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Suicide Seasonality

Theoretical and Clinical Implications

GEORGIOS MAKRIS



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Abstract

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Background: Although suicide seasonality has been well-documented, surprisingly little is known about its underlying mechanisms.

Methods: In this thesis, data from three Swedish registers (Cause of Death Register, National Patient Register, Prescribed Drugs Register) and data from the Swedish Meteorological and Hydrological Institute were used.

In *Study I*, the amplitude of suicide seasonality was estimated in completed suicides in 1992-2003 in individuals with different antidepressant medications or without antidepressants.

In *Study II*, monthly suicide and sunshine data from 1992-2003 were used to examine the association between suicide and sunshine in groups with and without antidepressants.

In *Study III*, the relationship between season of initiation of antidepressant treatment and the risk of suicidal behavior was explored in patients with a new treatment episode with antidepressant medication.

In *Study IV*, the complex association between sunshine, temperature and suicidal behavior was investigated in patients with a new treatment episode with an antidepressant in two exposure windows (1-4 and 5-8 weeks) before the event.

Findings: *Study I:* Higher suicide seasonality was found in individuals treated with selective serotonin reuptake inhibitors (SSRIs) compared with those given a different antidepressant treatment or those without any antidepressant treatment.

Study II: In individuals treated with SSRIs, there was a positive association between sunshine and suicide, with the association stronger in men treated with SSRIs compared with men treated with other antidepressants. An effect modification by age was observed.

Study III: The elderly (65+) had a higher risk of suicide when initiating antidepressant treatment in summer and a higher risk of suicide attempt when starting antidepressant therapy in spring and summer. Younger patients (0-24) demonstrated a higher risk of suicide attempt when treatment was initiated in autumn.

Study IV: In the elderly (65+), a harmful association was observed between the risk of suicide attempt and the average daily temperature during the four weeks before the suicide attempt, as well as with average daily sunshine during both exposure windows (1-4 and 5-8 weeks) before the suicide attempt.

Significance: Our results provide epidemiological support for the role of the serotonergic system in seasonality of suicide in which both medication and climate may be involved.

Keywords: suicide, season, antidepressants, sunshine, temperature

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*This thesis is dedicated to my parents,
Dimitrios and Krystallia, my wife,
Christina, and my children, Maria,
Dimitra, and Alexandros, for their
unconditional love and support.*

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Makris, GD, Reutfors, J, Osby, U, Isacsson, G, Frangakis, C, Ekbom, A, Papadopoulos, FC. (2013) Suicide seasonality and antidepressants: a register-based study in Sweden. *Acta Psychiatr Scand*, 127(2):117-25.
- II Makris, GD, Reutfors, J, Larsson, R, Isacsson, G, Osby, U, Ekbom, A, Ekselius, L, Papadopoulos, FC. (2016) Serotonergic medication enhances the association between suicide and sunshine. *J Affect Disord*, 1;189:276-81.
- III Makris, GD, Reutfors, J, Andersen, M, White, R, Ekselius, L, Papadopoulos, FC. (2017) Season of treatment initiation with antidepressants and suicidal behavior: a population-based study in Sweden. *J Affect Disord*, 6;215:245-255.
- IV Makris, GD, White, R, Reutfors, J, Ekselius, L, Andersen, M, Papadopoulos, FC. (2017) Sunshine, temperature and suicidal behavior in patients treated with antidepressants: an explorative nested case-control study. *Manuscript*.

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Abbreviations

AD	Antidepressants
BAT	Brown adipose tissue
Coef	Poisson coefficient in percent (%)
CSF	Cerebrospinal fluid
HR/ aHR	Hazard ratio, adjusted Hazard ratio
ICD	International Classification Of Diseases
LRT	Likelihood ratio test
OR	Odds ratio
PET	Positron emission tomography
RCG	Retina ganglion cell
RR	Relative risk
SAD	Seasonal affective disorder
SERT	Serotonin transporter
SIR	Standardized incidence ratio
SMHI	Swedish Meteorological and Hydrological Institute
SMR	Standardized mortality ratio
SPECT	Single-photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization

Introduction

Suicide

Suicide is a complex phenomenon that has led to copious scientific research and philosophical debate that continues to this day. The estimated yearly number of suicides worldwide is 800 000. The estimated mortality per year is 10.7 deaths per 100 000 people, which equals one death every 40 seconds. Suicide is the 17th leading cause of death worldwide and accounts for 1.4% of all deaths (WHO, 2017).

Suicide rates vary widely among countries (Figure 1). In Europe, the average suicide rate is 14.1 per 100 000 people, but rates are generally higher in northern European countries than in southern European countries, with former Soviet states ranking on the top of the list. In Sweden, suicide rates were about 11.3 per 100 000 inhabitants in 2016 (Socialstyrelsen, 2016). China, where 3.6% of all deaths are caused by suicide, accounts for more than 30% of suicides worldwide (Phillips et al., 2002).

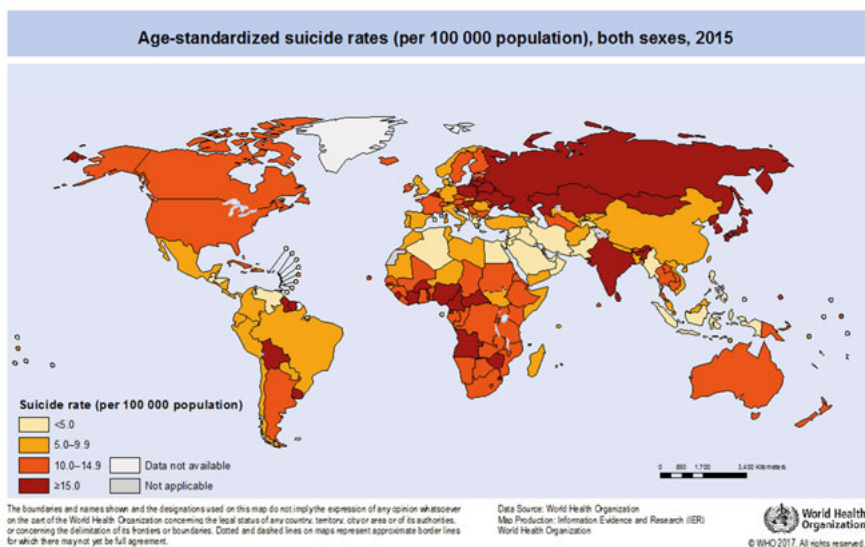


Figure 1. Suicide rates in different countries of the world, WHO 2015.

Sex

In developed countries, there is a male predominance and the ratio of male to female suicide is from 2-4:1. An exception to this male predominance is Asian countries, which show much lower male-to-female ratios (Phillips et al., 2002; Yip et al., 2008). In China, the trend is reversed, with women committing suicide more than men. In Sweden in 2016, 1134 suicides were committed: 783 by men and 351 by women, yielding a male to female ratio of 2.2:1. The corresponding rates were 15.75 per 100 000 men and 7.09 per 100 000 women (Socialstyrelsen, 2016). In general, men tend to choose more violent means (e.g., hanging or shooting) and women less violent methods (e.g., self-poisoning) (Denning et al., 2000). As many as 30% of global suicide deaths might involve ingestion of pesticides (Gunnell et al., 2007).

Age

Suicide rates are generally higher in elderly people (65+) in most countries. However, over the past half of the century, young people, in particular men, show increasing suicide rates (Wasserman et al., 2005) and elderly people decreasing rates (Pritchard and Hansen, 2005). In the past years, previously increased suicide rates in young males have decreased in some developed countries (Bridge et al., 2006). In Sweden, the age group with the highest rate for both sexes is 45-64 years with 23.3 per 100 000 inhabitants (Figure 2) (Socialstyrelsen, 2016).

Ethnicity

Differences in suicide rates between ethnic groups have occurred, with the general finding that Hispanic and African Americans have lower rates of suicide than European Americans (McKenzie et al., 2003).

Even within countries, there are variations between different ethnic groups. A study in Great Britain showed, for example, young Indian women in London have a higher suicide rate than other women, whereas young Afro-Caribbean women have very low rates. In the same study, men of Indian and African origin had lower rates than white men (Neeleman and Wessely, 1999).

Another noteworthy aspect is that indigenous populations in several countries worldwide have higher suicide rates compared with the rest of the population. Such examples are Native Americans in the USA, Métis and Inuit in Canada, Australian Aborigines and Maori in New Zealand (Hawton, 2007). Factors that might contribute to higher suicide rates in indigenous populations include marginalization, disintegration of traditional social support networks and cultural values, socioeconomic deprivation and alcohol misuse.

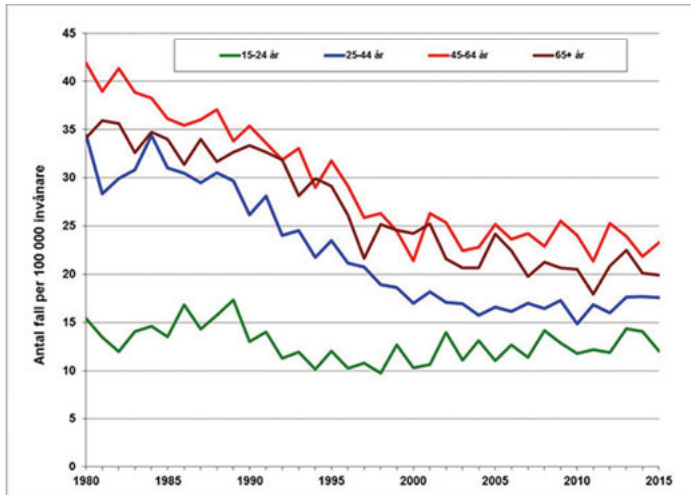


Figure 2. Suicide rates in Sweden by different age groups, NASP 2016

Psychiatric disorders

Using psychological autopsy (Hawton et al., 1998), many studies have shown that psychiatric disorders are present in about 90% of people who take their own life (Cavanagh et al., 2003). In China, again the pattern is different. There people who die by suicide seem to have less often psychiatric disorders, especially women and girls in rural areas (Yang et al., 2005).

In suicide victims, mood disorder is the most common psychiatric disorder, followed by substance (especially alcohol) misuse and schizophrenia. Co-morbidity of psychiatric disorders carries a higher risk for suicide. Not surprisingly, more than half of all people who die by suicide suffer from a current depressive disorder (Cavanagh et al., 2003). Furthermore, 10–15% of patients with bipolar disorder die by suicide, commonly early in the illness course (FK Goodwin, 2007). A more recent study from Denmark found a 6–10% risk for suicide in bipolar patients (Nordentoft et al., 2011).

Recent estimates suggest a 4–5% lifetime suicide risk in schizophrenia, with the risk being highest relatively early after onset of the disorder (Palmer et al., 2005).

A strong association between alcohol misuse, alcohol dependence, anorexia nervosa and suicide risk has also been documented (Mattisson et al., 2011; Papadopoulos et al., 2009; Schneider, 2009).

Attention deficit and hyperactivity disorder seem to have an increased risk of suicide not only because of the inherent impulsivity and aggression but also through increasing severity of co-morbidities in males (in particular, conduct disorder and depression) (James et al., 2004).

Approximately 30–40% of people who commit suicide suffer from a personality syndrome (Foster et al., 1997). The risk of suicide is higher in bor-

derline and antisocial personality disorders (Lieb et al., 2004). About 10% of individuals who die by suicide in most countries have no apparent psychiatric disorder.

Physical disorders

Several physical disorders are associated with suicide, including cancer (head and neck cancers in particular), HIV/AIDS, neurological disorders (Huntington's disease, multiple sclerosis, epilepsy), peptic ulcer, renal disease, spinal-cord injury, systemic lupus erythematosus and chronic pain (Harris and Barraclough, 1994; Stenager and Stenager, 1992; Tang and Crane, 2006; Webb et al., 2012).

