

Supplemental Methods

Selection of covariates for propensity score matching

We performed propensity score matching to reduce the bias associated with the non-experimental design of the study. The propensity score is defined as the probability of an individual receiving treatment given the individual's pre-treatment characteristics (1,2). The purpose of the propensity score matching is to balance the covariates between the treatment groups to mimic a randomized controlled trial (2). Covariates to be considered for inclusion in the propensity score are those associated both with exposure and with outcome (or at least with outcome) (3). Therefore, we evaluated whether the individual covariates, assessed prior to first prescription for SSRIs, were associated with both the exposure (statin treatment) and any outcome (i.e., psychiatric hospital contacts, psychiatric hospital contacts due to depression, all-cause mortality, and suicidal behavior) using logistic regression. This analysis showed that all covariates (except "lipid modifying agents other than statins") were associated with both exposure and outcome. However, since the treatment with other lipid-modifying agents are used for the same indication as statins, we performed the propensity score matching procedure as described below both with and without including treatment with other lipid-modifying agents, to see if this variable had any impact on the risk estimates.

Calculation of the propensity score

In order to obtain the propensity score, we calculated a logistical regression model for each individual. We included the following variables in the calculation of the propensity score: Sex, age, education level, previous diagnoses of mental disorders (depression, schizophrenia spectrum, bipolar disorder, anxiety, substance abuse, any other mental disorder) or medical diseases (myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate to severe renal disease, diabetes

with end organ damage, any tumor, leukemia, lymphoma, liver disease, metastatic solid tumor, AIDS), previous suicide attempts, start year of SSRI treatment, and use of the following drugs in the year prior to index (dichotomously defined: yes/no): corticosteroids, anti-inflammatory/anti-rheumatic agents, NSAIDs, antihypertensives, diuretics, peripheral vasodilators, vasoprotective agents, betablocking agents, calcium channel blockers, agents acting on the renin-angiotension system, lipid modifying agents other than statins (both included and not included – see above), antidepressants other than SSRI, antipsychotics, lithium, other mood-stabilizers, anxiolytics, benzodiazepine-like hypnotics.

Propensity score matching

We matched the individuals on the propensity score using nearest neighbour matching (3). Specifically, we matched an individual using both a SSRI and a statin with the individual using only a SSRI, which had the propensity score closest to that of the aforementioned SSRI+statin user. If there were more equally suited matches, we selected one randomly. Each matched pair of individuals was removed from the sample prior to the next matching. Individuals with no overlap in the propensity scores were excluded (trimming). Subsequently, we tested the balance between the propensity score matched groups using standardized differences, which were all below 10.0 % and the majority below 3%. In general, an absolute standardised difference of <10% and a variance ratio between 0.8 and 1.25 is considered to support the assumption of balance between groups (4,5). We also assessed the balance between groups graphically by comparing the distribution of the propensity scores of the unmatched cohorts with the distribution of the characteristics after matching.

Analyses

Within the propensity score matched cohort, we performed Cox regression analyses to calculate hazard ratios (HR) for the four outcomes: psychiatric hospital contact, psychiatric hospital contact due to depression, suicidal behavior, and all-cause mortality. The time since first SSRI prescription (index date) was used as underlying timescale. The crude analyses were adjusted for age and sex. The fully adjusted analyses included the following covariates: age, sex,

education level, previous diagnoses of mental disorders and medical diseases, previous suicide attempts, start year of SSRI treatment, and use of the following drugs in the year prior to index (dichotomously defined: yes/no): corticosteroids, anti-inflammatory/anti-rheumatic agents, NSAIDs, antihypertensives, diuretics, peripheral vasodilators, vasoprotective agents, betablocking agents, calcium channel blockers, agents acting on the renin-angiotension system, lipid modifying agents other than statins (both included and not included – see above), antidepressants other than SSRI, antipsychotics, lithium, other mood-stabilizers, anxiolytics, benzodiazepine-like hypnotics.

Sensitivity analyses

Finally, for each outcome, we calculated the HR in propensity-score percentiles (divided as follows: 0-5, 5-10, 10-25, 25-50, 50-75, 75-90, 90-95, and 95-100). This was done to investigate whether the HRs were consistent over different propensity-score groups.

