**TITLE PAGE**

**Title**

Association between statins and the risk of suicide attempt, depression, anxiety, and seizure: a population-based, self-controlled case series study

**Short title**

Association between statins and neuropsychological disorders

**Authors**

Xuxiao Ye, MSc[1*]; Joseph E. Blais, PhD[1,2*]; Vanessa W.S. Ng, BPharm[1]; David Castle, MD[3]; Joseph F. Hayes, PhD[4]; Yue Wei, MPH[1]; Wei Kang, MSc[1]; Le Gao, MSc[1]; Vincent K.C. Yan, BPharm[1]; Ian C.K. Wong, PhD[1,5,6,8]; Esther W. Chan, PhD[1,6,7,8]

[*] *share first authorship*

**Affiliations**

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, University of Hong Kong, Hong Kong SAR, China
[2]School of Public Health, LKS Faculty of Medicine, University of Hong Kong, Hong Kong SAR, China
[3]Department of Psychiatry, University of Toronto, Toronto, Canada
[4]Division of Psychiatry, University College London, London, United Kingdom
[5]Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom
[6]Laboratory of Data Discovery for Health, Hong Kong SAR, China
[7]Department of Pharmacy, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China
[8]The University of Hong Kong Shenzhen Institute of Research and Innovation, Shenzhen, China

**Corresponding author**

Dr Esther W Chan
Centre for Safe Medication Practice and Research
Department of Pharmacology and Pharmacy
General Office, L02-56 2/F
Laboratory Block LKS Faculty of Medicine
The University of Hong Kong
21 Sassoon Road, Pokfulam
Hong Kong SAR, China
Tel: +852 2831 5110
E-mail: ewchan@hku.hk

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## Highlights

- Previous studies of statins have suggested both an increased and decreased risk of suicide attempt, depression, anxiety and seizure.
- In this self-controlled case series study, we find that the risks of suicide attempt, depression, anxiety or seizure were elevated even before statin initiation; remained elevated after a statin was first prescribed; and returned to baseline (i.e. non-exposure period) after 1 year of continuous statin treatment.
- Our study does not support a direct association between statin use and suicide attempt, depression, anxiety and seizure, whose risks could be explained by cardiovascular events, for which statins were prescribed.

## ABSTRACT

**Background** Risk of suicide attempt, depression, anxiety and seizure and the association with statins is an ongoing debate. We aim to investigate the association between statins and the above neuropsychological outcomes, in specific pre- and post-exposure time windows.

**Methods** We identified patients aged 40-75 years old who were dispensed a statin between January 1, 2003 and December 31, 2012 from the Hong Kong Clinical Data Analysis & Reporting System (CDARS), an electronic medical records database. Patients with new onset of suicide attempt, depression, anxiety and seizure were derived from the original dataset separately, in a self-controlled case series study design. A non-parametric spline-based self-controlled case series model was built to measure continuous changes of risk.

**Results** We identified 396 614 statin users. The risk of each outcome was elevated prior to statin initiation with incidence rate ratios of 1.38 (95% CI, 1.09-1.74) for suicide attempt, 1.29 (95% CI, 1.15-1.45) for depression, 1.35 (95% CI, 1.19-1.53) for anxiety, and 1.45 (95% CI, 1.21-1.73) for seizure. The incidence rate ratios remained elevated after the initiation of statins during the first 90 and 91-365 days after statin prescription and decreased to the baseline level after 1 year of continuous prescription.

**Limitations** CDARS includes prescription data but not adherence data, which could lead to misclassification of exposure periods.

**Conclusions** Our study does not support a direct association between statin use and suicide attempt, depression, anxiety and seizure, whose risks could be explained by cardiovascular events, for which statins were prescribed.