Occupation

Unemployment is linked to high suicide rates, although this is in part associated with mental illness, which carries a risk for both unemployment and suicide (Blakely et al., 2003; Qi et al., 2015; S Platt, 2000). A recent review on unemployment suggested that it results in increased psychological distress and mental illness. The link between unemployment and suicide is weaker and might be better explained by pre-existing mental illness (Myles et al., 2017). Among occupational groups, there are some at increased risk of suicide, such as medical practitioners, especially female doctors, anesthesiologists and nurses (Agerbo et al., 2007; Hawton et al., 2001; Schernhammer and Colditz, 2004). Nurses and midwives are members of an occupation with high risk for suicide, with self-poisoning the most frequent method (Agerbo et al., 2007; Milner et al., 2016). Generally, professional groups that have access to potentially lethal substances are at higher risk (Milner et al., 2017).

Suicide attempt

A previous suicide attempt is a strong predictor of completed suicide. A history of suicide attempt increases the risk of suicide 40 times and approximately 40% of those who die from suicide have previously attempted suicide (Hawton and van Heeringen, 2009; Maris, 2002). The exact number of suicide attempts is hard to determine because not all suicide attempts come to the attention of health care professionals. A rough estimation, though, shows that suicide attempts are 10-20 times more common than completed suicides (WHO, 1999). In almost half of the completed suicides, at least one previous suicide attempt had occurred (Tidemalm et al., 2008). The proportion is higher among younger people (Runeson et al., 1996). In contrast to completed suicides, women are overrepresented among suicide attempters (constituting about 60% of these individuals). In Sweden, the highest suicide attempt rates are found in the age group 15-24 years for both sexes, and

thereafter the rates successively decrease with increasing age (Socialstyrelsen, 2016). In addition, severity of attempt or an attempt with a violent method increases the risk of subsequent suicide (Harriss et al., 2005; Holley et al., 1998; Runeson et al., 2016).

Suicide and antidepressants

Antidepressants have been extensively investigated in randomized clinical trials and in comprehensive meta-analyses to determine whether they trigger the emergence or worsening of suicidal ideation (Juurlink et al., 2006; Martinez et al., 2005; Olfson et al., 2006; Stone et al., 2009). The debate concerning whether selective serotonin reuptake inhibitors (SSRIs) increase the risk of suicide or suicidal thoughts began already in the 1990s when the first series of studies on adult patients with depression who might have been suicidal as a result of fluoxetine (Prozac) treatment was published (Teicher et al., 1990). Over the following years, several groups have reported that the risk of completed suicide was the same, regardless of treatment assignment (Hammad et al., 2006; Khan et al., 2000; Storosum et al., 2001), whereas others assumed that SSRIs increase the risk of suicide attempts and self-harm behavior (Fergusson et al., 2005; Gunnell et al., 2005; Martinez et al., 2005). Later on, it was suggested that there is a differential risk of antidepressant-induced suicide across the age spectrum, 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 (Brent, 2016; Martinez et al., 2005; Olfson et al., 2006; Stone et al., 2009). On the other hand, ecological studies have consistently reported an association between higher SSRIs prescribing and lower suicide rates (Gibbons et al., 2006; Isacson, 2000; Isacson et al., 2009).

Suicide seasonality

Early demographers in the 19th century, such as Guerry in 1829 and Casper in 1825 (Casper, 1825; Guerry, 1829), discovered that suicidal behavior peaks during the late spring and early summer and declines during mid-winter. Before their work, it was generally thought that suicide was most common during autumn months (Esquirol, 1838). This assumption probably originated from the common idea that autumn was a naturally melancholic period.

This seasonal phenomenon was so consistently found in many subsequent studies that most of the social philosophers of that period accepted it as truth (Kevan, 1980). On the other hand, the explanation of this phenomenon was a matter of debate. Two schools of thought evolved. The first one, led by Morselli, suggested that bioclimatic factors were of considerable importance and the second one, led by Durkheim, attributes the seasonal pattern to socioeconomic factors (Durkheim, 1897; Morselli, 1881).

Bioclimatic hypotheses

Morselli did not ignore the importance of socioeconomic and individual psychological factors. He understood the individual must be predisposed towards self-destruction before committing suicide. He was trying to argue a case in favor of the organic origin of suicide. In addition, he suggested that seasonal changes of weather could have detrimental effects upon poorly acclimatized predisposed people. Later, Fitt suggested that light could possibly interfere with the endocrine system thereby affecting processes that lead towards suicidal behavior (Fitt, 1941). Other authors, Petersen and Milliken in 1934 and Mills in 1934, 1939, suggested that the seasonal incidence of suicide is related to the general state of the atmosphere. The former authors considered that temperature changes and the latter author that changes in barometric pressure in relation to storms were important (Mills, 1934, 1939; Petersen and Milliken, 1934).

Sociological hypotheses

Durkheim argued against the bioclimatic hypothesis on the grounds that it could not explain why different areas that had nearly the same climatic conditions exhibited different seasonal distributions (Durkheim, 1897). Similarly, Durkheim found noteworthy the fact that suicide rates change from one historical period to another within the same geographical region, and most importantly, that the data that he collected from rural and urban populations living in the same region showed differential suicide rates. He suggested that it was much easier to explain suicide seasonality as seasonal changes of social behavior, such as increasing and decreasing social isolation. For Durk-

heim, any influence of weather conditions is exerted through their effect on social activities: during brighter or warmer periods, social life becomes more intense and the probability of conflicts and frustration increases.

Although Durkheim's ideas have been widely accepted among social theorists, other hypotheses concerned with socioeconomic factors have been proposed. Cavan suggested a possible link between suicide and causes of sudden economic crises; however, she did not elaborate a relation to seasonal variations of suicide (Cavan, 1928). Schmid, in the same year (i.e. 1928), proposed that immigrants could influence suicide patterns (Schmid, 1928). Nearly 40 years later, Whitlock and Schapira suggested that part of the explanation for the seasonal distribution of suicide could be related to economic conditions and the availability of alcohol (Whitlock and Schapira, 1967).

A later sociological approach to seasonality was the theory of "broken promises" (Gabennesch, 1988). This theory suggests that vulnerable individuals may be influenced by approaching holidays or new seasons. Holidays tend to promote expectations in people that they will feel better. When these expectations are not fulfilled, the resulting disappointment may trigger a suicidal reaction.

In 1998, Yip et al. suggested that social contacts and activities and their related lifestyle might play a role in seasonal effects on suicide (Yip et al., 1998). Ajdacic-Gross et al. (in 2005) supported the "availability of means" theory, finding that different suicide methods have different seasonality or lack seasonality. More specifically, suicide methods in which means are available evenly throughout the year (e.g., poisoning, cutting, shooting) lack seasonality. In contrast, drowning, jumping and hanging where the availability of means is higher in certain seasons but also the subjective perception of availability, i.e. the social circannual timing of activities such as swimming and climbing, shows a clear seasonal pattern (Ajdacic-Gross et al., 2005b). Other social, cultural determinants (e.g., marital status and employment) were also thought to influence seasonal variations in suicide rates (Nayha, 1982; Yamasaki et al., 2004).

Chew and McCleary (Chew and McCleary, 1994), based on the "opportunity structure concept", which was introduced in sociology by Cloward and Ohlin 1960, pointed to the importance of opportunity to commit suicide as opposed to sociological, biological and psychological theories for the cyclic incidence of suicide. According to them, the main factors in suicide opportunity are surveillance and the accessibility of lethal means. Holidays are periods when people change their routines, which may coincide with lower social interaction and decreased surveillance of those at risk. For younger people, Christmas and Easter can be a high-risk period because of interruption of school; for the elderly, summer can be a high-risk period when family and friends spend more time in outdoor activities.

In line with this conjecture, it has been suggested that females with school-aged children may experience additional stress in autumn because of

decreased social interaction and surveillance, which coincides with the beginning of the school year (Nayha, 1983).

Seasonality of suicide attempts

Seasonality of suicide attempts is less studied than seasonality of suicide. A recent systematic review of 29 studies in 16 countries reported spring and summer peaks as the most frequent finding. Differences in sex, age and method of suicide attempt were reported in some studies, i.e. older individuals and more violent attempts had a significant seasonal pattern (Preti and Miotto, 2000). Three studies did not find any seasonal pattern. Rhythmic analysis of data indicated a seasonal pattern with spring peak independent of sex and method of suicide attempt (Coimbra et al., 2016). Discrepancies in sample composition by sex and age, i.e. preponderance of females and young age, or lack of a distinction between methods used in suicide attempts might be the reason that some studies have failed to report seasonal patterns in suicide attempts.

Seasonality trends

The trend of suicide seasonality has been studied in the past by many researchers and in different countries, resulting in inconclusive results with decreasing, unchanged, or increasing trends.

In studies from Denmark and Switzerland, extended time series were used, including up to 120 (Denmark study) and 125 years (Switzerland study). Data from these studies indicate that a decrease in seasonality started by the end of the 19th century and the beginning of the 20th century. In the Swiss data, seasonality was already absent by the end of the 19th century in urban regions (Ajdacic-Gross et al., 2005b; Dreyer, 1959). In other countries with smaller data series, the same finding has been documented (Kalediene et al., 2006; Oravecz et al., 2006; Rihmer et al., 1998; Yip et al., 2000; Yip and Yang, 2004; Yip et al., 2006). In Finland, however, this decrease seems to have come later in the end of the 20th century (Nayha, 1981; Partonen et al., 2004a). Although the evidence seems to be strong, some of the studies cited above have used either short periods (Kalediene et al., 2006), small samples (Rihmer et al., 1998), or both, or have based their results by comparing their data with the results of previous studies in the same country (Yip et al., 2000). In Norway, Bramness et al., in a time-series of 39 years and using an advanced statistical method specifically designed for trend, found a declining amplitude of seasonality (Bramness et al., 2015).

Unchanged trend was found in studies from Japan, Romania, Italy and one from Austria with a span of 29, 19, 29 and 38 years, respectively. How-

ever, in the Romanian study, the findings of an unchanged trend are confined to suicides by hanging and to a single county of the country (Nader et al., 2011; Nakaji et al., 2004; Rocchi et al., 2007a; Voracek et al., 2002).

Increased seasonality was found in studies conducted in Australia, the USA and Ireland. Bridges et al., who studied 865 928 suicides in the USA between 1970 and 2000, observed a strong and increasing seasonality in those three decades. His results supported the results of other studies in the USA done by Warren et al. in 1983 and Lester et al. in 1988 (Lester and Frank, 1988a; Warren et al., 1983). In Australia, the same finding was replicated but it was largely male violent suicides that determined the increase (Rock et al., 2003). The most recent study from Ireland also found increasing seasonality (Casey et al., 2012).

A recent study from Italy on suicide seasonality trend observed an increase from 1969 onwards until 1990, and a decrease thereafter until 2003. The decrease was mainly attributed to female suicides (Preti and Lentini, 2016).

Numerous explanations have been offered by researchers about the trends in seasonality. Researchers supporting the decreasing trend, attribute this decrease to the shift of suicide to less violent methods, increased use of antidepressants or changes in living conditions, roles of males and females and communication patterns thought to influence social interaction. In the Australian study, where increased seasonality was observed and was mainly attributed to male violent suicides, the authors suggested that since impulsive individuals may be more prone to migrate, suicide rates among migrants are higher compared with the settled population and given the fact that impulsivity expressed as violence or violent suicide is seasonal, increased migration might have led to increased seasonality (Rock et al., 2003).

Those who observed unchanged seasonality trends suggest that the absolute suicide numbers are related to the strength of seasonality in suicides and that when the absolute suicide frequency is higher, seasonal variation increases. By taking this association into account when analyzing data, changes in trend of suicide seasonality may eventuate to be smaller and much more consistent across different countries.

Factors associated with suicide seasonality

Having briefly commented on the theories that have been proposed to explain suicide seasonality, it is worth examining some of the factors that have been investigated in the past.

Demographic factors

Sex

Seasonality is seen in both men and women but it seems that the pattern differs between the sexes. Most studies find one spring peak in men, whereas women show a bimodal pattern with one peak in spring and one in fall (Chew and McCleary, 1995; Hakko et al., 1998a; Liu et al., 2015; Meares et al., 1981; Micciolo et al., 1991; Nayha, 1982; Preti et al., 2000). A few studies have failed to find two peaks in women (Ho et al., 1997; Lester and Frank, 1988b; Rock et al., 2003; Yip et al., 1998). The peak in autumn was suggested to be related to psychosocial processes specific to western countries, although this suggestion was not supported in later studies (Yip and Yang, 2004). These contradictory results may be due to different statistical models that can be either more or less sensitive to detect two peaks in the distribution.

