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Use of antidepressants and risk of repeat self-harm in older adults 75+ with nonfatal self-harm: A 1-year prospective national study

Khedidja Hedna^{1,2} | Chiara Montuori³ | Alberto Forte³ | Maurizio Pompili³ | Margda Waern^{1,4}

¹Department of Psychiatry and Neurochemistry, AgeCap Center, Gothenburg University, Gothenburg, Sweden

²Statistik konsulterna AB, Gothenburg, Sweden

³Department of Neurosciences, Mental Health and Sensory Organs, Suicide Prevention Center, Sant'Andrea Hospital, Sapienza University, Rome, Italy

⁴Region Västra Götaland, Sahlgrenska University Hospital, Psychosis Clinic, Mölndal, Sweden

Correspondence

Khedidja Hedna, Department of Psychiatry and Neurochemistry, AgeCap Center, Gothenburg University, Gothenburg SE-413 45, Sweden.
Email: khedidja.hedna@neuro.gu.se

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Abstract

Purpose: To assess exposure to antidepressants (AD) before and after nonfatal self-harm (SH) in older adults and to examine 1-year rates and risk factors for subsequent SH.

Methods: Longitudinal national register-based retrospective cohort study of Swedish residents aged 75+ ($N = 2775$) with treatment at hospital or specialist outpatient clinic in connection with SH between January 1, 2006, and December 31, 2013. The cohort was followed for 1 year after the index episode. Exposure to AD was assessed at index and at subsequent SH. Cox regression analysis was used to assess factors associated with 1-year repeat SH.

Results: At the index episode, 51% were prevalent AD users; 23% started AD during the following year. Overall 12% of prevalent AD users, 8% of AD nonusers, and 6% of AD new users repeated SH or died by suicide. About two-thirds of these subsequent behaviors occurred within 3 months after the index episode. Men had increased risk of subsequent SH (Hazard ratio [HR] 1.38, 95% CI: 1.09–1.74); older age (>85 years) was associated with a lower risk (HR 0.72, CI 95% 0.55–0.93). Users of AD did not have an increased risk of repeat SH.

Conclusions: Half of older adults who self-harmed were prevalent AD users and a further one fourth started an AD within 1 year after the index SH. Antidepressant use was not associated with increased risk of subsequent SH in this high-risk cohort of older adults.

KEYWORDS

antidepressants, older people, register-based research, repetition of self-harm, suicide

1 | INTRODUCTION

Adults aged 75 and over have high suicide rates compared to younger age groups in many countries around the globe.¹ A previous episode of self-harm (SH) is considered a major risk factor for subsequent suicide in older adults.² Older people who SH were found to have a

stronger intent to die than their younger counterpart.³ In addition, SH is more often lethal in older adults due to a tendency to use more violent methods, especially in men.⁴

Older adults who die by suicide are often depressed, and the identification and treatment of depression is a major suicide prevention strategy in this age group.⁵ Surprisingly, the relationship between

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AD use and repeated SH in late-life was rarely studied,⁶ although older adults who SH constitute a group with high consumption of AD and a particularly high risk of subsequent SH.⁷ Some studies have suggested an increased risk of repetition of SH in those who were treated by AD at time of index SH,⁶ or at early stage after initiation of AD following the SH episode.⁸ However, the few studies that have examined repetition of SH in older adults have tended to include small and selective samples,^{9–13} or covered a wide age range including individuals in their 60's.^{4,14} Extrapolating results from the younger old group (65+) to the oldest segment of the population (75+) may not be appropriate, as medication use patterns, treatment response and side effects may differ due to higher levels of psychiatric and somatic comorbidities in the older group, as well as age-related physiological changes.¹⁵ Population-based studies provide a useful context to examine risk of fatal and nonfatal SH in the general population with enough power and with limited risk of inclusion bias.

The aim of the current study was to assess exposure to antidepressants (AD) in older adults aged 75 and above who self-harmed and to examine rates and risk factors for SH repetition by antidepressant use status within 1 year after the index SH episode.

2 | METHODS

2.1 | Study design and study population

We conducted a national register-based retrospective cohort study in all Swedish residents aged 75+ with an episode of SH with presentation at any hospital or specialized healthcare service between January 1, 2006 and December 31, 2013. We followed individuals for 1 year after the index SH episode to investigate the repeat of SH: nonfatal SH or suicide. Individuals were censored in case of death during the follow-up time.