**Key words**

Statins, suicide attempt, depression, anxiety, seizure, self-controlled case series

## INTRODUCTION

Statins, inhibitors of the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme, are the most widely prescribed class of lipid-lowering medications.(Blais et al., 2021) They are recommended in the 2019 ACC/AHA guidelines as the first-line treatment for the prevention of atherosclerotic cardiovascular disease (ASCVD) in people with clinical ASCVD, severe hypercholesterolemia, diabetes and those with an ASCVD 10-year risk over 7.5%.(Arnett et al., 2019) Statins are reported to have potential pleiotropic effects through antithrombotic, anti-inflammatory and antioxidative pathways on different diseases including mental health and neurological disorders.(Yu and Liao, 2021) Patients with cardiovascular diseases generally have a higher risk of suicide attempt,(Larsen et al., 2010) depression(Rutledge et al., 2006) and anxiety(Easton et al., 2016) and cardiovascular comorbidities are common in people with seizure.(Shmuely et al., 2017) Previous studies of statins have suggested both an increased and decreased risk of suicide attempt, depression, anxiety and seizure.(Cham et al., 2016; Quintana-Pájaro et al., 2018) The uncertainty of the association between statin use and these adverse events can impact statin prescribing negatively.

A within-individual study published by Molero et al. used a stratified Cox proportional hazards regression model to assess the relationship between statin use and suicide attempt, depression, anxiety and seizure.(Molero et al., 2020) Although this study found a lower risk of depression and no association with suicide attempt, anxiety or seizure, a similar reduction was observed with other non-psychotropic medications and it was proposed that the true association required further investigation to clarify the possible contribution of non-specific treatment factors. Randomized controlled trial and a recent systematic review and meta-analysis found no association between statin use and depression.(Lee et al., 2021; Muldoon et al., 2000) Thus, the overall relationship between statin prescription and the above outcomes is uncertain. Cardiovascular disease itself has psychological impacts(Dhar and Barton, 2016; Hare et al., 2013; Huffman et al., 2013) and previous studies have reported that time-varying risk periods (pre-exposure and each prescription period) were associated with different levels of risk.(Man et al.,

2017; Man et al., 2020) The association between statins and the above psychological disorders could also be confounded by the time-varying diagnoses of ASCVD, hypercholesterolemia and diabetes, which are also the main indications for initiating statin therapy(Arnett et al., 2019) and should be considered when investigating the association between statins and suicide attempt, depression, anxiety and seizure. This study sought to assess the association between statin use and risks of suicide attempt, depression, anxiety and seizure by employing a self-controlled case series (SCCS) design and non-parametric SCCS model to measure continuous trends in risk changes adjusted for ASCVD, hypercholesterolemia and diabetes.

## METHODS

### Data Source

We used data from the Clinical Data Analysis and Reporting System (CDARS), which is an electronic health record database developed by the Hong Kong Hospital Authority, the statutory body managing all public hospitals and their ambulatory clinics in Hong Kong. The Hospital Authority provides services to over 7.4 million Hong Kong residents covering around 80% of all hospital admissions.(Leung et al., 2005) Patient-specific data in CDARS include diagnoses, procedures, prescription records, laboratory tests, demographics, and date of hospital admissions and discharges for research and audit purposes; data are anonymized to protect patient confidentiality and have been used in various investigations of medication safety in neuropsychological outcomes and have reported to be reliable.(Chai et al., 2020; Man et al., 2017; Man et al., 2020) The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW21-399). Informed patient consent was not required as the data used in this study were anonymized.

### Study Design

We used the self-controlled case series study design(Whitaker et al., 2006) to investigate the association between statin use and the risk of suicide attempt, depression, anxiety and seizure. Each patient serves as their own control and therefore time-invariant variables, such as genetic factors and socioeconomic profile, can be implicitly controlled. The diagnoses of ASCVD, hypercholesterolemia and diabetes were adjusted as time-varying factors by modeling a variable of their diagnosis date in the SCCS model, since they can impact statin prescription patterns and the development of psychological diseases. The SCCS allows us to estimate risk at pre-exposure and each risk period to explore the short-term and long-term risk changes. The pre-exposure risk accounts for the possibility that events might be driven by other factors rather than statin use and the comparison between pre-exposure and exposure period just after statin initiation demonstrates the association of statin initiation on each outcome event. The use of

nonparametric SCCS model allows us to model the continuous trend of risk changes and can therefore serve as a validation of the standard SCCS model. The self-controlled case series study design has been used previously to assess the association between a variety of exposures and outcomes.(Man et al., 2017; Man et al., 2020)

