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Risk of repeated suicide attempt after redeeming prescriptions for antidepressants: a register-based study in Denmark

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Original Article

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Abstract

Background. It remains unclear how SSRIs and other antidepressants are associated with the risk of repeated suicide attempts. We aimed to analyse the association between redeemed antidepressant prescriptions and the risk of repeated suicide attempts, hypothesising that antidepressant treatment is associated with increased risk of repeated suicide attempts.

Methods. The study was based on Danish register data and a validated cohort of 1842 suicide attempts. We used three Cox regression models (crude, adjusted and propensity score matched) to analyse the data; these models included both static and dynamic time-dependent factors.

Results. 1842 individuals attempted suicide in the study period, with a total of 210 repeated attempts. Individuals redeeming antidepressant prescriptions were more likely to repeat a suicide attempt. All crude models showed all antidepressants to be significant risk factors (HR around 1.39), whereas all adjusted models showed all antidepressants to be insignificant risk factors.

Conclusion. We found no significant increased risk of repeated suicide attempts in individuals redeeming a prescription for any antidepressant (or only SSRIs) when considering the individuals' baseline risk of repetition. This study is based on validated suicide attempts, register data, and strong epidemiology designs, but it still has some limitations, and the results should be replicated and confirmed in other studies.

Introduction

Suicidal behaviour is a serious public health concern around the world. In Denmark, the suicide rate was 10.8 per 100 000 individuals in 2021, while the overall suicide attempt rate was estimated to be around 85 per 100 000 individuals in 2018 (Centre for Suicide Research, 2022). The strongest predictor of suicide is a previous suicide attempt, and the strongest predictor of repeated attempts is also previous attempts. Other strong predictors of non-fatal repetition are psychiatric disorders, ongoing psychiatric treatment, alcohol abuse and dependence, and sexual abuse. Weak associations have been found among demographic factors such as age, unmarried status and unemployment (Beghi, Rosenbaum, Cerri, & Cornaggia, 2013). Therefore, prevention of suicide attempts is highly important as they increase the risk of death by suicide.

Psychopharmacological treatment is one way of treating psychiatric disorders like depression, but some reviews have found treatment with antidepressants to be a risk factor for suicidal behaviour. The meta-analyses report inconsistent results, as they are based on a limited number of individual studies, which result in biased estimates, wide confidence intervals (CIs) and varying quality. Most individual studies lack long-term effects, do not properly consider the age-related adverse impact in young people, and inclusion and exclusion criteria have become more stringent over time (Zimmerman et al., 2015).

A systematic review, including a meta-analysis of 27 422 depressed adults from 131 randomised placebo-controlled trials found no statistical significant difference between a group using selective serotonin reuptake inhibitors (SSRIs) and a placebo group in terms of risk of suicide, suicide attempt and suicidal ideation. In this study, data on suicidal behaviour and the long-term effect was limited, and all trials were at high risk of bias (Jakobsen et al., 2017). Likewise, a meta-analysis by Hengartner et al., of 27 observational studies revealed no definite association between exposure to SSRIs and the risk of suicide or suicide attempts in patients with depression (Hengartner et al., 2021). Nevertheless, a large umbrella review of 45 meta-analyses of observational studies, including a total of 4471 individual studies, found strong evidence in support of the protective role of antidepressants against suicidality in adults (Dragioti et al., 2019).

A meta-analysis by Sharma et al., found significantly higher risk of suicidality and aggression in children and adolescents treated with SSRI or SNRI, but the risk was not present in adults (Sharma, Guski, Freund, & Gotzsche, 2016). Likewise, a meta-analysis by Stone et al., found that the association between risk of suicidality and antidepressants was strongly age dependent, as the increased risk was found only in adults under age 25 (Stone et al., 2009). A Cochrane review of 26 randomised trials analysing the effects on depression and suicide-related outcomes concluded that young people treated with new-generation antidepressants might have higher odds of suicide-related events (Hetrick et al., 2021). These variations in findings suggest that further studies should be made to identify a causal association between antidepressant use and adverse outcomes. It is known that treatment in early stages can have a stimulating effect, which can increase the risk of acting on suicidal impulse before the therapy effect materialises (Mayer-Gross, Slater, & Roth, 1960). Individuals treated with antidepressants (or similar treatment) might be at higher risk of suicidal behaviour in the early phase of the medical treatment, and the effect can be age-related (Sinclair et al., 2009).

A large study of young individuals found that the risk of suicide attempt was highest in the three months after redeeming a first prescription for SSRIs (Christiansen, Agerbo, Bilenberg, & Stenager, 2016). Another study of young people found a higher risk of suicidal behaviour on the date of the first prescription for SSRIs or tricyclic antidepressants (TCAs) (Wijlaars, Nazareth, Whitaker, Evans, & Petersen, 2013).

