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SSRIs and risk of suicide attempts in young people – A Danish observational register-based historical cohort study, using propensity score

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Christiansen E, Agerbo E, Bilenberg N, Stenager E. SSRIs and risk of suicide attempts in young people – A Danish observational register-based historical cohort study, using propensity score. Nord J Psychiatry 2015;Early Online:1–9.

Background: SSRIs are widely used in the treatment of mental illness for both children and adults. Studies have found a slightly increased risk of suicidal thoughts and suicide attempts in young people using SSRIs but SSRIs' impact on risk for suicides in youth is not well-established. *Aim:* Is there indication that SSRIs might raise risk for suicide attempts in young people? *Methods:* We used an observational register-based historical cohort design, a large cohort of all Danish individuals born in 1983–1989 (n = 392,458) and a propensity score approach to analyse the impact from SSRIs on risk for suicide attempts. Every suicide attempt and redeemed prescription of SSRIs was analysed by Cox regression. *Results:* We found a significant overlap between redeeming a prescription on SSRIs and subsequent suicide attempt. The risk for suicide attempt was highest in the first 3 months after redeeming the first prescription. The hazard ratio for suicide attempts after redeeming a prescription was estimated to 5.23, 95% CI 4.82–5.68. *Conclusion:* We conclude that the risk of suicide attempt is higher for young people in the first months after redeeming their first prescription for SSRIs, compared to non-users. For SSRI users with lower propensity score (fewer risk factors for SSRIs) the risk of suicide attempt is estimated to be highest. Although the design may miss some explicit reason for prescription of SSRIs and SSRIs might be a marker for those in high risk rather than a causal risk factor, we would recommend systematic risk assessment in the period after redeeming the first prescription.

• *SSRIs, suicide attempts, children and adolescents*

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Selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressant drugs licensed for treatment of depression and certain anxiety disorders. The relationship between SSRIs and the risk of suicide in young people has been subject to considerable public attention, as some studies have found a weak, but significant, association between taking SSRIs and an increased risk of suicidal behaviour.

This association has been the subject of a number of meta-analyses on paediatric randomized trials. A meta-analysis performed by Mosholder and Willy (1) included 22 randomized short-term placebo-controlled paediatric trials, involving nine different antidepressant drugs. They estimated the serious suicide attempts incidence rate ratio to be 1.89 (95% CI 1.18–3.04) for the group exposed to the active drug, compared to placebo. No completed suicides were found (1). Another meta-analysis of suicidality risk (suicidal ideation and behaviour), performed by Hammad and colleagues, estimated the risk ratio for SSRIs in depression paediatric trials to be 1.66 (95% CI: 1.02–2.68) compared to placebo. They found no suicides either (2). A third meta-analysis of the impact of SSRIs on the risk of suicide ideation and attempts analysed the impact on three different indications for drugs (major depressive disorder, obsessive–compulsive disorder (OCD) and non-OCD anxiety disorders). They found a significant pooled overall risk ratio of 1.7 (95% CI: 1.1–2.7) for SSRIs compared to placebo (3). A meta-analysis performed

DOI: 10.3109/08039488.2015.1065291

by Stone and colleagues found that association between risk of suicidality and antidepressants was strongly age dependent, such that raised risk was only seen among adults under 25 (4).

Suicide is relatively rare in young people, including depressed young people, but is still among the leading causes of death (5). This is why estimation of the impact of SSRIs on suicide risk in randomized trials can be difficult, as a high number of exposed and unexposed are needed in order to show significant associations. Observational studies can provide this and have therefore been used. The disadvantage of observational studies is that individuals are not randomized to SSRI treatment, and the obvious differences between SSRI users and non-users bias results. A review of six observational studies performed by Dudley and colleagues found no evidence to support the hypothesis that SSRIs raise the risk of suicide in young people (6). Another systematic review followed by a meta-analysis found that SSRIs did increase the risk (OR 1.92, 95% CI 1.51–2.44) of suicide and suicide attempts in depressed young people, but decreased the risk in adults. This meta-analysis was based on eight studies involving 200,000 depressed patients and was performed by Barbui and colleagues (7).

An original study carried out by Jick and colleagues of 555 cases and 2062 controls found a significantly increased risk of suicidal behaviour in the first 9 days after being prescribed antidepressants. The study estimated the risk ratio for that period to be 4.07 (95% CI 2.89–5.74) (8).

The literature provides us with some indications that SSRIs might slightly increase the risk of suicide ideation and suicide attempts in children and adolescents. Their impact on completed suicides is not well-established. As suicidal behaviour is a well-known part of depression, it is difficult to distinguish whether the impact on risk is from the drug (SSRIs) or from the indication for the drug (e.g. depression). In observational studies the imbalance in the underlying risk profile for SSRI users and SSRI non-users might bias results, as individuals are not randomized to SSRI treatment. In observational studies it is necessary to deal with this "confounding by indication" problem. Including a propensity score in the analysis is an attempt to reduce this problem, if the propensity score is modelled well (9).

It is well-known that treatment may have an early stimulating effect, i.e. increasing the risk that a depressed individual might act on suicidal impulses before the therapy (or anti-depressant) effect materializes (10). This drive-mood dissociation might also be present in SSRIs treatment of young people and might raise the risk of suicidal behaviour in the early phase of the treatment (11).

By using the detailed linkage opportunities afforded by Denmark's rich series of health, social and economic registers and an observational design, this study has aimed to answer the following two questions: is there indication that SSRIs might raise risk for suicide attempts in young people, and if yes, in which period is the risk the highest? This paper will also include a discussion on the use of a pseudo-randomized (propensity score method) design to test the hypothesis.