Supplemental Results

Due to computational restrictions, we performed the propensity score matching within a 20% subsample (n=174,180) of the total study population (n=872,216). Within this subsample, we were able to propensity-score match 44,956 individuals using the nearest neighbour matching procedure described above. The balance between groups after the propensity score matching is displayed in Figure S1 and Table 1. Since the inclusion/exclusion of the variable “lipid modifying agents other than statins” in the propensity score matching model and in the adjusted Cox regression analysis, respectively, had no noticeable effect on the results, we chose to report the results based on the models in which this variable was included (i.e., in both the propensity score matching and in the Cox regression).

Effects on psychiatric hospital contacts

According to the propensity score matched analyses, concomitant use of a SSRI and a statin was associated with a decreased risk for both psychiatric hospital contacts in general (adjusted HR=0.79 (95%-CI=0.60; 0.96)) and for psychiatric hospital contacts due to depression

specifically (adjusted HR=0.71 (95%-CI=0.49; 0.90)) compared to the use of a SSRI alone (Table S2). The risk for both psychiatric hospital contacts in general and contacts due to depression specifically were reduced significantly when the SSRIs were used in combination with either simvastatin or any one of the statins from the composite group of “other statins” (Table S2). The same was the case for the citalopram-simvastatin combination versus citalopram alone.

Adverse events

According to the propensity score matched analyses, the all-cause mortality of individuals using a SSRI and a statin concomitantly was similar to that of those using SSRI alone (adjusted HR=0.97 (95%-CI=0.79; 1.15)) (Table S2). Results were similar for the SSRI+simvastatin, SSRI+“other statins” and citalopram+simvastatin combinations. The analysis of suicidal behavior was affected by the very low number of events (wide confidence interval), but was not indicative of increased risk associated with the concomitant use of a SSRI and a statin (adjusted HR=1.06 (95%-CI=0.34; 3.20)).

Sensitivity analyses

The direction of the HRs across the propensity score percentiles was consistent with the overall results for each outcome (results not shown).

References

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4. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46:399-424
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TABLE S1. Baseline characteristics for the sub-population used for propensity score matching (i.e., a 20% sample from the original study population of 872,216 individuals) and for the propensity score matched population. For each of these groups, the characteristics are shown for the entire group (total) as well as for individuals using only a selective serotonin reuptake inhibitor (SSRI) and for individuals using an SSRI and a statin concomitantly (SSRI & Statin).

