# Antidepressant use and risk of self-harm among people aged 40 years or older: A population-based cohort and self-controlled case series study

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## Summary

**Background** Studies on the association between antidepressants and self-harm in adults were mostly conducted over a decade ago and have inconsistent findings. We aimed to compare self-harm risks by antidepressant classes among people aged 40 years or older with depression.

**Methods** Individuals aged ≥40 years with depression who initiated antidepressant treatment between 2001 and 2015 were retrieved from the Hong Kong Clinical Data Analysis & Reporting system, and were followed up until December 31, 2016. We conducted self-controlled case series (SCCS) analyses to estimate the incidence rate ratio (IRR) of self-harm comparing the pre-exposure (90 days before the first antidepressant use), index exposure (the first antidepressant use), and subsequent exposure (subsequent antidepressant use) periods to nonexposed periods. We applied Cox proportional hazard regressions to estimate the hazard ratio (HR) of self-harm comparing five antidepressant classes (tricyclic and related antidepressant drugs [TCAs], selective serotonin reuptake inhibitors [SSRIs], noradrenergic and specific serotonergic antidepressants [NaSSAs], serotonin−norepinephrine reuptake inhibitors [SNRIs], and others).

**Findings** A total of 48,724 individuals were identified. SCCS analyses (N = 3,846) found that the increased self-harm risk occurred during the pre-exposure (IRR: 22.24; 95% CI, 20.25-24.42), index exposure (7.03; 6.34-7.80), and subsequent exposure periods (2.47; 2.18-2.79) compared to the unexposed period. Cohort analyses (N = 48,724) found an association of higher self-harm risks in short-term (one year) for NaSSAs vs. TCAs (HR, 2.13; 95% CI, 1.53-2.96), SNRIs vs. TCAs (1.64; 1.01-2.68), and NaSSAs vs. SSRIs (1.75; 1.29-2.36) in the 40-64 years group. The higher risk remained significant in long-term (> one year) for NaSSAs vs. TCAs (1.55; 1.26-1.91) and NaSSAs vs. SSRIs (1.53; 1.26-1.87). In the 65+ group, only short-term differences were observed (SSRIs vs. TCAs [1.31; 1.03-1.66], SNRIs vs. SSRIs [0.44; 0.22-0.87], and SNRIs vs. NaSSAs [0.43; 0.21-0.87]).

**Interpretation** Within-person comparisons did not suggest that antidepressant exposure is causally associated with an increased risk of self-harm in people with depression. Between-person comparisons revealed differences in self-harm risks between certain pairs of antidepressant classes. These findings may inform clinicians' benefit-risk assessments when prescribing antidepressants.

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## Research in context

### *Evidence before this study*

We searched Web of Science and PubMed for peer-reviewed articles published between January 1, 2000, and December 31, 2021, using the search term [(self-harm) OR (self harm) OR (self-injur*) OR (suicid*)] AND [(antidepressant*) OR (TCAs) OR (SSRIs) OR (SNRIs) OR (NaSSAs)] AND [(depressi*)]. We did not apply any language restrictions. Previous studies on the association between antidepressants use and self-harm mainly focused on adolescents. The limited number of studies on middle-aged and older adults mainly were conducted in the last decades of the 20th century and have generated inconsistent findings. Although most studies indicated that there is no association between antidepressant use and self-harm risk in adults, a large-scale cohort study of people aged 65 years or older in the UK found that all types of antidepressants were associated with a significantly increased risk of self-harm compared to those non-users in older people with depression. Most existing studies employed only one study design, typically cohort analyses, which are susceptible to confounding by indication and residual confounding. Findings regarding the differences in self-harm risks associated with specific antidepressant classes are also mixed.

### *Added value of this study*

To our best knowledge, this is one of the first studies conducted both within- and between-person comparisons of self-harm risks in people aged 40 years or older who have an initiation of antidepressants in a single population-based cohort. We found an increased self-harm risk before and during the initiated antidepressants treatment, irrespective of age and drug type. Significant variations in risk were observed between antidepressant classes. Short- and long-term risk differences associated with specific antidepressant classes have been comprehensively reported in people aged 40-64 years and 65 years or older.

### *Implications of all the available evidence*

We found no evidence that antidepressants impose additional risks of self-harm in middle-aged and older adults in Hong Kong. This, together with previous studies, provides converging evidence that supports the efficacy of antidepressants for treating depression. Some antidepressant classes may offer less protection against self-harm than others; the prescribing of a specific antidepressant class should take into account treatment efficacy and self-harm risk management.

## Introduction

Antidepressants are recommended pharmacological interventions for patients with moderate to severe depression.[1] However, controversies exist regarding the association between antidepressants and suicidal behaviour in adults. Although clinicians have raised concerns on the early activating effects during the first weeks of antidepressant treatment,[2] it is difficult to conclude whether suicidal behaviours that develop during treatment are attributable to the initiation of antidepressants or the core symptoms of depression itself. To disentangle the effect of treatment from the illness itself, the US Food and Drug Administration (FDA) conducted a meta-analysis using data from randomized controlled trials (RCTs),[3] concluding that an increased risk of suicidal behaviour during antidepressant treatment was observed only in adults younger than 25. However, clinical trials generally have strict inclusion criteria and exclude people with comorbidity and polypharmacy, which paradoxically are the very reason why different treatment responses and side effects should be suspected and studied.[4]

Several observational studies have examined the association between the initiation of antidepressants and an increased risk of suicidal behaviour in middle aged and older adults using data from the US and the UK.[5–8] Although most studies confirmed the lack of association observed in clinical trials, a large-scale UK study of older people found that all classes of antidepressant drugs were associated with significantly increased risks of self-harm or suicide.[8] Findings on whether the risk of suicidal behaviour differs between commonly-used antidepressant classes are also inconsistent, with some studies showing considerably varied risks,[9–12] while others show no difference.[5,7,13–15]

A wide range of antidepressants are available in clinical practice, and clinicians are advised to make the best choice by weighing their efficacy and side effects.[16] In this study, we used population-representative electronic health records of people aged 40 or older in Hong Kong

to: 1) examine the association between antidepressants and self-harm by comparing self-harm risk before and after antidepressant treatments, and 2) compare the short- and long-term risk of self-harm associated with different antidepressant classes.

## Methods

### Data source

This study used electronic health records from the Clinical Data Analysis and Reporting System (CDARS) maintained by the Hong Kong Hospital Authority (HA). The HA is a territory-wide statutory body that manages all public hospitals and ambulatory clinics in Hong Kong.[17] CDARS has collected information on demographics, clinical diagnoses, hospital admission and discharge, and prescription records. Population-based pharmaco-epidemiological studies have extensively validated the reliability of CDARS data.[18–20]

### Ethics

All records were de-identified, and no patients were contacted. This study was approved by the Institutional Review Board (IRB) of the University of Hong Kong (UW 17-520).