Method

Population and follow-up period

Complete birth-cohort of every individual born in 1983–1989 and living in Denmark has been followed from birth or immigration and until first registered suicide attempt, death, emigration or end of follow-up (31 December 2011). Individuals who immigrated back into Denmark were not re-included in the study. We included data on two generations: data on the birth-cohort and data on their parents.

Factors

Data

We used seven longitudinal (historical) Danish registers and data from the period 1977–2011. The data were merged by using the unique civil registration number (CPR number) every Danish citizen has (12). We used data from the Danish Fertility Database (13), the Register of Causes of Death (14), the National Patient Register (15), the Danish Psychiatric Central Register (16) the Register of Families and Households, the Register of Unemployment and the Danish National Prescription Registry (17).

Outcome

First registered suicide attempt was the primary outcome. In keeping with previous studies (18–20), a suicide attempt was defined (with ICD-10) as:
contact with a somatic department when:

- the reason for contact was coded E4 (suicide attempts), and the diagnostic code was one of the following: S617–S619 (open wound of wrist and hand), T36x–T60x, T65 (poisoning/toxic effects by drug, substances etc.), and X60x–X84x (intentional self-harm),
- or a psychiatric disorder (F-code) as primary diagnosis, and a diagnostic code of T36x–T50x (poisoning by drugs), T52x–T60x (poisoning effects by substances), S51x (wound of forearm), S55x (injury of blood vessels at forearm), S59x (other injuries of forearm), S61x (wound of wrist and hand), S65x (injury of blood vessels at wrist and hand) or S69x (other injuries of wrist and hand) as the secondary diagnosis,

or contact with a psychiatric department when:

- given a diagnostic code of X60x–X84x (suicide attempt).

Exposure

For each individual, every prescription of SSRIs redeemed at any Danish pharmacy in the period 1 January 1995 to

31 December 2011, and prescribed by the primary or secondary health care section, was included in the analysis. We used the ATC code (N06AB) to identify prescriptions of SSRIs. All the prescriptions were coded into three different variations of using SSRIs: previous SSRI prescriptions (yes/no); first prescription of SSRIs (yes/no) coded as a time-varying factor, and prescribed SSRIs (yes/no) coded as time-varying factor for every quarter of the year. SSRIs were analysed in four different models (see Table 1).

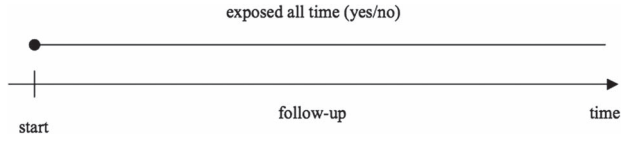
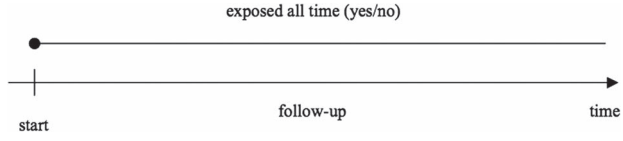
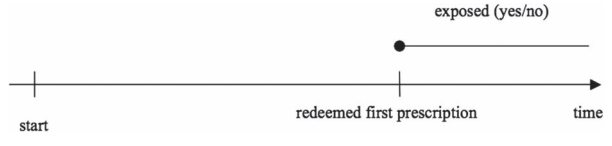
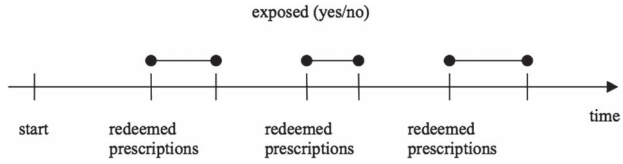
Confounding factors

For each individual we calculated a score measuring the likelihood of redeeming at least one prescription for SSRIs. To do so we used a logistic regressions model which included SSRI prescription as the outcome factor, and birth year, gender, adopted, own contact to mental department (substance abuse, psychotic and/or schizophrenia, affective, depression, anxiety and post-traumatic stress, behaviour disorders, personality disorder, patient type, number of contacts), study participants' use of psychopharmacological drugs (antipsychotics, anxiolytics, psychoanaleptics without SSRIs (including other types of antidepressant drugs), anti-epileptic drugs or drugs for substance dependence), all kinds of criminal offences, number of contacts to somatic department, place of living (county), death of parent, parental level of income, parental suicide attempt, parental use of psychopharmacological drugs, parents not living together, parental contact to mental health department and all kinds of parental offences, as independent variables. All the factors were coded as non-time-dependent dichotomy factors (yes/no) and we only included information that was collected prior to the first redeemed prescription on SSRIs. Many of the factors are associated with SSRIs and risk of suicide attempts (21).

The Propensity Score (PS)

Because the allocation of treatment (SSRIs) is not random, we try to reduce bias in estimated effect, by including the above-mentioned propensity score (PS) in our analysis. Whether actually receiving the treatment or not, the logistic regression model returns an estimate of the probability of being allocated to treatment. The study participants were grouped into 50 mutually exclusive strata according to the PS value, so that individuals in a specific stratum have almost the same probability of redeeming a prescription no matter whether they actually redeem a prescription or not. A detailed description of the propensity score method is to be found in Williamson et al. (22). We assessed the predictive ability to distinguish between SSRI user and non-user, and for this we

Table 1. Models used to test the impact of SSRIs on risk of suicide attempts in a young cohort.

