for men and 37 days for women. In 70% of the patients, antidepressant treatment was initiated in primary care, 17% in psychiatric care and 13% in somatic care (i.e. other medical specialties). The most common type of antidepressant prescribed was SSRI (66%). Only 17% of the population had a psychiatric diagnosis in the NPR, which is because this register does not include diagnoses from primary care. Among those with an available diagnosis, 42% had a diagnosis of mood disorder, 33% a diagnosis of anxiety, dissociative, stress-related, somatoform and other non-psychotic mental disorders and 6.9% a diagnosis of mental and behavioral disorders due to psychoactive substance use.

Fig. 1 presents the mean number of filled antidepressant prescriptions by month and in three age groups between July 2006 and December 2012. As can be seen in the figure, a trough in the prescription of antidepressants was observed during July.

3.1. Completed suicides

In completed suicides, no statistically significant seasonality was observed for the whole population or within sex (Table 2 and Fig. 2).

3.1.1. Age

The interaction term between age and seasonality was borderline statistically significant with a p-value of 0.12 (Table 2 and Fig. 3). Stratifying for age, patients aged ≥65 years presented a statistically significant seasonality pattern (p=0.04), with the highest risk for suicide occurring when starting antidepressants in the summer (HR (summer vs. winter) =2.27, 95% CI: 1.25–4.11) whereas patients between 0–24 and 25–64 years of age presented no statistically significant seasonal pattern.

Sub-analysis of completed suicides in the ≥65 age group.

Because the over-65 age group presented a statistically significant seasonality pattern and because the interaction term of age was lower than 0.15, we performed further analysis in this age group according to sex (Table 2 and Fig. 4). No statistically significant seasonality pattern was found. Sub-analyses by history of previous suicide attempt and prescription setting were not conducted because of the very small number of cases within these strata.

3.2. Attempted suicides

In attempted suicides, no statistically significant seasonality was observed for the whole population or within sex (Table 2 and Fig. 5).

3.2.1. Age

The interaction term of age and seasonality reached statistical significance (p=0.01) (Table 2 and Fig. 6). A trend similar to the one in completed suicides was observed, i.e. patients ≥65 years had a higher risk for suicide attempt when starting antidepressant treatment in the spring and summer (HR (spring vs. winter)=1.50 with 95% CI: 0.9–2.49, HR (summer vs. winter)=1.52 with 95% CI: 0.9–2.54); this

Table 2
P-values derived from Likelihood Ratio Test (LRT) for seasonality and interaction terms, and Cox-regression derived hazard Ratios (aHR) along with 95% Confidence Intervals (CIs) for suicide and suicide attempts in different seasons compared to winter, adjusting for confounders.

			aHR (95%CIs)+				
		P-value for seasonality LRT*	Spring vs Winter	Summer vs Winter	Autumn vs Winter	P-value for interaction LRT**	Figure
Suicide							
All	All	0.36	1.03 (0.74–1.43)	1.15 (0.83–1.61)	0.85 (0.61–1.19)		Fig. 2
Sex	Males	0.47	1.15 (0.78–1.68)	1.20 (0.81–1.76)	0.91(0.62–1.34)	0.70	Fig. 2
	Females	0.54	0.72 (0.36–1.43)	1.03 (0.53–1.98)	0.70 (0.36–1.35)		
Age	0–24 yrs	0.94	0.84 (0.22–3.15)	1.26 (0.36–4.36)	0.92 (0.26–3.17)	0.12	Fig. 3
	25–64 yrs	0.23	0.95 (0.63–1.42)	0.75 (0.48–1.19)	0.68 (0.44–1.03)		
	65+	**0.04**	1.36 (0.71–2.59)	2.27 (1.25–4.11)	1.39 (0.75–2.60)		
Setting	Primary	0.24	1.00 (0.68–1.49)	1.15 (0.77–1.70)	0.76 (0.51–1.14)	0.91	SFig. 1
	Somatic	0.76	2.02 (0.50–8.12)	1.82 (0.43–7.63)	1.48 (0.35–6.19)		
	Psychiatric	0.99	0.93 (0.46–1.86)	1.04 (0.52–2.11)	1.02 (0.53–2.00)		
65+	Males	0.14	1.64 (0.80–3.36)	2.20 (1.11–4.39)	1.52 (0.75–3.10)	0.34	Fig. 4
	Females	0.10	0.50 (0.09–2.47)	2.48 (0.76–8.06)	1.01 (0.27–3.76)		
Suicide attempts							
All	All	0.45	0.92 (0.78–1.09)	1.06 (0.90–1.26)	1.01 (0.86–1.18)		Fig. 5
Sex	Males	0.56	0.97 (0.74–1.26)	0.97 (0.74–1.28)	0.84 (0.65–1.09)	0.16	Fig. 5
	Females	0.13	0.90 (0.73–1.12)	1.13 (0.91–1.40)	1.12 (0.92–1.36)		
Age	0–24 yrs	**0.04**	0.85 (0.66–1.11)	0.94 (0.72–1.22)	1.19 (0.95–1.50)	**0.01**	Fig. 6
	25–64 yrs	0.24	0.90 (0.70–1.15)	1.10 (0.86–1.40)	0.88 (0.69–1.11)		
	65+	0.09	1.50 (0.90–2.49)	1.52 (0.91–2.54)	0.92 (0.53–1.58)		
Setting	Primary	0.16	0.98 (0.78–1.27)	1.21 (0.96–1.53)	0.93 (0.74–1.17)	0.14	SFig.2
	Somatic	0.69	0.91 (0.44–1.87)	1.03 (0.50–2.11)	0.68 (0.33–1.42)		
	Psychiatric	0.11	0.86 (0.67–1.10)	0.92 (0.71–1.19)	1.13 (0.90–1.42)		
Previous attempt	No	0.70	0.95 (0.79–1.13)	1.04 (0.87–1.24)	0.95 (0.80–1.12)	0.06	Fig. 7
	Yes	**0.03**	0.80 (0.47–1.34)	1.32 (0.82–2.12)	1.51 (0.98–2.32)		
0–24	Males	0.15	0.62 (0.37–1.06)	0.84 (0.51–1.40)	1.08 (0.70–1.67)	0.56	SFig.3
	Females	0.19	0.95 (0.71–1.29)	0.98 (0.71–1.33)	1.24 (0.95–1.63)		
0–24	No previous. att.	0.26	0.87 (0.66–1.14)	0.93 (0.70–1.23)	1.12 (0.87–1.43)	0.27	SFig.4
	With previous att.	**0.05**	0.80 (0.34–1.85)	1.01 (0.44–2.28)	1.91 (0.97–3.75)		
65+	Males	**0.04**	2.02 (0.98–4.18)	1.61 (0.75–3.43)	0.76 (0.32–1,82)	0.31	Fig. 8
	Females	0.71	1.07 (0.52–2.23)	1.44 (0.72–2.90)	1.03 (0.51–2.08)		

