Understanding the association between antidepressants and the risk of being diagnosed with dementia in older people: a self-controlled case series study

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ABSTRACT

BACKGROUND: Given concerns about adverse outcomes for older people taking antidepressants in the literature, we investigated whether taking antidepressants elevates the risk of dementia.

OBJECTIVE: This study aims to investigate the putative association of antidepressants with the risk of dementia.

***METHODS*:** We conducted a population-based self-controlled case series analysis of older people with dementia and taking antidepressants, using territory-wide medical records of 194,507 older patients collected by the Hospital Authority of Hong Kong, to investigate the association between antidepressant treatment and the risk of developing dementia in older people.

RESULTS: There was a significantly higher risk of being diagnosed with dementia during the pre-drug-exposed period (incidence rate ratio (IRR) 20.42 (95% CI: 18.66-22.34)) compared to the non-drug-exposed baseline period. The IRR remained high during the drug-exposed period (IRR 8.86 (7.80-10.06)) before returning to a baseline level after washout (IRR 1.12 (0.77-1.36)).

CONCLUSIONS: The higher risk of dementia before antidepressant treatment may be related to emerging psychiatric symptoms co-occurring with dementia, which trigger medical consultations that result in a decision to begin antidepressants. Our findings do not support a causal relationship between antidepressant treatment and the risk of dementia.

Key words: Dementia, Alzheimer's disease, Antidepressants, Self-controlled case series studies, Causal associations

INTRODUCTION

Dementia is a major cause of disability and dependency in older people [1]. It has become increasingly prevalent worldwide as the population ages, and it is associated with significant healthcare and economic burden [1],[2],[3]. However, there is convincing evidence that dementia is not inevitable in the course of ageing [2]. Significant efforts are thus being made to identify potentially-modifiable risk factors of dementia in older people, especially those that influence the early stage of the disease progression, when intervention might provide the most therapeutic benefit [4]. Potentially-modifiable risk factors for dementia include hypertension, obesity, hearing loss, depression, physical inactivity, social isolation and diabetes [5]. Among the risk factors that have been studied, the relationship between antidepressants and dementia in the elderly remains contentious. For instance, whilst concerns have been raised that taking tricyclic antidepressants (TCA) poses an increased risk for the onset of dementia in older people [5,6], there is conflicting evidence that treatment of depression in the elderly using TCA is associated with a reduced [7], or a negligible [8], risk of dementia.

These controversial findings are likely caused by the complex confounding effects on the association between taking antidepressants and dementia, of pre-existing mental health conditions, coupled with the high prevalence of comorbid mental health issues in patients treated with antidepressants [9]. For example, depression is a potential confounder for dementia [10], and the disease processes

itself may also lead to the onset of dementia [10]. Thus the reason for being prescribed antidepressants may underlie this argument. Moreover, antidepressants can also be prescribed for the management of health concerns other than depression. It has been reported that approximately 50% of antidepressants are prescribed for other conditions (such as off-label indications for prescription e.g. schizophrenia, insomnia or incontinence) [11]. These conditions might indicate other issues of cognitive distress or body systems deterioration, for which diseases of the nervous system and cerebral cortex (including dementia) are important complications [12–14].

Consequently, research designs applied to test causal associations between antidepressants and dementia must take account of potentially-complex confounding variables. Research to date has used standard epidemiological case-control and cohort study designs to examine associations between antidepressants and dementia. These studies reported the possibility of causal relationships between antidepressant drugs and dementia, but controlled for none or only some, mental health-related disorders [5–8]. This paper reports the use of a self-controlled study design (Self-Controlled Case Series (SCCS)) developed to investigate associations between an exposure (antidepressant prescriptions) and an outcome of interest (dementia), using only data on cases. The within-individual inference enabled controlling for any fixed covariate effect.

MATERIALS AND METHODS

ETHICS APPROVAL

The study protocol was approved by the Hospital Authority of Hong Kong ethics committee KC/KE-19-0001/ER-2.

AIM

This study aimed to characterize the association of taking antidepressants with the risk of being diagnosed with dementia, in people aged 65 years and over.

DATA SOURCE

Access to comprehensive territory-wide deidentified electronic inpatient health records was provided by the Hospital Authority of Hong Kong (HKHA), a statutory body that manages all Hong Kong public hospitals and their ambulatory clinics. The HKHA services are available to all Hong Kong residents (>7.3 million), reflecting approximately 80% of all hospital admissions [15]. The HKHA collects and collates public-sector inpatient, outpatient, and emergency department admissions records. The HKHA electronic health records have been validated, and previously used for investigations of medication safety [16–21]. The patient-level data includes diagnosis, prescription, information on hospital admissions and discharges, payment method, and prescription and dispensing information.

OBSERVATION PERIODS

For this study, the observation periods began on January 1, 2008, or the 65th birthday of the patient (whichever was later) and ended on December 31, 2010, or date of registered death (whichever was earlier) (a three year study period). We also imposed a five-year pre-study window as a historical period for index dementia diagnosis.

SELECTION CRITERIA

INCLUSION CRITERIA

Eligible participants were aged 65 years or older with a first-ever (index) diagnosis of dementia, which occurred any time during the three-year study period. Dementia diagnoses were identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of Alzheimer disease (331.0), frontotemporal dementia (331.1), dementia with Lewy bodies (331.82), mild cognitive impairment (331.83), vascular dementia (290.4x), and other/nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.1, 294.2x, and 294.8). This method of identifying people with dementia is consistent with previous studies [22,23]. We further included ICD-9-CM codes 296.x, 296.90, 300.4, 309.0, 309.28 and 311 as depression-related disorders[24] for the *post-hoc* analysis (Refer to Table S1 for detailed names).