Age

Several studies have reported an association between age and seasonal variation of suicide. One of the first studies examining this issue was done in Japan and indicated that people in the age group 15-24 years committed suicide more frequently in late winter and early spring, whereas people >65 years more frequently committed suicide in late spring and early summer (Takahashi, 1964). Later, a study from Germany found that the elderly tend to commit suicide in spring, whereas younger in autumn months (Danneel, 1975). In Finland, a bimodal seasonality was noted in younger females. It was suggested that it might be due to modernization of society because such a secondary peak was not evident in Finland before the 1920s and that social factors in the young (such as transition from holidays or from school to work or university that occurs in autumn) could expose people to stressful events (Nayha, 1982). Maes et al. (Maes et al., 1993a) documented that seasonality exists in younger people in spring and older adults in late summer. McCleary et al. (McCleary et al., 1991) found seasonal peaks in young adults in the fall-winter and the elderly in the summer. In Italy, Pretti reported clear seasonality in older age groups and a less marked seasonal pattern in younger age groups (Preti and Miotto, 1998). In Finland, Lahti et al. observed that shooting suicides in victims aged less than 18 years peaked in autumn, whereas suicides in adults peaked in spring (Lahti et al., 2006). In Ireland, Casey et al. found that, after controlling for other socioeconomic factors,

middle-aged adults have a spring suicide peak. Finally, in a study from Canada, only younger individuals showed a spring peak (Marion et al., 1999).

There is probably an interaction between age and other factors, including sex, psychopathology and method of suicide. Younger people generally, and especially women, have a bimodal seasonality, with peaks in autumn and spring. This autumn peak is coupled to lighter psychopathology, more related to social factors and non-violent suicides. Elderly, and especially men, on the other hand, have a classical unimodal pattern with a peak in spring, which is related to the recurrence of mood disorders that are more prevalent with increasing age and violent suicides.

Rural-urban differences

The most devastating argument of Durkheim against the bioclimatic school was that in his study rural populations showed a greater amplitude of seasonality than the urban populations in the same region, with the peak occurring earlier in the cities. Despite the substantial number of studies investigating seasonality, there are very few studies on rural-urban variation. Only in the past 20 years have researchers renewed interest in the topic. Surprisingly, all have found that the amplitude of seasonality is higher in rural areas compared with urban areas (Ajdacic-Gross et al., 2005b; Chew and McCleary, 1995; Flisher et al., 1997; Herea and Scripcaru, 2012; Jung et al., 2009; Kalediene et al., 2006; Lester and Moksony, 2007; Micciolo et al., 1991; Sun et al., 2011; Zhang et al., 2011).

Relative to the rural-urban variation in seasonality seems to be the occupation of suicide victims. Two studies from Finland found that outdoor workers showed a seasonal peak in spring in contrast to indoor workers who had a peak in autumn (Koskinen et al., 2002; Nayha, 1982).

These findings may imply that people who are more exposed to outdoor environments are more affected by environmental factors (such as temperature, sunlight, allergens) and thus show greater seasonal patterns.

Season of birth

Although many studies have been done to determine whether there is an association between season of birth and suicide or suicidal behavior, only one looked for an association between season of birth and suicide seasonality; however, in that study no association was found (Rock et al., 2006).

Environmental factors

Meteorological factors

Many studies have examined the possible association of weather parameters and suicide seasonality. Most of the studies have found an association but

the results have been inconclusive and sometimes contradictory. The two most studied variables are temperature and sunlight.

Temperature was positively associated with suicide in a number of studies (Bando et al., 2017; Deisenhammer et al., 2003; Dixon et al., 2014; Hiltunen et al., 2014; Holopainen et al., 2014; Kim et al., 2016; Kim et al., 2011; Lee et al., 2006; Lin et al., 2008; Page et al., 2007; Preti et al., 2007; Tsai and Cho, 2012) but negatively associated in others (Ajdacic-Gross et al., 2007; Inoue et al., 2012; Ishii et al., 2013; Lester, 1999; Marion et al., 1999; Souetre et al., 1990; Wu et al., 2014) or both (Holopainen et al., 2013).

Sunlight was also associated with suicide in numerous studies (Jee et al., 2017; Lambert et al., 2003; Maes et al., 1994; Papadopoulos et al., 2005; Partonen et al., 2004a; Petridou et al., 2002; Preti, 1997; Preti and Miotto, 1998; Salib, 1997; Salib and Gray, 1997; Souetre et al., 1987; Vyssoki et al., 2014; Vyssoki et al., 2012), negative in others (Kadotani et al., 2014; Linkowski et al., 1992; Terao et al., 2002; Tietjen and Kripke, 1994; Vyssoki et al., 2014; Yang et al., 2011) or no association at all (Chiu, 1988). Studies about precipitation and other meteorological factors have been inconclusive (Ajdacic-Gross et al., 2007; Deisenhammer, 2003; Lin et al., 2008).

The main reason for the inconsistency is probably differences in methodology. Apart from the fact that they deal with different numbers and types of weather variables, there is no unified hypothesis on whether climate has an acute or more chronic effect on suicide, and consequently, daily, weekly, monthly or annual meteorological data have been used. Studies with a more standard methodology are needed to enhance our knowledge of the relationship between weather and suicide.

Allergens

Some studies have linked suicide with allergens (Postolache et al., 2008; Qin et al., 2011) and seasonality of suicide with seasonal peaks of ambient pollen concentration (Postolache et al., 2005). The evidence thus far suggests that such a co-occurrence is more prominent for suicide victims with a history of mood disorders (Postolache et al., 2010).

In the USA, Messias et al. found a positive association between history of seasonal allergies and history of suicidal ideation, but no association between history of seasonal allergies and history of suicide attempts (Messias et al., 2010). In Finland, Timonen et al. reported that seasonality of suicide was higher in victims previously hospitalized for atopic disorders. In a recent study from the USA, the association between pollen counts and suicide could not be replicated (Woo et al., 2012a), but the same group in another study in Denmark found an association even after controlling for region, calendar time, temperature, cloud cover and humidity (Qin et al., 2013).

Geographical location

Europe

Suicide seasonality has been noted in most European countries. Studies from southern Europe (Italy, France, Spain, Portugal, Greece) (Altamura et al., 1999; Chew and McCleary, 1995; Petridou et al., 2002; Preti, 1997; Rocchi et al., 2007a; Souetre et al., 1987), from Eastern Europe (Romania, Slovenia, Hungary) (Lester and Moksony, 2007; Oravec et al., 2006; Voracek et al., 2002), from central Europe (Switzerland, Belgium) (Ajdacic-Gross et al., 2005a; Maes et al., 1993a) and from Northern Europe (the UK, Finland, Greenland, Sweden) have all shown that seasonality is evident (Bjorksten et al., 2005; Hakko et al., 1998a, b; Koskinen et al., 2002; Meares et al., 1981; Partonen et al., 2004a; Partonen et al., 2004c; Reutfors et al., 2009).

North and South America

With the exception of one study (Tietjen and Kripke, 1994), all studies from the USA and Canada have found substantial seasonality in suicides (Bridges et al., 2005; Kim et al., 2004; Kposowa and D'Auria, 2010; Lester and Frank, 1988b; Marion et al., 1999). Two studies from Brazil have yielded different results (Bando and Volpe, 2013; Nejar et al., 2007), with one finding seasonal patterns and the other failing to find any seasonality in suicides.

Asia

In Asia, almost all studies have found evidence for seasonality but with differences in the seasonal pattern of women, with some finding a unimodal and other a bimodal pattern (Ho et al., 1997; Lee et al., 2006; Lin et al., 2008; Liu et al., 2013; Nakaji et al., 2004; Nazari Kangavari et al., 2017; Sun et al., 2011; Tsai and Cho, 2011; Zhang et al., 2011). Only one study from Hong Kong failed to find seasonal variation of suicides but did find such a variation in suicide attempts (Yip and Yang, 2004). Finally, one study from the equator reported no seasonality (Parker et al., 2001).

Australia

Studies from Australia have also found seasonality of suicides but again with differences between sexes or diminishing trends over the years (Lambert et al., 2003; Parker and Walter, 1982; Rock et al., 2003; Yip et al., 1998).

Africa

One study from South Africa reported that suicide incidence increases in the spring and that this is more pronounced in rural areas and in colored people (Flisher et al., 1997).

Other factors

Other factors such as viruses and pollutants that follow seasonal patterns have been thought of as potential factors in suicide seasonality.

Human immunodeficiency virus (HIV) has been studied as a risk factor for suicide but no seasonal pattern was observed. Influenza, which has a seasonal pattern of infectivity, has been studied as a risk factor for suicidal behavior but not in relation to seasonality.

Air pollution has been associated with an increase in emergency visits for depression and suicide attempts in studies from Canada and the USA (Strahilevitz et al., 1979; Szyszkowicz, 2007; Szyszkowicz et al., 2016; Szyszkowicz et al., 2010). Furthermore, studies in South Korea, China, Japan and Belgium observed an association between air pollution and risk for suicide but these studies did not consider the interaction of season and pollution (Casas et al., 2017; Kim et al., 2015; Lin et al., 2016; Ng et al., 2016).

In a German study, levels of ozone have also been studied for an association with suicide and seasonality. An association between ozone levels and suicide in summer was found, but no association between ozone and suicide attempts (Biermann et al., 2009).

More studies are needed to study these (and potentially other) factors and their association to suicide seasonality.

Clinical factors

Methods of suicide

According to the International Classification of Diseases (ICD), suicides are classified as violent (hanging, shooting, drowning, jumping, cutting or self-immolation) or non-violent (intoxication). Massing and Angermeyer were the first to report on seasonality in suicides by hanging but found no relationship between seasonality and suicides by poisoning (Massing and Angermeyer, 1985). Many studies have since determined whether there is a difference in seasonality depending on suicide method. Overall, the majority of studies from different countries reported that violent suicides have a more pronounced seasonal pattern (Ajdacic-Gross et al., 2010; Ajdacic-Gross et al., 2005b; Bjorksten et al., 2005; Bjorksten et al., 2009; Kalediene et al., 2006; Lahti et al., 2006; Lester and Frank, 1988b; Lin et al., 2008; Rasanen et al., 2002). Moreover, this effect was mainly attributed to men and those of older age (Christodoulou et al., 2009; Maes et al., 1993a; Preti and Miotto, 1998; Preti et al., 2000). However, a UK study showed a peak in March for drowning mainly in elderly women (Salib and Gray, 1997).

However, the Swiss data demonstrated that there is seasonality in some violent methods but not all and that the timing of the peak differed between methods (e.g., hanging occurs earlier than drowning or jumping) (Ajdacic-Gross et al., 2003).

There is some disagreement as to whether the differentiation of suicides into violent and non-violent groups is too crude and that maybe the seasonal context and not the method is a more relevant factor. An argument favoring such a position is suicide by poisoning, although a non-violent method has been found to have a seasonal pattern for pesticide poisonings. Conversely, suicide by stabbing and firearms are not that seasonal compared with jumping and drowning.

Psychiatric diagnosis

It is well described in the literature -- and noted earlier in this thesis -- that psychiatric disorders are associated with suicide. Almost 90% of persons who commit suicide suffer from a psychiatric disorder. Hypotheses on the relationship between seasonal occurrence or exacerbation of psychiatric disorders and seasonal peaks of suicide have been formulated.

Eastwood et al., in Canada, was the first to find that seasonal peaks of suicide frequency are consistent with the seasonal peaks of hospitalization for psychiatric illness, especially depression (Eastwood and Peacocke, 1976).

By studying hospital admissions, Parker et al., in Australia, later found that certain affective disorders (mania, psychotic depression) peak in spring, whereas others (bipolar depression) peak in winter. He also noted that peaks of suicide in women, but not in men, coincided with the peak of admission for affective disorders (Parker and Walter, 1982).