+-Adjusted hazard ratios for the following covariates: calendar year, age, sex, setting of prescription and previous suicide attempt.
* -The seasonality LRT was achieved by comparing the full model plus three dummy variables representing spring, summer and autumn to the full model excluding the dummy variables representing the seasons.
** -The interaction LRT was achieved by comparing the full model plus three dummy variables representing spring, summer and autumn and the variable of interest to the full model that included interaction terms between the seasonality dummy variables and the variable of interest.

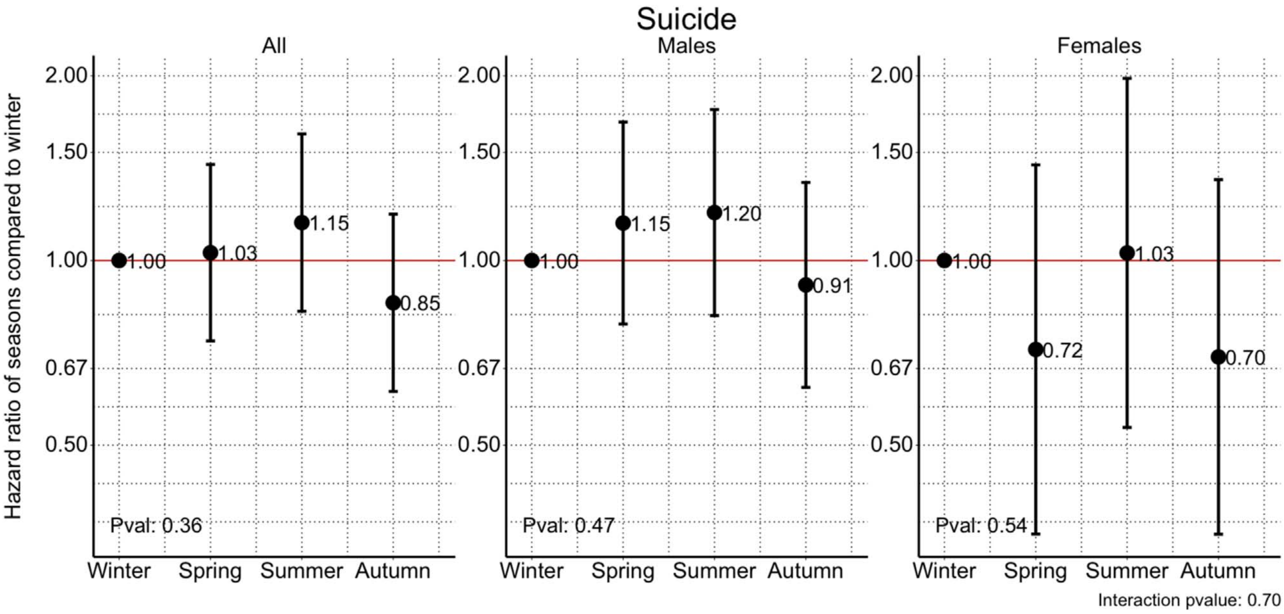

Fig. 2. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for suicide by season of antidepressant treatment initiation, with winter as the reference stratified by sex. The p-value within each graph was derived from the seasonality likehood ratio test (LRT) while the interaction term's p-value was derived from the LRT comparing the full model with the full model plus the interaction terms between the dummy variables of season and sex.