The findings of the above-mentioned studies indicate that young people might have increased risk of suicidal behaviour in the period after starting on antidepressant treatment. Despite a long list of individual studies and meta-analyses of the association between SSRIs and risk of suicidal behaviour, the results are still unclear. There seems to be some indication that young people are at increased risk of suicidal behaviour when starting on SSRIs, although the association may not be causal (Dragioti et al., 2019). There is a need for more high-quality studies, but long-term effects of psychopharmacological drugs are difficult to estimate in randomised controlled trials (RCTs), and ethical issues might interrupt the study. Therefore, alternatives are needed, and observational cohort studies seem to be the best alternative (Ranganathan & Aggarwal, 2019; Witt et al., 2021).

Most of the previous studies on the association between antidepressants and risk of suicidal behaviour have analysed the risk of suicidal behaviour after initiation of antidepressant treatment. However, they do not analyse the association between use of antidepressants and the risk of repeated suicide attempt in a high-risk suicidal group, as individuals with suicidal behaviour are often excluded from the trials. Treatment with antidepressants might reduce, increase or leave unchanged the risk of suicidal relapse (e.g. repetition of suicidal behaviour). However, the general knowledge on this topic is very sparse and should be expanded. The usual RCT designs are unlikely to be able to address this issue because of the long duration and large sample size required. Population-based epidemiological studies using a register-based prospective cohort design would be feasible and able to provide some answers (Witt et al., 2021).

In this study, we aimed to estimate the magnitude and direction of the association between treatment with any antidepressant or only SSRIs (exposures) and repeated suicide attempt (outcome).

Methods

Data

This study used Danish register data, which can be linked through the unique civil registration number (CPR) assigned to all Danish citizens at birth or immigration. This number makes it possible to combine data from different registers. The Register for Suicide Attempts contains information about suicide attempts, and this information has been validated for specific geographical regions of Denmark (Christiansen & Jensen, 2004). In the register, a suicide attempt is defined as 'an act with a non-fatal outcome, in which an individual deliberately initiates a non-habitual behaviour that, without intervention from others, will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognized therapeutic dose, and which is aimed at realizing changes which the subject desired via the actual or expected physical consequences' (Bille-Brahe, 1998; World Health Organization, 1986). The procedure for the validation of the suicide attempt ensures that events without suicidal intention, such as non-suicidal self-injury or repetitive self-injurious behaviour (repetitive self-harm) were not included in Register for Suicide Attempts and therefore not included in this study. In this retrospective cohort study, we used populations from the North Denmark Region and Region Zealand. We included suicide attempts for the period from 1 January 2012 to 31 December 2015 and analysed this data in a time-to-event setup (survival analysis). The date (quarter and year) of the suicide attempts was chosen as the beginning of the follow-up period, and individuals were followed until first repetition, death (all reasons), emigration (or moving out of the county) or end of follow-up in 2015. The applied time unit was quarters of a year, which was the only available time-unit from the Danish Medicines Agency.

We obtained data on mental illness from the Danish National Patient Registry (Schmidt et al., 2015), data on redeemed prescriptions for psychopharmacological drugs from the Danish National Prescription Registry (Kildemoes, Sorensen, & Hallas, 2011), data on income from the Income Statistics Register (Baadsgaard & Quitzau, 2011) and data on household structure, offspring, death, emigration and inter-regional migration from the Danish Civil Registration System (Pedersen, 2011).

The study was approved by the Danish Data Protection Agency.

Variables

The two exposure variables, i.e. 'any antidepressant' (Anatomical Therapeutic Chemical (ATC) code: N06A) and 'only SSRIs' (ATC code: N06AB), were included in the Cox regression analysis in three different models. In model 1, the variable was included as a static dichotomous covariate. In model 2, the variable was included as a time-dependent dichotomous covariate changing value from 0 to 1 at the time (quarter) when the person redeemed a prescription for any antidepressant or SSRIs. In model 3, the variable was included as a dynamic time-dependent dichotomous covariate with a value of 1 in the quarters of the follow-up period when the person had redeemed a prescription and with 0 in the other quarters. Each model was designed to explore the changes in estimates from a simple variable model to the most realistic variable model. All models are illustrated in Fig. 1.

Data on contact to mental departments was coded into two groups: contact during follow-up period (yes, no) and contact prior to the suicide attempt (no, yes within two years, yes before

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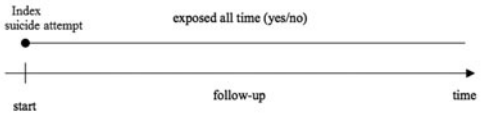
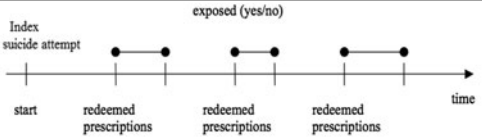
Variable structure	Covariates	Exposure ("any antidepressants" or "SSRIs only")	Outcome	Illustration
Structure 1	Static	Dichotomy exposure.	Risk of repeated suicide attempt if ever exposed (HR)	
Structure 2	Time-dependent dichotomised	Dichotomy exposure.	Risk of repeated suicide attempt from first time exposed (HR)	
Structure 3	Dynamic time-dependent	Dichotomy repeated time-varying exposure. Dummies that indicate time of exposure.	Risk of repeated suicide attempt in exposed times (HR)	

Fig. 1. Variable structure used to test the impact of antidepressants (or SSRIs only) on risk of repeated suicide attempts.

two years). Psychiatric contact was used as a proxy for past and present mental illness. Data on psychopharmacological drugs was dichotomised and included as redeemed prescriptions before and after the index suicide attempt: antidepressants (ATC code: N06A), SSRIs (ATC code: N06AB), antipsychotics (ATC code: N05A), anxiolytics (ATC code: N05B), hypnotics and sedatives (ATC code: N05C). If possible, variables were coded as time-dependent variables. Data on offspring was included and defined as having a minimum of one child aged under 15 (yes, no). Data on household was included as living alone (yes, no). Data on income was included as fractiles (lowest third, middle third, highest third).