Because of the concerns that repeat coding of the index dementia diagnosis might be found within the database, we considered only those potentially-eligible people with no dementia diagnosis in their historical electronic medical records (five years before study entry). This assumed that the index dementia event was correctly identified as occurring during the study period. Subsequent dementia diagnoses (if

any) were excluded from the analysis.

Potentially eligible participants also required at least one antidepressant medicine to be prescribed during the study period. Antidepressants were identified using British National Formulary (BNF) codes 4.3.x, specifically, tricyclic and related antidepressant drugs (4.3.1), monoamine-oxidase inhibitors (4.3.2), selective serotonin re-uptake inhibitors (4.3.3), and other antidepressant drugs (4.3.4). Refer to supplementary Table S2 for detailed drug names and their distributions within the database.

EXCLUSION CRITERIA

Potential subjects were excluded if (a) their antidepressant drug-exposure was shorter than seven days (to eliminate the impact of potentially-ineffective exposures) and/or (b) the washout period and subsequent exposure to antidepressants overlapped (thus violating model assumptions) [25].

STUDY DESIGN

A Self-Controlled Case Series (SCCS) design was used [25]. This design relies on within-person comparisons in a population of individuals who have experienced both the outcome and exposure of interest. A major advantage of this design over classic case-control and cohort study designs is that it allows for controlling for potential effects of measured and unmeasured time-invariant confounders that vary between individuals, such as underlying health status, genetic factors, hospital location,

underlying frailty, socio-economic status, etc. Using this design also enabled us to adjust for time-varying factors, such as age, which is a known associate of the onset of dementia [2].

MEASUREMENT PERIODS AND EVENT DATE

The default *baseline period*, and four *measurement periods* were defined. Firstly, the drug-exposed period was defined as time receiving antidepressants, with the duration between prescription start and end dates recorded within the database for each prescription episode. Drug-exposed period was further classified as *index drug-exposed period* and *subsequent drug-exposed period.* The index drug-exposed period was defined as the first time subjects received antidepressant medication. There were two other measurement periods: *pre-exposure period (50 days prior to index antidepressant prescription)* and *post-exposure period (washout period)*. The pre-exposure and post-exposure periods enabled comparison of dementia rates prior to, and after, index antidepressant episode. The washout period was applied after index drug-exposure ceased, as drugs generally require time to be excreted from body systems. We applied a washout period only after the index antidepressant administration, because subsequent washout periods (if any) might be influenced by previous drug administrations. All remaining time within the observation period constituted the baseline period, to which the measurement periods were compared. Each participant at baseline was allocated a (default) risk of dementia (risk=1).

It was possible that (presumed) continuous drug-exposed periods might have

been interrupted for a range of reasons [17,26]. We designed an algorithm (see *pseudo-codes* in the supplementary information) to obtain continuous treatment periods. We set the lengths of pre-exposure period and washout period to an arbitrary 50 days, and relevant sensitivity analyses were performed to examine the effects of the settings of the lengths of pre-exposure period and washout period. The study design and data capture periods are outlined in Figure 1.

The date of first lifetime dementia diagnosis in the HKHA Electronic Health Record (EHR) was defined as the event date. Only the first recorded dementia event for each patient during the study period was included in the analysis.

##########Figure 1#########

Figure 1. Illustration of different periods and study design for a hypothetical patient. The symbol “]” indicated that the corresponding day was included in the interval to the left.

ANALYSES

MAIN ANALYSIS

The association between antidepressant treatment and dementia diagnosis was calculated by comparing the rate of dementia diagnosed during the four measurement periods, with that during the baseline period. Specifically, the crude incidence rate per 1000 patient-days (CIR) (unadjusted by age) was calculated by dividing the number of events by the patient-days for each period [16]. The age-adjusted Incident Rate Ratio (IRR) was calculated in the standard SCCS analysis by modeling dementia diagnoses within individuals as a non-homogeneous, age-dependent Poisson process and contrasting incident rates within the same individual's person-time [25], using age in 365-day bands.

In addition to standard SCCS analysis, the nonparametric spline-based SCCS approach was applied to investigate risk changes during the observation period [27].

A significance level of 5% was applied in all statistical analyses. Python (version 3.6) and R (version 3.3.2) were used for data processing and analysis. Relevant codes are publically available (https://github.com/zhongzhixu/SCCS).

SENSITIVITY ANALYSES

Sensitivity analyses were conducted for: (a) gender differences; (b) the length of the washout period; (c) the length of the pre-exposure period; (d) the exclusion of individuals who died during the study period; (e) the exclusion of individuals whose drug duration was less than 30 days; (f) age-adjustment using 200-day age bands

and 500-day age bands; and (g) the association of dementia and sub-categories of antidepressant drugs (i.e. BNF 4.3.1-4.3.4).

POST-HOC ANALYSIS

Post-hoc analysis was conducted to investigate whether depression-related disorders may confound the case-control study designs and cohort study designs, using the whole population within the database, to test prevalence among different subsets.