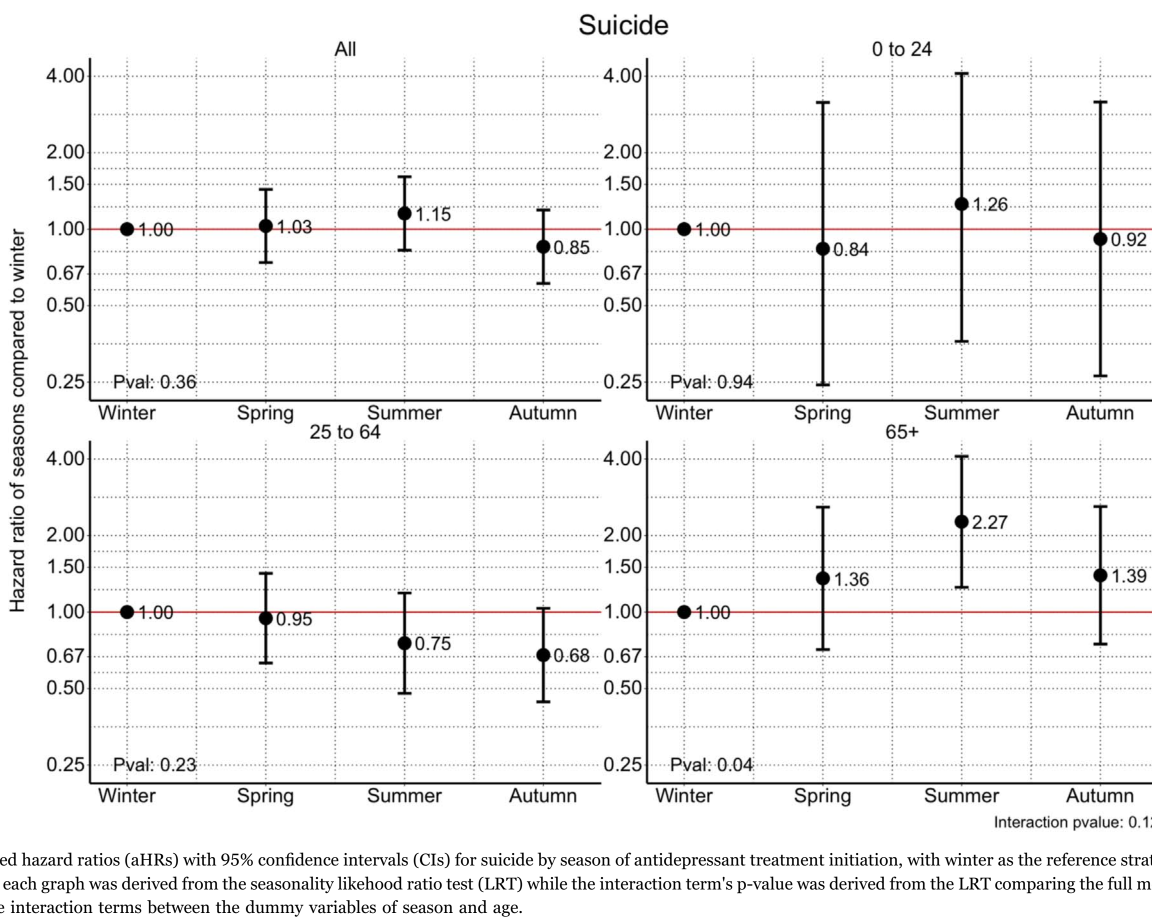

Fig. 3. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for suicide by season of antidepressant treatment initiation, with winter as the reference stratified by age. The p-value within each graph was derived from the seasonality likehood ratio test (LRT) while the interaction term's p-value was derived from the LRT comparing the full model with the full model plus the interaction terms between the dummy variables of season and age.

seasonal pattern was borderline significant (p=0.09). In patients from 25 to 64 years of age no significant seasonal pattern was found (p=0.24). However, younger patients (0–24 years old) had a significant seasonal pattern (p=0.04), with a higher risk to attempt suicide when treated in the autumn (HR (autumn vs. winter) =1.19 with 95% CI: 0.95–1.50).

3.2.2. *Previous suicide attempt*

The interaction term of previous suicide attempt and seasonality was borderline significant (p=0.06) (Table 2 and Fig. 7). For those with previous suicide attempt, a seasonal pattern was seen with a higher risk for suicide attempt when starting antidepressant treatment in the summer and autumn (HR (summer vs. winter)=1.32 with 95% CI

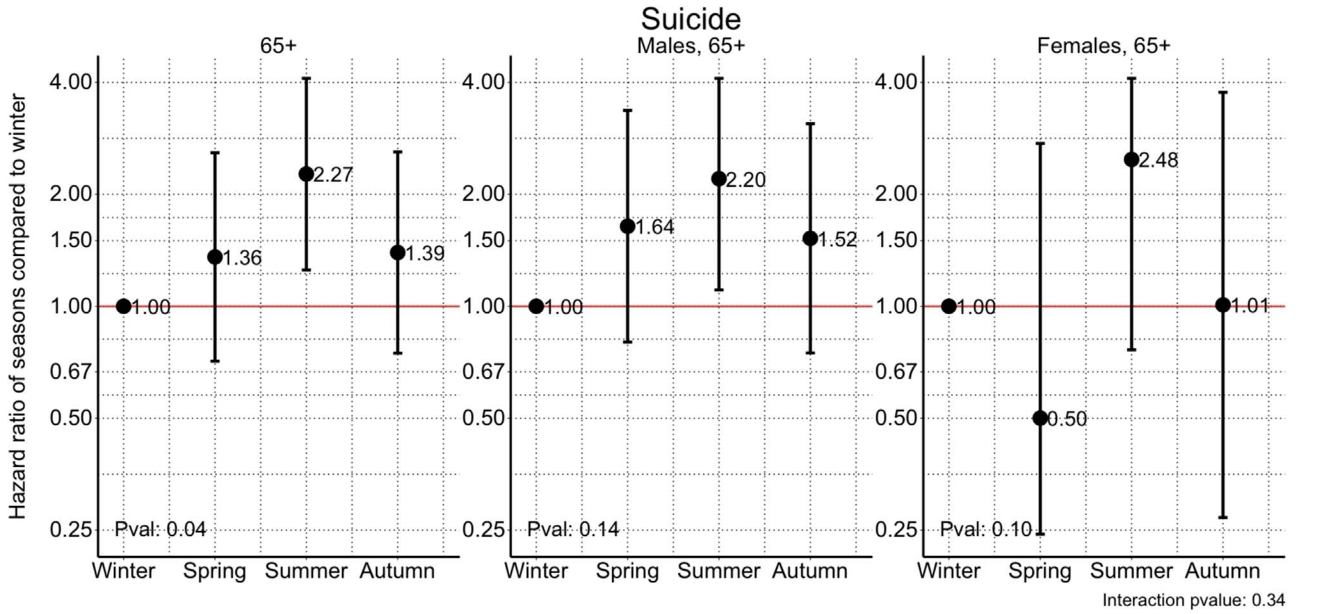

Fig. 4. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for suicide only in those aged ≥65 by sex and season of antidepressant treatment, with winter as the reference stratified by sex. The p-value within each graph was derived from the seasonality likehood ratio test (LRT) while the interaction term's p-value was derived from the LRT comparing the full model with the full model plus the interaction terms between the dummy variables of season and sex.

0.82–2.12, and HR (autumn vs. winter)=1.51 with 95% CI 0.98–2.32, p=0.03 for seasonality LRT). No significant seasonal pattern was seen in those without previous suicide attempt (p=0.70).