Statistical models

Three different statistical models were used: a crude model (model 1) including only exposure (antidepressant), an adjusted model (model 2) including exposure and other factors/confounders, and a propensity score-matched model (model 3) including exposure stratified by level of the propensity score.

The propensity score was calculated in a logistic regression model as the probability of redeeming a prescription for antidepressants during follow-up. The model included the use of antidepressants prior to the index attempt, (ever) contact to a mental department, (ever) redeemed a prescription for antipsychotics, anxiolytics, hypnotics or sedatives, age group, having children, gender, level of income and living alone as independent factors, whereas redeeming a prescription for antidepressants during follow-up was set as the dependent variable. Participants in the same subgroup (based on the propensity score) will have the same probability of redeeming a prescription for antidepressants. Effects from redeeming a prescription for antidepressants on the risk of repeated suicide attempts can be estimated in specific propensity score subgroups, which, in theory, will give an unbiased estimate of the effect. Individuals were grouped into 10 strata according to their level of the propensity score. All three models were stratified by year at index suicide attempt and were used to analyse the risk of repetition during the follow-up period.

Analysis

Each case was followed from the date of the suicide attempt until the first repetition, censored or end of follow-up. This information was used to estimate survival curves for repeated suicide attempts and to calculate repetition proportion. The Kaplan-Meier method was used to estimate survival curves (Allison, 2010).

The variables were analysed in a proportional Cox regression model, stratified by year and returning hazard ratios (HRs), CIs and p values. The hazard ratio is a measure of the relative difference in hazard rates between an exposed and an unexposed group. The hazard rate is the likelihood of having the outcome in the next time period. The model assumed proportional HRs over time, and this could be verified by testing for statistically significant interaction between time and exposure ('any antidepressant' or 'only SSRIs'). All interactions were non-significant. Therefore, the assumptions of proportionality were fulfilled for the two factors (Allison, 2010).

Results

A total of 1842 individuals survived a suicide attempt in 2012–2015 and were followed from the date of the attempt until the first repetition or end of follow-up. This resulted in 2052 cases and included 210 repetitions. The total follow-up time of the cohort was 2974.50 years (average: 1.61 years, S.D.: 1.15, min: 0, max: 16), with a total of 2824.50 years (average: 1.73 years, S.D.: 1.14, min: 0, max: 16) for those without repetition and a total of 150 years (average: 0.71 years, S.D.: 0.78, min: 0, max: 14) for those with repetition.

Survival analysis

An estimate of the Kaplan-Meier survival curve for repetition was calculated (figure not shown). The curve was steepest at the beginning of the follow-up period, which indicates higher risk in the period immediately after a suicide attempt. The risk decreased as the time since the last suicide attempt increased. The risk of repetition was estimated to be 17.69% in the follow-up period.

Figure 2 shows the risk of repeated suicide attempt in individuals who redeemed a prescription for any antidepressant compared to individuals who did not redeem a prescription. The highest risk of repetition was seen for the group who redeemed a prescription, and the difference was statistically significant (log-rank test $p = 0.0142$). The two groups showed the same overall