Prevalent users of AD were defined as those who were already on AD during the year preceding the index SH episode. New users of AD were defined as those who redeemed an AD after the SH episode, with no fills for any AD during the year prior the index SH episode. The 1-year period was selected to allow a sufficiently long wash out period prior to the index antidepressant prescription.

2.2 | Data sources

Multiple national registers were linked using the unique personal identity number.¹⁶ The National Patient Register was used to identify individuals with episodes of nonfatal SH. This register includes diagnoses for specialized inpatient and outpatient psychiatric and somatic healthcare based on the International Classification of Diseases, 10th version (ICD-10).¹⁷ It was also used to identify individuals with depression requiring specialized healthcare (ICD 10 codes: F31.3-F31.6 and F32-F33). These persons were considered to have serious depression, as those with less serious psychopathology are treated in primary care in Sweden.¹⁸ The Swedish Prescribed Drug Register (SPDR) was used to identify AD users and

patterns of prescription drug use, for both ADs and other psychotropic medications.¹⁹ The SPDR has full coverage of filled prescriptions in outpatient care and in residential institutions. Data on the cause of death, including suicide, were collected from the Cause of Death Register.²⁰ Sociodemographic data for the year preceding the entrance to the cohort were collected from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) and the Total Population Register, held by Statistics Sweden. Persons residing in institutions were identified from the Care and Social Services Register.

2.3 | Sociodemographic factors

Patient characteristics included sex, age group (75–79, 80–84, 85–89, and >90 years), and marital status (married, single, divorced, and widow/widower). Country of birth was grouped into three categories: Sweden, other Nordic countries, and outside Nordic countries.

2.4 | Medication use patterns

Antidepressants were defined as substances included in the Anatomic Therapeutic Class N06A. We grouped them into major classes: selective serotonin reuptake inhibitors (SSRIs; N06AB), serotonin-norepinephrine reuptake inhibitors and noradrenergic and specific serotonergic AD (SNRIs/NaSSA; N06AX), and tricyclic AD (TCAs; N06AA).

The psychoactive medications were classified as: antipsychotics (N05A, except Lithium (N05AN01), which is used as a mood stabilizer), anxiolytics (N05B), hypnotics (N05C), and anti-dementia drugs (N06D). Their use was assessed within 90 days prior the index SH and repeat episode. This period was chosen based on the Swedish Pharmaceutical Benefits Scheme, by which patients can purchase 3 months' supply and in practice, packages of approximately 100 units are often dispensed.

2.5 | Outcome measure

Study outcomes were (a) a new episode of nonfatal SH (identified from the national patient register), (b) suicide (identified by the Cause of Death Register for suicide, and (c) either nonfatal SH or suicide. The composite outcome (c) was employed in the regression analyses to provide sufficient power. SH methods were categorized into nonviolent (poisoning; ICD-10: X60-X69), and violent methods (including use of sharp objects, hanging and drowning; ICD-10: X70-X82), and other/undetermined (X83-X84).

2.6 | Statistical analysis

We used Cox logistic regression to assess factors associated with the repeat of SH in the total cohort and based on AD use. Persons were

censored if they died of causes other than suicide during the 1-year follow-up time. In order to avoid an immortal bias, the follow-up time started at index SH episode for all groups and the antidepressant use status was assessed both at index SH and at the time of the repeat SH episode. For those with more than one episode of SH during the study period, the first one was considered in the regression and the AD use exposure assessed. We calculated the 95% confidence interval and the *p*-value. The independent variables included in the regression model were selected based on the previous associations found with SH in the 75+ population.^{18,21} We considered gender, age group (75–85 and >85), use of AD, use of specialized healthcare for depression as a marker of serious depression. Milder forms of depression are treated within primary care in Sweden while more serious cases are referred to specialized care.²² The use of anxiolytics or hypnotics was also considered as they were associated with SH in our recent study among new users of AD.²³ The method of index SH was included as violent methods were found to be associated with increased risk of suicide.⁴ The robustness of the multivariable Cox regression model was explored by using the forward stepwise selection process. Statistical analysis was performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

No consent was required from patients as the study was based solely on national register data. All data were matched by Statistics Sweden and analyzed anonymously. The study was approved by the Regional Ethical Review Board in Gothenburg (approval number: 111-15).