3.2.3. Sub-analysis of attempted suicide in the age groups 0–24 and ≥65

In the age group 0–24 years there was no seasonal pattern after stratifying for sex (Table 2 and supplemental Figure 3). Further, the interaction term of seasonality and sex in this age group was not statistically significant (p=0.56). The interaction term of seasonality and previous suicide attempt did not reach significance (p=0.27). However, the seasonal pattern for patients aged 0–24 years might be numerically driven by patients aged 0–24 years who had a previous suicide attempt (p=0.05), with the highest risk for attempted suicide when starting antidepressant treatment in the autumn (HR (autumn vs. winter) =1.91 with 95% CI 0.97–3.75) (Table 2 and supplemental Figure 4).

The interaction term between seasonality and sex in patients ≥65 years was not significant (p=0.31) (Table 2 and Fig. 8). However, the finding does appear to be mostly numerically driven by males (p=0.04), who show a seasonal pattern with highest risk for attempted suicide when they start antidepressant treatment in the spring and summer (HR (spring vs. winter) =2.02 with 95% CI: 0.98–4.18, HR (summer vs. winter) =1.61 with 95% CI: 0.75–3.43). As opposed to males, females did not present significant seasonality (p=0.71).

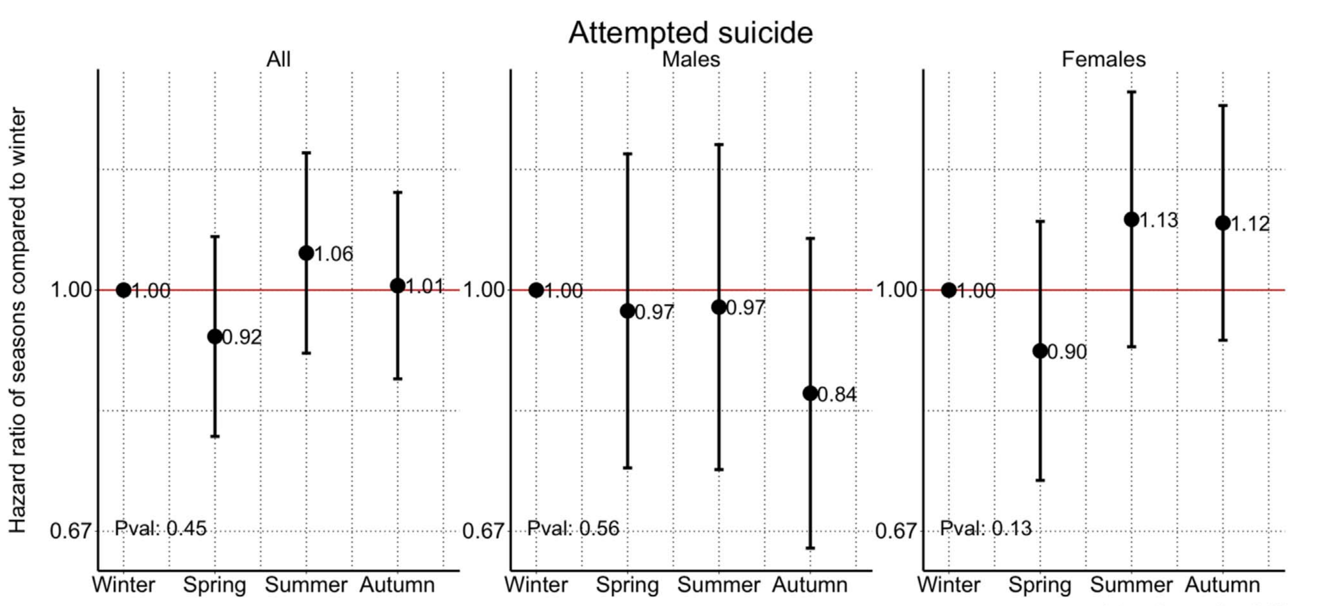

Fig. 5. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for suicide attempt by season of antidepressant treatment, with winter as the reference stratified by sex. The p-value within each graph was derived from the seasonality likehood ratio test (LRT) while the interaction term's p-value was derived from the LRT comparing the full model with the full model plus the interaction terms between the dummy variables of season and sex.