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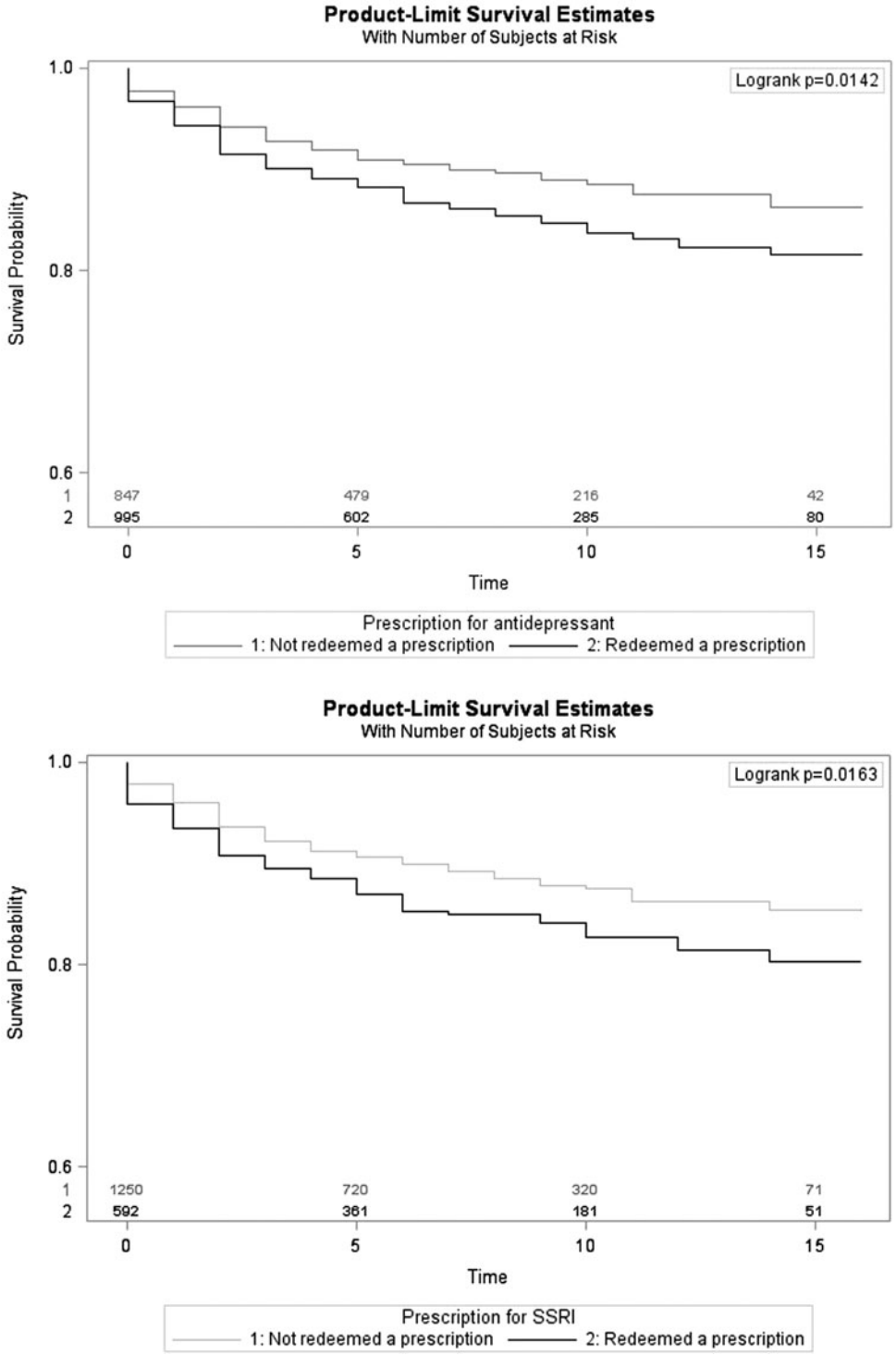

Fig. 2. Risk of repeated suicide attempt and antidepressants.

pattern, but the prescription group was more likely to make a repetition at any time during the follow-up period. Similar results were seen for redeemed prescriptions for only SSRIs (also shown in Fig. 2). After 1.5 years, the risk of repetition in the next period of time seemed to be approximately the same in the SSRI group and the group redeeming no SSRI prescriptions (the two curves are parallel and have similar slopes).

Cox regression models

In Table 1, the risk of repetition is shown as HRs. In the simplest model (crude estimate), the association between 'any antidepressant' (or 'only SSRIs') and the risk of repetition was significantly higher for those redeeming a prescription; this was seen in all models (HR: 1.38 to 1.81). The crude estimates were not

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Table 1. Estimates of hazard ratio on repetition of suicide attempts, by structure and type of model

	Structure 1[a]		Structure 2[b]		Structure 3[c]	
Crude estimate (model 1)	HR	CI	HR	CI	HR	CI
Antidepressant ($n = 995$)	1.39*	(1.05–1.85)	1.81**	(1.36–2.40)	1.56*	(1.20–2.07)
Adjusted estimate (model 2)						
Antidepressant ($n = 995$)	0.87	(0.62–1.22)	1.25	(0.89–1.76)	1.08	(0.79–1.48)
Propensity score estimate (model 3)						
Antidepressant ($n = 995$)	0.96	(0.69–1.34)	1.38	(0.99–1.92)	1.13	(0.83–1.55)
Crude estimate (model 1)						
SSRI ($n = 592$)	1.38*	(1.05–1.82)	1.75**	(1.33–2.31)	1.79*	(1.32–2.43)
Adjusted estimate (model 2)						
SSRI ($n = 592$)	0.97	(0.71–1.33)	1.26	(0.91–1.73)	1.31	(0.94–1.82)
Propensity score estimate (model 3)						
SSRI ($n = 592$)	1.02	(0.75–1.39)	1.35	(0.99–1.84)	1.35	(0.97–1.88)

*$p < 0.01$, **$p < 0.0001$.
[a]Antidepressant included as static dichotomous covariate.
[b]Antidepressant included as time-dependent dichotomous covariate.
[c]Antidepressant included as dynamic time-dependent dichotomous covariate.

controlled for possible confounders, and this could have biased the estimated association. In all advanced models (models 2 and 3), the HR was above 1, and the redeeming group was thus more likely to make a repetition. When model 2 was used, 'any antidepressant' and 'only SSRIs' showed similar risk level, with an increased risk around 30% (HR≈1.30). When model 3 was used, 'only SSRIs' showed slightly higher risk (HR≈1.30) for repetition compared to 'any antidepressant' (HR≈1.10). Therefore, model 3 was representing the real world the best. In model 2 (adjusted estimate) and model 3 (propensity score estimates), the association became statistically insignificant in all models.

