**Contents**

[eFigure 1. Flowchart describing the construction of the study cohort and case-control selection 3](#_Toc3389499)

[eTable 1. Crude and adjusted rate ratios of ischemic stroke/TIA associated with current use of antidepressants strongly inhibiting serotonin reuptake compared with antidepressants weakly inhibiting serotonin reuptake (stratified by sex, chronic kidney disease, and history of cardiovascular disease) 4](#_Toc3389500)

[eTable 2. Crude and adjusted rate ratios of ischemic stroke/TIA associated with current use of antidepressants strongly inhibiting serotonin reuptake compared with antidepressants weakly inhibiting serotonin reuptake in sensitivity analyses 6](#_Toc3389501)

[eTable 3. Characteristics of cases with myocardial infarction and matched controls a 8](#_Toc3389502)

[eTable 4. Crude and adjusted rate ratios of myocardial infarction associated with current use of antidepressants strongly inhibiting serotonin reuptake compared with antidepressants weakly inhibiting serotonin reuptake (stratified by sex, chronic kidney disease and history of cardiovascular disease) 10](#_Toc3389503)

[eTable 5. Crude and adjusted rate ratios of myocardial infarction associated with current use of antidepressants strongly inhibiting serotonin reuptake compared with antidepressants weakly inhibiting serotonin reuptake in sensitivity analyses 12](#_Toc3389504)

[eTable 6. Crude and adjusted rate ratios of ischemic stroke/TIA associated with current use of SSRIs strongly inhibiting serotonin reuptake compared with SSRIs intermediately inhibiting serotonin reuptake (stratified by sex, chronic kidney disease and history of cardiovascular disease) 14](#_Toc3389505)

[eTable 7. Crude and adjusted rate ratios of ischemic stroke/TIA associated with current use of SSRIs strongly inhibiting serotonin reuptake compared with SSRIs intermediately inhibiting serotonin reuptake in sensitivity analyses 16](#_Toc3389506)

[eTable 8. Crude and adjusted rate ratios of myocardial infarction associated with current use of SSRIs strongly inhibiting serotonin reuptake compared with SSRIs intermediately inhibiting serotonin reuptake (stratified by sex, chronic kidney disease and history of cardiovascular disease) 18](#_Toc3389507)

[eTable 9. Crude and adjusted rate ratios of myocardial infarction associated with current use of SSRIs strongly inhibiting serotonin reuptake compared with SSRIs intermediately inhibiting serotonin reuptake in sensitivity analyses 20](#_Toc3389508)

[eTable 10. Characteristics of patients initiating treatment with antidepressants strongly inhibiting serotonin reuptake and propensity score matched patients initiating treatment with antidepressants weakly inhibiting serotonin reuptake for the outcome ischemic stroke/TIA 22](#_Toc3389509)

[eTable 11. Characteristics of patients initiating treatment with antidepressants strongly inhibiting serotonin reuptake and propensity score matched patients initiating treatment with antidepressants weakly inhibiting serotonin reuptake for the outcome myocardial infarction 24](#_Toc3389510)

[eTable 12. Hazard ratios of ischemic stroke/TIA or myocardial infarction associated with the use of antidepressants strongly inhibiting serotonin reuptake compared with the use of antidepressants weakly inhibiting serotonin reuptake 26](#_Toc3389511)

# **eFigure 1. Flowchart describing the construction of the study cohort and case-control selection**

Patients registered in CPRD with at least one prescription for an SSRI or a third-generation antidepressant, after 18 years of age, and being in a UTS practice for at least one year, between January 1, 1995 and

June 30, 2014

(n = 1,348,245)

- Prescription for an antidepressant in the year prior to cohort entry

(n = 409,630)

- Prescription for both an SSRI and a third-generation antidepressant at cohort entry

(n = 227)

Cohort of incident users of SSRIs or third-generation antidepressants

(n = 938,388)

Matched controls for ischemic stroke/TIA

(n = 473,712)

Matched controls for myocardial infarction (n = 258,022)

Cases of ischemic stroke/TIA

(n = 15,860)

Cases of myocardial infarction

(n = 8626)

Abbreviations: CPRD, Clinical Practice Research Datalink; SSRI, selective serotonin reuptake inhibitor; UTS, up-to-standard; TIA, transient ischemic attack

# **eTable 1. Crude and adjusted rate ratios of ischemic stroke/TIA associated with current use of antidepressants strongly inhibiting serotonin reuptake compared with antidepressants weakly inhibiting serotonin reuptake (stratified by sex, chronic kidney disease, and history of cardiovascular disease)**