RESULTS

Of the 194,507 people aged 65+ years in the database, 24,646 (12.6%) received a diagnosis of dementia during the period under study, and of these, 18,825 received their first lifetime diagnoses of dementia. Moreover, 3,757 (20.0%) had been prescribed antidepressants during the study period. We further excluded 1,300 people whose drug exposure periods were less than seven days or not available, and 71 patients whose washout period and subsequent drug-exposed period overlapped. As a result, 2,386 eligible participants were included for SCCS modeling (837 (35.1%) men; mean sample (SD) age at the point of enrolment was 81.7 (7.26) years). The characteristics of the included participants are described in Table 1. 837 men and 1549 women had developed dementia during the observation period (Table 1). The ratio between women and men is 1.85, which is aligned with previous studies showing that women with Alzheimer's disease, the most common cause of dementia, outnumber men by nearly 2 to 1 [28–31]. Researchers have hypothesized that this is due to longer life expectancy of female and the neurobiological vulnerability in postmenopausal females [32,33].

##########Table 1##########

During the study period, 3.6% (85/2,386) eligible participants died and their observation periods were censored by the date of death. Figure 2 empirically demonstrates the event-exposure time-series patterns, by illustrating the distribution of the number of patients with different time intervals. The CIRs of developing dementia in the different risk windows are summarized in Table 2.

##########Figure 2#########

Figure 2. Distribution of the number of patients with different time intervals. The time interval of a patient is defined as the gap between the date receiving a diagnosis of dementia and the date initiating drugs.

The standard SCCS analysis indicated some association between the decision to start antidepressant treatment and dementia (Table 3). More specifically, a higher risk of receiving a diagnosis of dementia was observed during the index drug-exposed period (IRR, 8.86, 95% confidence interval, 7.80 to 10.06) and subsequent drug-exposed period (IRR, 4.83, 95% CI, 3.28-7.13), relative to the baseline period. The IRR during the pre-exposure period (IRR 20.42; 95% CI 18.66-22.34) was significantly higher than any other period. The IRR during the washout period was 1.12 (95% CI: 0.77-1.36) (similar to baseline).

############Table 2###########

############Table 3###########

Subsequent analysis using the nonparametric, spline-based SCCS demonstrated that the risk of developing dementia increased significantly before the initiation of antidepressant treatment, and peaked within 50 days before treatment (Figure 3). The risk pattern is consistent with the results from the standard SCCS

analysis.

##########Figure 3#########

Figure 3. Association between the timing of drug exposure and the risk of dementia using spline-based Self-Controlled Case Series. The solid line is the estimated Incidence Rate Ratio (IRR) curve, the dashed blue lines indicate the 95% CI.

We further examined the association of dementia diagnosis with different antidepressant types. During the study period, 22 different antidepressant drugs were prescribed. Considering the major drug classes, of the 2386 participants, 987 (41.37%) were prescribed tricyclic and related antidepressant drugs (TCAs, BNF 4.3.1), three (0.13%) were prescribed monoamine-oxidase inhibitors (MAOIs, BNF 4.3.2), 1338 (56.08%) were prescribed selective serotonin re-uptake inhibitors (SSRIs, BNF 4.3.3), and 300 (12.57%) patients were prescribed other antidepressant drugs (BNF 4.3.4). There was a higher number of antidepressant drugs (2631) prescribed than the total number of participants (2386) (average 1.1 types per-patient).

Tables 4-6 report the CIRs and SCCS analyses for the three major drug subcategories respectively, using the same population as the main analysis. Analysis was not undertaken on subjects who took MAOIs because of the small numbers. Figure 4 and Supplementary Table S2 reports a detailed distribution of the number of patients using different drugs. The analyses for each subcategory (Table 4-6), each gender (Table S3-S4), and the additional sensitivity analyses (supplementary Table S5-S12), are consistent with the main results

##############Tables 4-6############

##########Figure 4#########

Figure 4. Distribution of the number of patients using different drugs.

Post-hoc analysis indicated that during the study period, the prevalence of receiving a first-ever dementia diagnosis among people experiencing depression-related disorders was 26.6% (648/2432) which was 2.7 times higher than the prevalence of a first-ever dementia diagnosis among the whole population (9.7%, 18825/194507).

We examined the time intervals between two dementia diagnoses (which could have been the result of repeated coding). The mean (SD) of the time interval between two dementia diagnoses in the whole population was 114.14 (157.27) days. This indicated that our admission criterion of five years' retrospective was appropriately strict to ensure that we captured people who truly had a first lifetime development of dementia within the study timeframe.

DISCUSSION

This pharmacoepidemiologic SCCS analysis, conducted in a large-sample, comprehensive, territory-wide electronic health record database, found an elevated risk of being diagnosed with dementia during the index exposure to antidepressants, compared to baseline. This is consistent with findings from other case-control and cohort studies [5–8,11]. However, our results do not support earlier conclusions [5–8] that a causal association between antidepressant treatment and the development of

dementia may exist (i.e. antidepressant drugs may increase the risk of dementia). We present the following evidence to support our claims: (a) both the main analysis and the sensitivity analyses supported a higher risk of being diagnosed with dementia during the 50-day pre-exposure period, higher even than the index drug-exposed period. This finding was also supported by the nonparametric spline-based SCCS analysis, where the IRR peaked before the index drug initiation date, then decreased. A possible explanation for such a risk pattern is that the observed increased risk of developing dementia is not due to antidepressant treatment but in fact precedes it, perhaps reflecting changes in comorbid depressive complications and/or associated impairment that lead to a medical consultation, which in turn may contribute to the decision to prescribe antidepressant drugs; (b) both the main analysis and the sensitivity analyses indicated that the IRR of developing dementia during the washout period was similar to the default risk allocated to the baseline period. Since there was no obvious washout effect, it was reasonable to deduce that there is no effect of antidepressant drugs on dementia; and (c) the post-hoc analysis indicated that during the study period, the prevalence of a first-ever diagnosis of dementia among people diagnosed with depression was approximately three times as high as the dementia prevalence among the general population. This indicates that depression-related disorders may be closely associated with dementia and this should be strictly controlled in correlation models for prescription of antidepressant drugs and the development of dementia. Earlier studies [5–8] reporting a potential causal-relationship between antidepressant drugs and the risk of being diagnosed

with dementia controlled for none or only part of depression-related disorders.