**Case Identification**

We defined cases as individuals aged 40 to 75 years who had received at least one statin prescription and experienced any one of the investigated events (suicide attempt, depression, anxiety and seizure) during the observation period. Individuals aged 40 to 75 years were included as they are the target population, according to the 2019 ACC/AHA guidelines, for the initiation of statins for primary prevention of ASCVD.(Arnett et al., 2019) Patients with each event were extracted separately for the corresponding analyses and patients who had more than one kind of event were included in each analysis separately (eFigure 1 in Supplement). Outcome events were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostics codes from the inpatient, outpatient and emergency department diagnosis records (eTable 1 in Supplement). Only the first diagnosis of each event was included in the main analysis as multiple diagnoses of the studied outcomes could be the same episode and one occurrence of event should not modify the risk of subsequent events.(Whitaker et al., 2006) Patients with previous diagnosis of suicide, depression, anxiety, and seizure before the start of the observation period (January 1, 2003) were excluded in the main analysis and were later included in one of the sensitivity analyses. If an individual developed more than one outcome during the observation period, the individual was included in the analyses of both outcomes, separately. The observation period of the main analyses was from Jan 1, 2003 to Dec 31, 2012 or the registered date of death, whichever was earlier. Patients who were given a statin prescription during the observation period were followed up until Dec 31, 2017 with an extra 5 years added to the observation period in the sensitivity analysis.

## Exposures

We identified all statin prescriptions and outcome events including suicide attempt, depression, anxiety and seizure. Statin prescriptions were defined as all formulations and strengths of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. As different statins might have different effects on the studied outcomes and most patients were prescribed simvastatin in Hong Kong, we also conducted sensitivity analysis to include only patients prescribed with simvastatin. We did not conduct analysis only evaluating patients prescribed with other statins because the sample size is too small. Exposed periods were defined as the duration between prescription start and end dates recorded in CDARS within the study period. Overlapped prescription records were integrated from the earliest start date of prescription until the latest end date of prescription. Drug discontinuation was defined as over 30 days of no prescription recorded and different discontinuation scenarios were considered in the sensitivity analysis. Risk periods for each patient encompassed 90 days before statin initiation (pre-exposure period), the 0-90 days exposure, 91 to 365 days exposure and >365 days exposure (subsequent prescription period); these periods were compared with >90 days before statin initiation (non-exposure periods excluding the 90 days pre-exposure period), which served as the baseline risk level. The study design and observation period category determination are illustrated in Figure 1. The event date was identified as the corresponding date of suicide attempt, depression, anxiety or seizure.

## Statistical Analysis

The association between statin use and the risk of suicide attempt, depression, anxiety and seizure was estimated by comparing the incidence rates of each event during the specific studied periods with the baseline periods to estimate incidence rate ratio (IRR) using conditional logistic regression. Age was adjusted by using 20 quantiles of the age distribution for patients with corresponding events. We conducted subgroup analysis stratified by different sex groups. In addition to the standard SCCS study design, we also used the non-parametric splined-based SCCS approach to model exposure time as a

continuous variable. A 5% significance level was considered statistically significant in all analyses. R, version 4.0.3 (http://www.R-project.org) was used for all data analysis.

**Sensitivity Analyses**

A series of sensitivity analyses were conducted to assess the robustness of this study: excluding patients diagnosed with the event on the first day of prescription; including individuals who experienced the events before the study period; extending follow-up of the same cohort until December 31, 2017; using 40 quantiles of the age distribution for age adjustment; different drug discontinuation scenarios considering less than 90 days of drug discontinuation as a continuous prescription; antipsychotics prescriptions were adjusted as time-varying factors; only including patients who were prescribed simvastatin; only including the first statin prescription period for each individual; including patients who were under 40 or over 75 years; diagnosis of myocardial infarction was used as a positive control as statins have demonstrated efficacy in treating or reducing the risk of myocardial infarction;(Chou et al., 2016) diagnosis of tinnitus was used as a negative control as it has no known association with statins and has previously been used as a negative control in other studies of statin therapy.(Burkard et al., 2018; Canis et al., 2011)

**Patient and public involvement**

Patients and the public were not involved in the design, conduct, reporting or dissemination plans for this research. The study was based on retrospective evaluation of existing electronic health records and all data used in this study were anonymized.