|  | **Cases\*****(n =** **15,860)** | **Controls\*****(n = 473,712)** | **Crude RR** | **Adjust RR^****(95% CI)** |
| --- | --- | --- | --- | --- |
| **Male sex** | 6093 | 181,660 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 861 (14.1) | 25,310 (13.9) | 0.85 | 0.86 (0.74 - 1.00) |
| Weak inhibitors of serotonin reuptake\*\* | 226 (3.7) | 5630 (3.1) | Reference | Reference |
| **Female sex** | 9767 | 292,052 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 1,416 (14.5) | 41,267 (14.1) | 0.89 | 0.90 (0.79 - 1.02) |
| Weak inhibitors of serotonin reuptake\*\* | 333 (3.4) | 8614 (2.9) | Reference | Reference |
|  |  |  |  |  |
| **Chronic kidney disease** | 549 | 1585 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 61 (11.1) | 153 (9.7) | 1.24 | 1.26 (0.71 - 2.25) |
| Weak inhibitors of serotonin reuptake\*\* | 27 (4.9) | 86 (5.4) | Reference | Reference |
| **No chronic kidney disease** | 15,196 | 439,715 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 2196 (14.5) | 63,170 (14.4) | 0.85 | 0.86 (0.78 - 0.95) |
| Weak inhibitors of serotonin reuptake\*\* | 529 (3.5) | 12,547 (2.9) | Reference | Reference |
|  |  |  |  |  |
| **History of cardiovascular disease#** | 1023 | 2800 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 137 (13.4) | 405 (14.5) | 0.68 | 0.70 (0.45 - 1.08) |
| Weak inhibitors of serotonin reuptake\*\* | 48 (4.7) | 111 (4.0) | Reference | Reference |
| **No history of cardiovascular disease** | 14,621 | 410,542 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 2106 (14.4) | 57,406 (14.0) | 0.90 | 0.91 (0.82 - 1.01) |
| Weak inhibitors of serotonin reuptake\*\* | 503 (3.4) | 12,132 (3.0) | Reference | Reference |

Abbreviations: TIA; transient ischemic attack; RR, rate ratio; CI, confidence interval.

\* Cases and controls were matched for sex, age, duration of follow-up, and calendar time.

\*\* Current use of intermediate inhibitors of serotonin reuptake, multiple users, and non-users were also included in the model.

^ Rate ratios were additionally adjusted for obesity, smoking status, alcohol abuse, arterial hypertension, atrial fibrillation, congestive heart failure, myocardial infarction, other coronary artery disease, peripheral vascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, chronic obstructive pulmonary disease, cancer, use of anticoagulants, antiplatelets, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, antipsychotics, other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, trazodone), lithium, hormone replacement therapy, and number of physician visits.

# History of cardiovascular disease was defined as history of myocardial infarction, other coronary artery disease, or peripheral vascular disease.

# **eTable 2. Crude and adjusted rate ratios of ischemic stroke/TIA associated with current use of antidepressants strongly inhibiting serotonin reuptake compared with antidepressants weakly inhibiting serotonin reuptake in sensitivity analyses**

|  | **Cases\*** | **Controls\*** | **Crude RR** | **Adjusted RR^****(95% CI)** |
| --- | --- | --- | --- | --- |
| **60-day period of current use** | n = 15,860 | n = 473,712 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 2457 (15.5) | 72,021 (15.2) | 0.88 | 0.89 (0.81 - 0.98) |
| Weak inhibitors of serotonin reuptake\*\* | 575 (3.6) | 14,819 (3.1) | Reference | Reference |
|  |  |  |  |  |
| **Excluding TIA** | n = 9354 | n = 279,235 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 1345 (14.4) | 39,409 (14.1) | 0.85 | 0.85 (0.75 - 0.96) |
| Weak inhibitors of serotonin reuptake\*\* | 350 (3.7) | 8706 (3.1) | Reference | Reference |
|  |  |  |  |  |
| **Adjusting for covariates at cohort entry** | n = 15,860 | n = 473,712 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 2277 (14.4) | 66,577 (14.1) | 0.87 | 0.86 (0.78 - 0.94) |
| Weak inhibitors of serotonin reuptake\*\* | 559 (3.5) | 14,244 (3.0) | Reference | Reference |
|  |  |  |  |  |
| **Multiple imputation** | n = 15,860 | n = 473,712 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 2277 (14.4) | 66,577 (14.1) | 0.87 | 0.88 (0.80 - 0.97) |
| Weak inhibitors of serotonin reuptake\*\* | 559 (3.5) | 14,244 (3.0) | Reference | Reference |
|  |  |  |  |  |
| **hdPS based trimming** | n = 8949 | n = 266,168 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 1917 (21.4) | 56,051 (21.1) | 0.92 | 0.92 (0.81 - 1.04) |
| Weak inhibitors of serotonin reuptake\*\* | 322 (3.6) | 8610 (3.2) | Reference | Reference |

Abbreviations: TIA; transient ischemic attack; hdPS, high-dimensional propensity score; RR, rate ratio; CI, confidence interval.

\* Cases and controls were matched for sex, age, duration of follow-up, and calendar time.

\*\* Current use of intermediate inhibitors of serotonin reuptake, multiple users, and non-users were also included in the model.

^ Rate ratios were additionally adjusted for obesity, smoking status, alcohol abuse, arterial hypertension, atrial fibrillation, congestive heart failure, myocardial infarction, other coronary artery disease, peripheral vascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, chronic obstructive pulmonary disease, cancer, use of anticoagulants, antiplatelets, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, antipsychotics, other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, trazodone), lithium, hormone replacement therapy, and number of physician visits.