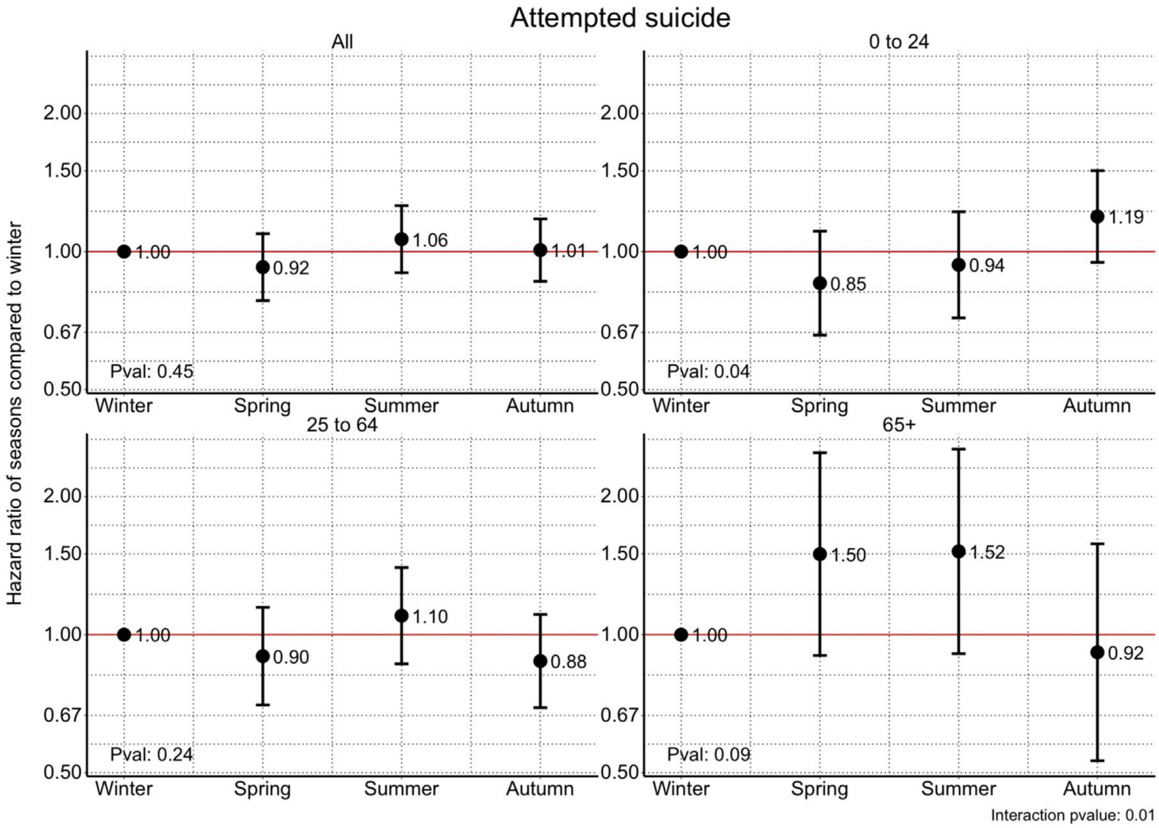

Fig. 6. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for suicide attempt by season of antidepressant treatment, with winter as the reference stratified by age. The p-value within each graph was derived from the seasonality likehood ratio test (LRT) while the interaction term's p-value was derived from the LRT comparing the full model with the full model plus the interaction terms between the dummy variables of season and age.

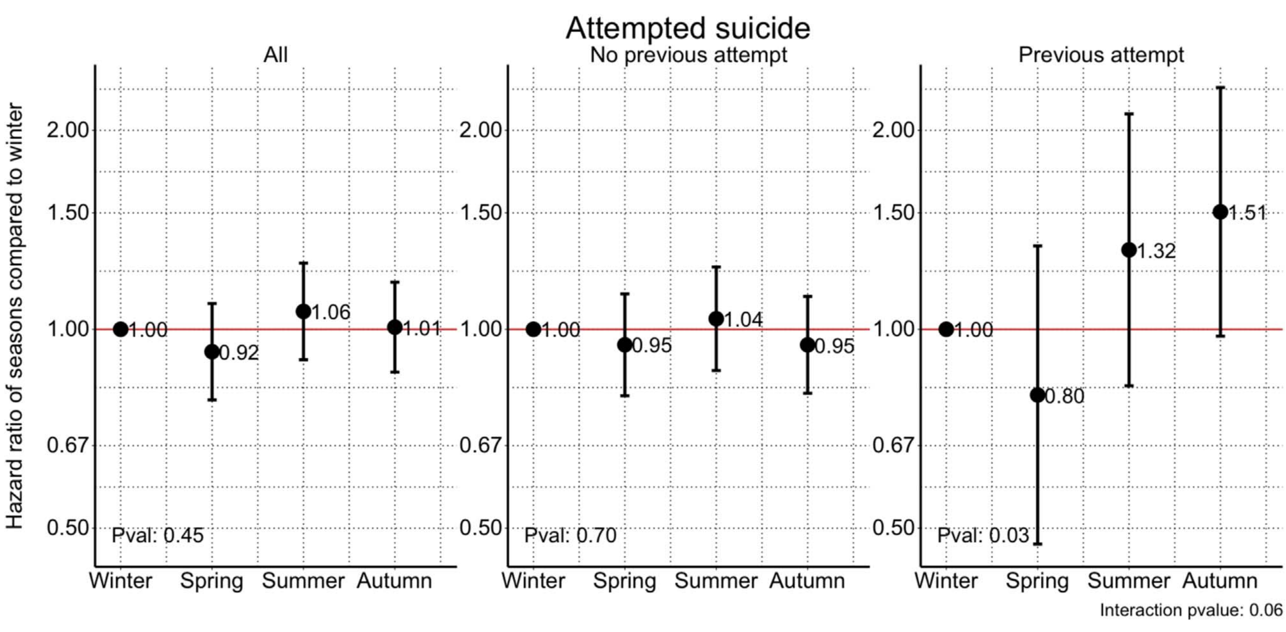

Fig. 7. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for suicide attempt by season of antidepressant treatment, with winter as the reference stratidfied by history of previous suicide attempt. The p-value within each graph was derived from the seasonality likehood ratio test (LRT) while the interaction term's p-value was derived from the LRT comparing the full model with the full model plus the interaction terms between the dummy variables of season and history of previous suicide attempt.

3.3. Sensitivity analyses

The age stratified analyses that excluded July did not alter the significant seasonal pattern for males aged ≥65 with a higher risk for attempted suicides when starting antidepressant treatment in the spring (p=0.03), although no significant seasonal pattern was longer observed for suicide. In the age group 0–24, excluding July did not modify the results, i.e. the interaction of seasonality and age remained significant with highest risk for attempted suicide when starting antidepressant treatment in the autumn.