### Study cohort

We included people aged 40 years or older with a diagnosis of depression (ICD-9-CM codes, 296.2-3, 300.4, and 311) and with a new prescription of antidepressants between January 01, 2003, and December 31, 2015 (the calendar years 2001 and 2002 were assigned as the screening period for determining a new prescription). The end of the study period was December 31, 2016.

Antidepressant prescription was identified by the British National Formulary (BNF) chapter 4.3 and classified into five mutually exclusive classes: 1) tricyclic and related antidepressant drugs (TCAs); 2) selective serotonin reuptake inhibitors (SSRIs); 3) noradrenergic and specific serotonergic antidepressants (NaSSAs); 4) serotonin–norepinephrine reuptake inhibitors (SNRIs); and 5) others. The classification was determined according to the BNF major categories, the proposed mechanisms of actions of drugs,[9] and consideration of statistical power. Drugs included in each class are reported in Supplementary eTable 1. Individuals who were prescribed multiple classes of antidepressants at the initiation of prescription were excluded since this may reflect a more severe level of depression.[7,12] Figure 1 provides a flowchart describing the cohort selection procedure.

### Outcomes

The primary outcome was self-harm (both non-fatal and fatal) during the study period. ICD-9-CM codes E950-59 and E980-89 were used to identify non-fatal self-harm, consistent with previous research.[21,22] ICD-10-CM codes X60-84 and Y10-34 were used to identify fatal cases (suicide) as the cause of death in CDARS was stored in ICD-10-CM codes.

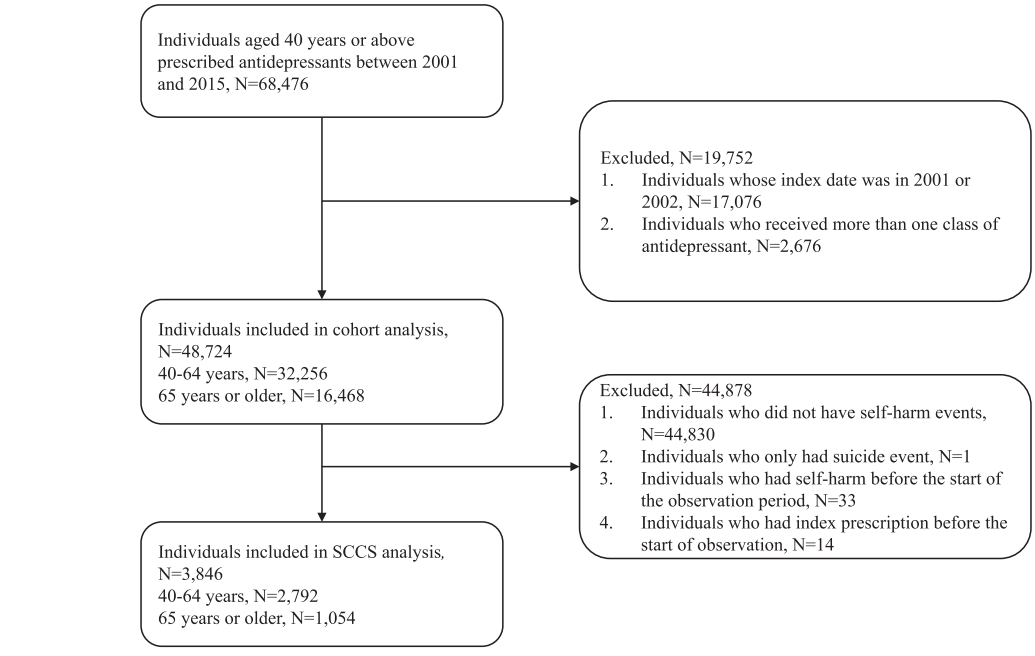


**Figure 1.** Study cohort selection procedure.

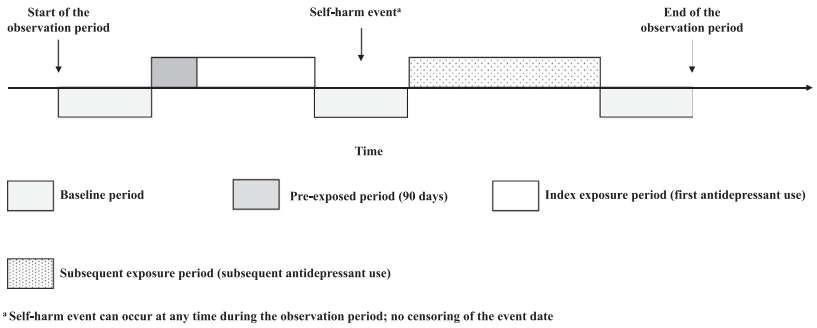


**Figure 2.** The SCCS study design of a hypothetical individual.

### Within-person comparison of self-harm risk

We used a self-controlled case series (SCCS) study design to account for potential indication bias. In this design, only those people who have both the exposure (antidepressants) and outcome of interest (self-harm) were included. Individuals served as their own control, and within-person comparisons were conducted by comparing the difference in self-harm incidences between the medication exposure period and all other periods.[23] Time-invariant confounders, such as genetic factors, socioeconomic status, and disease severity at baseline, were implicitly addressed.[24] This study design has been widely used to investigate associations between drugs and health outcomes.[18,25–27]

The SCCS design may generate biased results if the outcome is death since no exposure can occur after the event.[23] Therefore, we removed fatal self-harm (suicide) cases. Individuals who had at least one non-fatal self-harm record during the observation period were included in this analysis. The individual observational period commenced on January 01, 2001, or the 40$^{th}$ birthday (whichever was later), and ended on December 31, 2015, or the date of death (whichever was earlier). People who had a self-harm diagnosis before the start of the observation period were excluded (see Figure 1).[23]

All antidepressant prescriptions during the observation period were included for each individual. The index antidepressant exposure periods were defined as the time between the start and the end dates of firstly receiving a single class of antidepressants. If the same class of antidepressant was re-prescribed within 30 days after the end date of the last prescription, it was considered as a same exposure period (i.e., 30-day grace period). The date of switching to another class of antidepressants was defined as the start of the subsequent exposure period. All subsequent periods of antidepressant exposure were combined into one exposure category. The pre-exposure period was only considered for the first antidepressant prescription. The individual observation period was segmented into four mutually exclusive categories according to the antidepressant exposure status:[23,24] 1) the pre-exposure period (90 days before the first antidepressant exposure); 2) the index exposure period (the first antidepressant use); 3) the subsequent exposure period; and 4) the baseline period (all remaining time within the observation period). Only the first self-harm event for each person during the observation period was considered since recurrences of self-harm are not independent of each other.[23,28] To investigate the impact of excluding recurrent events, we did a sensitivity analysis in which all self-harm events within each individual during the observation period were included. Figure 2 shows the SCCS study design for a hypothetical individual.