The same confounders were included in both the adjusted models of 'any antidepressant' and the adjusted models of 'only SSRIs', and they showed similar estimates. Therefore, we report only the HR estimates based on the 'any antidepressant' models (Table 2).

Table 2 includes estimates of HRs for all other factors (confounders). The factors can be divided into two domains: demographic conditions and treated mental illness. Only a few of the demographic factors are significant, the most important being that individuals with the lowest income have the highest risk, HR 1.98, CI (1.38–2.82). Not all mental illness factors were significant in the adjusted analysis, but contact to a psychiatric department during follow-up tripled the risk, HR 3.09, CI (2.00–4.77), use of SSRIs prior to the index attempt increased the risk, HR 1.53, CI (1.02–2.31), use of antipsychotics before the index attempt increased the risk, HR 1.51 (CI 1.02–2.31), and use of anxiolytics during follow-up increased the risk of repetition, HR 1.68, CI (1.19–2.36). All these factors were statistically significant, although with relatively wide CIs.

The likelihood of redeeming a prescription for antidepressants or SSRIs during follow-up (the propensity score) was estimated, and both means and standard deviations of the redeeming and non-redeeming groups are reported in Table 3.

As expected, the likelihood for redeeming a prescription was higher in the redeeming groups. Both redeeming and non-redeeming individuals were, in every propensity score, matched with groups using 'any antidepressant' and 'only SSRIs' (not shown). Therefore, the propensity score approach was appropriate and balanced.

Discussion

Key findings

This study included 1842 individuals registered with one validated suicide attempt in the period 2012–2015. The risk of repetition was estimated to be 17.69% and was highest in the period just after the index attempt. In the crude model, 'any antidepressant' (and 'only SSRIs') were statistically significant risk factors for repetition, but this was not seen in any of the adjusted models (adjusted or propensity score matched). One demographic factor increased the risk significantly (low income), and some mental health factors increased the risk significantly (contact to psychiatric department during follow-up, use of antipsychotics before the index event and use of anxiolytics during follow-up). The results were consistent across the different models and very similar for 'any antidepressant' and 'only SSRIs'.

Comparison with the literature

We found a high risk of repetition in the period after a suicide attempt. Other studies have also found similar results (Christiansen & Jensen, 2007; Owens, Horrocks, & House, 2002). In this high-risk period, the individuals are very vulnerable and in serious need of treatment, support and monitoring to prevent repetition. It might be possible to support and treat these individuals as all individuals had received somatic treatment for the suicide attempt, and some had also received psychiatric treatment and are, therefore, known to the medical staff.

The crude estimates indicated that redeeming a prescription for SSRIs or other types of antidepressant drugs might be a proxy for high risk of repetition. The risk of repetition was estimated to be approximately 50% higher for those redeeming a prescription compared to those not redeeming a prescription in the follow-up period. This group might have more severe symptoms

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Table 2. Adjusted model estimates of hazard ratio

Adjusted model estimates[a]	HR	CI
Having a child ($n = 345$)	0.72	(0.48–1.08)
Living alone ($n = 797$)	1.04	(0.78–1.40)
Age:		
10-29 years ($n = 818$)	0.84	(0.59–1.19)
30-49 years ($n = 551$) (bl)	1.00	–
>50 years ($n = 473$)	0.73	(0.49–1.09)
Sex:		
Male ($n = 681$) (bl)	1.00	–
Female ($n = 1161$)	1.34	(0.99–1.82)
Income:		
Lowest third ($n = 586$)	1.98*	(1.38–2.82)
Middle third (bl) ($n = 587$) (bl)	1.00	–
Highest third ($n = 586$)	1.41	(0.93–2.13)
Unknown ($n = 83$)	1.55	(0.73–3.29)
Psychiatric contacts prior:		
No contact ($n = 794$) (bl)	1.00	–
Within two years ($n = 243$)	1.44	(0.90–2.30)
More than two years ($n = 805$)	1.25	(0.84–1.88)
Psy. contacts in follow-up ($n = 1344$)	3.09**	(2.00–4.77)
SSRI pre. ($n = 563$)	1.53*	(1.02–2.31)
Antidepressant pre. ($n = 853$)	0.70	(0.44–1.23)
Hypnotics, sedatives pre ($n = 422$)	1.21	(0.84–1.75)
Anxiolytic pre. ($n = 404$)	0.80	(0.55–1.17)
Antipsychotic pre. ($n = 527$)	1.51*	(1.02–2.31)
Hypnotics, sedatives in follow-up ($n = 500$)	0.91	(0.63–1.28)
Anxiolytic in follow-up ($n = 447$)	1.68*	(1.19–2.36)
Antipsychotics in follow-up ($n = 756$)	1.40	(0.98–1.99)

*$p < 0.01$, **$p < 0.0001$.
[a]Antidepressant included as dynamic time-dependent dichotomous covariate.