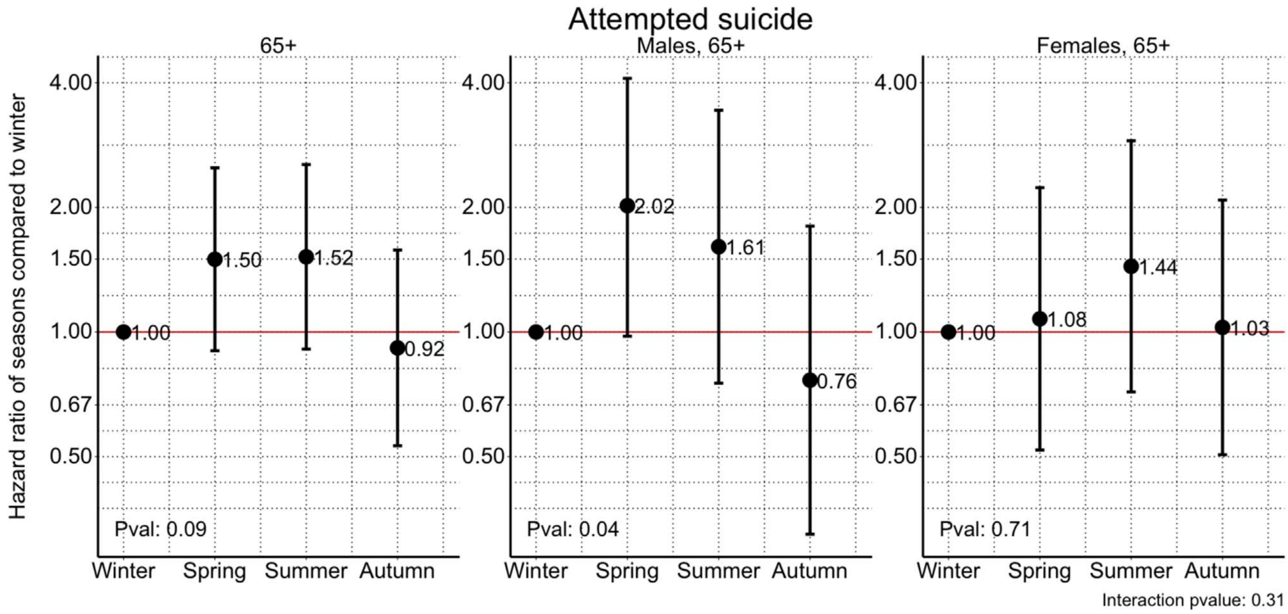

Fig. 8. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for suicide attempt in only older people (> 65) by season of antidepressant treatment, with winter as the reference, and stratified by sex. The p-value within each graph was derived from the seasonality likehood ratio test (LRT) while the interaction term's p-value was derived from the LRT comparing the full model with the full model plus the interaction terms between dummy variables of season and sex.

3.3.1. Standardized mortality ratios for suicide (SMRs) and standardized incidence ratios for suicide attempt (SIRs)

In the Tables 3a, 3b we present the calculated SMR for completed suicides and SIR for attempted suicides during the period July 2006 and December 2012.

In completed suicides, the SMR was increased in summer in the age groups of 0–24 and 65+, while in winter in the age group of 25–64 years old. In males, the same pattern was observed in the different age

Table 3a
Standardized Mortality Ratios (SMR) for suicides in Sweden between July 2006 and December 2012.

Sex	Age	Season	Age-specific suicide mortality rate per 100000	Person-time	Observed	Expected	SMR	Lower CI	Upper CI
Total	**0–24**	Autumn	0.0116	1416983	5	0.1642	30.45	9.81	71.07
		Spring	0.0125	1205963	4	0.1508	26.52	7.14	67.91
		Summer	0.0126	1008658	5	0.1270	39.38	12.69	91.91
		Winter	0.0119	1234820	5	0.1466	34.12	10.99	79.62
	25–64	Autumn	0.0375	7773163	39	2.9142	13.38	9.52	18.30
		Spring	0.0423	6501445	45	2.7533	16.34	11.92	21.87
		Summer	0.0399	5457243	30	2.1752	13.79	9.30	19.69
		Winter	0.0373	6500535	50	2.4240	20.63	15.31	27.19
	65+	Autumn	0.0414	3465771	26	1.4360	18.11	11.82	26.53
		Spring	0.0434	2969862	22	1.2898	17.06	10.69	25.83
		Summer	0.0407	2737409	35	1.1128	31.45	21.90	43.74
		Winter	0.0342	2875565	16	0.9847	16.25	9.28	26.39
Females	**0–24**	Autumn	0.0082	904546	3	0.0746	40.21	8.08	117.48
		Spring	0.0088	761892	0	0.0668	0.00	–	–
		Summer	0.0080	644120	0	0.0515	0.00	–	–
		Winter	0.0071	781118	2	0.0558	35.87	4.03	129.51
	25–64	Autumn	0.0223	4963443	8	1.1065	7.23	3.11	14.25
		Spring	0.0241	4099776	12	0.9862	12.17	6.28	21.26
		Summer	0.0219	3437083	8	0.7522	10.64	4.58	20.96
		Winter	0.0221	4028916	14	0.8893	15.74	8.60	26.42
	65+	Autumn	0.0217	2244762	5	0.4880	10.25	3.30	23.91
		Spring	0.0246	1918770	2	0.4716	4.24	0.48	15.31
		Summer	0.0202	1734148	9	0.3508	25.65	11.71	48.70
		Winter	0.0175	1835256	4	0.3215	12.44	3.35	31.85
Males	**0–24**	Autumn	0.0147	512437	2	0.0755	26.48	2.97	95.62
		Spring	0.0160	444071	4	0.0712	56.19	15.12	143.86
		Summer	0.0169	364538	5	0.0617	81.08	26.13	189.21
		Winter	0.0163	453702	3	0.0741	40.48	8.14	118.29
	25–64	Autumn	0.0522	2809720	31	1.4679	21.12	14.35	29.98
		Spring	0.0601	2401669	33	1.4436	22.86	15.73	32.10
		Summer	0.0573	2020160	22	1.1577	19.00	11.90	28.77
		Winter	0.0521	2471619	36	1.2868	27.98	19.59	38.73
	65+	Autumn	0.0647	1221009	21	0.7901	26.58	16.45	40.63
		Spring	0.0657	1051092	20	0.6907	28.96	17.68	44.72
		Summer	0.0648	1003261	26	0.6500	40.00	26.12	58.61
		Winter	0.0540	1040309	12	0.5619	21.36	11.02	37.31

Table 3b
Standardized Incidence Ratios (SIR) for suicide attempts in Sweden between July 2006 and December 2012.