Model	Name	Covariants	Exposure (SSRIs)	Illustration
1	Crude estimate	None	Dichotomy exposure. Ever exposed	
2	Adjusted estimate	Adjusted for PS by the use of strata and unbalanced covariants by the use of dummies§	Dichotomy exposure. Ever exposed	
3	Adjusted time-varying estimate	Adjusted for PS by the use of strata and unbalanced covariants by the use of dummies§	Dichotomy time-varying exposure. Dummies that indicate time of first exposure	
4	Adjusted time-varying repeated estimate	Adjusted for PS by the use of strata and imbalanced covariants by the use of dummies§	Dichotomy repeated time-varying exposure. Dummies that indicate exposure for every quarter of a year in the entire follow-up period	

§Insufficiently adjusted factors were gender, depression, anxiety and post-traumatic stress, behaviour disorders, personality disorder, type of contact with psychiatric department, use of antipsychotics, contacts to somatic department, parental level of income and parental use of psychopharmacological drugs.

used the C statistic. It was found to be 0.729, which indicates acceptable ability to distinguish between SSRI users and non-users (23). We included the strata in the logistic regression with SSRI as the outcome and all the above-mentioned covariants. We found that some factors were still significant, which indicates that some covariants were not sufficiently adjusted for through the use of strata. They were therefore, together with the strata, included in all of the Cox regression models of the impact of SSRI on risk of suicide attempts. The factors were gender, depression, anxiety and post-traumatic stress, behaviour disorders, personality disorder, type of contact to psychiatric department, use of antipsychotics, contacts to somatic department, parental level of income and parental use of psychopharmacological drugs.

Analysis

Based on the cohort of individuals redeeming a prescription for SSRIs and a matched non-redeeming comparison group, we estimated the survival distribution function in order to estimate the risk of suicide attempt as a function of time. The comparison group was matched on the PS value (strata), and they were all in the study at the time when the user redeemed the first prescription for SSRIs. The two cohorts were followed from the time when the first prescription for SSRIs was redeemed until the time of suicide attempt or end of follow-up. We estimated the survival distribution function by using the Kaplan Meier method in Proc Lifetest in SAS. The procedure returns an estimate of survival (no suicide attempt) for every time interval and a confidence interval, and based on that we calculate the risk of attempting suicide after starting on SSRIs.

The impact of SSRIs on the risk of suicide attempt was analysed by Cox proportional hazards models, which assume a constant hazard ratio (HR) across time, and by extended Cox models, which extend the Cox model to include time variation in covariants. We estimated the impact of SSRIs on risk of suicide attempts in four different dichotomized models. All the models are shown in Table 1.

Model 1 is the simplest and returns an unadjusted estimate of the impact. Model 4 is the most complicated and returns an adjusted estimate of the impact. Model 4 models "reality" most realistically, as it assumes individuals to be exposed and unexposed in some time intervals (quarters of years).

Proc Phreg in SAS was used to perform regression analysis of the time-to-event data on the Cox proportional hazards model (24). Age was the time-unit. The procedure returns a HR, a p-value and a confidence interval. The hazard is the risk of having a suicide attempt in the next time-unit, given not having had a suicide attempt until then. The HR is the ratio between hazards for exposed and unexposed to SSRIs. When SSRI use is analysed as a time-dependent covariant, the resulting HR represents the effect on suicide attempt after redeeming the first prescription of SSRIs. The repeated time-dependent covariant estimates the effect for any quarter during which the individual is exposed.

A crude estimate of the HR was calculated for each of the 50 strata. The estimates were plotted into a figure and inspected for trend by use of simple linear regression modelling. We used Proc Reg in SAS for this.

We tested for proportionality for SSRI by testing for time-dependent covariants of SSRI. We included an interaction term of SSRI and the logarithm of time and inspected its p-value. We found a p-value below 0.05, which indicates presents of non-proportionality. This was done for each stratum, and proportionality assumptions were not met for all strata. Strata with low values of PS were more likely to meet the assumptions.

Results

A total of 392,458 individuals were followed from turning 7.0 years of age and until suicide attempt or 31 December 2011. The mean follow-up time was 17.77 years (SD 3.00 (0.01–21.99)), which gives a total of 6,973,647.7 follow-up years. A total of 45,902 (11.7%) redeemed a prescription for SSRIs during follow-up. The mean age when they redeemed the first prescription for SSRIs was 21.17 years (SD 3.17 (7.64–28.94), 14.92% were below 18 years old). A total of 6364 (1.62%) had a suicide attempt during follow-up. The mean age at the index suicide attempt was 19.38 years (SD 3.27 (10.07–28.80), 35.86% were below 18 years old). During follow-up 2067 persons died (181 by suicide), and 30 of the attempters died by suicide. Among those who redeemed a prescription for SSRIs, 215 died, 43 of them by suicide and therefore only 23.8% had redeemed a prescription for SSRIs prior to the suicide.

A cross-table between SSRIs and suicide attempts is presented in Table 2. The table shows that 4.2% of all the individuals redeeming a prescription for SSRIs were registered with a suicide attempt at some point later in life. Furthermore, 30 % of all the suicide attempters had redeemed at least one prescription for SSRIs earlier in their life.

The estimate of the risk of suicide attempt after redeeming the first prescription for SSRIs is shown in Figure 1. The figure is based on only 41,710 users and 41,710 non-users (matched reference group), as it was

Table 2. Cross-table between use of SSRIs and registered suicide attempt.