# **eTable 3. Characteristics of cases with myocardial infarction and matched controls a**

| **Characteristic b** | **Cases** | **Controls** |
| --- | --- | --- |
| **(n = 8626)** | **(n = 258,022)** |
| Age in years, mean (SD) | 68.0 (14.5) | 67.8 (14.4) |
| Follow-up in years, mean (SD) | 4.7 (3.9) | 4.7 (3.9) |
| Male sex, n (%) | 4510 (52.3) | 134,846 (52.3) |
| Body mass index in kg/m2, n (%) |  |  |
| <30 | 5556 (64.4) | 172,703 (66.9) |
| ≥30 | 2171 (25.2) | 55,276 (21.4) |
| Unknown | 899 (10.4) | 30,043 (11.6) |
| Smoking status, n (%) |  |  |
| Never | 1794 (20.8) | 81,737 (31.7) |
| Ever | 6619 (76.7) | 167,106 (64.8) |
| Unknown | 213 (2.5) | 9179 (3.6) |
| Alcohol abuse, n(%) | 104 (1.2) | 2629 (1.0) |
| Comorbidities, n (%) |  |  |
| Arterial hypertension | 4593 (53.2) | 112,223 (43.5) |
| Atrial fibrillation | 159 (1.8) | 3847 (1.5) |
| Congestive heart failure | 159 (1.8) | 2379 (0.9) |
| Ischemic stroke | 78 (0.9) | 2143 (0.8) |
| Transient ischemic attack | 91 (1.1) | 1800 (0.7) |
| Other coronary artery disease | 666 (7.7) | 9739 (3.8) |
| Peripheral vascular disease | 113 (1.3) | 1498 (0.6) |
| Hyperlipidemia | 2745 (31.8) | 65,100 (25.2) |
| Diabetes mellitus | 1398 (16.2) | 26,002 (10.1) |
| Chronic kidney disease | 354 (4.1) | 7492 (2.9) |
| Liver disease | 17 (0.2) | 466 (0.2) |
| Depression | 1257 (14.6) | 33,103 (12.8) |
| Chronic obstructive pulmonary disease | 592 (6.9) | 10,554 (4.1) |
| Cancer | 218 (2.5) | 6795 (2.6) |
| Comedications, n (%) |  |  |
| Anticoagulants | 515 (6.0) | 12,152 (4.7) |
| Antiplatelets | 3541 (41.1) | 65,215 (25.3) |
| Acetylsalicylic acid | 3220 (37.3) | 59,299 (23.0) |
| Others | 1059 (12.3) | 11,472 (4.4) |
| Lipid lowering drugs | 3357 (38.9) | 69,099 (26.8) |
| Non-steroidal anti-inflammatory drugs | 2059 (23.9) | 53,068 (20.6) |
| Opioids | 3872 (44.9) | 85,910 (33.3) |
| Beta-blockers | 2395 (27.8) | 44,240 (17.1) |
| Thiazides | 1392 (16.1) | 40,119 (15.5) |
| Angiotensin-converting enzyme inhibitors | 2442 (28.3) | 47,692 (18.5) |
| Angiotensin II receptor blockers | 904 (10.5) | 20,264 (7.9) |
| Calcium channel blockers | 2252 (26.1) | 46,671 (18.1) |
| Antipsychotics | 939 (10.9) | 24,146 (9.4) |
| Other antidepressants c | 873 (10.1) | 22,235 (8.6) |
| Lithium | 39 (0.5) | 1149 (0.4) |
| Hormone replacement therapy d | 375 (9.1) | 11,870 (9.6) |
| Number of physician visits, n (%) |  |  |
| 0-3 | 1237 (14.3) | 58,583 (22.7) |
| 4-6 | 1265 (14.7) | 51,129 (19.8) |
| >=7 | 6124 (71.0) | 148,310 (57.5) |

Abbreviation: SD, standard deviation.

a Cases and controls were matched on sex, age (±1 year), date of cohort entry (±1 year), and duration of follow-up.

b Characteristics measured 366 to 730 days before the index date.

c Other antidepressant includes tricyclic antidepressants, monoamine oxidase inhibitors, and trazodone.

d Hormone replacement therapy frequency and percentage are reported only among women.

# **eTable 4. Crude and adjusted rate ratios of myocardial infarction associated with current use of antidepressants strongly inhibiting serotonin reuptake compared with antidepressants weakly inhibiting serotonin reuptake (stratified by sex, chronic kidney disease and history of cardiovascular disease)**