In Belgium, Maes et al. found a significant positive correlation between the severity of depression and the peak of suicide but not homicide (Maes et al., 1993b).

In Sweden, Bradvik et al. studied the seasonality of suicide in depressed patients and patients with alcohol addiction. She found a spring peak in suicides of patients with alcohol addiction but not in patients with depression. Suicides in depressed patients peaked in October-November (Bradvik, 2002; Bradvik and Berglund, 2002). At the same time, in Norway, Morken et al. found that admission for depression peaked in November for women and in April for men and that suicides in men had a high correlation with admission for depression and mania (Morken et al., 2002).

Later, in Canada, Kim et al. studied male suicides, detecting that 63% of suicides in males with major depressive disorder occurred in spring-summer. However, a closer examination revealed that 83% of the suicides in males with major depressive disorder but without co-morbid cluster B personality disorder occurred in spring-summer; no seasonality was found in those with co-morbidity.

On the other hand, 88% of suicides in males with schizophrenia occurred in fall-winter (Kim et al., 2004). In Denmark, Yip et al. found that psychiatric illness in males but not in females may play a role in seasonal variation of suicide (Yip et al., 2006).

In Italy, Rocchi et al., in a cohort of 57 796 suicides, found that suicides due to psychiatric or somatic illness mainly happen in spring-summer and those due to economic difficulties mainly occur in December (Rocchi et al., 2007b). The same group observed that unintentional drug overdose peaked slightly in December, January and August in both sexes.

In Sweden, Reutfors et al., in a cohort of 14 030 suicides, reported that inpatient-treated psychiatric disorder is associated with increased seasonality of suicide. In detail, males with a history of depression and females with a history of a neurotic, stress-related, or somatoform disorder showed significant seasonal peaks (Reutfors et al., 2009).

In a recent Danish study, Postolache et al. showed that suicide victims with a history of mood disorder presented with an increased amplitude of spring peak (Postolache et al., 2010). A negative study on the topic was done by Posternak et al. in the USA, where they could not find a correlation between seasonality of suicides and psychiatric disorders (Posternak and Zimmerman, 2002). A review study on seasonality of bipolar disorder in the Netherlands reported that manic and mixed episodes peak during spring-summer and manic to a lesser extent in autumn; depressive episodes peak in early winter and to a lesser extent in summer (Geoffroy et al., 2014).

In summary, mood disorders have a well-documented recurrent course and an elevated risk for suicidal behavior. There is some evidence that there is seasonal recurrence of episodes that may coincide with the seasonal pattern of suicide.

Social factors

Social factors (e.g., unemployment, socioeconomic status, marital status and occupation) have been studied with reference to suicide seasonality. In a study from Finland, a classical early summer peak, but also a secondary rise in autumn, were reported, particularly in those with modern occupations (technical, administrative, clerical, sales and service work), suggesting that the autumn peak is of later origin and typical of those living in a human-made environment (Nayha, 1982). The same researcher found that married or widowed women and divorced or widowed men had a higher risk for suicide in autumn. In Japan, seasonality of suicide decreased with economic prosperity and increased with economic decline, although this finding was not replicated in a study from England (Lester, 1993). Souetre et al. did not find any association between seasonality of suicide and unemployment (Souetre et al., 1987).

In a cross-national study on suicide seasonality, Chew and McCleary found that gross national product per capita was associated with suicide rates but did not affect seasonality (Chew and McCleary, 1995). Rich countries had higher suicide rates than poor countries but were less seasonal.

Rocchi et al., in Italy, reported that suicides related to a psychiatric diagnosis showed a higher seasonal pattern than suicides related to somatic illness, sentimental reasons or economic factors (Rocchi et al., 2007b).

Two studies from Australia have reported associations between social factors and suicide. The first one reported that maximum temperature, unemployment rate, the proportion of indigenous population and the proportion of population with low individual income were statistically significantly and positively associated with suicide. The second one also reported a significant and positive association between unemployment and suicide. An interaction between temperature difference and unemployment on suicide was found such that increased temperature amplified the strength of the association between unemployment and suicide (Qi et al., 2015; Qi et al., 2009).

In a study from Taiwan, unemployment and labor force participation rates were not associated with suicide rates. Monthly temperature increase was the most influential factor, and climatic factors had a more significant effect than economic factors (Tsai and Cho, 2012).

Generally, studies have yielded contradicting results, which might be due to several factors. One significant problem, though, is that little is known about the lag time of unemployment and suicide or the duration of unemployment and suicide or other social factors.

Possible explanations

Although suicide seasonality is a robust and highly replicated finding in psychiatric epidemiology worldwide, studies on the association of environmental, demographic and clinical factors with suicide seasonality has yielded inconsistent results and therefore little is known about the underlying mechanisms. Several mechanisms have been suggested but a multifactorial stress-diathesis model is most probable (Figure 3).

Sunlight-serotonin

Suicide and suicidal behavior have been associated with abnormalities in different neurotransmitters, although of all the neurotransmitters, serotonin is the most studied. Studies on serotonin, its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF), serotonin receptors, serotonin transporter (SERT) *in vivo* and post-mortem in suicide victims give support to this association. Dysregulation of serotonin is also associated with impulsivity and aggression (Mann, 2003).

Serotonergic neurotransmission also has been shown to follow a circannual rhythm. Changes of several serotonin-related measures in plasma and whole blood of healthy individuals have been reported to vary throughout the year, with highest values occurring in the summer and lowest values in the fall. In contrast, 5-HIAA follows an opposite seasonal pattern (Brewerton et al., 1988; Sarrias et al., 1989). Post-mortem studies have also reported the same finding (Carlsson et al., 1980). PET studies reported significantly higher SERT binding in the fall and winter compared with spring and summer (Buchert et al., 2006; Kalbitzer et al.; Praschak-Rieder et al., 2008). Another study from the Netherlands using SPECT replicated this seasonal variation in SERT binding (Ruhe et al., 2009).

Serotonin turnover, assessed by measuring concentrations of serotonin in the internal jugular vein in healthy individuals, was found to be lowest in the winter and inversely associated with duration of bright sunlight (Lambert et al., 2002). Particularly noteworthy is that serotonin turnover in unmedicated depressed patients was found to be elevated and reduced after successful SSRI treatment. (Barton et al., 2008). Seasonality of SERT binding capacity in association with sunlight was also supported in one PET study (Praschak-Rieder et al., 2008).

Light acts upon the human eye and apart from stimulating the classical image forming system, which is responsible for vision, stimulates the non-image forming system that contributes to regulation of many circadian functions such as the sleep-wake cycle, cognition and mood in the human organism. The retinal ganglion cells (RGCs) that are involved in this system contain the photopigment melanopsin and send efferent nerves to various parts of the brain. A well-known circuit (retinohypothalamic tract) goes from

RGCs to the suprachiasmatic nucleus (SCN), the master clock of the human organism and then to the pineal body to regulate the secretion of melatonin. Other projections of RGCs terminate to the amygdala, hippocampus and dorsal raphe nucleus (DRN). In animal studies, RGCs have been found to regulate serotonergic activity in the DRN. There is evidence that light either indirectly (i.e. through disruption of circadian rhythms and sleep) or directly affects mood and cognition (LeGates et al., 2014).

Another possible mechanism is through the effect of sunlight on skin. Vitamin D is synthesized in the skin in response to light and has a role in regulating serotonin synthesis by modulating the tryptophan-hydroxylase enzyme. Some studies reported vitamin D deficiency in psychiatric disorders and in persons who committed suicide or attempted suicide. Moreover, the seasonal pattern of vitamin D coincides with the peak of suicides (Patrick and Ames, 2015).

Temperature-serotonin

Ambient temperature has been associated with an increase in serotonin turnover in animals (Aghajanian and Weiss, 1968; Hale et al., 2011), platelet [3H]-paroxetine and [3H]-citalopram binding studies and 5-HT_{2A} receptor responsiveness in humans (Callaway et al., 2005; D'Hondt et al., 1996; Zhang and Tao, 2011). 5-HT_{2A} receptors are implicated in mood and suicidal behavior (Pandey, 2013). These findings imply that temperature modulates serotonin (5-HT) function and leads to variations in human behavior. A recent study from Finland reported an association between temperature, peripheral serotonin measures and violence (Callaway et al., 2005). This finding is in line with previous studies indicating that low 5-HIAA CSF levels are associated with violent suicide (Asberg et al., 1986).

Ambient temperature has also been studied in association with cognitive functions. There is evidence that increased temperature is associated with impaired cognitive performance and decision making (Taylor et al., 2015; Trezza et al., 2015).

Temperature- Brown adipose tissue (BAT)

A recently proposed hypothesis is that of over-activated brown adipose tissue (BAT) as formulated by Holopainen et al. (Holopainen et al., 2013). BAT is abundant in human adults and has a role in heat and cold tolerance. It is activated by cold and inhibited by heat. When activated, it generates heat by a process known as non-shivering thermogenesis (Cypess et al., 2009). Photoperiod also has an effect on BAT with a long photoperiod having an inhibitory effect. Normally cold and short photoperiods activate BAT to adapt in fall and winter temperatures while heat and a long photoperiod inhibit BAT to adapt to spring and summer temperatures. Studies in depressed

patients have reported thermoregulation disorders (Caroff et al., 1981); more precisely, elevated nocturnal and decreased daytime body temperatures have been observed (Avery et al., 1999; Avery et al., 1982; Elithorn et al., 1966; Souetre et al., 1989). In addition, activated BAT has been reported to produce a hypermetabolic change in the right inferior parietal lobule and a hypometabolic change in the left insula, brain regions involved in depression (Huang et al., 2011).

In temperate climates, there are rapid temperature changes twice a year (during fall and summer). In these periods, BAT becomes activated and resistant to become quiescent (Zukotynski et al., 2010), with the consequence that the inhibitory effect of the photoperiod is lost (Heldmaier et al., 1981). This mismatch that comes with long, sunny but still chilly days in spring leads BAT in an over-activated state.

In its over-activated state, BAT releases physiological responses that mimic melancholic depression, such as loss of appetite, insomnia, weight loss and lack of mood reactivity (Wallberg-Henriksson and Zierath, 2009). This event might be of particular importance for people already depressed (Partonen et al., 2004b). There are preliminary data that over-activated BAT was found in two suicides of depressed individuals (Huttunen and Kortelainen, 1990).

Allergy-inflammation

Aeroallergens, such as pollen, can induce inflammatory reactions in the nasal mucosa of susceptible individuals. This allergic reaction involves production of T-helper 2 cells and several cytokines. In animal models, both T-cells and cytokines have been associated with symptoms such as increased anxiety, aggression and reduced social interaction (Tonelli et al., 2008a; Tonelli et al., 2009). All of the above behaviors can be thought of as endophenotypes of suicidal behavior. In humans, Tonelli et al. found that suicide victims have an increased gene expression of cytokines in the orbitofrontal cortex, a brain region implicated in suicide (Tonelli et al., 2008b).

Seasonal variations of allergens may potentially worsen symptoms in susceptible individuals with affective disorders and subsequently increase the risk of suicidal behavior.

Vitamin D and inflammation

Vitamin D, apart from other functions, has an immuno-modulating effect. Low levels of vitamin D have been suggested to contribute to different psychiatric disorders and suicidal behavior. Several studies indicate that a dysregulated immune system could be related to depression and possibly to suicidality.

Post-mortem studies have shown that patients who die from suicide independently of their psychiatric diagnoses have an increased level of neuroinflammation. A study on attempted suicides showed elevated levels of interleukin-6 (IL-6) in the CSF and vitamin D deficiency (Grudet et al., 2014).