	No suicide attempt	Suicide attempt	All
No use of SSRIs	342.101 (98.71%)	4,455 (1.29%)	346,556
Use of SSRIs	43,993 (95.84%)	1,909 (4.16%)	45,902
All	385,673 (98.38%)	6,364 (1.62%)	392,458

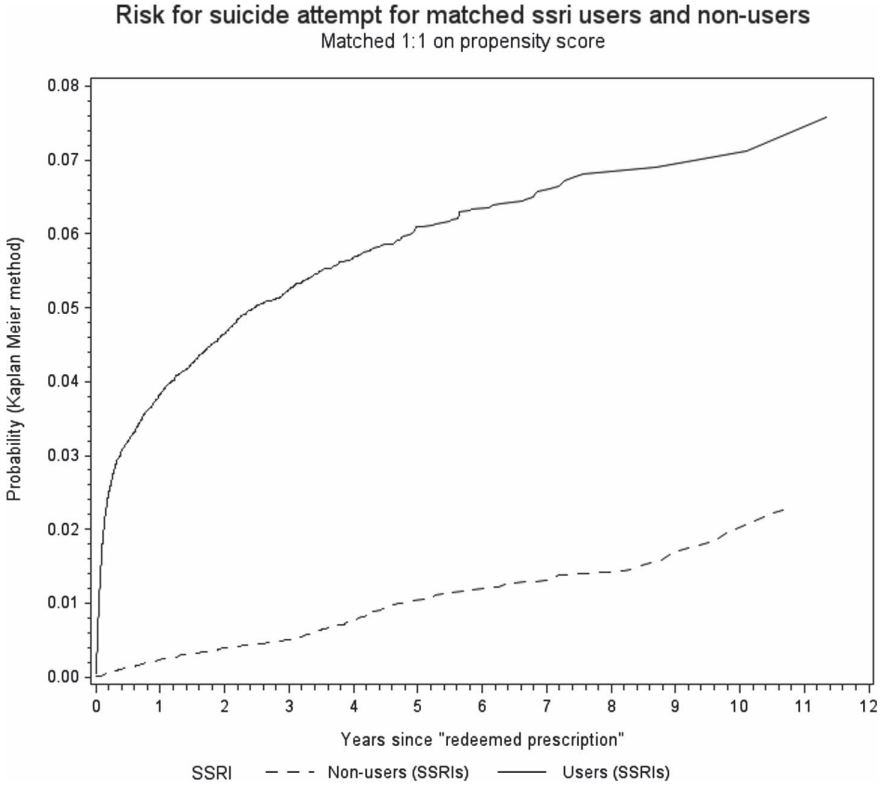


Fig. 1. Risk of suicide attempts after starting on SSRIs compared to matched (on PS) non-users.

not possible to find qualified non-users for all the users. The probability of having had a suicide attempt within 10 years after taking SSRIs is estimated to be around 7%. As can been seen from Figure 1 the risk increases considerably in the first 3 months after the first SSRI prescription. This analysis does not differentiate between individuals who have been prescribed SSRIs continuously and those whose prescriptions have stopped, and it cannot be used to prove causality. The figure tells us that individuals redeeming a prescription are at a much higher risk of suicide attempt within the first months after redeeming the prescription compared to the matched reference group, but it does not tells us that the risk is high because of SSRIs. After approximately 1 year, the risk is almost the same for the two groups.

In order to draw the figure, it was necessary to exclude 4,192 SSRI users from the analysis as it was not possible to find comparable non-SSRI users (with high PS value). The excluded users had the highest probability of redeeming a prescription, and Figure 2 shows that the group with the highest probability for redeeming has no negative impact from SSRI on the risk of suicide attempt. Therefore the figure might be slightly biased towards higher risk of suicide attempt.

The mean value of the propensity score was calculated for SSRI users and was 0.20 (lower quartile 0.10, median 0.14, upper quartile 0.24, SD 0.17) and for non-SSRI users 0.11 (lower quartile 0.06, median 0.09, upper quartile 0.13, SD 0.08). The distribution of the propensity score was different for the two SSRI groups, but very low and very high values were represented in both groups. However, more very high values were represented in the SSRI-user group. A more detailed analysis of the propensity score is given in Appendix 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/08039488.2015.1065291.

The estimates from the Cox regression models are reported in Table 3. In all models, prescription for SSRIs is a statistically significant risk factor for suicide attempts. The effect of prescription for SSRIs is lowered in the adjusted analysis compared to the crude level. Model number 3 has the lowest AIC value and is therefore to be preferred in a statistical context, but does not represent the real world situation. Model 4 models the real world most correctly and is in many ways the preferred model. As can been seen, the risk is relatively high (~5 times) in periods where the individual is exposed to SSRIs. The interpretation of the HR is the same for all the models, but an important difference is the way the exposure periods are modelled.

In Figure 2 estimates of HR (log(HR)) for each of the 50 strata are reported. A trend test showed significantly decreasing estimates (log(HR)) with increasing strata (increasing likelihood of receiving treatment (SSRI)). The parameter value was estimated to -0.00297 (t value: -9.48, p value < 0.0001).

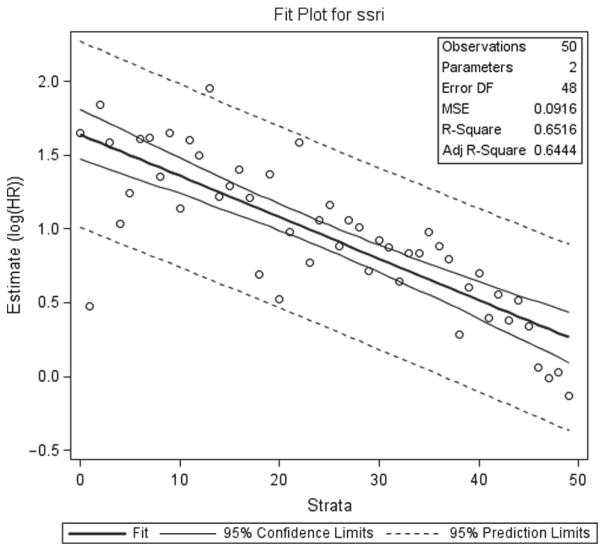


Fig. 2. Unadjusted point estimates of hazard ratio for the 50 strata.