|  | **Cases\*****(n = 8626)** | **Controls\*****(n = 258,022)** | **Crude RR** | **Adjust RR^****(95% CI)** |
| --- | --- | --- | --- | --- |
| **Male sex** | 4510 | 134,846 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 603 (13.4) | 17,554 (13.0) | 1.00 | 0.97 (0.80 - 1.17) |
| Weak inhibitors of serotonin reuptake\*\* | 135 (3.0) | 3875 (2.9) | Reference | Reference |
| **Female sex** | 4116 | 123,176 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 583 (14.2) | 16,897 (13.7) | 1.06 | 1.04 (0.85 - 1.27) |
| Weak inhibitors of serotonin reuptake\*\* | 120 (2.9) | 3666 (3.0) | Reference | Reference |
|  |  |  |  |  |
| **Chronic kidney disease** | 274 | 786 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 27 (9.9) | 81 (10.3) | 1.43 | 1.59 (0.59 - 4.27) |
| Weak inhibitors of serotonin reuptake\*\* | 8 (2.9) | 43 (5.5) | Reference | Reference |
| **No chronic kidney disease** | 8272 | 240,705 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 1148 (13.9) | 32,596 (13.5) | 1.01 | 0.99 (0.86 - 1.15) |
| Weak inhibitors of serotonin reuptake\*\* | 242 (2.9) | 6726 (2.8) | Reference | Reference |
|  |  |  |  |  |
| **History of cardiovascular disease#** | 668 | 1594 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 122 (18.3) | 230 (14.4) | 1.37 | 1.42 (0.77 - 2.63) |
| Weak inhibitors of serotonin reuptake\*\* | 20 (3.0) | 52 (3.3) | Reference | Reference |
| **No history of cardiovascular disease** | 7764 | 221,037 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 1034 (13.3) | 29,179 (13.2) | 0.99 | 0.98 (0.84 - 1.14) |
| Weak inhibitors of serotonin reuptake\*\* | 229 (2.9) | 6311 (2.9) | Reference | Reference |

Abbreviations: RR, rate ratio; CI, confidence interval.

\* Cases and controls were matched for sex, age, duration of follow-up, and calendar time.

\*\* Current use of intermediate inhibitors of serotonin reuptake, multiple users, and non-users were also included in the model.

^ Rate ratios were additionally adjusted for obesity, smoking status, alcohol abuse, arterial hypertension, atrial fibrillation, congestive heart failure, ischemic stroke, transient ischemic attack, other coronary artery disease, peripheral vascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, chronic obstructive pulmonary disease, cancer, use of anticoagulants, antiplatelets, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, antipsychotics, other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, trazodone), lithium, hormone replacement therapy, and number of physician visits.

# History of cardiovascular disease was defined as history of other coronary artery disease, peripheral vascular disease, or ischemic stroke/transient ischemic attack.

# **eTable 5. Crude and adjusted rate ratios of myocardial infarction associated with current use of antidepressants strongly inhibiting serotonin reuptake compared with antidepressants weakly inhibiting serotonin reuptake in sensitivity analyses**

|  | **Cases\*** | **Controls\*** | **Crude RR** | **Adjusted RR^****(95% CI)** |
| --- | --- | --- | --- | --- |
| **60-day period of current use** | n = 8626 | n = 258,022 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 1297 (15.0) | 37,061 (14.4) | 0.99 | 0.97 (0.85 - 1.11) |
| Weak inhibitors of serotonin reuptake\*\* | 279 (3.2) | 7856 (3.0) | Reference | Reference |
|  |  |  |  |  |
| **Adjusting for covariates at cohort entry** | n = 8626 | n = 258,022 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 1186 (13.7) | 34,451 (13.4) | 1.03 | 0.99 (0.86 - 1.14) |
| Weak inhibitors of serotonin reuptake\*\* | 255 (3.0) | 7541 (2.9) | Reference | Reference |
|  |  |  |  |  |
| **Multiple imputation** | n = 8626 | n = 258,022 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 1186 (13.7) | 34,451 (13.4) | 1.03 | 1.00 (0.87 - 1.15) |
| Weak inhibitors of serotonin reuptake\*\* | 255 (3.0) | 7541 (2.9) | Reference | Reference |
|  |  |  |  |  |
| **hdPS based trimming** | n = 5027 | n = 149,894 |  |  |
| Strong inhibitors of serotonin reuptake\*\* | 995 (19.8) | 29,922 (20.0) | 0.95 | 0.93 (0.79 - 1.11) |
| Weak inhibitors of serotonin reuptake\*\* | 163 (3.2) | 4633 (3.1) | Reference | Reference |

Abbreviations: RR, rate ratio; CI, confidence interval.

\* Cases and controls were matched for sex, age, duration of follow-up, and calendar time.

\*\* Current use of intermediate inhibitors of serotonin reuptake, multiple users, and non-users were also included in the model.

^ Rate ratios were additionally adjusted for obesity, smoking status, alcohol abuse, arterial hypertension, atrial fibrillation, congestive heart failure, ischemic stroke, transient ischemic attack, other coronary artery disease, peripheral vascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, chronic obstructive pulmonary disease, cancer, use of anticoagulants, antiplatelets, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, antipsychotics, other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, trazodone), lithium, hormone replacement therapy, and number of physician visits.