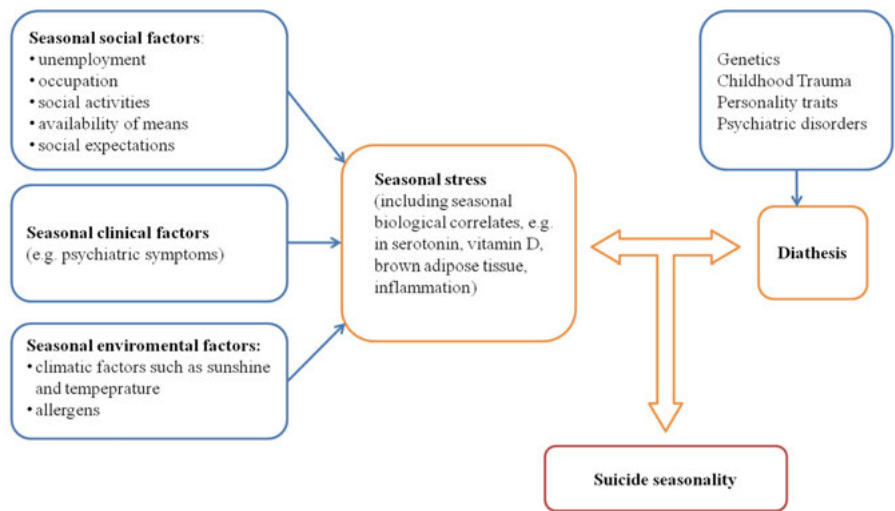


Figure 3. Stress-diathesis model in suicide seasonality.

Aims and scope

The aim of *Study I* was to study the amplitude of the seasonal effect in suicide victims positive for different classes of antidepressants at the time of death, as well as in those without any antidepressants.

The aim of *Study II* was to examine whether there is an association between sunshine and suicide after adjustment for season, in suicide victims positive for different classes of antidepressants at the time of death, as well as in those without any antidepressants.

The aim of *Study III* was to explore the relationship between season of initiation of antidepressant treatment and the risk of suicide or suicide attempt.

The aim of *Study IV* was to investigate the association between the exposure of sunlight and temperature and the risk for suicide or suicide attempt in patients starting a new treatment episode with antidepressants.

Methods

Data sources

Data were obtained from the National Board of Health and Welfare and Statistics Sweden. All Swedish registers use a 10-digit national registration number (NRN), a unique personal identifier assigned to all Swedish residents. The availability of the NRN allows 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 ICD. It has full coverage of all inpatient care in Sweden 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 comprises 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.

Toxicological analyses providing information about therapeutic levels of medication detected in the femoral blood of suicide victims (Druid and Holmgren, 1997) are carried out exclusively at the Department of Forensic Chemistry of the National Board of Forensic Medicine in Linköping, Sweden as a routine procedure for all unnatural deaths. The following antidepressants are included in routine analyses: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amitriptyline, clomipramine, desipramine, imipramine, maprotiline, mianserin, moclobemide, mirtazapine, nortriptyline, reboxetine, trimipramine and venlafaxine.

From the Swedish Meteorological and Hydrological Institute (SMHI), we gathered data for monthly sunlight duration from 11 meteorological stations for the years 1992-2003. The meteorological stations were in Luleå, Umeå, Östersund, Borlänge, Karlstad, Stockholm, Norrköping, Göteborg, Visby, Växjö and Lund. We also gathered data for daily sunshine using the STRÅNG model, which, since 1999, calculates several solar radiation measurements on a grid covering northern Europe (SMHI, 2017). The model grid covers the geographic area of Scandinavia with a resolution of 11 x 11 km.

By giving information on latitude, longitude and time, the model provides data for daily sunshine hours in a specific location under a certain period. Data for temperature were collected from SMHI historic open data in all Swedish counties for the years 2006-2012.

The Swedish Prescribed Drug Register contains patient identities for all dispensed prescribed drugs in Sweden for the entire Swedish population since July 2005.

Study populations

Study I and II

During 1992 to 2003, all certain suicides (n=14 455) were identified in the Swedish Cause of Death Register. Suicides lacking information about the month of death were excluded from the analyses (n=425).

Forensic data from the National Board of Forensic Medicine were available for 13 076 suicides (93.2%). Individuals that showed toxic levels of antidepressants were excluded from the analyses (n=628).

The remaining 12 448 (86%) individuals were linked to the Swedish Hospital Discharge Register (NPR, 2009). Psychiatric disorders as a primary or secondary diagnosis within five years before death were in this way identified (Figure 4).

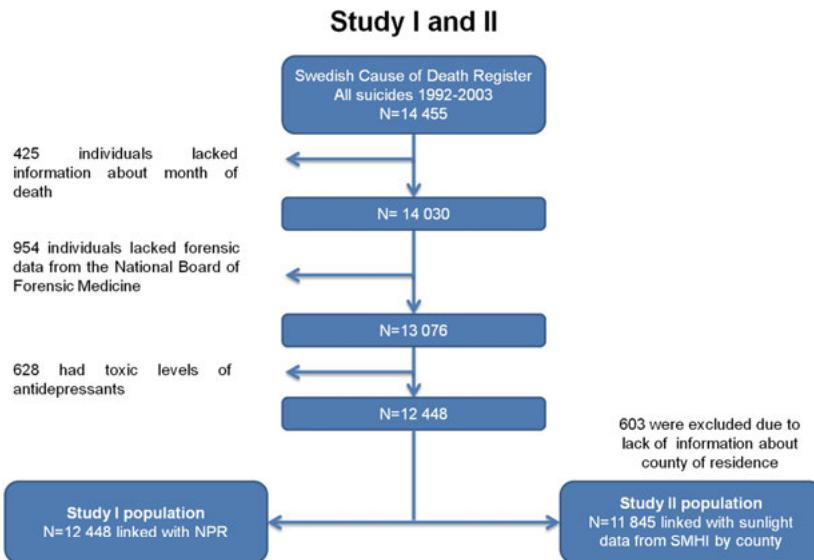


Figure 4. Study populations for Study I and II.

For *Study II*, an additional 603 individuals were excluded because of lack of information for county of residence. Thus, the final sample consisted of 11 845 individuals. Data for monthly sunshine duration for the years 1992-2003 were obtained by the SMHI for 11 of 21 Swedish counties with weather stations. For the counties with no weather station, the average number of sunshine hours from neighboring counties was imputed. Thereafter, a monthly sunshine variable was computed based on a population-weighted average sunshine value.

Study III and IV

In *Study III*, we identified 1 027 666 individuals that redeemed a prescription of at least one antidepressant between July 2006 and December 2012. Patients who had redeemed another prescription (antidepressants, antipsychotics, mood stabilizers) had been hospitalized the previous year, had a date of dispense that was after the date of death, or had invalid information in the prescription register were excluded. After exclusion, the total population comprised 1 014 708 individuals. The total population was then divided into four groups according to seasons of treatment initiation and was followed up to three months for suicide or suicide attempt. During the follow-up, individuals that moved from Sweden or dispensed afterwards another medicine (antidepressants, antipsychotics, mood stabilizers) were censored at that time.

In *Study IV*, we used the same population as in Study III but excluded those that were lacking information about county of residence. Data about temperature and sunshine duration were obtained from the Swedish Meteorological and Hydrological Institute. In this study, we explored the association of sunshine and temperature and suicide behavior in two time windows (1-4 weeks and 5-8 weeks) before suicide or suicide attempt (Figure 5).

Ethics

Studies I and II were approved by the research ethics committee in Stockholm, Sweden (Dnr 2005/1098-31).

Studies III and IV were approved by the research ethics committee in Stockholm, Sweden (Dnr 2011/1358-31/3 and 2013/1775-32).

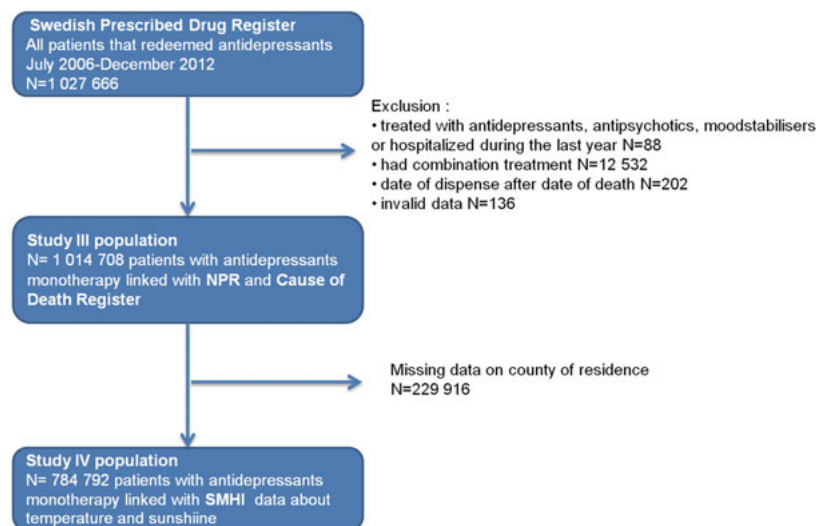


Figure 5. Study population of Study III and IV.

Statistical analyses

Study I

Seasonality was estimated with a Poisson regression variant of the circular normal distribution of completed suicide, as modified by Frangakis & Varadhan (Frangakis and Varadhan, 2002). It provides an estimate of the peak month for suicide with 95% confidence intervals (CIs) and an estimate of the relative risk (RR) of committing suicide during the peak month and 95% CIs for RR and a test for significance.

Stratification by sex, history of inpatient treatment for mental disorder and method of suicide (violent, non-violent) was performed. In each of these categories, the seasonal variation of suicide was estimated for individuals with positive forensic screening for SSRIs or other antidepressants and individuals with negative forensic screening for antidepressants.

The distribution-free test was used to test for differential degree of seasonality between two groups (i.e. that RR1 is different from RR2 for groups say 1 and 2).

The SAS software (version 9.1) and R (version 2.10) were used for the statistical analyses.

Study II

We used Poisson regression for our analysis because our dependent (outcome) variable was discrete. Three models were used.

The first model assessed the association of sunshine hours and monthly number of suicides by sex and age. In the second, we controlled for time trend by using a quadratic model because the number of suicides varies over time during our study period. In the third model, we controlled for season by using the dummy variable April-August for men; for women, we used March-May and October because two suicide peaks were evident during the study period. In each model, we tested the null hypothesis of no over dispersion using the Pearson goodness of fit statistic (od-test). The od-test with values <0.05 indicates a bad model fit and that more explanatory variables are needed in the model.

The same analyses were subsequently conducted on different treatment groups (no antidepressant, SSRIs, other antidepressants).

Different treatment groups were then compared with each other by using the likelihood ratio test (LRT) of equal coefficients to ascertain whether the difference in coefficients is statistically significant.

Data management was performed using SAS (version 9.1) and all calculations were performed in Matlab 7.10.0.

Study III

In this cohort study, the season of treatment initiation with an antidepressant agent was the exposure and suicide or suicide attempt during the three-month follow-up was the outcome measure.

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

Cox regression analyses were performed to obtain hazard ratios (HRs) and 95% CIs. We adjusted for the following covariates: calendar year, age, sex, setting of prescription and previous suicide attempt.

To determine the significance of variables, we performed two LRTs. The first was made to identify whether season had an association with the outcome of suicide or suicide attempt within various strata. 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.

Sensitivity analysis

The prescriptions of antidepressants showed a stable pattern during the study period, with a lower number of prescriptions in July. This observation led us to perform a sensitivity analysis that excluded July.

Comparison with SMR and SIR

To adjust for the underlying seasonal pattern in completed and attempted suicides, we calculated standardized mortality ratios (SMRs) for suicides and standardized incidence ratios (SIRs) for suicide attempts in patients recently prescribed an antidepressant treatment. If the seasonal suicidal behavior of patients starting on antidepressants was identical to the seasonal pattern of the whole Swedish population, we would expect a stable SMR and SIR throughout the year.

Study IV

In *Study IV*, we used a nested case control design and conditional logistic regression analyses. Completed and attempted suicides were included as cases. Ten controls were matched to each case using risk-set sampling. The mean daily temperature and the mean daily sunshine over the weeks 1-4 and 5-8 before suicide or suicide attempt were the main exposure variables. We used three models in our analyses: 1) crude model with no confounder and a single exposure (sunshine or temperature), 2) base model with confounders such as county, year and season and 3) climatic model, which is the base model with an additional exposure of the other climatic variable. An effect modification by season, age and sex was studied by using regression models with interaction terms.