Furthermore, diagnosed depression is not the only factor that should be controlled for in a case-control study design or a cohort study design that examines an association between antidepressant drugs and dementia. This is because almost half of the antidepressant prescriptions are for other (on or off-label) indications of other mental health-related disorders such as anxiety disorders, schizophrenia and insomnia [11], with which dementia usually co-occurs [34]. Indeed, mental health-related disorders of antidepressant drug users might indicate cognitive deterioration (co-occurring with diseases of the nervous system and cerebral cortex (including dementia)). Thus, a strong association between dementia and antidepressant drugs under these circumstances again may not indicate a true causal relationship [9]. However, even if all of these factors are considered, misdiagnosis (both over- and under-diagnosis) for mental disorders is not uncommon [35,36]. As a result, information on relevant diagnoses may not be available for patients who are experiencing mental disorders [35]. This may well bias findings, and lead to concerns about unmeasured confounders.

Consequently, a case-control or a cohort study design may not be the most appropriate for studies aiming to conclude causal associations, because those designs may not have the capacity to comprehensively control for important confounding variables. We propose that an SCCS design may be a better way of examining whether an exposure truly represents a risk factor for an event because the design eliminates all time-invariant confounders among individuals (including

mental disorders) and introduces temporal awareness around the event of interest. This approach has been successfully applied in other epidemiological studies which, for example, explore the association between herpes zoster and stroke [37], or the association between methylphenidate treatment with suicide attempts [16], psychosis [17] and seizures [18].

Given that this study's results do not support the argument that antidepressant treatment is causally associated with dementia, suggestions to reduce exposure to antidepressant drugs in older people [5] must be prudently considered, because of the potential harm of stopping antidepressant drugs that could worsen symptoms of depression, incontinence, or pain, for which antidepressants have been prescribed. Although our findings do not support a causal relationship between antidepressant treatment and the risk of dementia, the risk of dementia is still very high (IRR 8.86) following the exposure to antidepressants (Table 3 and Figure 3). This indicates that, the psychiatric symptoms of patients who begin antidepressants may be triggered by the progression of cognitive disorders. Therefore, we recommend follow up including the cognitive testing to identify these patients, so that cognitive disorders including dementia can be treated early.

There were only three patients who were prescribed MAOIs (BNF 4.3.3) during the study period. This is probably because MAOIs are older types of antidepressants with a wide range of side effects. According to the Hong Kong drug office [38], this drug is only suggested as a second-line intervention if other antidepressants are not effective.

The SCCS method has been adopted in many publications previously. However, we have observed several drawbacks: (a) Standard SCCS only accepts non-overlapping segments, whereas some studies may not ensure this. Our study potentially faced the same pitfalls, where there was a possibility that the washout period and period of subsequent antidepressant use may overlap. We attempted to exclude these individuals (71) to fulfill the SCCS model assumption; (b) The spline-based SCCS [27,39] use splines to smooth the exposure effect. As a result, the potential association trend between the timing of drug exposures or other risks, and adverse events, can be continuously depicted. However, we found that the spline-based SCCS method is underutilized by researchers to date.

Study limitations. Our study design had potential limitations. For example, a possible time lag between the time of developing dementia and the time of a formal clinical diagnosis of dementia may exist. However, to the best of our knowledge, extracting diagnoses from electronic medical records is the most efficient (if not the only feasible) way to access comprehensive and large-scale database information (including prescriptions) among a population with dementia. More importantly, in this study, if there was a time lag between developing dementia and its diagnosis, this will not contradict our conclusions.

CONCLUSIONS

The observed higher risk of dementia before the commencement of antidepressant treatment may reflect emerging psychiatric symptoms, which can co-occur with dementia. These symptoms could trigger medical consultations where a decision is made to begin antidepressant treatment. Therefore, the findings of this pharmaco-epidemiologic study do not support a causal association between antidepressant treatment and the risk of being diagnosed with dementia.

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Conflicts of interest

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DECLARATIONS

Ethics approval:

The study protocol was approved by the Hospital Authority of Hong Kong ethics committee KC/KE-19-0001/ER-2.

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Authors' contributions:

ZX, JY, QZ and ICKW formulated the idea. ZX, ICKW and KKL performed the literature review. ZX and JY developed the model and conducted the experiments. ZX, JY, ICKW, QZ and SFPY analysed and interpreted the results. ZX, KKL, ICKW, QZ and SFPY wrote the article. All authors read and approved the final manuscript.

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Table 1. Characteristics of participants.

Characteristics	No. of patients	Age at the point of enrolment, Mean (SD)	Number of days of the drug duration (Range)	Drug-exposed period		Other periods	
				No. of events	Patient-days	No. of events	Patient-days
All	2386	81.70 (7.26)	55 (7 - 363)	403	131884	1983	2480786
Men	837	79.42 (7.15)	58 (7 - 297)	139	48274	698	868241
Women	1549	82.93 (7.02)	54 (7 – 363)	264	83610	1285	1612545

Table 2. CIRs of dementia being diagnosed in different periods.