# **eTable 6. Crude and adjusted rate ratios of ischemic stroke/TIA associated with current use of SSRIs strongly inhibiting serotonin reuptake compared with SSRIs intermediately inhibiting serotonin reuptake (stratified by sex, chronic kidney disease and history of cardiovascular disease)**

|  | **Cases\*****(n = 15,860)** | **Controls\*****(n = 473,712)** | **Crude RR** | **Adjust RR^****(95% CI)** |
| --- | --- | --- | --- | --- |
| **Male sex** | 6093 | 181,660 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 818 (13.4) | 24,448 (13.5) | 0.95 | 0.94 (0.85 - 1.04) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 891 (14.6) | 25,390 (14.0) | Reference | Reference |
| **Female sex** | 9767 | 292,052 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 1365 (14.0) | 40,034 (13.7) | 0.99 | 1.00 (0.93 - 1.08) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 1558 (16.0) | 45,613 (15.6) | Reference | Reference |
|  |  |  |  |  |
| **Chronic kidney disease** | 549 | 1585 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 57 (10.4) | 141 (8.9) | 1.36 | 1.39 (0.92 - 2.11) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 109 (19.9) | 365 (23.0) | Reference | Reference |
| **No chronic kidney disease** | 15,196 | 439,715 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 2108 (13.9) | 61,294 (13.9) | 0.96 | 0.97 (0.91 - 1.03) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 2319 (15.3) | 64,127 (14.6) | Reference | Reference |
|  |  |  |  |  |
| **History of cardiovascular disease#** | 1023 | 2800 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 131 (12.8) | 385 (13.8) | 0.89 | 0.88 (0.65 - 1.18) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 176 (17.2) | 472 (16.9) | Reference | Reference |
| **No history of cardiovascular disease** | 14,621 | 410,542 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 2019 (13.8) | 55,629 (13.6) | 0.99 | 0.99 (0.93 - 1.06) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 2245 (15.4) | 61,099 (14.9) | Reference | Reference |

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; TIA; transient ischemic attack; RR, rate ratio; CI, confidence interval.

\* Cases and controls were matched for sex, age, duration of follow-up, and calendar time.

\*\* Current use of third-generation antidepressants, multiple users, and non-users were also included in the model.

^ Rate ratios were additionally adjusted for obesity, smoking status, alcohol abuse, arterial hypertension, atrial fibrillation, congestive heart failure, myocardial infarction, other coronary artery disease, peripheral vascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, chronic obstructive pulmonary disease, cancer, use of anticoagulants, antiplatelets, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, antipsychotics, other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, trazodone), lithium, hormone replacement therapy, and number of physician visits.

# History of cardiovascular disease was defined as history of myocardial infarction, other coronary artery disease, or peripheral vascular disease.

# **eTable 7. Crude and adjusted rate ratios of ischemic stroke/TIA associated with current use of SSRIs strongly inhibiting serotonin reuptake compared with SSRIs intermediately inhibiting serotonin reuptake in sensitivity analyses**

|  | **Cases\*** | **Controls\*** | **Crude RR** | **Adjusted RR^****(95% CI)** |
| --- | --- | --- | --- | --- |
| **60-day period of current use** | n = 15,860 | n = 473,712 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 2357 (14.9) | 69,826 (14.7) | 0.96 | 0.96 (0.91 - 1.02) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 2639 (16.6) | 75,575 (16.0) | Reference | Reference |
|  |  |  |  |  |
| **Excluding TIA** | n = 9354 | n = 279,235 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 1294 (13.8) | 38,242 (13.7) | 0.99 | 0.98 (0.90 - 1.06) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 1444 (15.4) | 42,386 (15.2) | Reference | Reference |
|  |  |  |  |  |
| **Adjusting for covariates at cohort entry** | n = 15,860 | n = 473,712 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 2183 (13.8) | 64,482 (13.6) | 0.98 | 0.97 (0.92 - 1.04) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 2449 (15.4) | 71,003 (15.0) | Reference | Reference |
|  |  |  |  |  |
| **Multiple imputation** | n = 15,860 | n = 473,712 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 2183 (13.8) | 64,482 (13.6) | 0.98 | 0.98 (0.92 - 1.04) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 2449 (15.4) | 71,003 (15.0) | Reference | Reference |
|  |  |  |  |  |
| **hdPS based trimming** | n = 13,125 | n = 391,645 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 1893 (14.4) | 56,394 (14.4) | 0.96 | 0.97 (0.90 - 1.03) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 2151 (16.4) | 62,059 (15.8) | Reference | Reference |

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; TIA; transient ischemic attack; hdPS, high-dimensional propensity score; RR, rate ratio; CI, confidence interval.

\* Cases and controls were matched for sex, age, duration of follow-up, and calendar time.

\*\* Current use of third-generation antidepressants, multiple users, and non-users were also included in the model.

^ Rate ratios were additionally adjusted for obesity, smoking status, alcohol abuse, arterial hypertension, atrial fibrillation, congestive heart failure, myocardial infarction, other coronary artery disease, peripheral vascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, chronic obstructive pulmonary disease, cancer, use of anticoagulants, antiplatelets, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, antipsychotics, other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, trazodone), lithium, hormone replacement therapy, and number of physician visits.