	Subsample of the original study population			Propensity score matched population		
	Total N (%)	SSRI N (%)	SSRI & Statin N (%)	Total N (%)	SSRI N (%)	SSRI & Statin N (%)
Total:	174,180 (100)	151,554 (87.0)	22,626 (13.0)	44,956 (100)	22,478 (50.0)	22,478 (50.0)
Gender:						
Female	107,352 (61.6)	93,996 (62.0)	13,356 (59.0)	26,528 (59.0)	13,264 (59.0)	13,264 (59.0)
Male	66,828 (38.4)	57,558 (38.0)	9,270 (41.0)	18,428 (41.0)	9,214 (41.0)	9,214 (41.0)
Median age, IQR:	47.9 (33.4; 67.7)	45.6 (31.6; 68.1)	56.3 (47.1; 66.7)	56.3 (46.3; 67.1)	56.3 (45.1; 67.4)	56.3 (47.1; 66.7)
Age groups:						
10-29	34,162 (19.6)	33,666 (22.2)	496 (2.2)	970 (2.1)	485 (2.2)	485 (2.2)
30-49	58,614 (33.7)	51,847 (34.2)	6,767 (29.9)	13,478 (30.0)	6,739 (30.0)	6,739 (30.0)
50-69	41,840 (24.0)	30,646 (20.2)	11,194 (49.5)	22,170 (49.3)	11,085 (49.3)	11,085 (49.3)
70-89	36,092 (20.7)	31,973 (21.2)	4,119 (18.2)	8,238 (18.3)	4,119 (18.3)	4,119 (18.3)
90+	3,472 (2.0)	3,422 (2.3)	50 (0.2)	100 (0.2)	50 (0.2)	50 (0.2)
Education:						
Primary school	73,293 (42.1)	62,812 (41.5)	10,481 (46.3)	20,868 (46.4)	10,471 (46.6)	10,397 (46.3)
Secondary school	6,707 (3.9)	6,384 (4.2)	323 (1.4)	706 (1.6)	384 (1.7)	322 (1.4)
Vocational	338 (0.2)	306 (0.2)	32 (0.1)	77 (0.2)	45 (0.2)	32 (0.1)
Short higher	41,300 (23.7)	34,704 (22.9)	6,596 (29.2)	12,886 (28.9)	6,333 (28.2)	6,553 (29.2)
Medium higher	25,780 (14.8)	22,446 (14.8)	3,334 (14.7)	6,702 (14.9)	3,379 (15.0)	3,323 (14.8)
University	26,762 (15.4)	24,902 (16.4)	1,860 (8.2)	3,717 (8.3)	1,866 (8.3)	1,851 (8.2)
Index year:						
1997	12,959 (7.4)	10,331 (6.8)	2,628 (11.6)	5,246 (11.7)	2,651 (11.8)	2,595 (11.5)
1998	11,648 (6.7)	9,415 (6.2)	2,233 (9.9)	4,456 (9.9)	2,239 (10.0)	2,217 (9.9)
1999	10,421 (6.0)	8,497 (5.6)	1,924 (8.5)	3,894 (8.7)	1,986 (8.8)	1,908 (8.5)
2000	10,525 (6.0)	8,712 (5.8)	1,813 (8.0)	3,684 (8.2)	1,885 (8.4)	1,799 (8.0)
2001	12,068 (6.9)	9,913 (6.5)	2,155 (9.5)	4,190 (9.3)	2,050 (9.1)	2,140 (9.5)
2002	11,547 (6.6)	9,527 (6.3)	2,020 (8.9)	4,021 (8.9)	2,019 (9.0)	2,002 (8.9)
2003	12,577 (7.2)	10,511 (6.9)	2,066 (9.1)	4,046 (9.0)	1,993 (8.9)	2,053 (9.1)
2004	10,305 (5.9)	8,782 (5.8)	1,523 (6.7)	3,008 (6.7)	1,489 (6.6)	1,519 (6.8)
2005	11,240 (6.5)	9,726 (6.4)	1,514 (6.7)	2,931 (6.5)	1,421 (6.3)	1,510 (6.7)
2006	11,130 (6.4)	9,842 (6.5)	1,288 (5.7)	2,539 (5.7)	1,252 (5.6)	1,287 (5.7)
2007	10,997 (6.3)	9,907 (6.5)	1,090 (4.8)	2,141 (4.8)	1,055 (4.7)	1,086 (4.8)
2008	10,164 (5.8)	9,399 (6.2)	765 (3.4)	1,513 (3.4)	751 (3.3)	762 (3.4)