Periods	No. of events	Patient-days	CIR per 1000 patient-days
Pre-exposure period	1010	117355	8.61
Index drug-exposed period	362	109631	3.30
Washout period	50	114490	0.44
Subsequent drug-exposed period	41	22253	1.84
Baseline period	923	2254234	0.41

Table 3. Results of the standard SCCS analysis

Periods	IRR (95% CI)	P-value
Baseline period	(default) 1	
Pre-exposure period	20.42 (18.66-22.34)	<0.001
Index drug-exposed period	8.86 (7.80-10.06)	<0.001
Washout period	1.12 (0.77-1.36)	<0.1
Subsequent drug-exposed period	4.83 (3.28-7.13)	<0.001

Table 4. Sensitivity analysis restricting to patients taking TCAs (No. of patients = 987)

Periods	No. of events	Patient-days	CIR per 1000 patient-days	IRR (95% CI)	P-value
Pre-exposure period	424	48602	8.72	22.06 (19.15-25.42)	<0.001
Index drug-exposed period	167	48105	3.47	10.16 (8.38-12.33)	<0.001
Washout period	21	47382	0.44	1.12 (0.72-1.74)	<0.1
Subsequent drug-exposed period	18	8882	2.03	5.38 (2.99-9.70)	<0.001
Baseline period	357	929503	0.38	1	

Table 5. Sensitivity analysis restricting to patients taking SSRIs (No. of patients = 1338)

Periods	No. of events	Patient-days	CIR per 1000 patient-days	IRR (95% CI)	P-value
Pre-exposure period	555	65849	8.43	19.34 (17.16-21.79)	<0.001
Index drug-exposed period	197	61754	3.19	8.16 (6.88-9.67)	<0.001
Washout period	27	64286	0.42	0.95 (0.64-1.39)	<0.1
Subsequent drug-exposed period	26	14421	1.80	4.92 (3.04-7.94)	<0.001
Baseline period	533	1262431	0.42	1	

Table 6. Sensitivity analysis restricting to patients taking other antidepressant drugs (No. of patients = 300)

Periods	No. of events	Patient-days	CIR per 1000 patient-days	IRR (95% CI)	P-value
Pre-exposure period	116	14503	8.00	17.73 (13.74-23.89)	<0.001
Index drug-exposed period	46	12728	3.61	9.15 (6.42-13.04)	<0.001
Washout period	8	14455	0.55	1.22 (0.60-2.50)	<0.1
Subsequent drug-exposed period	8	4104	1.95	2.57 (0.78-8.53)	<0.01
Baseline period	122	284274	0.43	1	

Figure 1

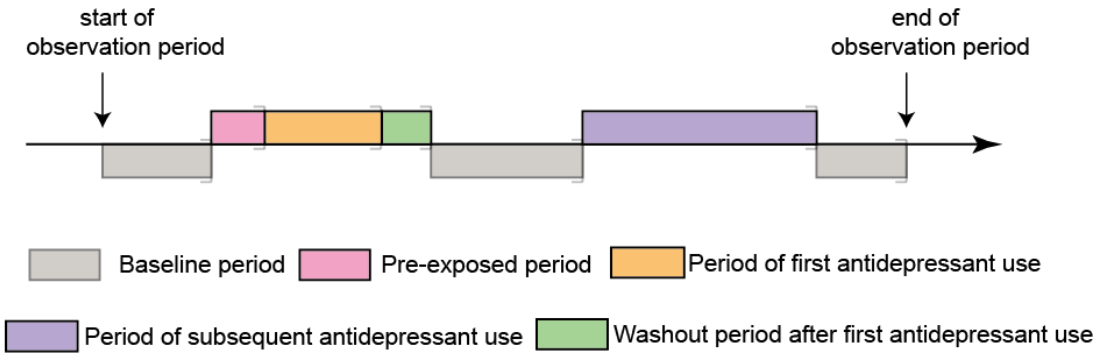

Figure 1. Illustration of different periods and study design for a hypothetical patient. The symbol “]” indicated that the corresponding day was included in the interval to the left.

Figure 2

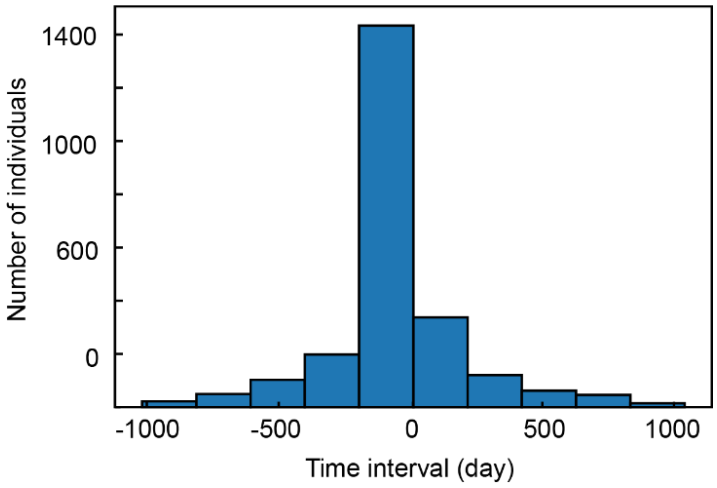

Figure 2. Distribution of the number of patients with different time intervals. The time interval of a patient is defined as the gap between the date receiving a diagnosis of dementia and the date initiating drugs.