# **eTable 8. Crude and adjusted rate ratios of myocardial infarction associated with current use of SSRIs strongly inhibiting serotonin reuptake compared with SSRIs intermediately inhibiting serotonin reuptake (stratified by sex, chronic kidney disease and history of cardiovascular disease)**

|  | **Cases\*****(n = 8626)** | **Controls\*****(n = 258,022)** | **Crude RR** | **Adjust RR^****(95% CI)** |
| --- | --- | --- | --- | --- |
| **Male sex** | 4510 | 134,846 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 572 (12.7) | 16,957 (12.6) | 1.14 | 1.12 (0.99 - 1.27) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 513 (11.4) | 17,252 (12.8) | Reference | Reference |
| **Female sex** | 4116 | 123,176 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 558 (13.6) | 16,351 (13.3) | 1.05 | 1.06 (0.94 - 1.20) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 615 (14.9) | 18,926 (15.4) | Reference | Reference |
|  |  |  |  |  |
| **Chronic kidney disease** | 274 | 786 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 26 (9.5) | 74 (9.4) | 0.91 | 0.96 (0.54 - 1.73) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 65 (23.7) | 175 (22.3) | Reference | Reference |
| **No chronic kidney disease** | 8272 | 240,705 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 1094 (13.2) | 31,584 (13.1) | 1.11 | 1.10 (1.01 - 1.20) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 1053 (12.7) | 32,875 (13.7) | Reference | Reference |
|  |  |  |  |  |
| **History of cardiovascular disease#** | 668 | 1594 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 117 (17.5) | 218 (13.7) | 1.38 | 1.46 (1.01 - 2.11) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 107 (16.0) | 274 (17.2) | Reference | Reference |
| **No history of cardiovascular disease** | 7764 | 221,037 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 985 (12.7) | 28,243 (12.8) | 1.08 | 1.08 (0.98 - 1.18) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 996 (12.8) | 30,518 (13.8) | Reference | Reference |

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; RR, rate ratio; CI, confidence interval.

\* Cases and controls were matched for sex, age, duration of follow-up, and calendar time.

\*\* Current use of third-generation antidepressants, multiple users, and non-users were also included in the model.

^ Rate ratios were additionally adjusted for obesity, smoking status, alcohol abuse, arterial hypertension, atrial fibrillation, congestive heart failure, ischemic stroke, transient ischemic attack, other coronary artery disease, peripheral vascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, chronic obstructive pulmonary disease, cancer, use of anticoagulants, antiplatelets, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, antipsychotics, other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, trazodone), lithium, hormone replacement therapy, and number of physician visits.

# History of cardiovascular disease was defined as history of other coronary artery disease, peripheral vascular disease, or ischemic stroke/transient ischemic attack.

# **eTable 9. Crude and adjusted rate ratios of myocardial infarction associated with current use of SSRIs strongly inhibiting serotonin reuptake compared with SSRIs intermediately inhibiting serotonin reuptake in sensitivity analyses**

|  | **Cases\*** | **Controls\*** | **Crude RR** | **Adjusted RR^****(95% CI)** |
| --- | --- | --- | --- | --- |
| **60-day period of current use** | n = 8626 | n = 258,022 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 1239 (14.4) | 35,859 (13.9) | 1.09 | 1.08 (0.99 - 1.17) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 1227 (14.2) | 38,417 (14.9) | Reference | Reference |
|  |  |  |  |  |
| **Adjusting for covariates at cohort entry** | n = 8626 | n = 258,022 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 1130 (13.1) | 33,308 (12.9) | 1.09 | 1.08 (0.99 - 1.18) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 1128 (13.1) | 36,178 (14.0) | Reference | Reference |
|  |  |  |  |  |
| **Multiple imputation** | n = 8626 | n = 258,022 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 1130 (13.1) | 33,308 (12.9) | 1.09 | 1.09 (1.00 - 1.19) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 1128 (13.1) | 36,178 (14.0) | Reference | Reference |
|  |  |  |  |  |
| **hdPS based trimming** | n = 7189 | n = 214,801 |  |  |
| SSRIs strongly inhibiting serotonin reuptake\*\*  | 995 (13.8) | 29,163 (13.6) | 1.09 | 1.08 (0.99 - 1.19) |
| SSRIs intermediately inhibiting serotonin reuptake\*\* | 1007 (14.0) | 32,137 (15.0) | Reference | Reference |

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; hdPS, high-dimensional propensity score; RR, rate ratio; CI, confidence interval; TIA, transient ischemic attack.

\* Cases and controls were matched for sex, age, duration of follow-up, and calendar time.

\*\* Current use of third-generation antidepressants, multiple users, and non-users were also included in the model.

^ Rate ratios were additionally adjusted for obesity, smoking status, alcohol abuse, arterial hypertension, atrial fibrillation, congestive heart failure, ischemic stroke, TIA, other coronary artery disease, peripheral vascular disease, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, chronic obstructive pulmonary disease, cancer, use of anticoagulants, antiplatelets, lipid-lowering drugs, non-steroidal anti-inflammatory drugs, opioids, beta-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, antipsychotics, other antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, trazodone), lithium, hormone replacement therapy, and number of physician visits.