3 | RESULTS

3.1 | Characteristics of individuals with SH episodes and use of AD

Overall, 2775 persons aged 75 years and over had a nonfatal SH episode during the observation period. Among them, 1419 (51%) were prevalent users of AD (Table 1). Users of AD were younger, more often women, tended to have concomitant treatment with other psychoactive drugs, and had greater use of specialized care for depression compared to those who were not AD users at the time of the index SH episode. Furthermore, 644 (23%) started treatment with an AD during the year following the SH episode.

3.2 | Repeated SH

A total of 303 (11%) individuals (153 women and 150 men) repeated SH (nonfatal SH or suicide) within 1 year after the index episode; 188 (62%) used poisoning, while 104 (34%) used violent methods. The repeated SH occurred in a median time of 53 days after the index SH. The first subsequent episode occurred within 3 months in two-thirds (*n* = 194) of those who repeated SH. Four out of five (*n* = 241) repeated within 6 months after the index SH.

Repeat SH was observed in 170 (12%) of those who were prevalent users of AD, in 96 (8%) of those who were not on AD, and in 37 (6%) of those who were new users of AD. Noteworthy, 44 initiated an AD after a new SH episode. Overall, 72 (3%) died of suicide (43 (3%) in prevalent users of AD, 19 (3%) in nonusers of AD, and 10 (2%) in the AD new users). In addition, 478 persons (17%) died of causes other than suicide, and 13% of all of the deaths registered in this cohort were suicides.

3.3 | Use of AD

The most frequently prescribed AD were mirtazapine and citalopram. Mirtazapine was more commonly prescribed in those who initiated an AD after the SH episode compared to the prevalent AD users (Table 2). Three-fourths initiated their AD treatment within 3 months after the index SH episode. Four out of 10 initiated their AD therapy within psychiatric or substance use services; for about one third, the treatment was started in primary care (Table 3).

3.4 | Factors associated with repeat Self-harm

In the total cohort, men had increased risk of repeated SH (hazard ratio (HR) 1.38, 95% CI: 1.10–1.75; Table 4 and Figure 1). Use of specialized care for depression (HR 1.26, 95% CI 0.96–1.66) showed associations of similar magnitude and confidence. Users of AD did not have an increased risk of repeated SH compared to the nonusers. Most associations were no longer significant in the AD use subgroup analyses, which could be related to the relatively small number of cases, especially the group of AD new users.

The forward stepwise regression confirmed that men have significantly increased risk for repeat SH.

4 | DISCUSSION

In this national cohort of adults aged 75 years and above, half of those who self-harmed were on AD, and about one-fourth initiated AD treatment within a year after the index SH episode. Two-thirds repeated SH within 3 months. The 1-year repeat rate was the lowest in those who initiated an AD after the SH episode. Use of AD was not associated with increased risk of repeated suicidal behavior. Increased risk for repeated SH was found in men.

We could not find studies investigating the reoccurrence of SH in the general 75+ population with and without AD use for comparison. The proportion of repeat SH in our 75+ population was within the range (7.9%) of a small Swedish cohort of hospitalized suicide attempters aged 70+,¹³ and similar to the rate (12.8%) observed in a British clinical cohort,⁴ and a hospital-based study in New Zealand,⁶ conducted in older adults with a lower mean age.

TABLE 1 Baseline characteristics of adults aged 75+ with self-harm episode by antidepressant use status