Figure 3

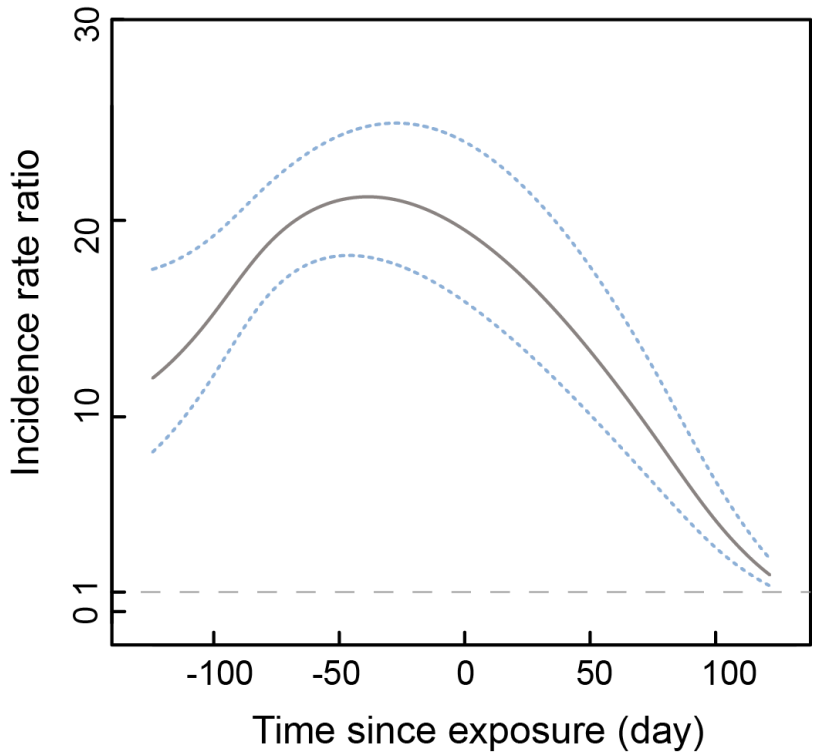

Figure 3. Association between the timing of drug exposure and the risk of dementia using spline-based Self-Controlled Case Series. The solid line is the estimated Incidence Rate Ratio (IRR) curve, the dashed blue lines indicate the 95% CI.

Figure 4

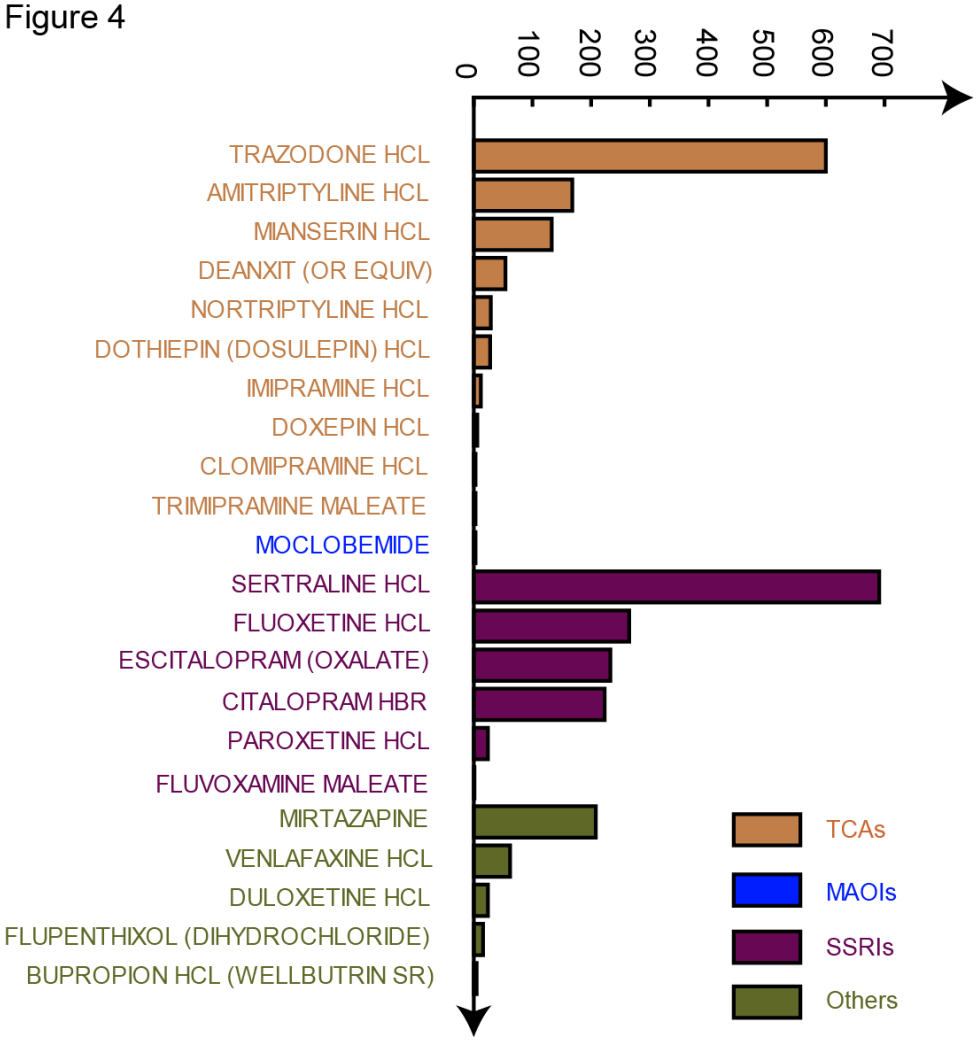

Figure 4. Distribution of the number of patients using different drugs.