# **eTable 10. Characteristics of patients initiating treatment with antidepressants strongly inhibiting serotonin reuptake and propensity score matched patients initiating treatment with antidepressants weakly inhibiting serotonin reuptake for the outcome ischemic stroke/TIA**

| **Characteristic** | **Strong inhibitors of serotonin reuptake****(n = 40,293)** | **Weak inhibitors of serotonin reuptake****(n = 40,293)** | **Standardized difference** |
| --- | --- | --- | --- |
| Age in years, mean (SD) | 52.9 (20.7) | 53.5 (21.4) | -0.0294 |
| Male sex, n (%) | 20,466 (50.8) | 19,224 (47.7) | 0.0617 |
| Body mass index (kg/m2) |   |   | . |
| <30 | 26,555 (65.9) | 26,749 (66.4) | -0.0102 |
| ≥30 | 6213 (15.4) | 6423 (15.9) | -0.0143 |
| Unknown | 7525 (18.7) | 7121 (17.7) | 0.026 |
| Smoking status |   |   | . |
| Never | 11,671 (29.0) | 11,998 (29.8) | -0.0178 |
| Ever | 26,544 (65.9) | 26,290 (65.2) | 0.0133 |
| Unknown | 2078 (5.2) | 2005 (5.0) | 0.0083 |
| Alcohol abuse, n (%) | 1115 (2.8) | 1135 (2.8) | -0.003 |
| Comorbidities, n (%) |   |   | . |
| Arterial hypertension | 11,914 (29.6) | 12,153 (30.2) | -0.013 |
| Atrial fibrillation | 550 (1.4) | 557 (1.4) | -0.0015 |
| Congestive heart failure | 340 (0.8) | 389 (1.0) | -0.0128 |
| Myocardial infarction | 172 (0.4) | 217 (0.5) | -0.0161 |
| Other coronary artery disease | 1033 (2.6) | 1209 (3.0) | -0.0266 |
| Peripheral vascular disease | 134 (0.3) | 171 (0.4) | -0.015 |
| Hyperlipidemia | 6792 (16.9) | 7072 (17.6) | -0.0184 |
| Diabetes mellitus | 2366 (5.9) | 2675 (6.6) | -0.0317 |
| Chronic kidney disease | 937 (2.3) | 1046 (2.6) | -0.0175 |
| Liver disease | 113 (0.3) | 127 (0.3) | -0.0064 |
| Depression | 13,046 (32.4) | 12,993 (32.2) | 0.0028 |
| COPD | 1170 (2.9) | 1268 (3.1) | -0.0142 |
| Cancer | 1630 (4.0) | 1734 (4.3) | -0.0129 |
| Comedications, n (%) |   |   | . |
| Anticoagulants | 1308 (3.2) | 1455 (3.6) | -0.0201 |
| Antiplatelets | 6184 (15.3) | 6511 (16.2) | -0.0223 |
| Acetylsalicylic acid | 5750 (14.3) | 5983 (14.8) | -0.0164 |
| Others | 991 (2.5) | 1251 (3.1) | -0.0392 |
| Lipid lowering drugs | 6547 (16.2) | 6893 (17.1) | -0.023 |
| NSAIDs | 8695 (21.6) | 8499 (21.1) | 0.0119 |
| Opioids | 12,629 (31.3) | 12,443 (30.9) | 0.01 |
| Beta-blockers | 5521 (13.7) | 5664 (14.1) | -0.0103 |
| Thiazides | 3832 (9.5) | 3649 (9.1) | 0.0157 |
| ACE inhibitors | 4673 (11.6) | 4957 (12.3) | -0.0217 |
| Angiotensin II receptor blockers | 1559 (3.9) | 1814 (4.5) | -0.0316 |
| Calcium channel blockers | 4303 (10.7) | 4286 (10.6) | 0.0014 |
| Antipsychotics | 4746 (11.8) | 4938 (12.3) | -0.0147 |
| Lithium | 162 (0.4) | 186 (0.5) | -0.0091 |
| Number of physician visits, n (%) |   |   | . |
| 0-3 | 9728 (24.1) | 9408 (23.3) | 0.0187 |
| 4-6 | 9064 (22.5) | 8996 (22.3) | 0.004 |
| ≥7 | 21,501 (53.4) | 21,889 (54.3) | -0.0193 |

Abbreviation: TIA, transient ischemic attack; SD, standard deviation; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme

The two groups were matched on closest propensity score using a caliper of 0.2.