Sex	Age	Season	Age-specific incidence rate per 100000	Person-time	Observed	Expected	SIR	Lower CI	Upper CI
Total	**0–24**	Autumn	0.270	1412062	190	3.809	49.88	43.04	57.50
		Spring	0.293	1202498	123	3.529	34.86	28.97	41.59
		Summer	0.252	1005331	111	2.536	43.77	36.01	52.72
		Winter	0.284	1230374	144	3.500	41.14	34.70	48.44
	25–64	Autumn	0.230	7768927	171	17.904	9.55	8.17	11.09
		Spring	0.249	6496852	151	16.158	9.35	7.91	10.96
		Summer	0.241	5452804	153	13.150	11.64	9.86	13.63
		Winter	0.243	6496162	168	15.762	10.66	9.11	12.40
	65+	Autumn	0.094	3464134	45	3.246	13.86	10.11	18.55
		Spring	0.108	2968686	48	3.195	15.02	11.07	19.92
		Summer	0.102	2735461	56	2.779	20.15	15.22	26.17
		Winter	0.093	2874226	41	2.666	15.38	11.03	20.86
Females	**0–24**	Autumn	0.382	901294	137	3.447	39.74	33.36	46.98
		Spring	0.414	759276	92	3.141	29.29	23.61	35.92
		Summer	0.339	641649	80	2.173	36.81	29.19	45.81
		Winter	0.397	777807	103	3.090	33.34	27.21	40.43
	25–64	Autumn	0.254	4961125	98	12.579	7.79	6.32	9.49
		Spring	0.277	4097520	76	11.345	6.70	5.28	8.38
		Summer	0.263	3434430	92	9.031	10.19	8.21	12.49
		Winter	0.267	4026792	81	10.745	7.54	5.99	9.37
	65+	Autumn	0.097	2243991	24	2.175	11.04	7.07	16.42
		Spring	0.114	1918150	22	2.187	10.06	6.30	15.23
		Summer	0.098	1733288	27	1.699	15.89	10.47	23.13
		Winter	0.090	1834533	21	1.647	12.75	7.89	19.49
Males	**0–24**	Autumn	0.163	510768	53	0.834	63.54	47.59	83.11
		Spring	0.180	443222	31	0.797	38.88	26.41	55.19
		Summer	0.171	363682	31	0.620	49.96	33.94	70.92
		Winter	0.178	452567	41	0.806	50.89	36.51	69.04
	25–64	Autumn	0.208	2807802	73	5.842	12.50	9.79	15.71
		Spring	0.221	2399332	75	5.311	14.12	11.11	17.70
		Summer	0.220	2018374	61	4.440	13.74	10.51	17.65
		Winter	0.219	2469370	87	5.411	16.08	12.88	19.83
	65+	Autumn	0.090	1220143	21	1.097	19.14	11.84	29.25
		Spring	0.100	1050536	26	1.051	24.73	16.15	36.24
		Summer	0.106	1002173	29	1.061	27.34	18.31	39.27
		Winter	0.096	1039693	20	1.001	19.98	12.20	30.85

groups, while in females the age group of 0–24 had a higher SMR in autumn, and the age groups 25–64 and 65+ in winter and summer respectively.

An almost two-fold SMR for suicide in the summer in the older patients (≥65) was observed as compared with the SMRs in other seasons, although with overlapping CIs among seasons (SMR for summer: 31, 95% CI: 22–44; SMR for autumn: 18, 95% CI: 12–27; SMR for winter: 16, 95% CI:9–26; SMR for spring: 17, 95% CI: 11–26).

In attempted suicides an increased SIR was observed in autumn in the age groups of 0–24 and in summer in the age groups of 25–64 and 65+. In females the same pattern was observed in the different age groups, while in males the age group of 0–24 had a higher SIR in autumn and the age groups 25–64 and 65+ in winter and summer respectively.

An increased SIR for suicide attempt when starting antidepressant treatment in the autumn was observed in younger patients (0–24), also with overlapping CIs with the SIRs in the other seasons (SIR for autumn: 50, 95% CI: 43–58; SIR for winter: 41, 95% CI: 35–48; SIR for spring: 35, 95% CI: 29–42; SIR for summer: 44, 95% CI: 36–53).

4. Discussion

Ecological studies have consistently reported a higher risk for completed suicide in the spring and summer compared with winter and autumn (Christodoulou et al., 2012). Our group has also reported an increased seasonality pattern in patients treated with antidepressants (Makris et al., 2013). In that study, information on antidepressant treatment was derived from toxicological analyses at the time of death. Thus, information about the start or duration of treatment was not available. This is the first time seasonal patterns were studied in detail in a large population-based cohort with a new treatment episode with antidepressants. No overall association between season of antidepressant treatment initiation and suicide or suicide attempt was found. Nor was a statistically significant seasonal pattern evident after stratifying for sex. However, when stratifying for age, a clear seasonal pattern with a two-fold increased risk for suicide and suicide attempt was observed in patients ≥65 years of age who filled an antidepressant prescription in the summer or spring compared with the winter. An almost two-fold increased risk for suicide attempt when starting antidepressant treatment in the autumn, in comparison with the winter, was also seen in the young patients (0–24) with a history of previous suicide attempt.