Results

Study I

There was a general pattern of an increased suicide incidence in late spring and summer in both sexes but only men showed a significant seasonality with a peak in suicide incidence in June (RR=1.14, $p<0.001$, Figure 6).

In the different treatment groups, no seasonality was observed in women. On the other hand, men with no antidepressant treatment were found to have a 12% increased risk of suicide (RR=1.12, $p<0.001$), while men with SSRI treatment were found to have a 42% increased risk of suicide in June compared with December (RR=1.42, $p<0.001$). A notable finding was that men with another antidepressant treatment did not show a statistically significant seasonal pattern (RR=1.07, $p=0.81$) (Figure 6).

Direct comparison of the seasonal amplitude among men with SSRI treatment and those with no antidepressants yielded a statistically significant difference ($p=0.02$) (Table 1).

Suicide seasonality was observed in the group of men with a history of inpatient psychiatric treatment (RR=1.19, $p<0.001$). Those with a history of inpatient psychiatric treatment and SSRI treatment showed a borderline significant trend in seasonal pattern (RR=1.37, $p=0.10$), whereas those with no antidepressants had a statistically significant suicide peak (RR=1.20, $p=0.01$).

In the group of men without a history of inpatient psychiatric treatment, suicide seasonality was also observed (RR=1.12, $p=0.01$). Those without a history of inpatient psychiatric treatment who screened positive for SSRI showed the highest seasonal amplitude, with a 56% increased risk of suicide in June (RR=1.56, $p<0.001$); there was also a borderline significant seasonal peak in those screened negative for antidepressants (RR=1.10, $p=0.06$) (Figure 7). The difference in seasonal amplitude between these two groups was statistically significant ($p=0.008$) (Table 1).

In women with and without a history of inpatient treated mental disorder, no statistically significant seasonality was observed and therefore a comparison of RRs between groups was not applied.

In the group of suicides by violent methods, significant peaks in June for both men (RR=1.18, $p<0.001$) and women (RR=1.17, $p=0.05$) were observed. In men, the group with SSRI treatment had an increased seasonality for violent suicide (RR=1.49, $p<0.001$) compared with those without antidepressants (RR=1.16, $p<0.001$), and this difference was borderline significant

($p=0.06$) (Figure 8, Table 1). Females with violent suicide methods did not show statistically significant seasonal peaks in the different treatment groups.

For non-violent suicides, no statistically significant seasonal peaks could be detected in either sex.

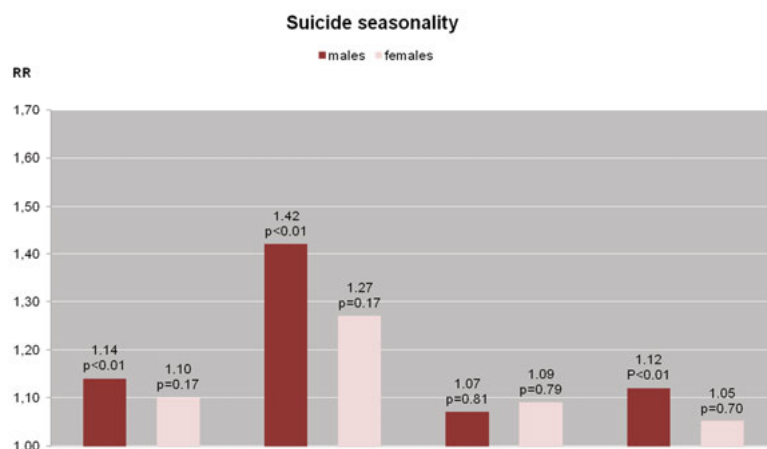


Figure 6. Relative risk of suicide (maximum over minimum frequency) by sex and treatment group

Table 1. Comparison of the amplitude of suicide seasonality in different groups

Men	RR1 (SSRI positive)	RR2 (no antidepressants)	Ratio = RR1/RR2	P-value
Total	1.42	1.12	1.27	0.02
No inpatient treated mental disorder	1.56	1.10	1.42	0.008
Violent suicide	1.49	1.16	1.28	0.06

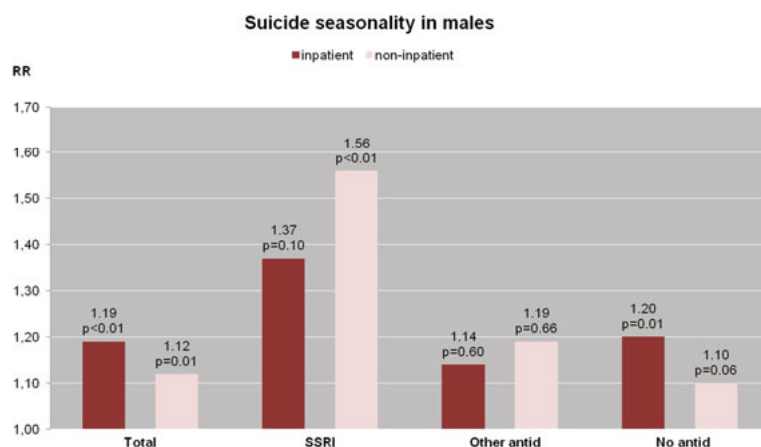


Figure 7. Relative risk of suicide (maximum over minimum frequency) in males by inpatient treatment and treatment group

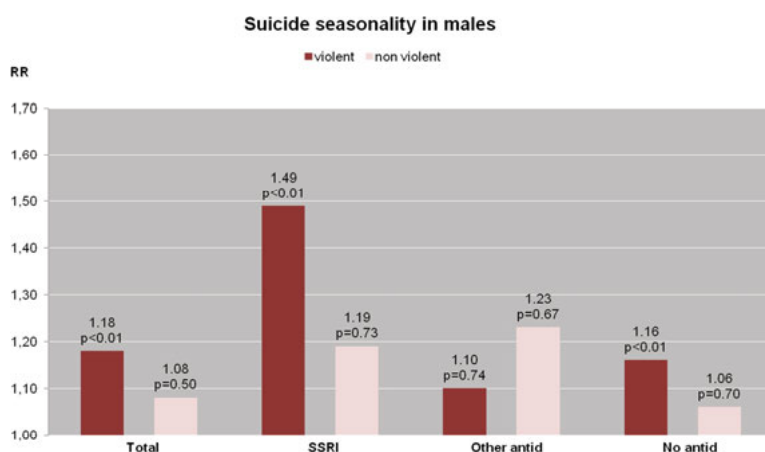


Figure 8. Relative risk of suicide (maximum over minimum frequency) by method and treatment group

Study II

Sunshine and suicide

The association between sunshine and suicide was statistically significant for both men and women. An increase by one hour of sunshine a day was associated with an increase of the average number of monthly suicides by 1.6% ($p<0.001$) in men and 1.2% ($p=0.05$) in women (model 1, Table 2). However, overdispersion was evident, suggesting a bad model fit.

Adding a quadratic time trend in the model did not improve the fit of the model while the results remained unchanged (model 2). This association seems to be mostly driven by the elderly (65+) in both sexes.

Adding season to the model, the association with sunshine was no longer significant in either men ($p=0.66$) or women ($p=0.15$) but season was significant instead, although overdispersion was evident (model 3).

In the fully extended model, though, the association with sunshine was maintained in only men in the 65+ age group. Moreover, no overdispersion was observed in the model, suggesting a good model fit. Specifically, an increase by one hour of sunshine a day was associated with an increase of the average number of monthly suicides by 2.1% ($p=0.009$).

Table 2. Poisson regression-derived estimates of suicide risk (expressed in % change) by increasing sunshine hours in different treatment groups.

	N	Model 1 ^a		Model 2 ^b		Model 3 ^c	
Men		Coef	p-value	Coef	p-value	Coef	p-value
Total	9016	1.6% ^e	<0.001	1.6% ^e	<0.001	0.3% ^e	0.66
<65	6631	1% ^d	0.02	1% ^d	0.02	0.4% ^d	0.61
>65	2385	3.5% ^e	<0.001	3.5% ^e	<0.001	2.1% ^d	0.009
No AD^f	7366			1.4% ^e	<0.001	-0.3% ^e	0.69
<65	5505			0.8% ^d	0.08	-0.7% ^d	0.38
>65	1861			3.5% ^d	<0.001	0.9% ^d	0.49
SSRI	783			4.8% ^e	<0.001	5.4% ^e	0.008
<65	508			2.8% ^e	0.06	3% ^e	0.26
>65	275			8.4% ^d	<0.001	10.4% ^d	0.004
Other AD	653			0.5% ^d	0.67	0.07% ^d	0.97
<65	473			1.6% ^d	0.28	0.87% ^d	0.76
>65	180			-2.4% ^d	0.34	-1.9% ^d	0.65
Women							
Total	3432	1.2% ^e	0.05	1.2% ^e	0.05	0.8% ^e	0.15
<65	2419	0.7% ^d	0.3	0.7% ^d	0.3	0.4% ^d	0.57
>65	1013	2.2% ^e	0.04	2.2% ^d	0.04	1.9% ^d	0.07
No AD^f	2372			0.9% ^e	0.2	0.6% ^e	0.39
<65	1711			0.5% ^e	0.54	0.2% ^e	0.85
>65	661			1.9% ^e	0.15	1.75% ^e	0.19
SSRI	502			3.5% ^d	0.027	3.1% ^d	0.048
<65	346			2.5% ^d	0.17	2.4% ^d	0.2
>65	156			5.4% ^d	0.054	4.75% ^d	0.1
Other AD	455			-0.4% ^d	0.77	-0.65% ^d	0.68
<65	314			-1.3% ^d	0.49	-1.5% ^d	0.43
>65	141			1.4% ^d	0.61	1.2% ^d	0.67

^a Poisson regression for monthly suicides: linear model including monthly sunshine hours

^b Poisson regression for monthly suicides: linear model including monthly sunshine hours and quadratic time trend

^c Poisson regression for monthly suicides: linear model including monthly sunshine hours, quadratic time trend and season

^d odtest > 0.05 means good model fit

^e odtest < 0.05 means bad model fit

^f antidepressants

Effect of sunshine on suicide in different treatment groups

In the different treatment groups, men not treated with antidepressants had a significant association between sunshine hours and monthly suicide ($p < 0.001$), but this association disappeared after adjustment for season ($p = 0.69$) and season was instead significant.

For both models, no significant association between sunshine hours and monthly suicide was found in women not treated with antidepressants.

In both sexes, a significant association was detected between sunshine and suicide in individuals treated with SSRIs. In the fully adjusted model, an increase by one hour of sunshine a day was associated with an increase of the average number of monthly suicides by 5.4% in men ($p = 0.008$) and 3.1% in women ($p = 0.048$). Again, this association in men is mostly driven by the 65+ age group with an increase of 10.4% in suicides for each hour increase in sunshine ($p = 0.04$).

No significant associations were noted in the group treated with other antidepressants.

The differential association of sunshine and monthly suicides found in different treatment groups in men was statistically significant (Figure 9). No statistically significant differences between different treatment groups were found in women.

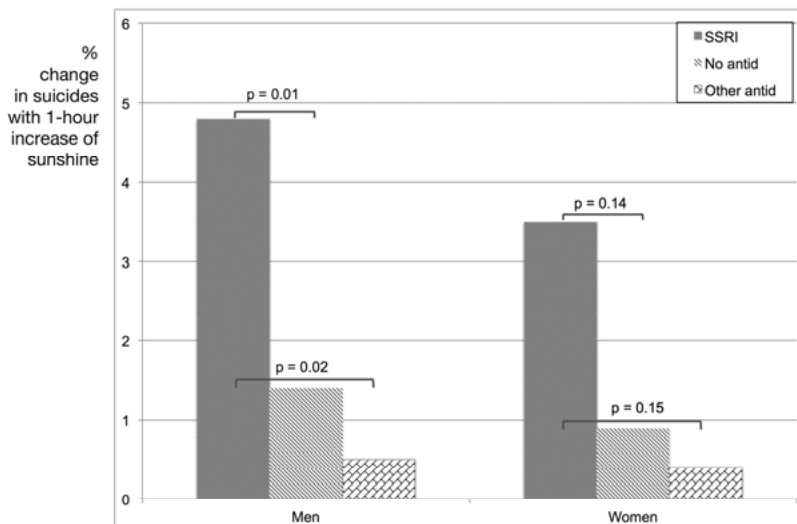


Figure 9. Pair comparison of coefficients (%) in different treatment groups when controlling for time trend

Study III

Completed suicides

In completed suicides, no statistically significant seasonality was observed for the whole population or in either sex (Table 3).