2009	11,041 (6.3)	10,386 (6.9)	655 (2.9)	1,329 (3.0)	675 (3.0)	654 (2.9)
2010	10,948 (6.3)	10,440 (6.9)	508 (2.3)	1,013 (2.3)	507 (2.3)	506 (2.3)
2011	8,610 (4.9)	8,335 (5.5)	275 (1.2)	563 (1.3)	290 (1.3)	273 (1.2)
2012	8,000 (4.6)	7,831 (5.2)	169 (0.8)	382 (0.9)	215 (1.0)	167 (0.7)
Previous mental disorders:						
No contact	140,280 (80.5)	121,157 (79.9)	19,123 (84.5)	37,074 (82.5)	18,085 (80.5)	18,989 (84.5)
Any contact	33,900 (19.5)	30,397 (20.1)	3,503 (15.5)	7,882 (17.5)	4,393 (19.5)	3,489 (15.5)
Depression	9,133 (5.2)	8,149 (5.4)	984 (4.4)	2,154 (4.8)	1,173 (5.2)	981 (4.4)
Schizophrenia spectrum	4,613 (2.7)	4,107 (2.7)	506 (2.2)	1,164 (2.6)	658 (2.9)	506 (2.3)
Bipolar disorder	1,140 (0.7)	1,018 (0.7)	122 (0.5)	255 (0.6)	133 (0.6)	122 (0.5)
Anxiety	4,876 (2.8)	4,332 (2.9)	544 (2.4)	1,267 (2.8)	726 (3.2)	541 (2.4)
Substance abuse	7,144 (4.1)	6,220 (4.1)	924 (4.1)	2,055 (4.6)	1,132 (5.0)	923 (4.1)
Other psychiatric^a	13,699 (7.9)	12,466 (8.2)	1,233 (5.5)	2,720 (6.1)	1,494 (6.7)	1,226 (5.5)
Previous medical diseases:						
No disorders	131,775 (75.7)	115,324 (76.1)	16,451 (72.7)	31,685 (70.5)	15,343 (68.3)	16,342 (72.7)
Any disorder	42,405 (24.3)	36,230 (23.9)	6,175 (27.3)	13,271 (29.5)	8,208 (31.7)	6,136 (27.3)
Myocardial infarct	4,103 (2.4)	3,382 (2.2)	721 (3.2)	1,430 (3.2)	718 (3.2)	712 (3.2)
Congestive heart failure	2,766 (1.6)	2,489 (1.6)	277 (1.2)	705 (1.6)	429 (1.9)	276 (1.2)
Peripheral vascular disease	4,009 (2.3)	3,341 (2.2)	668 (3.0)	1,346 (3.0)	683 (3.0)	663 (3.0)
Cerebrovascular disease	4,465 (2.6)	3,730 (2.5)	735 (3.3)	1,383 (3.1)	652 (2.9)	731 (3.3)
Dementia	2,031 (1.2)	1,945 (1.3)	86 (0.4)	318 (0.7)	232 (1.0)	86 (0.4)
Chronic pulmonary disease	10,705 (6.2)	9,359 (6.2)	1,346 (6.0)	3,094 (6.9)	1,749 (7.8)	1,345 (6.0)
Connective tissue disease	3,959 (2.3)	3,374 (2.2)	585 (2.6)	1,241 (2.8)	658 (2.9)	583 (2.6)
Ulcer disease	5,712 (3.3)	4,821 (3.2)	891 (3.9)	1,918 (4.3)	1,034 (4.6)	884 (3.9)
Mild liver disease	1,553 (0.9)	1,356 (0.9)	197 (0.9)	478 (1.1)	283 (1.3)	195 (0.9)
Diabetes	3,280 (1.9)	2,402 (1.6)	878 (3.9)	1,363 (3.1)	490 (2.2)	873 (3.9)
Hemiplegia	308 (0.2)	277 (0.2)	31 (0.1)	74 (0.2)	44 (0.2)	30 (0.1)
Moderate to severe renal disease	1,557 (0.9)	1,361 (0.9)	196 (0.9)	466 (1.0)	271 (1.2)	195 (0.9)
Diabetes with end organ damage	1,790 (1.0)	1,314 (0.9)	476 (2.1)	766 (1.7)	292 (1.3)	474 (2.1)
Any tumor	12,729 (7.3)	11,393 (7.5)	1,336 (5.9)	3,500 (7.8)	2,169 (9.7)	1,331 (5.9)
Leukemia	324 (0.2)	302 (0.2)	22 (0.1)	66 (0.2)	44 (0.2)	22 (0.1)
Lymphoma	701 (0.4)	634 (0.4)	67 (0.3)	193 (0.4)	127 (0.6)	66 (0.3)
Liver disease	145 (0.1)	130 (0.1)	15 (0.1)	42 (0.1)	27 (0.1)	15 (0.1)
Metastatic solid tumor	1,413 (0.8)	1,354 (0.9)	59 (0.3)	303 (0.7)	244 (1.1)	59 (0.3)
AIDS	191 (0.1)	170 (0.1)	21 (0.1)	43 (0.1)	23 (0.1)	20 (0.1)
Prior CV-drug use:						
No prior use	121,508 (69.8)	108,293 (71.5)	13,215 (58.4)	25,462 (56.6)	12,293 (54.7)	13,169 (58.6)
Any use	52,672 (30.2)	43,261 (28.5)	9,411 (41.6)	19,494 (43.4)	10,185 (45.3)	9,309 (41.4)
Antihypertensives	912 (0.5)	710 (0.5)	202 (0.9)	415 (0.9)	220 (1.0)	195 (0.9)
Diuretics	30,069 (17.8)	25,171 (17.2)	4,898 (21.7)	10,265 (22.8)	5,424 (24.1)	4,841 (21.5)
Peripheral vasodilators	53 (0.1)	40 (0.1)	13 (0.1)	20 (0.1)	9 (0.1)	11 (0.1)
Vasoprotective agents	8,121 (4.7)	6,993 (4.6)	1,128 (5.0)	2,522 (5.6)	1,401 (6.2)	1,121 (5.0)