### Between-person comparison of self-harm risk

Cohort analyses with pairwise comparisons were conducted between different antidepressants to compare self-harm risks associated with different antidepressants. A propensity score with the inverse probability of treatment weighting (IPTW) approach was applied to balance the characteristics of the study population to address the potential confounding effect of non-randomized treatment assignment.[29] The propensity score was estimated by the Generalized Boosted Model (GBM).[30] These weights were then retrieved to obtain the average treatment effect among antidepressant classes. Covariates used to estimate the weights comprised gender, age in years, living status, educational level, family history of mental illness at baseline; and self-harm behaviour, antipsychotic use (BNF code, 4.2.1), and psychiatric (comprising bipolar disorders, alcohol and tobacco use disorders, personality disorders, anxiety disorders, schizophrenia, and drug use disorders) and physical (comprising congestive heart disease, arthritis, hypertension, diabetes, stroke, cancer, dementia, epilepsy, Parkinson's disease, hypothyroidism, and asthma) comorbidities before or at baseline. Supplementary eTable 2 reports the ICD-9-CM codes for all comorbidities of interest.

The standardized mean difference (SMD) was used to assess the covariate balance among antidepressant classes with the threshold of 0.1.[31] Covariates with a

maximum pairwise SMD greater than 0.1 after IPTW were further adjusted in the regression model.

The entire sample was included in the cohort analyses (see Figure 1). Only the first prescription of a single class of antidepressant was considered and the date of the first prescription of antidepressants was designated as the index date. Individuals were followed from the index date until the occurrence of self-harm, death (other than suicide), or the end of the study period (one year for short-term risk, and December 31, 2016, for long-term risk), whichever came first. Since the phenomenology of adult depression may be different at younger and older ages,[32] analyses was stratified into two subgroups by age at the index date (40-64 years and 65 years or older).

### Statistical analysis

We tabulated sample characteristics at baseline for each antidepressant class. The SCCS analyses were conducted first to compare the self-harm incidence rate during the pre-exposure, index exposure, and subsequent exposure periods with the baseline period, using the incident rate ratio (IRR) estimated from conditional Poisson regression, adjusting for age in years.[24] We also conducted subgroup analyses by age groups and by antidepressant classes.

In the cohort analyses, we estimated the crude and weighted short-term (one-year) and long-term (whole observation period) incidence of self-harm per 100 person-years for each antidepressant class. The Cox proportional hazards model with IPTW was applied to estimate the hazard ratio (HR) for short-term and long-term risk of self-harm between antidepressant classes, stratified by age groups.

To consider the potential unmeasured confounders, E-values for all statistically significant IRRs and HRs were calculated to estimate the minimum strength of the association between unmeasured confounders with both antidepressant exposure and self-harm were needed, conditional on the measured covariates, to explain away the observed association(s).[33] A sensitivity analysis was conducted by only including people who initiated antidepressants after or within 30 days before their first diagnosis of depression during the study period.

Packages *dplyr, SCCS, survival, twang,* and *Evalue* in statistical software R (version 4.0.2) were used for data analysis.[34]

### Role of the funding source

No funding reported.

## Results

We identified 48,724 people with a diagnosis of depression and receiving new antidepressant monotherapy between January 01, 2003, and December 31, 2015. Missing values were not present in the analytical sample. Table 1 summarizes the baseline characteristics of the study cohort. In the age 40-64 group, the most prescribed antidepressant class was SSRIs (18,843 [58.42%]), followed by TCAs (10,797 [33.47%]). In the age 65+ group (age range: 65-105 years), the most prescribed antidepressant class was also SSRIs (10,010 [60.78%]), followed by TCAs (3,974 [24.13%]). Supplementary eTable 1 shows frequencies of specific drugs included in each antidepressant class.

### Results from the SCCS analyses (within-person comparison of self-harm risk)

A subsample of 3,846 individuals with an average age of 54.64 years (SD, 13.24 years) at the start of the observation period met the inclusion criteria for the SCCS analyses. Table 2 reports the number of events, incidence, and IRRs of self-harm in the four risk windows defined by antidepressant exposure status. The highest incidence of 76.71 (95% CI, 71.27-82.43) per 100 person-years was observed in the pre-exposure period. The incidence decreased to 16.06 (15.03 to 17.13) per 100 person-years in the index exposure period. Compared with the baseline period, the risk of self-harm was higher in the antidepressants exposed period (index exposure: IRR, 7.03; 95% CI, 6.34-7.80; E-value, 13.54; subsequent exposure: 2.47; 2.18-2.79; 4.38). The risk was even higher during the pre-exposure period (22.24; 20.25-24.42; 43.97). The results were similar in the age-specific analyses (Supplementary eTable 3). Preliminary analysis indicated that very few people were prescribed only one class of antidepressants across the entire study period, the drug-class-specific analyses were therefore limited to TCAs ($N = 253$), SSRIs ($N = 1151$) and NaSSAs ($N = 181$) because only 49 and 4 people were prescribed SNRIs and Others, respectively (Supplementary eTable 4). Compared to the baseline period, self-harm risk was consistently higher in both exposure and pre-exposure periods. Results from sensitivity analyses of including all self-harm events were consistent with main analyses (eTable 5).

### Results from the cohort analyses (between-person comparison of self-harm risk)

In individuals aged 40-64, the SMDs of all characteristics were equal to or less than 0.1 after IPTW, except for family history of mental illness (maximum pairwise SMD, 0.11), anxiety disorder (0.15), and cancer (0.12). In the age 65+ group, exceptions were age (0.16), self-harm diagnosis before or at baseline (0.22), congestive heart disease (0.17), diabetes (0.20), dementia (0.22), epilepsy (0.12), and hypothyroidism (0.11) (Table 1). These characteristics were further adjusted in the regression model.