## RESULTS

Among 396 614 individuals aged 40 to 75 years with a statin prescription, half were male and most participants received simvastatin as their initial treatment (Table 1). The median (interquartile range [IQR]) age at commencement of observation was 58.43 (50.92-66.57) years and the median (IQR) duration of statin exposure for each individual was 746 (281-1443) days. The median length of each continuous prescription was 471 days (IQR, 150-1042 days). There were 577 patients who had attempted suicide and 2871, 3797, 1273 were diagnosed with depression, anxiety or seizure respectively before the start of observation period and were therefore removed from the analysis for each event (Supplement eFigure 1). This left 1701, 8361, 6968 and 3513 patients who had their first recorded suicide attempt, depression, anxiety or seizure, respectively, within the observation period and were thus included in further analyses.

The risks for all four outcomes of interest were elevated in the pre-exposure period with IRRs of 1.38 (95% CI, 1.09-1.74) for suicide attempt, 1.29 (95% CI, 1.15-1.45) for depression, 1.35 (95% CI, 1.19-1.53) for anxiety, and 1.45 (95% CI, 1.21-1.73) for seizure (Table 2) compared to baseline (>90 days before statin initiation). The risks remained elevated after statin initiation and gradually decreased after 1 year of continuous statin prescription with no evidence of a difference compared with the baseline period: respective IRRs were 0.87 (95% CI, 0.72-1.06), 0.95 (95% CI, 0.87-1.04), 1.02 (95% CI, 0.92-1.13) and 0.94 (95% CI, 0.83-1.08). Similar trends of time-varying risk were observed in the non-parametric SCCS model (Figure 2). Results from sensitivity analyses 1-9 and sex stratification analyses were consistent with the main analysis (Supplement eTables 2-11). The positive control analysis using myocardial infarction showed a 15-fold risk before statin initiation, which decreased to 0.72 (95% CI 0.68 to 0.76) after 90 days of statin treatment, compatible with statins having a direct preventive and treatment effect on acute myocardial infarction (eTable 12, Supplement eFigure 2A). Result from the negative control study showed no evidence of an association between statin use and new onset tinnitus throughout all exposure and non-exposure periods (eTable 13, Supplement eFigure 2B).

## DISCUSSION

In this study, we assessed the association between statin use and suicide attempt, depression, anxiety and seizure by using both standard SCCS and non-parametric SCCS models adjusted for diagnoses of ASCVD, hypercholesterolemia and diabetes during the pre-exposure period and specific exposure periods. Our results showed that the incidence of suicide attempt, depression, anxiety and seizure increased before statin initiation, and remained elevated during the first year of statin exposure, which suggests that the outcomes were not directly triggered by statin prescription. The elevated short-term risks after statin use could be driven by multiple factors or dynamic changes in physical status such as healthcare utilization, opportunity for diagnosis, and potential delay in diagnosing psychological disorders, which has been reported in previous studies.(Huerta-Ramírez et al., 2013; Kerr et al., 2016) After 90 days of prescription, the risk of the above events began to diminish, and returned to baseline levels after 1 year of prescription, suggesting that long-term use of statins was not directly related to any of the outcomes of interest.

Previous study reported that factors associated with cardiovascular disease could lead to psychological problems.(Dhar and Barton, 2016; Hare et al., 2013; Huffman et al., 2013) Statins were shown to have potential treatment effect for depressive symptoms(Yatham et al., 2019) while other large observational studies reported no association between statins and depression.(Köhler-Forsberg et al., 2019) The mixed effects of cardiovascular diseases, psychological disorders and direct pharmacological effects of statins are all relevant to this debate. Hence, we used the SCCS study design to enable measurement of risk changes at different periods of statin prescription. We explored the pre-exposure and specific exposure periods of statin use and found increased risks for the outcomes of interest, before statin prescription. This finding might be due to the concurrent events associated with cardiovascular disease, which later led to the decision to prescribe a statin. The differing duration of this risk-elevated period before the statin prescription can lead to varied results if we directly compare the risk of the whole exposure and non-exposure periods rather than specific exposure periods. Therefore, grouping the observation periods into

non-exposure, pre-exposure and specific exposure periods provided additional insight in measuring the risks. In this way, evidence of the time-varying relationship between statin initiation and suicide attempt, depression, anxiety and seizure could be better understood.