Betablocking agents	15,942 (9.2)	12,671 (8.4)	3,271 (14.5)	6,838 (15.2)	3,654 (16.3)	3,184 (14.2)
Calcium channel blockers	12,983 (7.5)	10,357 (6.8)	2,626 (11.6)	5,341 (11.9)	2,790 (12.4)	2,551 (11.4)
RAS-drugs	17,169 (9.9)	13,484 (8.9)	3,685 (16.3)	7,505 (16.7)	3,920 (17.4)	3,585 (16.0)
Other lipid-modifying agents	352 (0.2)	284 (0.2)	68 (0.3)	145 (0.3)	78 (0.3)	67 (0.3)
Prior anti-inflammatory drug use:						
No use	24,204 (13.9)	22,692 (15.0)	1,512 (6.7)	3,022 (6.7)	1,555 (6.9)	1,467 (6.5)
Any use	149,976 (86.1)	128,862 (85.0)	21,114 (93.3)	41,934 (93.3)	20,923 (93.1)	21,011 (93.5)
Corticosteroids	53,015 (30.4)	43,807 (28.9)	9,208 (40.7)	18,833 (41.9)	9,694 (43.1)	9,139 (40.7)
Antirheumatics	46 (0.1)	36 (0.1)	10 (0.1)	26 (0.1)	16 (0.1)	10 (0.1)
NSAIDs	141,815 (81.4)	121,531 (80.2)	20,284 (89.7)	40,073 (89.1)	19,892 (88.5)	20,181 (89.8)
Low-dose acetylsalicylic acid	18,511 (10.6)	15,581 (10.3)	2,930 (13.0)	5,913 (13.2)	3,024 (13.5)	2,889 (12.9)
Prior psychopharmaceutical use:						
No use	55,833 (32.1)	51,157 (33.8)	4,676 (20.7)	8,547 (19.0)	3,921 (17.4)	4,626 (20.6)
Any use	118,347 (67.9)	100,397 (66.3)	17,950 (79.3)	36,409 (81.0)	18,557 (82.6)	17,852 (79.4)
Other antidepressants than SSRI	16,221 (9.3)	13,788 (9.1)	2,433 (10.8)	5,305 (11.8)	2,894 (12.9)	2,411 (10.7)
Antipsychotics	13,557 (7.8)	11,910 (7.9)	1,647 (7.3)	3,658 (8.1)	2,013 (9.0)	1,645 (7.3)
Lithium	624 (0.4)	546 (0.4)	78 (0.3)	182 (0.4)	104 (0.5)	78 (0.4)
Other mood-stabilizers	12,958 (7.4)	10,863 (7.2)	2,095 (9.3)	4,668 (10.4)	2,596 (11.6)	2,072 (9.2)
Anxiolytics	93,511 (53.7)	78,470 (51.8)	15,041 (66.5)	30,317 (67.4)	15,365 (68.4)	14,952 (66.5)
Benzodiazepine-like hypnotics	59,776 (34.3)	50,159 (33.1)	9,617 (42.5)	19,782 (44.0)	10,231 (45.5)	9,551 (42.5)

Abbreviations: IQR=Inter quartile range; AI=Anti-inflammatory; RAS=Renin angiotension system; NSAIDs=Nonsteroidal anti-inflammatory drugs

^aOther psychiatric: Contact with any other psychiatric disorder than those mentioned.