The short- and long-term incidence of self-harm (both crude and weighted) by antidepressant classes

| 40–64 years | | | | | | Maximum Pairwise SMD | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **TCAs** | **SSRIs** | **NaSSAs** | **SNRIs** | **Others** | **Before IPTW** | **After IPTW** |
| **Individuals, *n*** | 10797 (33.47) | 18843 (58.42) | 1566 (4.85) | 887 (2.75) | 163 (0.51) | | |
| **Gender, *n (%)*** | | | | | | 0.19 | 0.10 |
| Female | 8020 (74.28) | 13308 (70.63) | 1028 (65.64) | 614 (69.22) | 109 (66.87) | | |
| Male | 2777 (25.72) | 5535 (29.37) | 538 (34.36) | 273 (30.78) | 54 (33.13) | | |
| **Mean age (SD), *y*** | 52.08 (6.00) | 52.98 (5.80) | 53.17 (6.12) | 52.72 (5.91) | 52.89 (6.06) | 0.19 | 0.02 |
| **Living status, *n (%)*** | | | | | | 0.10 | 0.04 |
| Alone | 1352 (12.52) | 2622 (13.91) | 220 (14.05) | 106 (11.95) | 25 (15.34) | | |
| With family or relatives | 7466 (69.15) | 13178 (69.94) | 1122 (71.65) | 670 (75.54) | 111 (68.10) | | |
| Others | 65 (0.60) | 168 (0.89) | 11 (0.70) | 4 (0.45) | 1 (0.61) | | |
| Unknown | 1914 (17.73) | 2875 (15.26) | 213 (13.60) | 107 (12.06) | 26 (15.95) | | |
| **Educational level, *n (%)*** | | | | | | 0.11 | 0.08 |
| Less than primary | 680 (6.30) | 928 (4.92) | 74 (4.73) | 33 (3.72) | 7 (4.29) | | |
| Primary | 3075 (28.48) | 4791 (25.43) | 398 (25.42) | 177 (19.95) | 33 (20.25) | | |
| Secondary | 4039 (37.41) | 7899 (41.92) | 640 (40.87) | 398 (44.87) | 68 (41.72) | | |
| Tertiary or above | 469 (4.34) | 1387 (7.36) | 131 (8.37) | 126 (14.21) | 21 (12.88) | | |
| Unknown | 2534 (23.47) | 3838 (20.37) | 323 (20.63) | 153 (17.25) | 34 (20.86) | | |
| **Family history of mental illness, *n (%)*** | 549 (5.08) | 773 (4.10) | 74 (4.73) | 59 (6.65) | 9 (5.52) | 0.12 | 0.11 |
| **Self-harm diagnosis before or at baseline, *n (%)*** | 221 (2.05) | 738 (3.92) | 85 (5.43) | 40 (4.51) | 7 (4.29) | 0.19 | 0.03 |
| **Antipsychotics use before or at baseline, *n (%)*** | 502 (4.65) | 1775 (9.42) | 194 (12.39) | 121 (13.64) | 31 (19.02) | 0.53 | 0.03 |
| **Psychiatric comorbidities before or at baseline, *n (%)*** | | | | | | | |
| Bipolar disorders | 28 (0.26) | 57 (0.30) | 4 (0.26) | 4 (0.45) | 1 (0.61) | 0.07 | 0.04 |
| Alcohol and tobacco use disorders | 128 (1.19) | 278 (1.48) | 32 (2.04) | 4 (0.45) | 1 (0.61) | 0.14 | 0.07 |
| Personality disorders | 54 (0.50) | 109 (0.58) | 13 (0.83) | 9 (1.01) | 0 (0.00) | 0.13 | 0.07 |
| Anxiety disorders | 361 (3.34) | 795 (4.22) | 67 (4.28) | 31 (3.49) | 3 (1.84) | 0.13 | 0.15 |
| Schizophrenia | 43 (0.40) | 133 (0.71) | 15 (0.96) | 5 (0.56) | 12 (7.36) | 0.87 | 0.03 |
| Drug use disorders | 134 (1.24) | 187 (0.99) | 51 (3.26) | 8 (0.90) | 3 (1.84) | 0.22 | 0.04 |
| **Physical comorbidities before or at baseline, *n (%)*** | | | | | | | |
| Congestive heart disease | 27 (0.25) | 109 (0.58) | 13 (0.83) | 2 (0.23) | 0 (0.00) | 0.12 | 0.07 |
| Arthritis | 46 (0.43) | 65 (0.34) | 6 (0.38) | 4 (0.45) | 0 (0.00) | 0.07 | 0.08 |
| Hypertension | 631 (5.84) | 1413 (7.50) | 106 (6.77) | 50 (5.64) | 9 (5.52) | 0.08 | 0.05 |
| Diabetes | 400 (3.70) | 977 (5.18) | 72 (4.60) | 27 (3.04) | 8 (4.91) | 0.10 | 0.06 |
| Stroke | 204 (1.89) | 628 (3.33) | 37 (2.36) | 23 (2.59) | 5 (3.07) | 0.09 | 0.10 |
| Cancer | 838 (7.76) | 1703 (9.04) | 146 (9.32) | 78 (8.79) | 10 (6.13) | 0.11 | 0.12 |
| Dementia | 7 (0.06) | 37 (0.20) | 1 (0.06) | 1 (0.11) | 0 (0.00) | 0.05 | 0.04 |
| Epilepsy | 42 (0.39) | 134 (0.71) | 16 (1.02) | 2 (0.23) | 1 (0.61) | 0.10 | 0.08 |
| Parkinson's disease | 26 (0.24) | 65 (0.34) | 11 (0.70) | 4 (0.45) | 1 (0.61) | 0.08 | 0.03 |
| Hypothyroidism | 53 (0.49) | 135 (0.72) | 12 (0.77) | 6 (0.68) | 0 (0.00) | 0.10 | 0.09 |
| Asthma | 93 (0.86) | 206 (1.09) | 15 (0.96) | 8 (0.90) | 1 (0.61) | 0.05 | 0.02 |
| **65 years or older Characteristics** | | | | | | | |
| **Individuals, *n (%)*** | 3974 (24.13) | 10010 (60.78) | 1879 (11.41) | 539 (3.27) | 66 (0.40) | | |
| **Gender, *n (%)*** | | | | | | 0.17 | 0.05 |
| Female | 2899 (72.95) | 6630 (66.23) | 1218 (64.82) | 365 (67.72) | 44 (66.67) | | |
| Male | 1075 (27.05) | 3380 (33.77) | 661 (35.18) | 174 (32.28) | 22 (33.33) | | |
| **Mean age (SD), *y*** | 74.66 (6.80) | 75.95 (7.32) | 76.22 (7.12) | 75.69 (7.36) | 74.67 (8.07) | 0.22 | 0.16 |
| **Living status, *n (%)*** | | | | | | 0.12 | 0.03 |
| Alone | 545 (13.71) | 1263 (12.62) | 273 (14.53) | 65 (12.06) | 7 (10.61) | | |
| With family or relatives | 2120 (53.35) | 5428 (54.23) | 1061 (56.47) | 304 (56.40) | 39 (59.09) | | |
| Others | 410 (10.32) | 1302 (13.01) | 199 (10.59) | 57 (10.58) | 7 (10.61) | | |