Figure 2 reports that individuals with the lowest indication for redeeming SSRIs (modelled by the propensity score) are in the highest risk for suicide attempts, after redeeming a prescription on SSRIs.

Discussion

Results short

In this analysis of time-to-event data, we estimate the risk of suicide attempt to be high in the first 3 months after redeeming SSRIs as prescription drugs for adolescents. We used four different models to analyse the impact from SSRIs on the risk of suicide attempt. In all our models, redeeming of SSRIs was significantly associated with suicide attempts, after trying to control for many important confounders that may bias impact, such as mental illnesses and severity of mental illness. As this study is an observational study, confounding by indication might still bias the impact from SSRIs on the risk of suicide attempt, and therefore we might have overestimated the real impact. We cannot exclude that SSRIs might be a marker for those in high risk rather than a causal risk factor. In the most real-life model (model 4), the risk was estimated to be significantly higher in the SSRI-user group. The significant finding is probably due to the increased risk that we found in connection with the start up of SSRI treatment.

Limitations

Based on factors from registers, we modelled a propensity score for SSRIs (23). Propensity score methods can only account for measured confounding. Therefore it is still possible that unmeasured confounders (such as doctors' decision to prescribe SSRIs to those most at risk for suicidal behaviour) have not been fully captured by the propensity scores included in this study. Low and high values of the PS were represented in both the non-SSRIs and SSRIs prescription group. We included the PS in our models as strata, and we found impact from SSRIs on the risk of suicide attempt. There are two possible explanations for our finding: either SSRIs have a real impact

Table 3. The impact of SSRIs on risk of suicide attempts – four different models.

Model	Impact on risk		Note and interpretation of HR
	HR	CI	
1. Crude	3.10**	2.94–3.27	Hazard for attempts is 3.1 times higher in the SSRIs group assuming exposed all the time during follow-up
2. Adjusted	1.54**	1.45–1.63	Hazard for attempts is 54% higher in the SSRIs group assuming exposed all the time during follow-up
3. Adjusted time-varying	7.81**	7.32–8.33	Hazard for attempts is 7.81 times higher in the SSRIs group, at the time of starting on SSRIs and never ending taking SSRIs
4. Adjusted repeated time-varying (Longitudinal exposure, SSRIs)	5.23**	4.82–5.68	Hazard for attempts is 5.23 times higher in any quarter of a year when exposed to SSRIs

**$p < 0.0001$.

on the risk of suicide attempt, or our modelling of the propensity score is insufficient as the PS approach does not balance unmeasured confounders. Suicidal ideation or behaviour may well be the distinct factor that triggers the prescription of SSRIs. Therefore we must expect our estimates of the impact from SSRIs on the risk of suicide attempt to be an absolute maximum estimate.

The outcome variable (suicide attempt) is created on the basis of recommendations suggested by a Danish research group. The variable does not include all the suicide attempts made by the entire cohort, as some suicide attempts may be incorrectly registered in the registers and therefore unknown to us (18). On the other hand, we are convinced that what we are analysing are real suicide attempts and not some other kind of event, e.g. accidents.

This study is very highly powered and is therefore capable of finding small effects from SSRIs on the risk of suicide attempt. High-powered studies offer many benefits but also some disadvantages, as very small or negligible effects become significant associations, which may be falsely interpreted as important associations. To achieve the greatest effect, a suicide behaviour prevention strategy should focus on the strongest association with the most exposed individuals.

The best Danish estimate of incidence of suicide attempt in youths (15–19 years) shows an increasing trend from 1990 (~150 per 100,000) to 2004 (~450 per 100,000), and then a falling trend until 2011 (to ~200 per 100,000) (25). The estimates are based on records of treatment of suicide attempts in the somatic secondary health care system (26). During the period 2001–2010, the number of SSRIs users in Denmark increased from ~200,000 to 320,000 per year (~56%). The prescription rate has increased in all age groups, including children and adolescents. In 2001 the number of SSRI users among children and adolescents (0–17 years) was 1,731; and in 2010 the number of users was 5,700. Thus, this age group has the highest relative increase in prescriptions, although not the nominally highest prescription rate. The age group with most prescriptions is women above the age of 65; 16.1% of this group has been prescribed SSRIs within the last 12 months, compared to only 0.8% of girls and 0.4% of boys in the youngest age group (27).

As can been seen from the above, the last decade has seen a co-occurrence of an increased prescription rate for SSRIs and a fall in suicide attempts for the youngest age group. An ecological study might conclude that medical treatment of depression and anxiety lowers the risk of suicide attempts, but ecological studies have difficulties documenting causality between factors. In the same period where SSRI users have increased, a national suicide prevention project has been implemented. The project has resulted in more knowledge of suicide behaviour and prevention, especially in young people, better treatment of suicidality, and more suicide prevention centres around the country. It is difficult to estimate how many suicides and suicide attempts the project has prevented, and based on ecological studies, it is also difficult to analyse the interaction between treatment with SSRIs and treatment of suicidality. Other study designs are needed.

Some researchers and clinicians have expressed concerns about restrictions on the use of SSRIs in children and adolescents, as a decrease in prescriptions might result in increasing rates of untreated depression, which again might lead to increasing rates of suicidal behaviour (28). Examinations of US and Dutch data have confirmed this hypothesis (29), but a UK ecological study analysing the impact on the incidence of suicide and non-fatal self-harm from regulatory action in 2003 to restrict the use of SSRIs found no indication that a reduction in the use of SSRIs had led to an increase in suicidal behaviour (30). Other study designs are needed in order to document this association.