Supplementary materials of the manuscript entitled

Understanding the association between antidepressants and the risk of being diagnosed with dementia in older people: a self-controlled case series analysis

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Table S1. Depression related diseases

ICD-9-CM code	Disease descriptor
296.0	Bipolar I disorder, single manic episode
296.1	Manic disorder, recurrent episode
296.2	Major depressive disorder, single episode
296.3	Major depressive disorder, recurrent episode
296.4	Bipolar I disorder, most recent episode (or current) manic
296.90	Unspecified episodic mood disorder
300.4	Dysthymic disorder
309.0	Adjustment disorder with depressed mood
309.28	Adjustment disorder with mixed anxiety and depressed mood
311	Depressive disorder, not elsewhere classified

Table S2. The distribution of antidepressant drug usage among participants

BNF code	Drug name and type	No. of patients
4.3.1	TRAZODONE HCL	600
	AMITRIPTYLINE HCL	168
	MIANSERIN HCL	133
	DEANXIT (OR EQUIV)	54
	NORTRIPTYLINE HCL	29
	DOTHIEPIN (DOSULEPIN) HCL	28
	IMIPRAMINE HCL	12
	DOXEPIN HCL	6
	CLOMIPRAMINE HCL	3
	TRIMIPRAMINE MALEATE	3
4.3.2	MOCLOBEMIDE	3
4.3.3	SERTRALINE HCL	691
	FLUOXETINE HCL	265
	ESCITALOPRAM (OXALATE)	233
	CITALOPRAM HBR	223
	PAROXETINE HCL	24
	FLUVOXAMINE MALEATE	1
4.3.4	MIRTAZAPINE	208
	VENLAFAXINE HCL	62

	DULOXETINE HCL	24
	FLUPENTHIXOL (DIHYDROCHLORIDE)	16
	BUPROPION HCL (WELLBUTRIN SR)	5

Table S3. Results of the standard SCCS analysis in men. (No. of patients = 837)

Periods	IRR (95% CI)	P-value
Baseline period	(default) 1	
Pre-exposure period	22.18 (19.03-25.86)	<0.001
Index drug-exposed period	9.84 (7.93-12.20)	<0.001
Washout period	1.06 (0.71-1.64)	<0.1
Subsequent drug-exposed period	6.34 (3.40-11.81)	<0.01

Table S4. Results of the standard SCCS analysis in women. (No. of patients = 1549)

Periods	IRR (95% CI)	P-value
Baseline period	(default) 1	
Pre-exposure period	19.43 (17.38-21.73)	<0.001
Index drug-exposed period	8.42 (7.19-9.87)	<0.001
Washout period	1.14 (0.82-1.54)	<0.05
Subsequent drug-exposed period	4.13 (2.51-6.80)	<0.001

Table S5. Results of the sensitivity analysis by setting the length of washout period to 30 days (No. of participants=2404)

Periods	IRR (95% CI)	P-value
Pre-exposure period	20.38 (18.64-22.29)	<0.001
Index drug-exposed period	8.88 (7.82-10.08)	<0.001
Washout period	1.20 (0.88-1.66)	<0.1
Subsequent drug-exposed period	4.84 (3.28-7.14)	<0.001
Baseline period	1	

Table S6. Results of the sensitivity analysis by setting the length of washout period to 70 days (No. of participants=2325)

Periods	IRR (95% CI)	P-value
Pre-exposure period	20.39 (18.63-22.32)	<0.001
Index drug-exposed period	8.89 (7.82-10.10)	<0.001
Washout period	1.15 (0.83-1.34)	<0.1
Subsequent drug-exposed period	4.83 (3.28-7.13)	<0.001
Baseline period	1	

Table S7. Results of the sensitivity analysis by setting the length of pre-exposure period to 30 days

Periods	IRR (95% CI)	P-value
Pre-exposure period	22.36 (19.84-25.11)	<0.001
Index drug-exposed period	8.42 (7.42-9.55)	<0.001
Washout period	1.08 (0.84-1.40)	<0.1
Subsequent drug-exposed period	4.63 (3.14-6.82)	<0.001
Baseline period	1	

Table S8. Results of the sensitivity analysis by setting the length of pre-exposure period to 70 days

Periods	IRR (95% CI)	P-value
Pre-exposure period	19.85 (18.48-21.34)	<0.001
Index drug-exposed period	9.11 (8.02-10.36)	<0.001
Washout period	1.16 (0.79-1.40)	<0.1
Subsequent drug-exposed period	4.90 (3.32-7.23)	<0.001
Baseline period	1	

Table S9. Results of the sensitivity analysis by excluding individuals who died during the study period. (No. of participants=2301)

Periods	IRR (95% CI)	P-value
Pre-exposure period	20.30 (18.54-22.24)	<0.001
Index drug-exposed period	8.18 (7.17-9.34)	<0.001
Washout period	1.03 (0.79-1.36)	<0.05
Subsequent drug-exposed period	4.68 (3.15-6.95)	<0.001
Baseline period	1	

Table S10. Results of the sensitivity analysis by excluding any individual with drug duration<30 (No. of participants = 1520)