Our result does not support a direct association between statin use and the outcomes of interest, including depression. This is consistent with a randomized controlled trial(Muldoon et al., 2000) and a recent systematic review and meta-analysis. In addition, Molero et al. reported findings consistent with those in our study in terms of suicide attempt, anxiety and seizure, but differed regarding depression, for which they found a reduction in risk.(Molero et al., 2020) The authors interpreted the depression outcome to be a reflection of non-specific treatment factors rather than a direct neuroprotective mechanism. Our results suggest that the risk of depression was already elevated before the statin initiation. A possible reason for the increased risk before starting statin treatment is the occurrence of cardiovascular symptoms which have been found to be associated with depression.(de Jonge and Roest, 2012) Therefore, the reported protective effects on depression could be caused by setting an elevated risk level of depression as baseline. The risk of depression returned to the baseline level after 1 year of statin therapy suggesting that long-term effect is unlikely. It is also worth noting that most residents of Hong Kong are of southern Chinese ethnicity, differing from those in the Molero et al. study, which was based in Sweden. Asian populations are reported to be prescribed lower doses of statin and there are ethnic differences in the cholesterol-lowering effect of statins.(Naito et al., 2017) Further study is needed for the investigation of racial difference on these outcomes.

We adjusted for the diagnoses of ASCVD, hypercholesterolemia and diabetes as time-varying factors in the SCCS model as they could both impact the decision to start statin treatment and also increase the risks of suicide attempt, depression, anxiety and seizure.(Dhar and Barton, 2016; Hare et al., 2013; Huffman et al., 2013) Patients with these conditions were the main groups defined in the 2019 ACC/AHA Guideline(Arnett et al., 2019) on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Some studies explained the association between statins and psychological

disorders through their pleiotropic effects, including plaque stability and vascular inflammation but the evidence supporting a direct pleiotropic effect of statins on neuropsychological disorders is limited.(Yu and Liao, 2021) Statins are reported to have a direct prevention and treatment effect on myocardial infarction.(Chou et al., 2016) In our positive control analysis, the risk of myocardial infarction dropped from 15-fold to baseline level, upon commencement of a statin. The negative control analysis showed no association between statins and tinnitus throughout all pre-exposure and exposure period. The observed time-trends for both the positive and negative control outcomes, therefore, differ from those for suicide attempt, depression, anxiety and seizure, which suggests that there is no direct association between statins and these outcomes.

**Limitations**

Our study has some limitations. First, CDARS includes prescription data but not adherence data, which could lead to misclassification of exposure periods. Therefore, we tested our findings on different drug discontinuation time periods and the results were consistent. Second, our results showed an increased risk during 0-90 days exposure compared to the 90 days pre-exposure period. Although we explained the acute risks possibly driven by healthcare utilization, opportunity for diagnosis, and potential delay in diagnosing psychological disorders, whether there is an acute risk after initiating statins requires further studies. Third, in our non-parametric models, trends of increased risk of depression, anxiety and seizure can be observed after 6 months of statin treatment. This could be explained by some patients discontinuing statins after a relatively long prescription period. The wide confidence intervals also demonstrate uncertainty and data are sparse for long-term statin users. Fourth, we only have records of antipsychotics but not antidepressants, antiepileptics and anxiolytics prescriptions for statin users in our dataset. We can only adjust antipsychotics prescriptions as time-varying factors and the results were consistent with the main analysis. Fifth, as CDARS only uses ICD-9-CM to code diagnosis records and we are not able to use ICD-10-CM for this study. Sixth, due to our data availability, we were not able to censor the patients for emigration. Seventh, only some of the studied outcomes were validated in previous

studies. However, as data were reported to be reliable in previous studies,(Chai et al., 2020; Man et al., 2017; Man et al., 2020) this was unlikely to affect our results. Last, CDARS only contains records of all public hospitals but not private hospital in Hong Kong and this could affect the generalizability of our results.

**Clinical implications**

To our knowledge, this is the first study using both standard and non-parametric SCCS study designs to investigate the association between statin use and risk of suicide attempt, depression, anxiety and seizure. We examined the risks at pre-exposure and specific exposure periods compared with non-exposure periods within the same individual, and adjusted the diagnoses of ASCVD, hypercholesterolemia and diabetes diagnoses as time-varying covariates. The results thus provide new evidence to inform the debate about statins and psychological disorders.(Köhler-Forsberg et al., 2019; Macedo et al., 2014; Yatham et al., 2019) As the risk of all outcomes increased before statin use, remained elevated after statin initiation and then returned to baseline levels, traditional observational study designs could miss the risk change during statin use at each prescription. The modelling of non-parametric SCCS provides a comprehensive description of continuous risk changes. This study also adds to the evidence of statin safety in non-white populations since most residents of Hong Kong are of southern Chinese ethnicity.