Table 3. Probability for redeeming prescription during follow-up

	#	Mean	Std. Dev.	Min.	Max.
Any antidepressant					
Yes	995	0.67	0.22	0.11	0.94
No	847	0.39	0.22	0.10	0.92
Only SSRI					
Yes	592	0.45	0.21	0.08	0.75
No	1250	0.26	0.17	0.06	0.75

of mental illness, be more ill or more vulnerable and, therefore, at higher risk of repetition. Consequently, the association between treatment with antidepressants and risk of repetition might not be causal. We found some indication of this, as the antidepressant factors became statistically insignificant when controlling for baseline risk of repetition. Similar findings have previously been reported in a literature review (Beghi et al., 2013), and Dragioti and colleagues explain the findings by an absence of reduction in depressive symptoms in young people treated with antidepressants (Dragioti et al., 2019). The association with any type of antidepressant might be slightly different from that based on 'only SSRIs', as the baseline risk of repetition might be different for the two populations using 'any antidepressant' and 'only SSRIs'. SSRIs are typically chosen for medical treatment of the first episode of depression, and the baseline risk of repetition might be higher in this group, which can explain the slightly higher risk in the exposure group.

The lack of statistical significance in the adjusted and propensity score matched analyses might partly be explained by the use of a mixed-age cohort. While previous studies have shown that young people tend to have a higher risk of suicidal behaviour in the period after starting antidepressant treatment (SSRIs and SNRIs), a similar risk is not found in adults (Dragioti et al., 2019; Sharma et al., 2016). In this study, these two opposing effects might have offset each other.

We used prescriptions of psychopharmacological drugs as proxies for diagnoses of mental illnesses and contact to a psychiatric department as confounders for severity and high suicidal risk in individuals with mental illness. Studies have found that anxiety, depression, emotionally unstable personality disorder and schizophrenia are some of the diagnoses that tend to increase the risk of suicide attempt and repetition (Christiansen & Jensen, 2007; Christiansen & Larsen, 2012; Hawton, Saunders, Topiwala, & Haw, 2013). Controlling for these diagnoses might have reduced bias in estimates. The calculated models showed statistically significant risk effects from medical treatment with antipsychotics and anxiolytics. These factors might be a measure of the severity of mental illness or high-risk diagnoses and, therefore, be more correlated with the repetition of the suicide attempt. In this study, the strongest risk factor was psychiatric contact in the follow-up period, which might be a proxy for present mental illness. These individuals are at high risk of repetition, and they need support, treatment and risk assessment. Including these factors in the model will control for part of the baseline risk of repetition of the suicide attempt.

Confounding by indication

Individuals redeeming a prescription for antidepressant drugs might have a higher baseline risk of repetition of suicide attempts, as they might be more ill and vulnerable. We included factors describing the baseline risk in order to get unbiased estimates, but this method might be insufficient (Bosco et al., 2010). We had access to information on contacts to mental departments, which is likely to include more severe mental illness. Still, we also had information on redeemed prescriptions for antidepressants prior to a suicide attempt, which could have included less severe mental illness, as such prescriptions are likely to have been given by GPs. We believe that this information is vital to control for confounding by indication. Including individuals who have redeemed prescriptions for antidepressants prior to a suicide attempt might have biased the cohort to a less or more risky cohort, but excluding them would have had more disadvantages. Therefore, we statistically controlled for redeeming prescriptions for antidepressants prior to a first suicide attempt. We have included a large range of factors in our efforts to control for confounding by indication; all factors are related to risk of repetition and redeeming prescriptions for antidepressants during

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follow-up. There is a risk that this adjustment could have removed important variations from redeemed antidepressant prescriptions during follow-up, and this might explain our finding of insignificant effects from antidepressants on the risk of the repeated suicide attempt. A good alternative would be a clinical trial study, where individuals were randomised into treatment with antidepressants after a suicide attempt and then followed for a period in order to estimate treatment effects and risk of suicide behaviour. Still, long-term effects are difficult to analyse in a clinical trial setup, as individuals are needed to be followed prospectively for a long time, and high numbers of individuals are needed to get sufficient statistical power. The RCT design will also raise some issues that will make it difficult to complete the study. We used the propensity score approach as an alternative to a randomised clinical trial, in which it is possible to analyse long-term effects such as suicide attempts in a large population. This design allows us to compare individuals redeeming antidepressant prescriptions during follow-up with individuals not redeeming prescriptions, but we can only compare individuals with the same probability for redeeming (matched on propensity score). This balancing is similar to that induced by randomisation in RCT studies, but the propensity score approach balances only measured covariates (and not unmeasured covariates as randomisation can do). Therefore, the data might not be balanced perfectly, which could have biased the results. We have included confounding variables to model the propensity score, which is a method that performs well (Austin, Xin Yu, Vyas, & Kapral, 2021). The propensity score approach is a good alternative to a randomised clinical trial and is described in more detail in the paper by E. Williamson and colleagues (Williamson, Morley, Lucas, & Carpenter, 2012).