# **eTable 11. Characteristics of patients initiating treatment with antidepressants strongly inhibiting serotonin reuptake and propensity score matched patients initiating treatment with antidepressants weakly inhibiting serotonin reuptake for the outcome myocardial infarction**

| **Characteristic** | **Strong inhibitors of serotonin reuptake****(n = 40,864)** | **Weak inhibitors of serotonin reuptake****(n = 40,864)** | **Standardized difference** |
| --- | --- | --- | --- |
| Age in years, mean (SD) | 53.2 (20.8) | 53.8 (21.5) | -0.0303 |
| Male sex, n (%) | 20,818 (50.9) | 19,503 (47.7) | 0.0644 |
| Body mass index (kg/m2) |   |   | . |
| <30 | 26,935 (65.9) | 27,153 (66.4) | -0.0113 |
| ≥30 | 6315 (15.5) | 6519 (16.0) | -0.0137 |
| Unknown | 7614 (18.6) | 7192 (17.6) | 0.0268 |
| Smoking status |   |   | . |
| Never | 11,839 (29.0) | 12,187 (29.8) | -0.0187 |
| Ever | 26,920 (65.9) | 26,647 (65.2) | 0.0141 |
| Unknown | 2105 (5.2) | 2030 (5.0) | 0.0084 |
| Alcohol abuse, n (%) | 1147 (2.8) | 1140 (2.8) | 0.001 |
| Comorbidities, n (%) |   |   | . |
| Arterial hypertension | 12,245 (30.0) | 12,556 (30.7) | -0.0166 |
| Atrial fibrillation | 614 (1.5) | 641 (1.6) | -0.0054 |
| Congestive heart failure | 351 (0.9) | 392 (1.0) | -0.0106 |
| Transient ischemic attack | 189 (0.5) | 248 (0.6) | -0.0198 |
| Ischemic stroke | 466 (1.1) | 575 (1.4) | -0.0238 |
| Other coronary artery disease | 1028 (2.5) | 1191 (2.9) | -0.0245 |
| Peripheral vascular disease | 137 (0.3) | 176 (0.4) | -0.0155 |
| Hyperlipidemia | 7027 (17.2) | 7425 (18.2) | -0.0255 |
| Diabetes mellitus | 2452 (6.0) | 2751 (6.7) | -0.03 |
| Chronic kidney disease | 973 (2.4) | 1068 (2.6) | -0.0149 |
| Liver disease | 116 (0.3) | 130 (0.3) | -0.0063 |
| Depression | 13,167 (32.2) | 13,101 (32.1) | 0.0035 |
| COPD | 1184 (2.9) | 1290 (3.2) | -0.0151 |
| Cancer | 1666 (4.1) | 1771 (4.3) | -0.0128 |
| Comedications, n (%) |  |  |  |
| Anticoagulants | 1383 (3.4) | 1586 (3.9) | -0.0266 |
| Antiplatelets | 6504 (15.9) | 6961 (17.0) | -0.0302 |
| Acetylsalicylic acid | 6024 (14.7) | 6329 (15.5) | -0.0208 |
| Others | 1122 (2.7) | 1452 (3.6) | -0.0463 |
| Lipid lowering drugs | 6775 (16.6) | 7243 (17.7) | -0.0304 |
| NSAIDs | 8813 (21.6) | 8583 (21.0) | 0.0138 |
| Opioids | 12,872 (31.5) | 12,663 (31.0) | 0.011 |
| Beta-blockers | 5579 (13.7) | 5774 (14.1) | -0.0138 |
| Thiazides | 4052 (9.9) | 3810 (9.3) | 0.0201 |
| ACE inhibitors | 4773 (11.7) | 5153 (12.6) | -0.0285 |
| Angiotensin II receptor blockers | 1640 (4.0) | 1890 (4.6) | -0.0301 |
| Calcium channel blockers | 4445 (10.9) | 4484 (11.0) | -0.0031 |
| Antipsychotics | 4893 (12.0) | 5055 (12.4) | -0.0121 |
| Lithium | 179 (0.4) | 189 (0.5) | -0.0037 |
| Number of physician visits, n (%) |   |   |  |
| 0-3 | 9761 (23.9) | 9428 (23.1) | 0.0192 |
| 4-6 | 9142 (22.4) | 9069 (22.2) | 0.0043 |
| ≥7 | 21,961 (53.7) | 22,367 (54.7) | -0.0199 |

Abbreviation: SD, standard deviation; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme

The two groups were matched on closest propensity score using a caliper of 0.2.

# **eTable 12. Hazard ratios of ischemic stroke/TIA or myocardial infarction associated with the use of antidepressants strongly inhibiting serotonin reuptake compared with the use of antidepressants weakly inhibiting serotonin reuptake**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Number of patients** | **Number of events** | **Person-years** | **Incidence rate a** | **HR b****(95% CI)** |
| **Ischemic stroke/TIA** |  |  |  |  |  |
| Strong inhibitors of serotonin reuptake  | 40293 | 224 | 20132 | 111.3 | 0.94 (0.75 - 1.18) |
| Weak inhibitors of serotonin reuptake | 40293 | 233 | 19763 | 117.9 | Reference |
|  |  |  |  |  |  |
| **Myocardial infarction** |  |  |  |  |  |
| Strong inhibitors of serotonin reuptake  | 40864 | 80 | 20669 | 38.7 | 1.00 (0.68 - 1.46) |
| Weak inhibitors of serotonin reuptake | 40864 | 78 | 20394 | 38.2 | Reference |

Abbreviations: HR, hazard ratio; CI, confidence interval; TIA, transient ischemic attack.

a Per 10,000 person-years.

b Matched on propensity score.