**Conclusions**

In this population-based study from Hong Kong, the risks of suicide attempt, depression, anxiety and seizure were elevated before statin use, remained elevated after statin initiation and gradually declined to the baseline level during the first year of therapy. Our study does not support a direct association between statin use and suicide attempt, depression, anxiety and seizure and there was no suggestion of a protective effect. These events are more likely caused by the medical conditions which lead to prescription of statins.

## Conflict of interest

JFH is supported by UKRI grant MR/V023373/1, the University College London Hospitals NIHR Biomedical Research Centre and the NIHR North Thames Applied Research Collaboration. JFH has received consultancy fees from Wellcome Trust and juli Health. ICKW reports research funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong RGC, and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, and also received speaker fees from Janssen and Medice in the previous 3 years. He is also an independent non-executive director of Jacobson Medical in Hong Kong. EWC has received honorarium from the Hospital Authority, research grants from Research Grants Council (RGC, HKSAR), Research Fund Secretariat of the Food and Health Bureau (HMRF, HKSAR), National Natural Science Fund of China, National Health and Medical research Council (NHMRC, Australia), Welcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, and Narcotics Division of the Security Bureau of HKSAR, outside the submitted work. All other authors declare no competing interests.

## Author contributions

All authors qualify for authorship based on ICMJE criteria. XY, JEB, ICKW and EWC designed the research. XY and JEB conducted the analyses, with support from VWSN, DC, JFH, YW, WK, LG and VKCY. XY wrote the paper, with detailed input from all co-authors. All authors contributed to the interpretation of the results, and have approved the final paper.

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**Availability of data and materials**

CDARS data is not available to the public.

**Ethical approval and consent to participate**

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW21-399). Informed patient consent was not required as the data used in this study were anonymized.

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Table 1. Characteristics of 396 614 individuals with statin prescriptions from 2003 to 2012

| **Characteristics** | |
|---|---|
| Sex | |
| Male | 205 625 (51.85%) |
| Age at start of study period, median (IQR) | 58.43 (50.92-66.57) |
| Days of statin exposure for each individual, median (IQR) | 746 (281-1443) |
| Days of a continuous prescription, median (IQR) | 471 (150-1042) |
| Statin drug at the start of treatment | |
| Simvastatin | 329 778 (83.15%) |
| Atorvastatin | 43 701 (11.02%) |
| Fluvastatin | 14 558 (3.67%) |
| Rosuvastatin | 7 743 (1.95%) |
| Pravastatin | 666 (0.17%) |
| Lovastatin | 168 (0.04%) |
| Individuals with new onset of outcome event during the overall study period / during exposure periods / during non-treatment period) | |
| Suicide attempt | 1 701 (899; 1 102) |
| Depression | 8 361 (3 474; 4 887) |
| Anxiety | 6 968 (2 309; 4 659) |
| Seizure | 3 513 (2 009; 1 504) |
| Follow-up time of individuals with new onset of outcome event during the overall study period / during exposure periods / during non-exposure periods, person-years | |
| Suicide attempt | 16 326 (4 612; 11 714) |
| Depression | 80 216 (24 736; 55 480) |
| Anxiety | 68 544 (19 664; 48 880) |
| Seizure | 31 933 (10 776; 21 157) |

Abbreviation: IQR, interquartile range.