Strengths and limitations

This study included only validated suicide attempts. For each suicide attempt, the hospital records have been reviewed, and it has been validated that the event fulfils the WHO definition of a suicide attempt (Christiansen & Jensen, 2004). Suicides were not considered as a follow-up repetition, as suicide and repetition of suicide attempts might be two different types of suicidal behaviour, with different pathology. Including suicide as an outcome might have biased effects from antidepressants on the risk of repetition. The study was based on register data of high quality without recall bias. It includes data from many different registers, which ensured the inclusion of relevant variables and made it possible to censor individuals from the study at the correct time of the censoring event. Therefore, we expect the follow-up time to have been estimated correctly, which reduced the risk of bias in the estimates of survival curves and HRs. The accessible time unit was a quarter of a year, which is a relatively large unit of time. Therefore, it was not possible to analyse details about time correlation within a quarter. This does not affect the overall temporal context in the study, but HRs and survival curves are estimated more roughly.

If treatment for a suicide attempt was given outside the catchment area of the included regional hospitals, the suicide attempt was not registered in our data and, therefore, not included in this study. We expect this to be a minor problem. An additional limitation was that it was not possible to include suicide attempts treated by general practitioners.

Conclusion

In this study, we found a higher risk of repeated suicide attempt in individuals redeeming an antidepressant prescription. However, the association became statistically insignificant when we controlled for baseline risk. This was done by two different methods, which showed similar results. Our study could not confirm the hypothesis that antidepressants or SSRIs are strongly associated with increased risk of repeated suicide attempts. The authors are aware of the limitations of this study and the potential impact on the results. Therefore, it is important that the results are confirmed in other studies. This study is adding to the literature, as it confirms that antidepressant use after a suicide attempt is correlated with increased risk of repetition. Our study indicates that the risk is not higher than the risk of repetition seen in individuals at baseline, but the limitations of the study make it necessary to repeat the study to confirm the results. Present and severe psychiatric problems or very low income seems to increase the risk of repetition the most. Therefore, systematic risk assessment and treatment of mental illness should be conducted; this is especially important in the period immediately after a suicide attempt.

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References

Allison, P. D. (2010). *Survival analysis using SAS: A practical guide*. Cary, NC: SAS Institute Inc.

Austin, P. C., Xin Yu, A. Y., Vyas, M. V., & Kapral, M. K. (2021). Applying propensity score methods in clinical research in neurology. *Neurology*, *97* (18), 856–863. doi:10.1212/WNL.0000000000012777

Baadsgaard, M., & Quitzau, J. (2011). Danish registers on personal income and transfer payments. *Scandinavian Journal of Public Health*, *39*(Suppl 7), 103–105. doi:10.1177/1403494811405098

Beghi, M., Rosenbaum, J. F., Cerri, C., & Cornaggia, C. M. (2013). Risk factors for fatal and nonfatal repetition of suicide attempts: A literature review. *Neuropsychiatric Disease and Treatment*, *9*, 1725–1736. doi:10.2147/NDT.S40213

Bille-Brahe, U. (1998). Suicidal behaviour in Europe. The situation in the 1990s. Retrieved from https://www.euro.who.int/__data/assets/pdf_file/0007/239938/E60709.pdf.

Bosco, J. L., Silliman, R. A., Thwin, S. S., Geiger, A. M., Buist, D. S., Prout, M. N., … Lash, T. L. (2010). A most stubborn bias: No adjustment method fully resolves confounding by indication in observational studies. *Journal of Clinical Epidemiology*, *63*(1), 64–74. doi:10.1016/j.jclinepi.2009.03.001

Centre for Suicide Research. (2022). Register for Suicide and Suicide Attempt. Retrieved from http://statistik.selvmordsforskning.dk/.

Christiansen, E., Agerbo, E., Bilenberg, N., & Stenager, E. (2016). SSRIs and risk of suicide attempts in young people – A Danish observational register-based historical cohort study, using propensity score. *Nordic Journal of Psychiatry*, *70*(3), 167–175. doi:10.3109/08039488.2015.1065291

Christiansen, E., & Jensen, B. F. (2004). Register for suicide attempts. *Danish Medical Bulletin*, *51*(4), 415–417.

Christiansen, E., & Jensen, B. F. (2007). Risk of repetition of suicide attempt, suicide or all deaths after an episode of attempted suicide: A register-based survival analysis. *Australian and New Zealand Journal of Psychiatry*, *41*(3), 257–265. doi:10.1080/00048670601172749

Christiansen, E., & Larsen, K. J. (2012). Young people's risk of suicide attempts after contact with a psychiatric department – a nested case-control design using Danish register data. *Journal of Child Psychology and Psychiatry*, *53* (1), 16–25. doi:10.1111/j.1469-7610.2011.02405.x

Dragioti, E., Solmi, M., Favaro, A., Fusar-Poli, P., Dazzan, P., Thompson, T., … Evangelou, E. (2019). Association of antidepressant use with adverse health

outcomes: A systematic umbrella review. *Journal of the American Medical Association Psychiatry*, *76*(12), 1241–1255. doi:10.1001/jamapsychiatry.2019.2859