The purpose of this study was only to analyse the impact from SSRIs on the risk of suicide attempt; not to evaluate the benefits of treatment of depressed children and adolescents with SSRIs. A Cochrane review of 19 randomized controlled trials, cross-over trials and cluster trials comparing newer generations of antidepressants with placebo in children and adolescents gave no compelling evidence for the effectiveness of SSRI drugs. The review found some evidence that the drugs reduce depression symptoms but also that they increase the risk of suicide-related behaviours (ideation and attempts). Still, it is important to bear in mind that untreated depression in children and adolescents can raise the risk of suicide significantly (31). As our study shows that the risk of suicide attempts is highest in the period after redeeming the first prescription, we recommend that clinicians keep close contact with the patient, especially during that period, and to practice systematic risk assessment. A relatively new study using self-controlled cases found a peak in risk for suicide attempts, self-harm and ideation on the day of prescription. We found similar results. The study analysed in more detail the temporal relationship between SSRIs (or TCAs) and risk for suicidal behaviour, as they estimated incidence rate ratios for each week (32). They explain the findings by an artefact of GP-recording behaviour, where an antidepressant is given as a consequence of a suicide-related event.

Our analysis of HR in each of the strata shows that the impact from SSRIs on the risk of suicide attempt is non-existent or very low for individuals with the highest likelihood of redeeming prescriptions for SSRIs. This finding needs to be replicated in other studies. Many different interpretations of the figure can be given. If the likelihood of prescribing SSRIs is high, more severe psychopathology is to be expected and therefore a higher

effect of treatment in that group. Individuals with a low propensity score and individuals with a high propensity score might be two different populations with significantly different baseline risks for suicide attempts. Individuals with high propensity scores might more often be diagnosed with mental illness in psychiatric departments, and might therefore have more access to support and treatment, whereas individuals with low propensity scores might be undiagnosed and not have the same access to support and treatment. This might result in different levels of risk for suicide attempts.

Conclusion

Our results are much in line with results from the meta-analysis (1–4), but we can add that the risk of suicide attempt is highest for young people in the first 3 months after redeeming their first prescription for SSRIs. This risk is then lowered and almost the same for SSRI users and non-users. For individuals estimated as having low indications for the drug (based on our propensity score), the risk of suicide attempt is high if they are redeeming prescriptions on SSRIs. It is important to emphasize that in this study individuals are not randomized as to treatment with SSRIs, and therefore we might have reported biased estimates of the impact on risk for suicide attempts, as our design may have missed some explicit reason for redeeming a prescription of SSRIs. SSRIs might be a marker (non-causal risk factor) for those at high risk, rather than a causal risk factor, but we would still recommend systematic suicide risk assessment for children and young people during the period after redeeming the first prescription.

Funding: This study has been financial supported by Helsefonden and Psykiatriens Forskningsfond i Region Syddanmark.

Conflict of interest: None.

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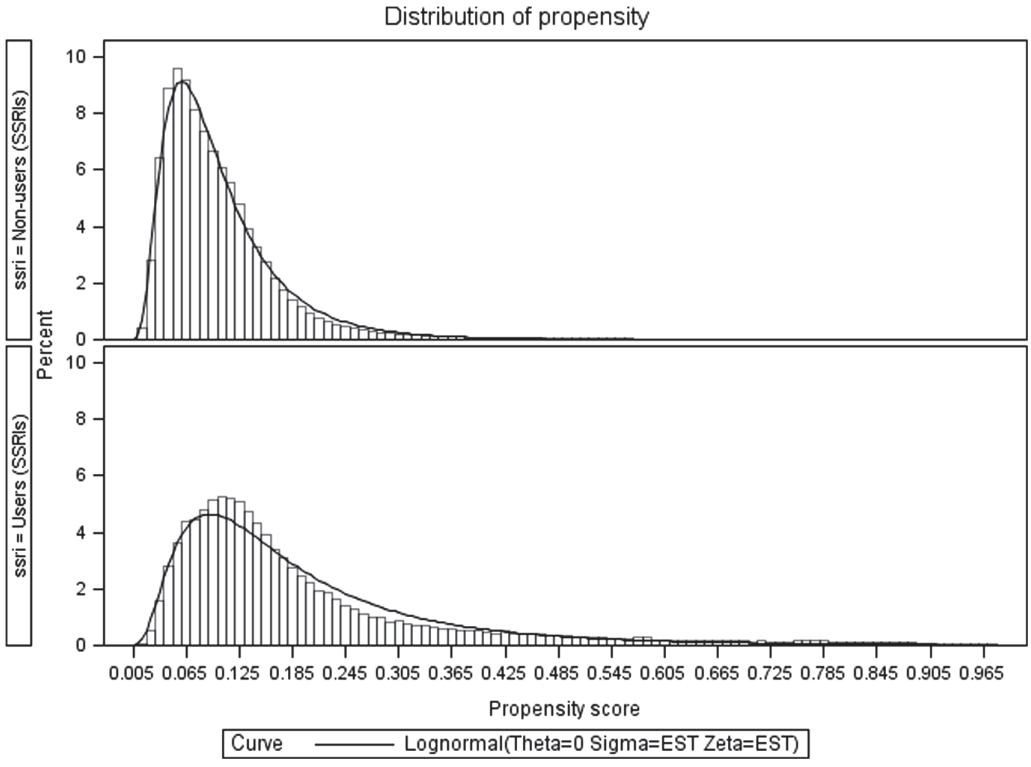
Supplementary material available online

Supplementary Appendix 1.

Supplementary material for Christiansen E. et al. SSRIs and risk of suicide attempts in young people – A Danish observational register-based historical cohort study, using propensity score, Nordic Journal of Psychiatry, 2015;doi: 10.3109/08039488.2015.1065291.