***Table 1*** *(Continued)*

| 40–64 years | | | | | | Maximum Pairwise SMD | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **TCAs** | **SSRIs** | **NaSSAs** | **SNRIs** | **Others** | **Before IPTW** | **After IPTW** |
| Unknown | 899 (22.62) | 2017 (20.15) | 346 (18.41) | 113 (20.96) | 13 (19.70) | | |
| **Educational level, *n (%)*** | | | | | | 0.07 | 0.03 |
| Less than primary | 1134 (28.54) | 2830 (28.27) | 570 (30.34) | 146 (27.09) | 18 (27.27) | | |
| Primary | 857 (21.57) | 2226 (22.24) | 400 (21.29) | 109 (20.22) | 15 (22.73) | | |
| Secondary | 495 (12.46) | 1377 (13.76) | 275 (14.64) | 69 (12.80) | 9 (13.64) | | |
| Tertiary or above | 171 (4.30) | 461 (4.61) | 109 (5.80) | 41 (7.61) | 3 (4.55) | | |
| Unknown | 1317 (33.14) | 3116 (31.13) | 525 (27.94) | 174 (32.28) | 21 (31.82) | | |
| **Family history of mental illness, *n (%)*** | 100 (2.52) | 203 (2.03) | 51 (2.71) | 13 (2.41) | 2 (3.03) | 0.07 | 0.04 |
| **Self-harm diagnosis before or at baseline, *n (%)*** | 117 (2.94) | 559 (5.58) | 118 (6.28) | 23 (4.27) | 1 (1.52) | 0.22 | 0.22 |
| **Antipsychotics use before or at baseline, *n (%)*** | 224 (5.64) | 860 (8.59) | 172 (9.15) | 68 (12.62) | 11 (16.67) | 0.40 | 0.05 |
| **Psychiatric comorbidities before or at baseline, *n (%)*** | | | | | | | |
| Bipolar disorders | 2 (0.05) | 16 (0.16) | 2 (0.11) | 3 (0.56) | 1 (1.52) | 0.38 | 0.03 |
| Alcohol and tobacco abuse | 16 (0.40) | 78 (0.78) | 16 (0.85) | 2 (0.37) | 1 (1.52) | 0.14 | 0.05 |
| Personality disorders | 8 (0.20) | 26 (0.26) | 7 (0.37) | 3 (0.56) | 1 (1.52) | 0.25 | 0.03 |
| Anxiety disorders | 161 (4.05) | 377 (3.77) | 86 (4.58) | 28 (5.19) | 6 (0.09) | 0.27 | 0.01 |
| Schizophrenia | 14 (0.35) | 31 (0.31) | 9 (0.48) | 5 (0.93) | 1 (1.52) | 0.20 | 0.05 |
| Drug use disorders | 37 (0.93) | 45 (0.45) | 24 (1.28) | 2 (0.37) | 1 (1.52) | 0.14 | 0.06 |
| **Physical comorbidities before or at baseline, *n (%)*** | | | | | | | |
| Congestive heart disease | 190 (4.78) | 751 (7.50) | 124 (6.60) | 19 (3.53) | 3 (4.55) | 0.16 | 0.17 |
| Arthritis | 23 (0.58) | 47 (0.47) | 10 (0.53) | 6 (1.11) | 1 (1.52) | 0.14 | 0.02 |
| Hypertension | 981 (24.69) | 3212 (32.09) | 577 (30.71) | 153 (28.39) | 30 (45.45) | 0.45 | 0.06 |
| Diabetes | 539 (13.56) | 1776 (17.74) | 275 (14.64) | 86 (15.96) | 8 (12.12) | 0.15 | 0.20 |
| Stroke | 385 (9.69) | 1542 (15.40) | 167 (8.89) | 51 (9.46) | 7 (10.61) | 0.19 | 0.07 |
| Cancer | 358 (9.01) | 1022 (10.21) | 228 (12.13) | 54 (10.02) | 5 (7.58) | 0.15 | 0.10 |
| Dementia | 133 (3.35) | 542 (5.41) | 83 (4.42) | 29 (5.38) | 1 (1.52) | 0.18 | 0.22 |
| Epilepsy | 31 (0.78) | 105 (1.05) | 17 (0.90) | 7 (1.30) | 1 (1.52) | 0.07 | 0.12 |
| Parkinson's disease | 73 (1.84) | 225 (2.25) | 62 (3.30) | 14 (2.60) | 2 (3.03) | 0.10 | 0.08 |
| Hypothyroidism | 37 (0.93) | 130 (1.30) | 28 (1.49) | 3 (0.56) | 0 (0.00) | 0.14 | 0.11 |
| Asthma | 96 (2.42) | 254 (2.54) | 55 (2.93) | 12 (2.23) | 4 (6.06) | 0.24 | 0.08 |

***Table 1*: Baseline characteristics of the study cohort.**
IPTW: Inverse probability of treatment weighting.
SD: Standardized deviation.
SMD: Standardized mean difference.
TCAs: Tricyclic and related antidepressant drugs.
SSRIs: Selective serotonin reuptake inhibitors.
NaSSAs: Noradrenergic and specific serotonergic antidepressants.
SNRIs: Serotonin–norepinephrine reuptake inhibitors.

stratified by age groups are shown in Table 3. In both age groups, the highest incidence (both short- and long-term) was found in NaSSAs.

Table 4 shows the unadjusted and adjusted results of the cohort analyses from pairwise comparisons between antidepressant classes. In terms of the short-term risk of self-harm in individuals aged 40-64, those prescribed NaSSAs (HR, 2.13; 95% CI, 1.53-2.96; E-value: 2.76) and SNRIs (1.64; 1.01-2.68; 2.18) carried elevated risks of self-harm compared to people prescribed TCAs. NaSSAs were also associated with an increased risk of self-harm compared to SSRIs (1.75; 1.29-2.36; 2.31). In terms of long-term risk, only the association of NaSSAs vs. TCAs (1.55; 1.26-1.91; 2.05) and NaSSAs vs. SSRIs (1.53; 1.26-1.87; 2.02) remained significant. In individuals aged 65 years or older, an association of increased short-term risk of self-harm was found in SSRIs vs. TCAs (1.31; 1.03-1.66; 1.70). A significantly lower short-term risk of self-harm was observed in SNRIs vs. SSRIs (0.44; 0.22-0.87; 2.91)

| Periods | Events, n | Total person-years | Incidence per 100 person-years (95% CI) | IRR (95% CI) | p value | E-value |
|---|---|---|---|---|---|---|
| Baseline period | 1380 | 36674.81 | 3.76 (3.56-3.96) | ref | | |
| Pre-exposure period | 727 | 947.68 | 76.71 (71.27-82.43) | 22.24 (20.25-24.42) | <0.0001 | 43.97 |
| Index exposure period | 892 | 5555.16 | 16.06 (15.03-17.13) | 7.03 (6.34-7.80) | <0.0001 | 13.54 |
| Subsequent exposure period | 847 | 12230.18 | 6.93 (6.47-7.40) | 2.47 (2.18-2.79) | <0.0001 | 4.38 |