Hawton, K., Saunders, K., Topiwala, A., & Haw, C. (2013). Psychiatric disorders in patients presenting to hospital following self-harm: A systematic review. *Journal of Affective Disorders*, *151*(3), 821–830. doi:10.1016/j.jad.2013.08.020

Hengartner, M. P., Amendola, S., Kaminski, J. A., Kindler, S., Bschor, T., & Ploderl, M. (2021). Suicide risk with selective serotonin reuptake inhibitors and other new-generation antidepressants in adults: A systematic review and meta-analysis of observational studies. *Journal of Epidemiology and Community Health*, *75*, 523–530. doi:10.1136/jech-2020-214611

Hetrick, S. E., McKenzie, J. E., Bailey, A. P., Sharma, V., Moller, C. I., Badcock, P. B., … Meader, N. (2021). New generation antidepressants for depression in children and adolescents: A network meta-analysis. *Cochrane Database of Systematic Reviews*, *5*(5). doi:10.1002/14651858.CD013674.pub2

Jakobsen, J. C., Katakam, K. K., Schou, A., Hellmuth, S. G., Stallknecht, S. E., Leth-Moller, K., … Gluud, C. (2017). Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and trial sequential analysis. *Boston Medical Center Psychiatry*, *17*(1), 58. doi:10.1186/s12888-016-1173-2

Kildemoes, H. W., Sorensen, H. T., & Hallas, J. (2011). The Danish national prescription registry. *Scandinavian Journal of Public Health*, *39*(Suppl 7), 38–41. doi:10.1177/1403494810394717

Mayer-Gross, W., Slater, E., & Roth, M. (1960). *Clinical psychiatry* (2nd ed.). London: Bailliére, Tindall & Cassell.

Owens, D., Horrocks, J., & House, A. (2002). Fatal and non-fatal repetition of self-harm. Systematic review. *British Journal of Psychiatry*, *181*, 193–199. doi:10.1192/bjp.181.3.193

Pedersen, C. B. (2011). The Danish civil registration system. *Scandinavian Journal of Public Health*, *39*(Suppl 7), 22–25. doi:10.1177/1403494810387965

Ranganathan, P., & Aggarwal, R. (2019). Study designs: Part 3 – analytical observational studies. *Perspectives in Clinical Research*, *10*(2), 91–94. doi:10.4103/picr.PICR_35_19

Schmidt, M., Schmidt, S. A., Sandegaard, J. L., Ehrenstein, V., Pedersen, L., & Sorensen, H. T. (2015). The Danish national patient registry: A review of content, data quality, and research potential. *Clinical Epidemiology*, *7*, 449–490. doi:10.2147/CLEP.S91125

Sharma, T., Guski, L. S., Freund, N., & Gotzsche, P. C. (2016). Suicidality and aggression during antidepressant treatment: Systematic review and meta-analyses based on clinical study reports. *British Medical Journal*, *352*. doi:10.1136/bmj.i65

Sinclair, L. I., Christmas, D. M., Hood, S. D., Potokar, J. P., Robertson, A., Isaac, A., … Davies, S. J. (2009). Antidepressant-induced jitteriness/anxiety syndrome: Systematic review. *British Journal of Psychiatry*, *194*(6), 483–490. doi:10.1192/bjp.bp.107.048371

Stone, M., Laughren, T., Jones, M. L., Levenson, M., Holland, P. C., Hughes, A., … Rochester, G. (2009). Risk of suicidality in clinical trials of antidepressants in adults: Analysis of proprietary data submitted to US food and drug administration. *British Medical Journal*, *339*, b2880. doi:10.1136/bmj.b2880

Wijlaars, L. P., Nazareth, I., Whitaker, H. J., Evans, S. J., & Petersen, I. (2013). Suicide-related events in young people following prescription of SSRIs and other antidepressants: A self-controlled case series analysis. *British Medical Journal Open*, *3*(9), e003247. doi:10.1136/bmjopen-2013-003247

Williamson, E., Morley, R., Lucas, A., & Carpenter, J. (2012). Propensity scores: From naive enthusiasm to intuitive understanding. *Statistical Methods in Medical Research*, *21*(3), 273–293. doi:10.1177/0962280210394483

Witt, K. G., Hetrick, S. E., Rajaram, G., Hazell, P., Taylor Salisbury, T. L., Townsend, E., & Hawton, K. (2021). Pharmacological interventions for self-harm in adults. *The Cochrane Database of Systematic Reviews*, *1*(1).

World Health Organization. (1986). Working Group on Preventive Practices in Suicide and Attempted Suicide, York, 22-26 September 1986. WHO Regional Office for Europe. Copenhagen.

Zimmerman, M., Clark, H. L., Multach, M. D., Walsh, E., Rosenstein, L. K., & Gazarian, D. (2015). Have treatment studies of depression become even less generalizable? A review of the inclusion and exclusion criteria used in Placebo-controlled antidepressant efficacy trials published during the past 20 years. *Mayo Clinic Proceedings*, *90*(9), 1180–1186. doi:10.1016/j.mayocp.2015.06.016