Our findings are in line with studies reporting a greater risk for suicide in the elderly in the summer (Preti and Miotto, 1998) and studies supporting that seasonality of suicide is a consequence of the seasonal pattern in underlying depression (Eastwood and Peacocke, 1976; Kim et al., 2004; Morken et al., 2002; Postolache et al., 2010; Reutfors et al., 2009; Rihmer et al., 1998). An alternative explanation is that the surveillance of the elderly decreases in the summer when family members and friends spend more time in outdoor activities and holidays, while accessibility of the lethal means for suicide increases (Chew and McCleary, 1994). This contention is partly supported by our sensitivity analyses that excluded July, which resulted in the elimination of the seasonal pattern in the elderly. July is the big Swedish holiday month and during this month the availability of health care and the quality of the follow-up after a prescription of antidepressant may suffer. The oldest age group (≥65 years) had also a higher risk for suicide attempt, when starting treatment during the spring and summer compared with the winter. This finding is consistent with other studies that found that older individuals and males show a seasonal pattern with increased incidence of suicide attempts in the spring and summer (De Maio et al., 1982; Mergl et al., 2010; Preti and Miotto, 2000). Excluding July from the analyses did not cause a significant difference in seasonal pattern for elderly males, who presented a clear increase in the risk for suicide attempt when starting treatment in the spring. This observation suggests that the observed seasonal pattern in this age group cannot be fully explained by health care availability differences across seasons.

The SERT has been reported to have a lower availability with increasing age (Chang et al., 2015). This in combination with a lower binding capacity of SERT in the spring and summer and treatment with an antidepressant that blocks the SERT, as well, can possibly lead to a higher risk for suicide in the elderly in the spring and summer. Particularly noteworthy is that the seasonal SERT binding is accentuated in people with the short allele of the SERT (Kalbitzer et al., 2010). This polymorphism is associated with anxiety-related traits and increased risk for depression in interaction with psychosocial adversity across the lifespan (Homberg and Lesch, 2011).

Seasonality of attempted suicides is less studied than seasonality of completed suicide and findings are less consistent (Barker et al., 1994; De Maio et al., 1982; Masterton, 1991; Mergl et al., 2010; Polewka et al., 2004; Preti and Miotto, 2000; Rock et al., 2005; Wenz, 1977; Yip and Yang, 2004). The majority of studies investigating seasonality of attempted suicides conclude that females have two peaks, one in the spring/summer and one in the autumn, whereas males may have a peak in the spring/summer if any at all. This might be explained by two factors: males attempt suicide less frequently than females and many studies have low statistical power to detect a clinically relevant difference. It seems that the method of suicide attempt has a role, with more violent attempts showing higher seasonality (these more violent attempts show similar characteristics with completed suicides). This finding may imply a spectrum-like explanation in which more potentially fatal attempts have more common characteristics and neurobiological background with completed suicides. The higher risk for suicide attempt in the autumn in the younger age group (0–24) is also documented in other studies (De Maio et al., 1982; Polewka et al., 2004; Yip and Yang, 2004) suggesting that the autumn peak may be due to the seasonal variation in communal and social activities found particularly in females and that the autumn peak is of later origin and typical of those living in a man-made environment. In our study the sex interaction term was not significant but there was a numerical trend of higher risk of suicide attempt in women during autumn compared with winter. The reason for the phenomenon of autumn peak in female suicides and suicide attempts in Western countries is still unclear.

In the 0–24 age group the risk for suicide attempt in the autumn was even higher in those with a past history of suicide attempt and a prescription within a psychiatric setting, suggesting more severe psychopathology. There are currently no studies suggesting a differential seasonal pattern of the SERT binding between males and females and thus the higher risk for suicide attempt in young females in the autumn is intriguing and cannot be explained by the suggested interaction between the endogenous serotonergic seasonality and serotonergic medication in this age group.

Attempted and completed suicides have probably different but overlapping neurobiological processes (Mann, 2003). Females are overrepresented in attempted suicide and have a higher incidence of suicide attempts than males. Males, on the other hand, have a higher incidence of completed suicides, which is at least in part due to the more violent and fatal nature of the methods they use (Hawton and van Heeringen, 2009). In the present study a trend was seen for a different seasonal pattern, with higher risk for suicide when starting treatment in the spring and summer in males and a higher risk for suicide attempt when starting treatment in the summer and autumn in females.

In summary, the season of treatment initiation with antidepressants was associated with increased risk for suicide and suicide attempt in some age groups (elderly ≥65 and younger persons 0–24). Our results indicate an interaction between biological and health care-related factors for the observed seasonal pattern, with a peak in the spring and summer in the elderly (≥65), whereas psychological and societal factors may be more important for the seasonality observed in the autumn in the younger group.

Our estimated SMRs and SIRs indicate that the association between season of initiation of antidepressant treatment and suicidal behavior in these groups is likely not entirely attributable to the underlying seasonal association seen in the general Swedish population. If the seasonal suicidal behavior of patients starting on antidepressants were identical to the seasonal pattern of the whole Swedish population, we would expect a stable SMR throughout the year.

4.1. Strengths and limitations

To our knowledge this is the first large population-based cohort study to investigate suicidal behavior in relation to season of antidepressant treatment initiation. The findings of this study need to be interpreted within the context of its limitations. An important limitation of our study is that we used information of filling antidepressant prescriptions as a proxy of actual antidepressant treatment. We know that this proxy might not reflect the patient's actual use of the medication in that up to 60% of patients that receive an antidepressant prescription do not follow the intended treatment (Sawada et al., 2009). While we cannot verify that the patients initiated antidepressant treatment, our analyses were performed in a valid "intention-to-treat" manner, which is a main-stay of analyses within the medical field." Intention to treat analysis allows for non-compliance and deviations from policy by clinicians". If a true association between antidepressants and suicide/suicide attempt when starting treatment in specific seasons were assumed, including patients with no compliance would only dilute our results. Thus, the associations found in this work could be even stronger if we were able to exclude non-compliant patients. Moreover, we have no indication according to the literature that non-compliance varies with season, something that could potentially affect our results. It cannot be excluded that other factors such as psychiatric diagnosis, which was not available for most of the study population, might also contribute to this association with suicide seasonality (Reutfors et al., 2009). The design of our study excludes patients with combination or augmentation therapy, as well as those switching to another antidepressant during follow-up. Thus, our results refer to less complicated psychopathology. Finally, because of the observational study design, it cannot prove causality between antidepressant medication initiation and suicidal behavior in different seasons.

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Conflict of interest

None.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jad.2017.03.028.

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