Appendix 1. Distribution of propensity score

Appendix 1. Distribution of propensity score

In this appendix the distribution of the propensity score (PS) is analyses and compared for SSRIs-users and non-users.

PS-distribution for SSRIs users and non-users.

Table 1.a. Statistical descriptors for the SSRIs users and non-users

SSRIs	n	Mean	Std. Dev.	Median	Min	Max
Non-users	346,556	0.1056	0.0828	0.0862	0	0.9899
Users	45,902	0.2029	0.1712	0.1449	0.014	0.9897

As can been seen from table 1.a the mean, standard deviation and the median of the propensity score are higher for the users, compared to the non-users. The range between the minimum and the maximum is the same for the users and the non-users, and therefore there exist a considerable overlap between the two exposure groups.

Test for equal means and medians for users and non-users:

Graphic inspection of histograms, QQ-plots and test for propensity scores goodness-of-fit for normality indicates, that the propensity score is not normal distributed, but the log-propensity score is normal distributed. Therefore a parametric test was used on the log transformation of the propensity score, and a non-parametric test was used on the mean.

Table 2.a. Test for equal distribution of propensity score for users and non-users

	t-test (parametric)	Wilcoxon Rank-Sum test (Non-parametric)
Propensity score	-	Z=159.91 p<0.0001
Log-propensity score (test of equal medians)	Satterthwaite t(54808)=-163.49 p<0.0001	-

Figure 1.a. Distribution of propensity score

Figure 1.a. about here

The two tests (table 2.a.) and inspection of the histogram (figure 1.a.) for the propensity score indicate that the distribution of the propensity score is not alike, for the two groups. Both groups have a large concentration of individuals with relatively low propensity score, but users are more likely to have higher values of the propensity score.

PS-distribution for SSRIs users and non-users, for the 50 strata.

Table 3.a. Statistical descriptors for the SSRIs users and non-users, for all strata

Strata	Exposed	N	Attempters	Min.	Max.	Mean	Std. Dev.
0	Non-users (SSRIs)	7,654	15	0	0.028	0.023	0.0037
	Users (SSRIs)	195	2	0.014	0.028	0.023	0.0033
1	Non-users (SSRIs)	7,638	22	0.028	0.032	0.03	0.0013
	Users (SSRIs)	211	1	0.028	0.032	0.03	0.0013
2	Non-users (SSRIs)	7,604	24	0.032	0.036	0.034	0.0010
	Users (SSRIs)	248	5	0.032	0.036	0.034	0.0010
3	Non-users (SSRIs)	7,580	23	0.036	0.039	0.037	0.0009
	Users (SSRIs)	266	4	0.036	0.039	0.037	0.0009
4	Non-users (SSRIs)	7,578	29	0.039	0.042	0.04	0.0008
	Users (SSRIs)	272	3	0.039	0.042	0.04	0.0008
5	Non-users (SSRIs)	7,548	21	0.042	0.044	0.043	0.0008
	Users (SSRIs)	301	3	0.042	0.044	0.043	0.0007
6	Non-users (SSRIs)	7,527	23	0.044	0.047	0.045	0.0007
	Users (SSRIs)	322	5	0.044	0.047	0.046	0.0007
7	Non-users (SSRIs)	7,534	23	0.047	0.049	0.048	0.0007
	Users (SSRIs)	315	5	0.047	0.049	0.048	0.0007
8	Non-users (SSRIs)	7,500	32	0.049	0.051	0.05	0.0007
	Users (SSRIs)	352	6	0.049	0.051	0.05	0.0007
9	Non-users (SSRIs)	7,498	24	0.051	0.053	0.052	0.0006
	Users (SSRIs)	348	6	0.051	0.053	0.052	0.0006
10	Non-users (SSRIs)	7,463	41	0.053	0.056	0.054	0.0006
	Users (SSRIs)	387	7	0.053	0.056	0.055	0.0006
11	Non-users (SSRIs)	7,548	35	0.056	0.058	0.057	0.0007
	Users (SSRIs)	381	9	0.056	0.058	0.057	0.0007
12	Non-users (SSRIs)	7,361	39	0.058	0.06	0.059	0.0006
	Users (SSRIs)	408	10	0.058	0.06	0.059	0.0006
13	Non-users (SSRIs)	7,390	24	0.06	0.062	0.061	0.0006
	Users (SSRIs)	460	11	0.06	0.062	0.061	0.0006
14	Non-users (SSRIs)	7,395	41	0.062	0.065	0.064	0.0007
	Users (SSRIs)	453	9	0.062	0.065	0.064	0.0007
15	Non-users (SSRIs)	7,381	38	0.065	0.067	0.066	0.0007
	Users (SSRIs)	470	9	0.065	0.067	0.066	0.0007
16§	Non-users (SSRIs)	7,374	41	0.067	0.069	0.068	0.0007
	Users (SSRIs)	474	11	0.067	0.069	0.068	0.0007
17	Non-users (SSRIs)	7,346	58	0.069	0.072	0.071	0.0007
	Users (SSRIs)	503	14	0.069	0.072	0.071	0.0007
18	Non-users (SSRIs)	7,343	49	0.072	0.075	0.073	0.0008
	Users (SSRIs)	506	7	0.072	0.075	0.073	0.0007
19	Non-users (SSRIs)	7,290	45	0.075	0.077	0.076	0.0008
	Users (SSRIs)	559	14	0.075	0.077	0.076	0.0008
20	Non-users (SSRIs)	7,298	53	0.077	0.08	0.078	0.0007
	Users (SSRIs)	551	7	0.077	0.08	0.078	0.0007