TABLE S2. Comparison of outcomes for individuals using a selective serotonin reuptake inhibitor (SSRI) and a statin concomitantly compared to individuals using a SSRI alone based on the propensity score matched sample of 44,956 individuals.

	Contacts with psychiatric hospital				Contacts with psychiatric hospital due to depression			
	N [^] (events)	Person- Years	Crude [§] HR (95%-CI)	Adjusted* HR (95%-CI)	N [^] (events)	Person- Years	Crude [§] HR (95%-CI)	Adjusted* HR (95%-CI)
SSRI only	3,333	21,084	1.0 (Ref.)	1.0 (Ref.)	1,321	21,275	1.0 (Ref.)	1.0 (Ref.)
Statins	1,119	7,715	0.77 (0.64; 0.90)	0.79 (0.60; 0.96)	301	7,833	0.70 (0.49; 0.87)	0.71 (0.49; 0.90)
Simvastatin	1,046	7,092	0.81 (0.68; 0.94)	0.82 (0.61; 0.98)	269	7,148	0.71 (0.56; 0.86)	0.72 (0.50; 0.97)
Other statins ^a	73	623	0.72 (0.56; 0.88)	0.73 (0.56; 0.90)	32	685	0.60 (0.48; 0.70)	0.62 (0.41; 0.83)
Citalopram only	1,825	11,256	1.0 (Ref.)	1.0 (Ref.)	711	11,487	1.0 (Ref.)	1.0 (Ref.)
Simvastatin	612	4,484	0.78 (0.61; 0.96)	0.79 (0.58; 0.98)	168	4,512	0.70 (0.52; 0.87)	0.71 (0.49; 0.96)
	All-cause mortality				Suicidal behavior			
	N [^] (events)	Person- Years	Crude [§] HR (95%-CI)	Adjusted* HR (95%-CI)	N [^] (events)	Person- Years	Crude [§] HR (95%-CI)	Adjusted* HR (95%-CI)
SSRI only	1,499	21,189	1.0 (Ref.)	1.0 (Ref.)	179	21,487	1.0 (Ref.)	1.0 (Ref.)
Statins	502	7,784	0.94 (0.71; 1.13)	0.97 (0.79; 1.15)	23	7,845	1.15 (0.43; 2.62)	1.06 (0.34; 3.20)
Simvastatin	457	7,115	0.96 (0.72; 1.17)	0.99 (0.70; 1.22)	n.a.	7,183	n.a.	n.a.
Other statins ^a	45	669	0.92 (0.69; 1.16)	0.96 (0.68; 1.19)	n.a.	662	n.a.	n.a.
Citalopram only	794	11,312	1.0 (Ref.)	1.0 (Ref.)	102	11,356	1.0 (Ref.)	1.0 (Ref.)
Simvastatin	283	4,497	0.95 (0.72; 1.16)	0.98 (0.71; 1.23)	15	4,421	1.09 (0.41; 2.12)	1.02 (0.33; 3.10)

Abbreviations and explanations: HR=Hazard ratio; 95%-CI=95% Confidence Interval; **Bold** numbers represent statistically significant results; n.a.=not applicable because of too few observations.

[§] Adjusted for age and gender.

*Adjusted for: age; gender; education level; SSRI index year, previous contacts for mental disorders and medical diseases; prior use of other anti-inflammatory medications, cardiovascular protective medications and psychopharmaceuticals within the year preceding the SSRI index date.

^a The other statins comprises lovastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin.

[^] The crude analyses were based on the number of events shown in the table. The adjusted analyses were based on slightly less events: Contacts with psychiatric hospital: 29 less for any SSRI and 11 less for citalopram; Contacts with psychiatric hospital due to depression: 12 less for any SSRI and 5 less for citalopram; All-cause mortality: 17 less for any SSRI and 6 less for citalopram; Suicidal behavior: 11 for any SSRI and 4 less for citalopram.

FIGURE S1. The distribution of the propensity scores of the unmatched cohort containing all subjects (left) with the distribution of the propensity scores after trimming (right), i.e., after excluding the subjects with the lowest and highest propensity scores.