Characteristics	Total N (%)	AD user N (%)	Non-AD user N (%)	P-value
Number of individuals	2775	1419	1356	
Age				
Age: median (range)	82,0 (75,0;103)	82,0 (75,0;100)	83,0 (75,0;103)	<0.001 ^a
75–79	893 (32)	517 (36)	376 (28)	
80–84	909 (33)	491 (35)	418 (31)	
85–89	643 (23)	288 (20)	355 (26)	
90+	330 (12)	123 (9)	207 (15)	
Gender				
Female	1573 (57)	902 (64)	671 (49)	<0.001 ^b
Marital status				
Married	1084 (39)	545 (38)	539 (40)	0.16 ^c
Single	203 (7)	93 (6.6)	110 (8.1)	
Divorced	434 (16)	238 (17)	196 (14)	
Widow/widower	1050 (38)	542 (38)	508 (37)	
Country of birth				
Sweden	2417 (87)	1251 (88)	1166 (86)	0.21 ^c
Other Nordic country	170 (6)	82 (6)	88 (7)	
Outside Nordic countries	188 (7)	86 (6)	102 (8)	
Residence in long-term care facility	67 (2)	45 (3)	22 (2)	0.01 ^b
Specialized care for depression ^d	653 (24)	577 (41)	76 (6)	<0.001 ^b
Use of other psychoactive medications				
Hypnotics	1679 (61)	987 (70)	692 (51)	<0.001 ^b
Zopiclone	923 (33)	570 (40)	353 (26)	<0.001 ^b
Zolpidem	391 (24)	221 (16)	170 (13)	<0.001 ^b
Anxiolytics	1101 (40)	796 (56)	305 (22)	<0.001 ^b
Oxazepam	744 (27)	536 (38)	208 (15)	<0.001 ^b
Diazepam	180 (6)	131 (9)	49 (4)	<0.001 ^b
Antipsychotics	283 (10)	207 (15)	76 (6)	<0.001 ^b
Anti-dementia drugs	71 (3)	49 (4)	22 (2)	0.002 ^b
Method of self-harm				
Nonviolent	2222 (80)	1159 (82)	1063 (78)	0.03 ^b
Violent	478 (17)	233 (16)	245 (18)	0.25 ^b
Other/non-determined	75 (2.7)	27 (2)	48 (4)	0.01 ^b

Abbreviations: AD, antidepressant; N, number of individuals in the category.

^aTwo sample *t*-test assuming unequal variance.

^bPearson's Chi²-test.

^cChi²-test for comparison between AD users and non-AD users to establish if there are differences between categories.

^dUp to 5 years before index self-harm episode.

We found no evidence of increased rate of SH in prevalent AD users, nor did we find increased risk of repeat SH in those prescribed AD after the index episode. This may be due to the close monitoring and assessment of the clinical response of older adults who SH. Furthermore, despite the active discussion on the possible causal association between AD or their adverse effects and SH,²⁴ older

adults with a previous episode of SH experienced that the benefits of antidepressant treatment outweighed the disadvantages.²⁵

Men had a significantly higher risk for repetition. Murphy et al. found that men older than 75 years had the highest risk of suicide after SH.⁴ This could in part be explained by the strong intent to die of older men who SH,²⁶ and their higher attempt lethality.²⁷ Taken

TABLE 2 Use of antidepressants^a in adults aged 75+ with a nonfatal self-harm episode

	Prevalent AD users at index SH episode	New AD users after SH episode	Use of AD at subsequent SH episode	
			Prevalent user	New user
Number of individuals	1419	644	142	27
SSRI	601 (42)	338 (52)	65 (46)	9 (33)
Citalopram	373 (26)	189 (29)	35 (25)	4 (15)
Sertraline	112 (8)	63 (10)	15 (11)	2 (7)
Escitalopram	77 (5)	80 (12)	10 (7)	3 (11)
SNRI/NaSSA	475 (34)	323 (50)	55 (39)	16 (59)
Mirtazapine	336 (24)	286 (44)	34 (24)	14 (52)
Duloxetine	34 (2)	20 (3)	6 (4)	0 (0)
TCA	94 (6)	23 (4)	6 (4)	3 (11)
Amitriptyline	64 (5)	20 (3)	2 (1)	3 (11)

Abbreviations: AD, antidepressant; SNRI/NaSSA, serotonin–noradrenaline reuptake inhibitor–noradrenaline and specific serotonergic antidepressant; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

^aGroups not mutually exclusive as some individuals were prescribed more than one antidepressant.

TABLE 3 Prescribing setting and number of days between index self-harm and initiation of antidepressant treatment in older adults aged 75+ who self-harmed (*n* = 644)

Characteristics	Number (%)
Type of healthcare facility	
Psychiatric or substance use services	256 (39.8)
Primary care	195 (30.3)
Internal medicine	98 (15.2)
Geriatric care	33 (5.1)
General inpatient or outpatient care	13 (2)
Acute and emergency care	7 (1.1)
Other	42 (7)
Time between the index self-harm and initiation of AD	
<30 days after self-harm	233 (36)
30–90 days after self-harm	236 (37)
91–365 days after self-harm	175 (27)

Abbreviation: AD, antidepressant.