***Table 2*: Results from the SCCS analyses: incidence and IRR of self-harm in different time periods.**
SCCS: Self-controlled Case Series.
IRR: Incidence rate ratio.

| 40-64 years | Short-term | | | | Long-term | | | |
|---|---|---|---|---|---|---|---|---|
| | Events, n | Total follow-up time, years | Crude incidence per 100 person-years (95% CI) | Weighed incidence per 100 person-years (95% CI)[a] | Events, n | Total follow-up time, years | Crude incidence per 100 person-years (95% CI) | Weighed incidence per 100 person-years (95% CI)[a] |
| TCAs | 146 | 10660 | 1.37 (1.16-1.60) | 1.51 (1.37-1.65) | 544 | 91782 | 0.59 (0.54-0.64) | 0.65 (0.62-0.68) |
| SSRIs | 354 | 18474 | 1.92 (1.72-2.12) | 1.84 (1.69-1.99) | 947 | 130840 | 0.72 (0.68-0.77) | 0.70 (0.66-0.73) |
| NaSSAs | 55 | 1515 | 3.63 (2.75-4.68) | 3.22 (3.02-3.43) | 126 | 10536 | 1.20 (1.00-1.42) | 1.06 (1.02-1.11) |
| SNRIs | 21 | 869 | 2.42 (1.53-3.60) | 2.47 (2.30-2.65) | 51 | 5997 | 0.85 (0.64-1.11) | 0.80 (0.76-0.84) |
| Others | 1 | 163 | 0.61 (0.035-2.70) | 0.90 (0.79-1.01) | 4 | 1220 | 0.33 (0.10-0.76) | 0.39 (0.36-0.42) |
| **65 years or older** | | | | | | | | |
| TCAs | 87 | 3806 | 2.29 (1.84-2.80) | 2.60 (2.36-2.87) | 242 | 26318 | 0.92 (0.81-1.04) | 1.03 (0.97-1.10) |
| SSRIs | 337 | 9293 | 3.63 (3.25-4.03) | 3.43 (3.14-3.73) | 607 | 51941 | 1.17 (1.08-1.26) | 1.12 (1.05-1.19) |
| NaSSAs | 66 | 1740 | 3.79 (2.95-4.78) | 3.52 (3.23-3.83) | 122 | 9236 | 1.32 (1.10-1.57) | 1.23 (1.15-1.31) |
| SNRIs | 10 | 508 | 1.97 (0.99-3.45) | 1.45 (1.27-1.66) | 28 | 3021 | 0.93 (0.63-1.31) | 0.86 (0.80-0.92) |
| Others | 1 | 64 | 1.56 (0.09-6.87) | 2.07 (1.81-2.35) | 6 | 382 | 1.57 (0.62-3.18) | 1.15 (1.07-1.23) |

***Table 3*: Results from the cohort analyses: the crude and weighted short-term and long-term incidence of self-harm for both age groups.**
[a] After inverse probability of treatment weighting.
Short-term: One-year observation period.
Long-term: The whole observation period.
TCAs: Tricyclic and related antidepressant drugs.
SSRIs: Selective serotonin reuptake inhibitors.
NaSSAs: Noradrenergic and specific serotonergic antidepressants.
SNRIs: Serotonin–norepinephrine reuptake inhibitors.

and SNRIs vs. NaSSAs (0.43; 0.21-0.87; 2.97). No significant association was detected in long-term observation in older people. We also reported Bonferroni corrected confidence intervals and p values and standardized mean differences transformed from HRs (Supplementary eTable 6).[35] Differences in SNRIs vs. TCAs in people aged 40-64 years, and SSRIs vs. TCAs, SNRIs vs. SSRIs, and SNRIs vs. NaSSAs in people aged 65 years or older were no longer significant after adjustment for multiple comparison.

Sensitivity analyses that only included people who had a depression diagnosis dated after or within 30 days before the first antidepressant prescription yielded similar results (Supplementary eTables 7 and 8). In the SCCS analyses, significantly elevated risks of self-harm were found in all three periods (pre-exposure period: IRR, 23.76; 95% CI, 21.33-26.47; E-value: 47.01; index exposure period: 6.45; 5.69-7.30; 12.38; subsequent exposure period: 2.02; 1.73-2.35; 3.46) compared to the baseline period. In the cohort analyses results from pairwise comparison in individuals aged 40-64, the significant differences were found in NaSSAs vs. TCAs (short-term: HR, 2.14; 95% CI, 1.43-3.20; E-value: 2.77; long-term: 1.63; 1.27-2.09; 2.15) and NaSSAs vs. SSRIs (short-term: 1.72; 1.23-2.43; 2.27 long-term: 1.52; 1.21-1.91; 2.01) for both the short-term and long-term observation periods. Additionally, the SNRIs also carried an increased risk of self-harm compared to TCAs in the short-term observation (1.94; 1.10-3.43; 2.54). In people aged 65 years or older, the short-term significant differences can be observed in SSRIs vs. TCAs (1.50; 1.07-2.12; 1.98) and NaSSAs vs. TCAs (1.73; 1.14-2.63; 2.28). An association of decreased risk of self-harm was found in SNRIs vs. SSRIs (short-term: 0.40; 0.16-0.98; 3.16) and SNRIs vs. NaSSAs (short-term: 0.35; 0.14-0.87; 3.52; long-term: 0.55; 0.32-0.95; 2.39).