When we stratified for age, only 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).

Further analysis in this age group according to sex (Table 3) yielded no statistically significant seasonality pattern.

Table 3. P-values derived from the likelihood ratio test (LRT) for seasonality and interaction terms and the Cox regression-derived adjusted hazard ratios (aHRs) along with 95% confidence intervals (CIs) for suicide in different seasons compared with winter after adjusting for confounders.

	P-value seasonality LRT*	aHR (95%CIs)+			P-value interaction LRT**
		Spring vs Winter	Summer vs Winter	Autumn vs Winter	
Suicide					
All	0.36	1.03 (0.74-1.43)	1.15 (0.83-1.61)	0.85 (0.61-1.19)	
Sex					
Males	0.47	1.15 (0.78-1.68)	1.20 (0.81-1.76)	0.91 (0.62-1.34)	0.70
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
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
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
Females	0.10	0.50 (0.09-2.47)	2.48 (0.76-8.06)	1.01 (0.27-3.76)	

+ aHRs for the following covariates: calendar year, age, sex, setting of prescription and previous suicide attempts.

* 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 (e.g., sex) to the full model that included interaction terms between the seasonality dummy variables and the variable of interest.

Attempted suicides

In attempted suicides, as in completed suicides, no statistically significant seasonality was observed for the whole population or in either sex (Table 4).

When we stratified for age, the interaction of age and season was significant ($p=0.01$). Patients 65+ had a borderline significant trend in seasonal pattern ($p=0.09$), with 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 and HR (summer vs. winter) = 1.52 with 95% CI: 0.9-2.54). 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 autumn (HR (autumn vs. winter) = 1.19 with 95% CI: 0.95-1.50). In patients 25-64 years of age, no significant seasonal pattern was found ($p=0.24$).

When we stratified for previous suicide attempt, the interaction of previous suicide attempt and seasonality was borderline significant ($p=0.06$) (Table 4). Those with a previous suicide attempt had a seasonal pattern, with a higher risk for suicide attempt in the summer and autumn (HR (summer vs. winter) = 1.32 with 95% CI 0.82-2.12 and HR (autumn vs. winter) = 1.51 with 95% CI 0.98-2.32, $p=0.03$ for seasonality LRT). Those without previous suicide attempts had no significant seasonal pattern ($p=0.70$).

In the age group 0-24 years, there was no seasonal pattern after stratifying for sex (Table 4). In addition, the interaction of seasonality-sex and seasonality and previous suicide attempts in this age group was not statistically significant (seasonality-sex: $p=0.56$, seasonality and previous suicide attempts: $p=0.27$). However, the seasonal pattern in this age group might be driven by those who had a previous suicide attempt ($p=0.05$), with the highest risk for attempted suicide in autumn (HR (autumn vs. winter) = 1.91 with 95% CI 0.97-3.75) (Table 4).

The interaction term between seasonality and sex in patients 65+ was not significant ($p=0.31$) (Table 4). However, the finding does appear to be mostly numerically driven by males ($p=0.04$), who show a seasonal pattern with highest risk for an 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 and HR (summer vs. winter) = 1.61 with 95% CI: 0.75-3.43). As opposed to males, females did not present significant seasonality ($p=0.71$).

In stratification analyses by diagnostic group and medication, no statistically significant interactions were revealed.

Table 4. P-values derived from the likelihood ratio test (LRT) for seasonality and interaction terms and Cox regression-derived adjusted hazard ratios (aHRs) along with 95% confidence intervals (CIs) for suicide attempts in different seasons compared with winter, adjusting for confounders.

	P-value seasonality LRT*	aHR 95%CIs)+			P-value interaction LRT**
		Spring vs Winter	Summer vs Winter	Autumn vs Winter	
Suicide attempts					
All	0.45	0.92 (0.78-1.09)	1.06 (0.90-1.26)	1.01 (0.86-1.18)	
Sex					
Males	0.56	0.97 (0.74-1.26)	0.97 (0.74-1.28)	0.84 (0.65-1.09)	0.16
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
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
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
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
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
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
Females	0.71	1.07 (0.52-2.23)	1.44 (0.72-2.90)	1.03 (0.51-2.08)	

+ aHRs 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 (e.g., sex) to the full model that included interaction terms between the seasonality dummy variables and the variable of interest.

Sensitivity analyses

In sensitivity analyses that excluded July, the significant seasonal pattern for males aged 65+ with a higher risk for attempted suicides in the spring ($p=0.03$) remained unchanged, although the seasonal pattern was no longer observed for suicide.

In the group aged 0-24 years, the sensitivity analysis that excluded July did not modify the results.

Standardized mortality ratios (SMRs) for suicide and standardized incidence ratios (SIRs) for suicide attempts

The SMR for suicide was increased in summer in the age group 65+ and in winter in the age group 25-64 years, regardless of sex. In the age group 0-24 years, the SMR was increased in summer in both sexes combined generally and in males, while females in the age group 0-24 years had a higher SMR in autumn.

In the older patients (65+), an almost twofold SMR for suicide in the summer was observed as compared with the SMRs in other seasons, but 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).

An increased SIR for suicide attempts was observed in autumn for the age group 0-24 years and in summer for the age group 65+ in both sexes. In the age group 25-64 years, an increased SIR was observed in summer generally and in females; males in this age group expressed a higher SIR in winter.

An increased SIR for suicide attempts when starting antidepressant treatment in autumn was observed in the younger patient group (0-24 years), 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).

Study IV

No overall association was found between the exposure of sunshine or temperature and suicide or suicide attempt.

Evidence for an effect modification by age was found mainly in suicide attempts but also a similar trend was seen in suicides.

In completed suicides this effect was borderline significant ($p=0.07$) for the daily average temperature 1-4 weeks before index. In the age stratified analysis, only the age group 65+ showed a positive (harmful) association with temperature during 1-4 weeks before the event and completed suicide. This association was no longer significant when we adjusted for other confounders in the full model.

In attempted suicides, the interaction term for age was significant for both sunshine and temperature during the past 4 weeks before index (sunshine, $p=0.001$ and temperature, $p=0.017$). A tendency to a significant effect modification by age was found for temperature during the past 5-8 weeks ($p=0.06$).

More indicatively, an increase of one hour in the average daily sunshine during weeks 1-4 and weeks 5-8 was associated with an 8% (adjusted OR [aOR]=1.08, 95% CI: 1.02-1.14) and a 7% increase (aOR= 1.07, 95% CI: 1.02-1.13) in the risk of suicide attempt, respectively, in older patients (65+). In the same age group, an increase of one degree Celsius in the daily average temperature during weeks 1-4 was associated with a 3% increase risk of suicide (aOR=1.03, 95% CI: 1.00-1.05).

On the other hand, in the younger patients (0-24 years), a negative association was observed between daily average sunshine during the four last weeks and attempted suicide (OR=0.97, 95%CI: 0.94-1.00 in the base model). This association was no longer significant after adjustment for temperature.

Discussion

Main findings

In *Study I*, we observed an overall peak of completed suicides in spring-summer in Sweden, which is in line with many studies globally (Christodoulou et al., 2012; Kevan, 1980; Woo et al., 2012b).

Moreover, we observed a higher seasonal variation in suicide for men and, more concretely, in men treated with SSRIs compared with those with other antidepressant treatment or without any antidepressant treatment. This finding was more evident for violent suicide methods and in individuals without a history of inpatient treatment for mental disorders.

In *Study II*, we found evidence of an association between monthly sunshine duration and suicide. This association was markedly attenuated when we adjusted for season but not in individuals treated with SSRIs antidepressants. Moreover, the degree of association between sunshine and suicide is stronger in the individuals treated with SSRIs antidepressants compared with individuals treated with other antidepressants or those not treated with antidepressants. Age (older men 65+) seems to play a significant role in this association.

In *Study III*, no overall association could be identified between season of antidepressant treatment initiation and suicidal behavior. Nor did sex stratification result in a statistically significant seasonal pattern.

However, age stratification led to a clear seasonal pattern. Older patients (65+) that initiated treatment with antidepressants in spring and summer had a twofold increased risk for suicide or suicide attempt. In the younger patients (0-24 years) with a history of a previous suicide attempt, an almost twofold increased risk was found if antidepressant treatment was initiated in autumn.

In *Study IV*, no robust overall associations were noted between sunshine, temperature and suicidal behavior. Stratifying for age, there was evidence of an effect modification, mainly in attempted suicides.

Our results suggest a positive (harmful) association between average daily temperature during the past four weeks and the risk of suicide attempt in older patients (65+), while the harmful association between average daily sunshine and suicide attempt in the same age group was evident during both the four weeks prior to but even during weeks 5-8 before the suicide event. A notable finding was that average daily sunshine exposure during the four

weeks before the event had a negative (protective) association with suicide attempts in the younger patients (0-24 years).

Potential explanations for the main findings

Study I

Sex differences

Most studies agree that there is a sex difference in suicide seasonality. Men usually have higher seasonality and one peak as opposed to women who may have a second suicide peak in fall (Liu et al., 2015; Preti and Miotto, 2000).

Our results show a statistically significant pattern only in men, which is most probably driven by violent suicides. That women in our study do not show any seasonality might be because of the inherent limitation of our method to detect two peaks.

Treatment with SSRIs

A novel finding is that men in different treatment groups showed statistically different seasonality, i.e. men treated with SSRIs antidepressants show higher suicide seasonality compared with those with other or no-antidepressant treatment. Many possible explanations of this finding can be offered.

Affective disorder is most probably the usual indication for treatment with antidepressants, which per se might have a higher risk for seasonal suicide or seasonal recurrence.

We did not perform an analysis by diagnosis in our study because of lack of power, but another study with an overlapping dataset and same methodology showed higher seasonality in inpatient-treated depression (Reutfors et al., 2009).

However, the amplitude of seasonality in men treated with SSRIs was almost double compared with the above-mentioned study. In addition, patients treated with other antidepressants did not show any seasonality at all.

An alternative explanation might be that increased seasonality in the patients treated with SSRIs is due to severity of the affective disorder or response failure. However, severity of the affective disorder or response failure cannot explain our findings because in that case the patients treated with other antidepressants would have shown the same or similar trend in seasonality. Moreover, inpatient-treated patients would show higher seasonality, which was not observed in our study. In contrast, outpatient-treated patients had higher seasonality.

Seasonal affective disorder (SAD) can be thought of as a possible explanation of our findings. However, SAD is a relatively rare condition with

female predominance and a seasonal pattern that does not coincide with suicide seasonality.

Another explanation for the higher seasonality in individuals treated with SSRIs could be that direct effects of medication such as psychomotor activation before any mood improvement has occurred, the development of akathisia-like symptoms and the short-term effects of SSRIs in impulse control and aggression might be responsible for this finding (Nutt, 2003; Sinclair et al., 2009).

Although ecological studies on antidepressants and suicide risk from different countries argue that decreasing suicide rates can at least in part be attributed to the increased use of antidepressants (Gibbons et al., 2005; Grunebaum et al., 2004; Isacson and Mathe, 2008; Milane et al., 2006), a meta-analysis of all antidepressant studies in the FDA database revealed no differences in suicide risk between different antidepressants and placebo (Khan et al., 2003).

If we assume that seasonality were attributable only to SSRIs acute adverse effects, suicide peaks should coincide with a peak of SSRIs prescription. However, data from the Swedish Drug Register on SSRIs prescriptions redeemed from 2000 to 2003 indicate that there is a peak in prescription in autumn and winter.