together these results highlight the particularly serious prognosis of SH in men aged 75 and above. The lower risk for repeated SH in the 85+ group might be explained in part by competing mortality due to other causes. Another partial explanation might be that suicidal persons aged 85+ have a greater tendency to die on their very first act of SH due to greater degree of frailty or higher medical lethality of the index act. The association between serious depression and reoccurrence of SH in the univariate model echoes findings from younger age groups,²⁸ and advocates on the importance to adequately manage and treat serious depression to avoid the repeat of SH.²⁹

4.1 | Methodological considerations

The use of national population-based data minimizes the risk of selection bias that may potentially arise in clinical cohort studies. Cases of mild–moderate depression could not be identified as these conditions are mainly managed in primary care in Sweden and thus not included in the national patient register. This is a limitation since even milder forms of depression may be associated with both nonfatal SH,³⁰ and suicide³¹ in older adults.

We could consider important covariates for SH in our analysis. However, individual level information on overall health, depression scores, and behavioral factors such as social isolation and use of alcohol and illegal substances were not available. Due to the rarity of suicidal behavior, and despite the composite outcome, we had to limit the number of variables in the regression models, and the subgroup analyses by AD use status lacked power. We did not have information about the indication for AD use, and we can therefore not rule out confounding by indication. This could be of particular relevance for TCA, which are nowadays used mainly to treat chronic pain in Sweden. However, only a very small proportion were on TCAs, and there is, therefore, a low probability this would affect our findings. We used a strict definition of AD new users. However, we could not distinguish between those who started an AD treatment for the very first time, and those who were previously on treatment but had discontinued at least a year before the index date. Further, the SPDR does not include medications administered in a hospital setting. We do not consider this a major limitation since AD treatment initiated in hospitals will, in almost all cases, be continued after discharge and thus captured in our study. We could not assess adherence to AD based on refill data due to the high use of multidose prescribing, which automatically creates high refill adherence. Noteworthy, in our previous study that involved all AD new users aged 75+,

TABLE 4 Factors associated with the repeat self-harm in adults aged 75+ by antidepressant use status

Variable	Number ^a	Univariate HR (95 CI)	Multivariable HR ^b (95 CI)
All 75+ population			
Men (reference: Women)	150/153	1.37 (1.09–1.71)**	1.38 (1.1–1.75)**
Age >85 years (reference: 75–84 years)	79/224	0.68 (0.52–0.88)**	0.72 (0.55–0.93)*
Use of specialized care for depression (reference: No use)	92/211	1.38 (1.08–1.77)**	1.26 (0.96–1.66)
Use of antidepressants (reference: No use)	170/133	1.19 (0.95–1.49)	1.06 (0.81–1.38)
Use of anxiolytics (Reference: No use)	134/169	1.21 (0.97–1.52)	1.17 (0.92–1.51)
Use of hypnotics (Reference: No use)	183/120	0.98 (0.78–1.23)	0.96 (0.76–1.22)
Violent method of self-harm at index (reference: nonviolent)	58/245	1.23 (0.93–1.64)	1.14 (0.85–1.52)
Prevalent users of antidepressants			
Men (reference: Women)	71/99	1.34 (0.98–1.81)	1.31 (0.95–1.79)
Age >85 years (reference: 75–84 years)	32/138	0.58 (0.39–0.85)**	0.6 (0.41–0.89)*
Use of specialized care for depression (reference: No use of specialized care for depression)	83/87	1.39 (1.03–1.88)*	1.27 (0.94–1.72)
Use of anxiolytics (Reference: No use of anxiolytics)	105/65	1.3 (0.95–1.77)	1.28 (0.93–1.75)
Use of hypnotics (Reference: No use of hypnotics)	117/53	0.95 (0.68–1.31)	0.95 (0.68–1.32)
Method of self-harm at index episode (violent vs. nonviolent)	35/135	1.43 (0.98–2.07)	1.31 (0.89–1.92)
New users of antidepressants			
Men (reference: Women)	15/12	1.13 (0.52–2.46)	1.38 (0.6–3.19)
Age >85 years (reference: 75–84 years)	9/18	0.65 (0.28–1.54)	0.67 (0.26–1.76)
Use of specialized care for depression (reference: No use of specialized care for depression)	5/22	0.33 (0.1–1.15)	0.24 (0.06–0.91)*
Use of anxiolytics (Reference: No use of anxiolytics)	8/19	1.33 (0.57–3.09)	1.55 (0.64–3.75)
Use of hypnotics (Reference: No use of hypnotics)	17/10	1.24 (0.55–2.77)	1.25 (0.52–3.01)
Method of self-harm at index episode (violent vs. nonviolent)	2/25	0.76 (0.17–3.31)	0.63 (0.09–4.27)
Non users of antidepressants			
Men (reference: Women)	64/42	1.57 (1.06–2.31)*	1.52 (1.02–2.26)*
Age >85 years (reference: 75–84 years)	38/68	0.83 (0.56–1.23)	0.87 (0.58–1.29)
Use of specialized care for depression (reference: No use of specialized care for depression)	4/102	0.65 (0.24–1.77)	0.65 (0.24–1.79)
Use of anxiolytics (Reference: No use of anxiolytics)	21/85	0.86 (0.53–1.39)	0.97 (0.6–1.59)
Use of hypnotics (Reference: No use of hypnotics)	49/57	0.83 (0.56–1.21)	0.89 (0.6–1.32)
Method of self-harm at index episode (violent vs. nonviolent)	21/85	1.19 (0.74–1.93)	1.06 (0.65–1.73)