| 40-64 years | Short-term | | | | | Long-term | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unadjusted | | Adjusted | | | Unadjusted | | Adjusted | | |
| | HR (95% CI) | *p* value | HR (95% CI) | *p* value | E-value | HR (95% CI) | *p* value | HR (95% CI) | *p* value | E-value |
| SSRIs vs. TCAs | 1.40 (1.15-1.69) | 0.00068 | 1.22 (0.99-1.49) | 0.056 | - | 1.13 (1.02-1.26) | 0.024 | 1.01 (0.90-1.13) | 0.85 | - |
| NaSSAs vs. TCAs | 2.63 (1.93-3.59) | <0.0001 | 2.13 (1.53-2.96) | <0.0001 | 2.76 | 1.88 (1.55-2.28) | <0.0001 | 1.55 (1.26-1.91) | <0.0001 | 2.05 |
| SNRIs vs. TCAs | 1.76 (1.11-2.78) | 0.015 | 1.64 (1.01-2.68) | 0.044 | 2.18 | 1.32 (0.99-1.76) | 0.056 | 1.14 (0.84-1.56) | 0.39 | - |
| Others vs. TCAs | 0.45 (0.063-3.22) | 0.43 | 0.60 (0.08-4.20) | 0.60 | - | 0.53 (0.20-1.41) | 0.20 | 0.57 (0.21-1.59) | 0.29 | - |
| NaSSAs vs. SSRIs | 1.89 (1.42-2.50) | <0.0001 | 1.75 (1.29-2.36) | 0.00029 | 2.31 | 1.66 (1.38-2.00) | <0.0001 | 1.53 (1.26-1.87) | <0.0001 | 2.02 |
| SNRIs vs. SSRIs | 1.26 (0.81-1.96) | 0.30 | 1.35 (0.85-2.15) | 0.21 | - | 1.17 (0.88-1.55) | 0.27 | 1.13 (0.84-1.53) | 0.42 | - |
| Others vs. SSRIs | 0.32 (0.045-2.30) | 0.26 | 0.49 (0.070-3.43) | 0.47 | - | 0.47 (0.17-1.24) | 0.13 | 0.57 (0.21-1.57) | 0.28 | - |
| SNRIs vs. NaSSAs | 0.67 (0.40-1.11) | 0.12 | 0.77 (0.45-1.32) | 0.35 | - | 0.71 (0.51-0.98) | 0.035 | 0.74 (0.52-1.05) | 0.089 | - |
| Others vs. NaSSAs | 0.17 (0.024-1.24) | 0.08 | 0.28 (0.039-2.00) | 0.20 | - | 0.28 (0.10-0.76) | 0.012 | 0.37 (0.13-1.04) | 0.060 | - |
| Others vs. SNRIs | 0.26 (0.034-1.90) | 0.18 | 0.36 (0.049-2.67) | 0.32 | - | 0.40 (0.14-1.10) | 0.076 | 0.50 (0.17-1.45) | 0.20 | - |
| **65 years or older** | | | | | | | | | | |
| SSRIs vs. TCAs | 1.57 (1.24-1.98) | 0.00019 | 1.31 (1.03-1.66) | 0.029 | 1.70 | 1.15 (0.99-1.33) | 0.073 | 0.99 (0.85-1.16) | 0.93 | - |
| NaSSAs vs. TCAs | 1.64 (1.19-2.25) | 0.0026 | 1.34 (0.97-1.87) | 0.079 | - | 1.27 (1.02-1.58) | 0.031 | 1.08 (0.86-1.36) | 0.51 | - |
| SNRIs vs. TCAs | 0.85 (0.44-1.64) | 0.64 | 0.57 (0.28-1.16) | 0.12 | - | 0.94 (0.64-1.39) | 0.76 | 0.78 (0.52-1.18) | 0.24 | - |
| Others vs. TCAs | 0.69 (0.096-4.95) | 0.71 | 0.94 (0.13-6.97) | 0.95 | - | 1.60 (0.71-3.60) | 0.25 | 1.22 (0.42-3.55) | 0.71 | - |
| NaSSAs vs. SSRIs | 1.04 (0.80-1.36) | 0.75 | 1.03 (0.78-1.35) | 0.84 | - | 1.11 (0.91-1.35) | 0.30 | 1.09 (0.89-1.33) | 0.40 | - |
| SNRIs vs. SSRIs | 0.55 (0.29-1.02) | 0.059 | 0.44 (0.22-0.87) | 0.018 | 2.91 | 0.82 (0.56-1.20) | 0.30 | 0.79 (0.53-1.17) | 0.22 | - |
| Others vs. SSRIs | 0.44 (0.062-3.13) | 0.41 | 0.72 (0.098-5.27) | 0.75 | - | 1.40 (0.63-3.12) | 0.42 | 1.23 (0.43-3.57) | 0.70 | - |
| SNRIs vs. NaSSAs | 0.52 (0.27-1.02) | 0.056 | 0.43 (0.21-0.87) | 0.020 | 2.97 | 0.74 (0.49-1.11) | 0.15 | 0.72 (0.47-1.11) | 0.14 | - |
| Others vs. NaSSAs | 0.42 (0.058-3.04) | 0.39 | 0.70 (0.094-5.20) | 0.73 | - | 1.26 (0.55-2.56) | 0.58 | 1.13 (0.39-3.32) | 0.82 | - |
| Others vs. SNRIs | 0.81 (0.10-6.31) | 0.84 | 1.64 (0.20-13.44) | 0.64 | - | 1.70 (0.71-4.12) | 0.24 | 1.57 (0.51-4.85) | 0.44 | - |

***Table 4*: Results from the cohort analyses: cox proportional hazard regression model using IPTW as weights.**
IPTW: Inverse probability of treatment weighting.
Short-term: One-year observation period.
Long-term: The whole observation period.
TCAs: Tricyclic and related antidepressant drugs.
SSRIs: Selective serotonin reuptake inhibitors.
NaSSAs: Noradrenergic and specific serotonergic antidepressants.
SNRIs: Serotonin–norepinephrine reuptake inhibitors.

## Discussion

In this population-based study, we conducted within- and between-person comparisons of self-harm risks in people aged 40 years or older across five antidepressant classes, stratified by age group. We found an increased risk of self-harm before and during the exposure of antidepressants compared with the baseline period. The pre-exposure period showed a higher risk, suggesting that self-harm might be an indication for antidepressants treatment. We also found the risks of self-harm varied between different classes of antidepressant.

The extent to which the risk of self-harm is attributable to antidepressant treatment rather than the disease process of depression itself has been an ongoing question. In the current study, we employed a within-subject comparison with the SCCS design and found a consistently lower self-harm risk following the initiation of antidepressant treatment in both age groups and all drug classes studied (TCAs, SSRIs, NaSSAs). In general, this concurs with findings from the meta-analysis of RCTs registered with the US FDA.[3] Although no association was observed in people aged 25-64 in the meta-analysis, this difference may be attributable to the difference in age groups defined. The finding further supports the hypothesis that self-harm behaviour is triggered by the core symptoms of depression itself and may reflect a deterioration of the condition, requiring timely medical consultation and intervention.