Table 2. Incidence rate ratios of each study outcome for each pre-exposure exposure period in Hong Kong from 2003-2012

| Risk Period | Number of events | Person-years | Crude incidence rate (per 100 person-years) | Adjusted IRR (95% CI) | *P* Value |
|---|---|---|---|---|---|
| Suicide Attempt (n = 1 701) | | | | | |
| Baseline | 1018 | 11127 | 9.1 | Reference | |
| 90 days pre-exposure | 84 | 587 | 14.3 | 1.38 (1.09-1.74) | 0.01 |
| 0-90 days exposure | 120 | 537 | 22.3 | 1.90 (1.54-2.33) | <.01 |
| 91-365 days exposure | 153 | 1189 | 12.9 | 1.05 (0.87-1.28) | 0.61 |
| >365 days exposure | 326 | 2886 | 11.3 | 0.87 (0.72-1.06) | 0.17 |
| Depression (n = 8 361) | | | | | |
| Baseline | 4567 | 52655 | 8.7 | Reference | |
| 90 days pre-exposure | 320 | 2825 | 11.3 | 1.29 (1.15-1.45) | <.01 |
| 0-90 days exposure | 910 | 2667 | 34.1 | 3.21 (2.96-3.49) | <.01 |
| 91-365 days exposure | 892 | 6088 | 14.7 | 1.34 (1.23-1.46) | <.01 |
| >365 days exposure | 1672 | 15981 | 10.4 | 0.95 (0.87-1.04) | 0.26 |
| Anxiety (n = 6 968) | | | | | |
| Baseline | 4381 | 46474 | 9.4 | Reference | |
| 90 days pre-exposure | 278 | 2406 | 11.6 | 1.35 (1.19-1.53) | <.01 |
| 0-90 days exposure | 536 | 2240 | 23.9 | 2.54 (2.30-2.80) | <.01 |
| 91-365 days exposure | 597 | 4955 | 12 | 1.26 (1.14-1.40) | <.01 |
| >365 days exposure | 1176 | 12469 | 9.4 | 1.02 (0.92-1.13) | 0.75 |
| Seizure (n = 3 513) | | | | | |
| Baseline | 1355 | 20037 | 6.8 | Reference | |
| 90 days pre-exposure | 149 | 1120 | 13.3 | 1.45 (1.21-1.73) | <.01 |
| 0-90 days exposure | 509 | 1050 | 48.5 | 3.32 (2.95-3.75) | <.01 |
| 91-365 days exposure | 528 | 2496 | 21.2 | 1.42 (1.25-1.60) | <.01 |
| >365 days exposure | 972 | 7230 | 13.3 | 0.94 (0.83-1.08) | 0.38 |

Abbreviation: IRR, incidence rate ratio.

Figure 1. Self-controlled case-series study design. * An outcome event can occur any time during the observation period.

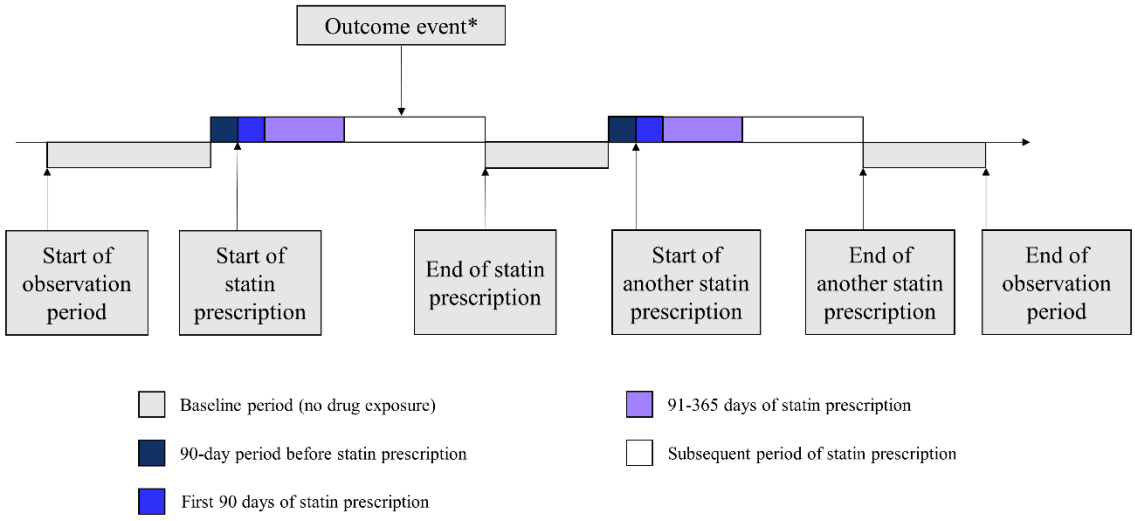

Figure 2. Results from the non-parametric spline-based self-controlled case series models for suicide attempt, depression, anxiety and seizure.