Abbreviations: AD, antidepressant; CI, confidence interval; HR, hazard ratio.

* $P < 0.05$. ** $P < 0.01$. ^aNumber of individuals in the comparison/reference group.

^bThe models included all variables considered in univariate models.

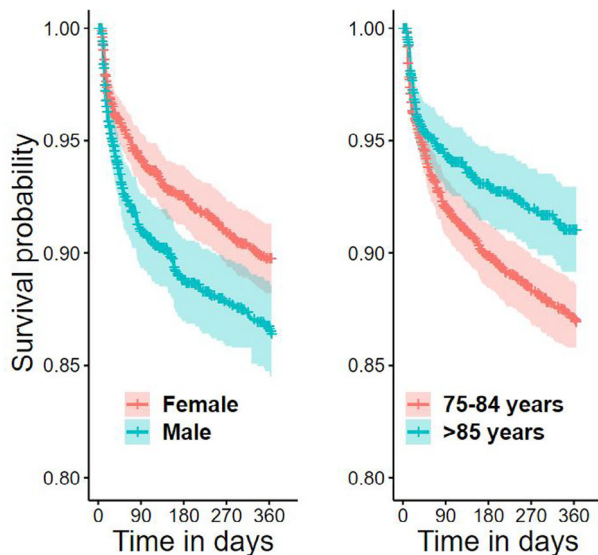


FIGURE 1 One-year survival curves from the multivariate Cox proportional hazard models* for factors significantly associated with repeat self-harm in adults aged 75+

discontinuation of AD was low, and not associated with increased risk of nonfatal SH and suicide.¹⁸

The National Patient Register does not distinguish between behavior with and without suicidal intent. This means that some non-fatal SH episodes that were identified in our study may actually have been non-suicidal SH.^{32,33} However, a Canadian study of the validity of SH ICD-10 codes to identify SH reported a fairly good positive predictive value of 75% for these codes relative to the clinical assessment. Some older adults may SH without seeking specialized healthcare, and these persons will be missed due to our study design. It is therefore possible that some older men who tend to use more lethal methods would be more likely hospitalized after SH and thus detected by our study design, while women, who in general use less lethal methods, may not present to hospital or specialized outpatient care after a SH episode. However, the inclusion of more severe cases of SH that required specialized healthcare is likely to increase the specificity of the outcome. A final consideration is that the Swedish Cause of Death register is based on death certificates, and can only capture suicides/deaths suspected to be suicides that are recorded as such by the physician who issues the death certificate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was approved by the Regional Ethical Review Board in Gothenburg (approval number: 111-15). No consent was required from patients as the study was based solely on national register data. All data were linked by Statistics Sweden and analyzed anonymously.

AUTHOR CONTRIBUTIONS

Khedidja Hedna designed and planned the study, organized data collection, participated in the statistical analysis and interpretation of the results, and drafted the manuscript. Chiara Montuori contributed to the statistical analysis, the interpretation of the results, and participated in manuscript writing. Alberto Forte and Maurizio Pompili contributed to the interpretation of the results and manuscript content. Margda Waern is the principal investigator of the project. She acquired funding and contributed to the design and planning of the study, to data collection and interpretation, and she took part in the writing of the manuscript. All authors declare that they have reviewed and approved the manuscript prior to its submission.

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