21	Non-users (SSRIs)	7,286	56	0.08	0.082	0.081	0.0008
	Users (SSRIs)	564	12	0.08	0.082	0.081	0.0008
22	Non-users (SSRIs)	7,221	55	0.082	0.085	0.084	0.0009
	Users (SSRIs)	628	24	0.082	0.085	0.084	0.0009
23§	Non-users (SSRIs)	7,206	60	0.085	0.088	0.087	0.0007
	Users (SSRIs)	643	12	0.085	0.088	0.087	0.0008
24	Non-users (SSRIs)	7,167	74	0.088	0.091	0.09	0.0009
	Users (SSRIs)	682	21	0.088	0.091	0.09	0.0009
25	Non-users (SSRIs)	7,140	89	0.091	0.094	0.092	0.0009
	Users (SSRIs)	709	29	0.091	0.094	0.093	0.0009
26	Non-users (SSRIs)	7,133	71	0.094	0.097	0.096	0.0009
	Users (SSRIs)	717	18	0.094	0.097	0.096	0.0009
27	Non-users (SSRIs)	7,038	70	0.097	0.1	0.099	0.0010
	Users (SSRIs)	778	23	0.097	0.1	0.099	0.0010
28	Non-users (SSRIs)	7,094	69	0.1	0.103	0.102	0.0009
	Users (SSRIs)	788	22	0.1	0.103	0.102	0.0009
29	Non-users (SSRIs)	7,045	86	0.103	0.107	0.105	0.0010
	Users (SSRIs)	804	21	0.103	0.107	0.105	0.0010
30	Non-users (SSRIs)	7,024	88	0.107	0.11	0.109	0.0010
	Users (SSRIs)	825	27	0.107	0.11	0.109	0.0010
31	Non-users (SSRIs)	6,990	84	0.11	0.114	0.112	0.0009
	Users (SSRIs)	859	26	0.11	0.114	0.112	0.0009
32	Non-users (SSRIs)	6,971	88	0.114	0.118	0.116	0.0011
	Users (SSRIs)	878	22	0.114	0.118	0.116	0.0011
33	Non-users (SSRIs)	6,944	106	0.118	0.122	0.119	0.0011
	Users (SSRIs)	905	33	0.118	0.122	0.12	0.0011
34	Non-users (SSRIs)	6,897	108	0.122	0.126	0.124	0.0012
	Users (SSRIs)	954	36	0.122	0.126	0.124	0.0012
35	Non-users (SSRIs)	6,887	90	0.126	0.13	0.128	0.0012
	Users (SSRIs)	995	36	0.126	0.13	0.128	0.0012
36	Non-users (SSRIs)	6,754	109	0.13	0.135	0.132	0.0014
	Users (SSRIs)	1,061	43	0.13	0.135	0.132	0.0014
37	Non-users (SSRIs)	6,764	108	0.135	0.14	0.137	0.0015
	Users (SSRIs)	1,082	40	0.135	0.14	0.137	0.0015
38§	Non-users (SSRIs)	6,716	143	0.14	0.145	0.142	0.0016
	Users (SSRIs)	1,137	34	0.14	0.145	0.142	0.0016
39	Non-users (SSRIs)	6,660	141	0.145	0.151	0.148	0.0018
	Users (SSRIs)	1,189	48	0.145	0.151	0.148	0.0019
40	Non-users (SSRIs)	6,642	130	0.152	0.158	0.155	0.0020
	Users (SSRIs)	1,232	50	0.152	0.158	0.155	0.0020
41	Non-users (SSRIs)	6,498	126	0.158	0.166	0.162	0.0023
	Users (SSRIs)	1,326	40	0.158	0.166	0.162	0.0023
42¶§	Non-users (SSRIs)	6,418	157	0.166	0.176	0.171	0.0029
	Users (SSRIs)	1,431	64	0.166	0.176	0.171	0.0029
43§	Non-users (SSRIs)	6,310	174	0.176	0.188	0.182	0.0034
	Users (SSRIs)	1,539	65	0.176	0.188	0.182	0.0034

44	Non-users (SSRIs)	6,137	163	0.188	0.204	0.196	0.0044
	Users (SSRIs)	1,713	79	0.188	0.204	0.196	0.0045
45	Non-users (SSRIs)	5,858	219	0.204	0.225	0.214	0.0062
	Users (SSRIs)	1,991	109	0.204	0.225	0.214	0.0062
46	Non-users (SSRIs)	5,614	215	0.225	0.258	0.24	0.0095
	Users (SSRIs)	2,235	94	0.225	0.258	0.24	0.0093
47¶§	Non-users (SSRIs)	5,227	245	0.258	0.318	0.284	0.0171
	Users (SSRIs)	2,622	126	0.258	0.318	0.285	0.0174
48¶§	Non-users (SSRIs)	4,470	258	0.318	0.452	0.373	0.0380
	Users (SSRIs)	3,379	206	0.318	0.452	0.378	0.0386
49¶§	Non-users (SSRIs)	3,595	373	0.452	0.99	0.626	0.1393
	Users (SSRIs)	4,254	401	0.452	0.99	0.642	0.1406

¶ Significant difference in means ($p<0.05$, t-test)
§ Significant difference in distributions ($p<0.05$, Wilcoxon)

As can been seen from table 3.a. the distribution of the propensity score within each strata is much alike. We tested for significant difference in distributions for each strata and found significant difference for strata 16, 23, 38, 42, 43, 47, 48 and 49. As the PS is getting higher, the more unequal are the distributions of the PS, for users and non-users.

Conclusion

This appendix is analysing the distribution of the PS for SSRIs users and non-users. Overall the distribution is not alike for the two groups, but within each stratum the users and non-users are having considerable overlap. Suicide attempts are also represented within each stratum and users/non-users.