Previous literature has identified variations of self-harm risk among different antidepressant classes. For instance, a large Taiwanese study of more than 0.75 million people aged ten years or older found an increased risk in SNRIs and NaSSAs compared to SSRIs.[9] A UK study of people aged 20-64 years reported a more than 2-fold higher suicide risk associated with the broad class of antidepressants, including SNRIs, NaSSAs, and others compared to SSRIs.[12] The results were similar when analyses were conducted in older people aged 65 and over.[8] Currently, SSRIs have been the most frequently prescribed drugs due to their relatively superior tolerability.[36,37] The NICE guideline recommends SSRIs as the first choice for pharmacological treatment of depression.[16] Hong Kong psychiatric care reflects this trend

where more than half of new antidepressant users were prescribed SSRIs. However, our study observed a lower self-harm risk in SSRIs compared with NaSSAs for only those aged 40-64 years. We also found a significantly higher short-term risk of self-harm in SSRIs vs. TCAs for people aged 65 years or above, consistent with the sensitivity analyses results of the Taiwan study.[9]

Two UK studies reported that venlafaxine, one of the major SNRIs, demonstrated a higher risk of self-harm than SSRIs drugs among people aged 10-90 years though subject to residual confounding.[11,38] Conversely, we found that people prescribed SNRIs had a lower risk of self-harm compared to SSRIs and NaSSAs in people aged 65 years or older. This divergence may be due to the different age effects of antidepressants. Given that older people are more likely to suffer from comorbidities,[39] the risk profiles may differ from those of their younger counterparts. Our results also show that TCAs had a lower short-term risk of self-harm compared to SNRIs and SSRIs, which is in contrast to the expected as TCAs are generally given to depressive people with more severe conditions. One possible explanation was that TCAs are associated with greater toxicity compared to SNRIs, NaSSAs, and SSRIs regarding self-poisoning,[40] and therefore, the prescription of TCAs for those considered at high risk of self-harm is avoided.[7] Moreover, the different self-harm risk patterns between short-term and long-term investigations may also reveal the distinct pharmacological efficacies referring to acute and chronic antidepressant treatment. Given the paucity of comparable evidence and results from the multiple comparison in this study, caution should be applied when generalizing our findings to other populations.

This population-based study supplements the body of evidence previously generated from RCTs that are often limited to a small number of events, inconsistent measures of suicidal behaviour, and short observational periods. As clinical trials may deliberately exclude people at high risk of suicide because of ethical concerns, suicide risk estimated from RCT participants may be lower than the true risk in all people treated with antidepressants.[41] The current study included all eligible patients (including those with excessive comorbidities), which increased the generalizability of the results, particularly in the older population.

Observational studies on antidepressant use and risk of self-harm are often susceptible to confounding.[42–44] To address these concerns, we adopted two study designs to understand the relationship between antidepressants and self-harm from both the within-person and between-person perspectives. To reduce indication bias in the cohort analyses, comparisons were restricted to people with a recorded diagnosis of depression who were treated with antidepressants. We applied propensity score with scores generated from the GBM for better comparison with multiple treatment arms.[31] To test the effect of missing covariates that were not recorded in the database (i.e., socioeconomic factors and clinical profiles) on the findings, we also calculated the E-values.[45] We conducted the SCCS analyses to compare the risk of self-harm before and after the initiation of a specific drug class within the same person, which also reduced the residual confounding from time-invariant factors.[24] However, biases and confounding might still exist. For instance, depression severity plays an important role in both the decision to prescribe pharmacological treatment and the selection of antidepressant type. However, no information regarding depression severity was available for our dataset. Though people prescribed multiple antidepressant classes who may represent the more complex situations were excluded to reduce potential bias, the absence of depression severity can still result in confounding by indication. Additionally, the indication for antidepressant prescription is unknown. Although antidepressant prescribing is primarily for the treatment of depression, it can also be for the treatment of other conditions (e.g., insomnia and anxiety).[46] Furthermore, most antidepressant classes included more than one specific drug, and the self-harm risk may also vary among individual drugs. Comparisons were only applied between broad antidepressant classes because of sample size limitations, which is the potential source of residual confounding.

This study has other limitations. First, both fatal (suicide) and non-fatal self-harm events were considered as outcomes in this study since ICD-9-CM codes do not provide enough information to determine suicide intention. Subject to the model assumption of SCCS analyses, all suicide cases without a prior self-harm diagnosis were excluded. However, only one person was identified (less than 0.1%), so the resulting bias should be minimal. Second, the study included hospital-presented self-harm cases only. The unavailability of information about self-harm cases managed outside hospitals, such as in community and long-term care settings, may have reduced the precision of our estimates. Third, fatal self-harm cases can affect the results since these suicides were not validated by a Coroner's court report. Another limitation is the number and duration of antidepressant withdrawal might have an effect on subsequent self-harm behaviour. Though we have adjusted for drug use disorders, which include the drug withdrawal (ICD-9-CM: 292.0), nevertheless, whether the withdrawal symptoms were caused by antidepressants cannot be determined. Furthermore, we used 2001 and 2002 as the screening period to determine whether an incident prescription in 2003 or subsequently was the first prescription. However, this two-year period may not be sufficient, as suggested by the identification of 2676 people taking multiple antidepressants at the index date. Finally, we did not consider the effect of drug dosage and prescription duration, which may also be associated with self-harm and suicide.[8]

## Conclusion

This study found an elevated risk of self-harm preceding the initiation of antidepressant treatment. The risk decreased during the treatment period compared to the pre-exposure period but remained higher than the baseline period. Though our results did not reveal a causal relationship between the antidepressant exposure and an elevated risk of self-harm, careful monitoring of self-harm risk is still required during the treatment stage. Varied risks in different antidepressant classes, influenced by age and the duration of observation, call for a comprehensive evaluation of prescribing that should take into account patients' characteristics, time effect, treatment efficacy, and self-harm risk management.

### Contributors

HL, KKCM, and ICKW initiated the study design. YC prepared the study protocol and conducted the formal data analysis. HL, KKCM, and WCYL provided expertise in statistics and cross check the analytical syntax. SKWC contributed clinical expertise and reviewed the study protocol. All authors contributed to the interpretation of data. YC and HL prepared the first draft of the manuscript. All authors substantially revised the drafts of the manuscript. All authors critically reviewed all drafts and approved the final version of the manuscripts.

### Data sharing statement

The CDARS dataset is managed by the Hong Kong Hospital Authority (HA). HA Data Sharing Portal provides various access channels to HA data for research purposes. The related information can be found online (https://www3.ha.org.hk/data).

### Declaration of interests

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### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100557.

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