Inpatient versus no inpatient treatment

We assume that patients without psychiatric inpatient treatment were likely to have been prescribed an SSRI, either by a general practitioner in primary care or by a specialist in somatic care, rather than by a psychiatrist. A possible explanation for the higher suicide seasonality among individuals treated with SSRIs and without a history of inpatient treatment could be that close follow-up is more difficult in this setting and therefore exacerbation of suicidal thoughts and behavior in the beginning of treatment in spring or early summer may not have been captured in time.

Violent suicides

Violent suicides are known to have a higher seasonal pattern and is hence probably the driving factor for overall seasonality. The higher amplitude of seasonality among violent suicides with positive screening for SSRIs is striking. A tempting explanation is that patients with affective disorders treated with SSRIs under a season of high serotonergic activity (increased serum 5-HT, decreased SERT-binding capacity and decreased 5-HIAA) can result in an excess of suicidal behavior, impulsive-aggressive behavior, or both. Seasonal variation in the availability of means to commit suicide as an alternative hypothesis cannot explain the difference in seasonality between violent suicides with positive screening for SSRIs and violent suicides with no antidepressants.

Study II

Sunshine duration and suicide

Our findings are consistent with those that reported an association between sunshine and suicide (Deisenhammer, 2003).

Not adjusting for season in such association studies is problematic because other factors with seasonal variation can act as confounders in the observed association with sunshine, which also presents a highly seasonal pattern.

When we adjusted for season in our study, the overall association between sunshine and suicide was greatly weakened and no longer significant, which replicates the results of a recent re-analysis of data from Australia, Greece and Norway, where the association between sunshine and monthly suicide after adjusting for seasonality failed to reach statistical significance (White et al., 2015).

Still, other studies have found an association of daily sunshine and suicide, even after adjusting for season. However, there was a problem with multiple statistical testing that was handled in different ways (Papadopoulos et al., 2005; Vyssoki et al., 2012).

Association of sunshine and suicide in SSRI-treated individuals

In people treated with SSRIs, the association between monthly sunshine and suicide remained significant, even after adjusting for time trend and season. This significant observation was more evident in men >65 years old.

This novel finding implies that a potential amplifying effect of sunshine and SSRIs on triggering suicide in susceptible individuals might prevail. A possible explanatory pathway may involve sunshine, altered serotonergic neurotransmission, impulsivity and suicidal acts.

Although higher prescription of SSRIs have been associated with lower suicide rates in the long term as mentioned above, our findings could suggest that in the short term SSRIs together with increased sunshine and its associated reduction in SERT binding may favor a state of increased impulsivity and or anxiety in some people, people who might then be more prone to suicide. A study on paroxetine treatment response found an association with monthly sunshine, which also supports a possible synergistic effect between SSRIs and sunshine (Tomita et al., 2012).

This finding is also in accordance with other studies that found that an increased risk for suicide in summer is associated with older age and attribute this age divergence to the difference in the prevalence of mood disorders (Preti and Miotto, 1998). Another explanation might be that the surveillance of the elderly (65+) may decrease in summer when family members and friends spend more time in outdoor activities while accessibility to lethal means for suicide increases in summer (Chew and McCleary, 1994).

Study III

The increased risk for suicide in older patients with antidepressants in spring and summer concurs with our previous study and other studies, supporting the notion that this may be due to the underlying seasonality of depression or decreased surveillance of the elderly during the summer period. The latter argument is in part supported by our sensitivity analysis showing that the seasonal pattern was eliminated after excluding the month of July.

The same did not apply for attempted suicides in the same age group, i.e. the sensitivity analysis did not alter the seasonal pattern. In this case, probably other factors than surveillance and availability of the healthcare system are involved.

An enticing explanation could be that elderly individuals have an accentuated seasonality as a combination effect of a lower availability of SERT with increasing age and an antidepressant treatment that also inhibits the SERT, which may lead to a higher risk for suicidal behavior in spring and summer (Chang et al., 2015; Kalbitzer et al., 2010). The short allele of SERT has been associated with anxiety-related traits and increased risk for depression in interaction with psychosocial stress (Homberg and Lesch, 2011).

The increased risk for attempted suicide in autumn in the younger age group (0-24 years), and particularly those with a previous attempt, accords with other studies that suggested that this peak is driven mostly by women and is related to seasonal social activities (De Maio et al., 1982; Polewka et al., 2004; Yip and Yang, 2004). Unfortunately, there are no studies examining differences in SERT seasonality in relation to sex and thus no interpretations can be made regarding a possible interaction of serotonergic neurotransmission and serotonergic medication during autumn.

Study IV

In a population of patients starting antidepressants, no robust association between sunshine, temperature and suicidal behavior was detected. This finding is in line with *Study III*, where no consistent seasonal pattern was observed for the general population but age stratification resulted in a clear seasonal pattern in the older (65+) and younger (0-24 years) age groups.

Of interest in *Study IV*, was evidence for an effect modification of age, mainly in attempted suicides in the same age groups (i.e. 65+ and 0-24).

We identified a harmful association between average daily temperature 1-4 weeks before the event and suicide attempt in older patients. This finding is in agreement with studies reporting the same association, although there are some inconsistencies (Ajdacic-Gross et al., 2007; Deisenhammer, 2003; Kim et al., 2016; Kim et al., 2011; Lee et al., 2006; Lin et al., 2008; Page et al., 2007; Tsai and Cho, 2012). This discrepancy is likely due to different

methodologies, time frames and statistical analyses used, that do not account for season or other climatic variables (White et al., 2015).

The literature describes possible mechanisms on how temperature can be involved in suicidal behavior, such as its interaction with the serotonergic system (D'Hondt et al., 1996; Tiihonen et al., 2017), over activation of BAT (Holopainen et al., 2014) and the effect of temperature or heat stress in cognitive performance or decision making (Taylor et al., 2015; Trezza et al., 2015).

A harmful association between average daily sunshine and suicide attempt was found in our older group (65+), both four weeks and 5-8 weeks before the event. In addition, a protective association between average daily sunshine and suicide attempt four weeks before the event was seen in the younger patients (0-24 years). Other studies have also reported the same association without adjusting for season (Deisenhammer, 2003; Lambert et al., 2003; Petridou et al., 2002; Vyssoki et al., 2012). In our study, adjustment for season, temperature and sunshine was done. Two studies that controlled for season reported the same associations but in different time windows. The first, from Greece, found an association between sunshine duration 1-4 days before the event and suicide while the second study, from Austria, found a harmful association between daily sunshine and suicide up to 10 days before suicide and a protective association from 14-60 days (Papadopoulos et al., 2005; Vyssoki et al., 2014).

Our results are not directly comparable with the aforementioned studies because of the different populations used as well as climatic differences between countries. A longer and more accumulative effect in older people was observed in our study.

Generally, the findings in the older group are in accordance with studies that observed an increased risk in the elderly for suicide and suicide attempt in summer when temperature and sunshine duration increases (Kim et al., 2011; Makris et al., 2017; Marion et al., 1999; Preti and Miotto, 1998; Preti et al., 2000; Salib, 1997).

Strengths and limitations

The major strengths of *Study I* and *II* are the size of the population studied and the high quality of the registers that allowed us to analyze data in different strata. Given the population-based data, our results can be generalized to similar populations. By excluding suicides with toxic levels of antidepressants, we secured individuals that were probably compliant to treatment. In *Study II*, we chose to include season in our model to control for other seasonal confounders, which is usually a problem in most of the studies in the field.

In *Study III* and *IV*, we used a large population-based cohort to study the association of suicidal behavior in relation to season of treatment initiation with antidepressants, as well as to the exposure of sunshine and temperature, which is a novel approach in the field of suicide seasonality. Our statistical analyses were comprehensive and strict and our models included interaction terms, season and other climatic variables as confounders.

Limitations of *Study I* include the lack of outpatient diagnoses from primary care and psychiatric settings and the lack of data on the timing of the initiation of the antidepressant therapy. Moreover, although our statistical method is very sensitive to detect one-peak seasonality patterns, it is not appropriate when two or more peaks are present. This limitation may have resulted in statistically nonsignificant results in our women population.

Study II needs to be interpreted within the context of two limitations. First, it cannot be excluded that other meteorological variables might have contributed to increased seasonality. Second, by excluding suicides with toxic levels of antidepressants to be more accurate in the association of sunshine and suicide in different treatment groups, we risk the possibility that our results will not generalize to the group of nonviolent suicides by intoxication.

In *Study III* and *IV*, we used filling of antidepressant prescriptions as a proxy for the actual antidepressant treatment, although this might not reflect the patient's actual use according to studies that show that up to 60% of patients are non-compliant to treatment. However, we performed an intention-to-treat analysis that allows for non-compliance. In addition, even if we have included non-compliant patients, this would, if anything, have led to underestimation of the hypothesized effect. Moreover, there are no studies suggesting that non-compliance has a seasonal variation.

Other factors (such as psychiatric diagnoses that were not available in our data) could contribute to the observed seasonal pattern. At last, the exclusion of patients with combination therapy or switching antidepressants constricts our results to patients with less severe psychopathology, which might have led to the nonsignificant overall seasonal pattern in *Study III* and the nonsignificant overall associations with climatic factors in *Study IV*.

A general limitation that applies to all our studies is that because of the ecological design, we cannot claim causality between variables that are studied and suicide seasonality but rather can only support previous hypotheses.

Theoretical and clinical implications

By studying completed suicides, we found evidence for suicide seasonality in Sweden and that it is probably stable throughout the years if we compare with previous studies (Chew and McCleary, 1995; Petridou et al., 2002). Seasonality is more prominent in men and violent suicide. The novel finding is that men treated with SSRIs have increased amplitude of seasonality compared with those without antidepressants; this effect is more evident in violent suicides and those individuals without inpatient treatment. The positive association between sunshine and suicide is enhanced by SSRIs and there is an effect modification by age.

In the study of patients treated with antidepressants, we could not detect an overall association between season of treatment initiation and suicidal behavior but an age modification effect was found for increased risk for suicide and suicide attempt in the 65+ age group when starting treatment in spring and summer and in the 0-24 age group for suicide attempt when starting treatment in autumn.

No overall association between temperature or sunshine and suicidal behavior in those treated with antidepressants was observed, although an effect modification by age was evident. Increased risk for suicide attempts was observed with increased sunshine up to two months before the event and with increased temperature up to one month before the event in the 65+ age group.

The above findings offer some more evidence to the implication of the serotonergic system in suicide seasonality. In susceptible individuals, the circannual variation of the endogenous serotonergic system may be further accentuated by seasonal environmental factors (such as sunshine or temperature) and exogenous administered serotonergic medication leading to seasonal suicidal behavior. Season of treatment initiation with antidepressants in some age groups might constitute a risk factor for suicide or suicide attempt in the clinical setting.

Conclusions

- We found a higher amplitude of suicide seasonality in males treated with SSRIs compared with those treated with other antidepressant treatments or those not given antidepressant therapy. Among males treated with SSRIs, those with violent suicide and those without a history of inpatient treatment for a psychiatric disorder had an even higher seasonal amplitude.
- We found an association between monthly sunshine duration and suicide in individuals treated with SSRIs, which remained significant even after adjusting for season. The degree of the association between sunshine and suicide is stronger in the individuals treated with SSRIs compared with the individuals given other antidepressants or those without antidepressants. Age (i.e. men 65+) seems to play a significant role in this association.
- No overall association was noted between season of antidepressant treatment initiation and suicidal behavior. However, older patients (65+) that initiated treatment with antidepressants in spring and summer had a twofold increased risk for suicide or suicide attempt. In the younger patients (0-24 years) with a history of a previous attempt, an almost two-fold increased risk for suicide attempt was found when starting antidepressant treatment in autumn.
- No overall associations were revealed between sunshine, temperature and suicidal behavior. However, when we stratified for age, there was evidence of an effect modification in attempted suicides.
A positive (harmful) association between average daily temperature during the past four weeks and the risk of suicide attempt in older patients was found. A harmful association between average daily sunshine and suicide attempt in the same age group was evident during both the four weeks before the event and even during weeks 5-8 before the event. Interestingly, average daily sunshine exposure during the four weeks before the event had a negative (protective) association with suicide attempts in the younger patients (0-24 years).

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