Periods	IRR (95% CI)	P-value
Pre-exposure period	19.96 (17.80-22.37)	<0.001
Index drug-exposed period	6.96 (5.99-8.08)	<0.001
Washout period	0.96 (0.69-1.37)	<0.1
Subsequent drug-exposed period	4.27 (2.83-6.44)	<0.001
Baseline period	1	

Table S11. Results of the sensitivity analysis using 200-day age bands

Periods	IRR (95% CI)	P-value

Pre-exposure period	20.42 (18.66-22.35)	<0.001
Index drug-exposed period	8.88 (7.82-10.09)	<0.001
Washout period	1.13 (0.88-1.47)	<0.1
Subsequent drug-exposed period	4.81 (3.26-7.10)	<0.001
Baseline period	1	

Table S12. Results of the sensitivity analysis using 500-day age bands

Periods	**IRR (95% CI)**	**P-value**
Pre-exposure period	20.34 (18.60-22.26)	<0.001
Index drug-exposed period	8.87 (7.81-10.07)	<0.001
Washout period	1.13 (0.87-1.47)	<0.1
Subsequent drug-exposed period	4.83 (3.27-7.12)	<0.001
Baseline period	1	

Pseudo codes for calculating the continuous drug duration

Algorithm 1 Drug-exposed Periods Processing for One Month

Input:

Dispense date $D = \{d_i\}_{i=1}^{n}$ and corresponding duration length $L = \{l_i\}_{i=1}^{n}$

Algorithm:

if $n = 1$ **then**

Exposure period start is dispense date d_1

Exposure period end is (dispense date + duration l_1)

else then

Exposure period start is the first dispense date d_1

Exposure period end is (the last dispense date + the duration of last prescription l_n)

end if

Output:

Exposure period start date and end date

Algorithm 2 Drug-exposed Periods Processing for Continues Months

Input:

Dispense date of the first month $D_1 = \{d_{1i}\}_{1i=0}^{n_1}$ and corresponding duration length $L_1 = \{l_{1i}\}_{1i=0}^{n_1}$

Dispense date of the last month $D_m = \{d_{mi}\}_{mi=0}^{n_m}$ and corresponding duration length $L_m = \{l_{mi}\}_{mi=0}^{n_m}$

Algorithm:

Exposure period start is the first dispense date of the first month d_{1i}

Exposure period end is (the last dispense date of the last month d_{mn_m}+ duration l_{mn_m})

Output:

Exposure period start date and end date

Algorithm 3 Separating the dispense months according to the continuity and threshold

Input:

Month list $MO = \{mo_i\}_{i=1}^{m}$, and corresponding total duration length $LT = \{lt_i\}_{i=0}^{m}$, and duration threshold T

Algorithm:

Initialize two pointers $s = 0, e = 0$

while $e \neq m$ **then**

if $e = m - 1$ and $e = s$ and $lt_e \geq T$ **then**

Append result list with (s, e)

else if $e = m - 1$ and $e \neq s$ and $\sum_{i=s}^{e} lt_i \geq T * (e - s)$ **then**
Append result list with (s, e)
end if
if $\mathrm{mo_t} - \mathrm{mo_s} = \mathrm{e} - \mathrm{s}$ **then**
$e = e + 1$
else then
if $\sum_{i=s}^{e-1} lt_i \geq T * (e - 1 - s)$ **then**
Append result list with $(s, e - 1)$
end if
$\mathrm{s} := \mathrm{e}$
end if
end while
Output:
Result list

Algorithm 4 Obtaining Continuous Exposure periods for a Patient
Input:
Dispense data list $D = \{d_{11}, d_{12}, \ldots d_{1n_1}, d_{21}, d_{22}, \ldots, d_{mn_m}\}$, corresponding duration length list $L = \{l_{11}, l_{12}, \ldots l_{1n_1}, l_{21}, l_{22}, \ldots, l_{mn_m}\}$, and threshold T
Algorithm:
if $m = 1$ and $\sum_{i=1}^{n_1} l_{1i} \geq T$ **then**
Exposure period of this month is from **Algorithm 1** with input
$D = \{d_{11}, d_{12}, \ldots d_{1n_1}\}$ and $L = \{l_{11}, l_{12}, \ldots l_{1n_1}\}$
Append exposed-period list with this Exposure period
else then
Obtain month list $MO = \{mo_i\}_{i=1}^{m}$ from
$D = \{d_{11}, d_{12}, \ldots d_{1n_1}, d_{21}, d_{22}, \ldots, d_{mn_m}\}$
Obtain separating month list R from **Algorithm 3** with input
$MO = \{mo_i\}_{i=1}^{m}$, and $LT = \{\sum_{i=1}^{n_1} l_{1i}, \ldots, \sum_{i=1}^{n_m} l_{1i}\}_{i=0}^{m}$, and threshold T
for (s, e) in R **do**
if $s = e$ **then**
Exposure period of this month is from **Algorithm 1** with input
$D = \{d_{s1}, d_{s2}, \ldots d_{sn_s}\}$ and $L = \{l_{s1}, l_{s2}, \ldots l_{sn_s}\}$
Append exposed-period list with this Exposure period
else then
Exposure period of this period is from **Algorithm 2** with input
$D = \{d_{s1}, d_{s2}, \ldots d_{sn_s}, d_{e1}, d_{e2}, \ldots d_{en_e}\}$ and
$L = \{l_{s1}, l_{s2}, \ldots l_{sn_s}, l_{e1}, l_{e2}, \ldots l_{en_e}\}$
Append exposure period list with this Exposure period
end if
end for
end else
Output:
Exposure period list