**Supplement 3**

Supplement to “Safety Outcomes of Selective Serotonin Reuptake Inhibitors in Adolescent Attention–Deficit/Hyperactivity Disorder: The ASSURE Study”

Graphical user interface

Description automatically generated

Figure S1. Schematic visualization for the cohort definition and as–treated follow–up strategy

Table S1. Baseline characteristics, comorbidities, and concomitant drugs in adolescent ADHD patients with depression before the propensity score matching

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **SSRI (n = 6 746)** | **MPH–only (n =2 917)** | **Fluoxetine**  **(n= 2 381)** | **Escitalopram**  **(n=3 364)** |
| **Socio-demographics, n (%)** |  |  |  |  |
| Male | 3,193 (47.3) | 1,740 (59.7) | 1,093 (45.9) | 1,615 (48.0) |
| 10–14 years | 2,315 (34.3) | 1,380 (47.3) | 802 (33.7) | 1,162 (34.5) |
| 15–19 years | 4,431 (65.7) | 1,537 (52.7) | 1,579 (66.3) | 2,202 (65.5) |
| Race, Korean | 6,746 (100.0) | 2,917 (100.0) | 2,381 (100.0) | 3,364 (100.0) |
| **Index year, n (%)** |  |  |  |  |
| 2017 | 1,205 (17.9) | 554 (19.0) | 457 (19.2) | 579 (17.2) |
| 2018 | 1,797 (26.6) | 675 (23.1) | 643 (27.0) | 874 (26.0) |
| 2019 | 1,951 (28.9) | 872 (29.9) | 678 (28.5) | 986 (29.3) |
| 2020 | 1,793 (26.6) | 816 (28.0) | 603 (25.3) | 925 (27.5) |
| **Medical history, n (%)** |  |  |  |  |
| Anxiety disorder | 2,085 (30.9) | 865 (29.7) | 628 (26.4) | 1,097 (32.6) |
| Autism spectrum disorder | 142 (2.1) | 78 (2.7) | 53 (2.2) | 69 (2.1) |
| Bipolar disorder | 622 (9.2) | 297 (10.2) | 207 (8.7) | 292 (8.7) |
| Conduct disorder | 441 (6.5) | 279 (9.6) | 180 (7.6) | 205 (6.1) |
| Intellectual disability | 209 (3.1) | 155 (5.3) | 91 (3.8) | 83 (2.5) |
| **Medication use, n (%)** |  |  |  |  |
| Anticholinergics | 2,866 (42.5) | 823 (28.2) | 864 (36.3) | 1,547 (46.0) |
| Antiepileptics | 482 (7.1) | 178 (6.1) | 143 (6.0) | 264 (7.8) |
| Antipsychotics | 1,832 (27.2) | 693 (23.8) | 604 (25.4) | 932 (27.7) |
| Anxiolytics | 1,574 (23.3) | 249 (8.5) | 429 (18.0) | 899 (26.7) |
| SSRI: selective serotonin reuptake inhibitor; MPH: methylphenidate; | | | | |



Figure S2. Empirical equipoise between the comparison groups.   
MPH: methylphenidate; SSRI: selective serotonin reuptake inhibitor; FLX: fluoxetine; ECP: escitalopram; Preference score: prevalence–adjusted propensity score1

Table S2. Incidence of outcome events between the SSRI and MPH–only groups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **SSRI group (n = 2,650)** | | | **MPH–only group (n = 2,650)** | | |
| **Number of events** | **Person–years** | **Incidence rate**§ | **Number of events** | **Person–years** | **Incidence rate**§ |
| **Primary endpoint** | | | | | | |
| Mania | 22 | 1 079.5 | 20.38 | 11 | 926.1 | 11.88 |
| Psychosis | 40 | 1 064.1 | 37.59 | 33 | 900.8 | 36.63 |
| Sleep disorder | 66 | 1 057.0 | 62.44 | 39 | 901.0 | 43.29 |
| Suicide | 1 | 1 117.5 | 0.89 | 2 | 939.1 | 2.13 |
| Tic disorder | 61 | 1 058.6 | 57.62 | 46 | 883.4 | 52.07 |
| Hospitalization | 26 | 1 117.9 | 23.26 | 12 | 929.7 | 12.91 |
| **Secondary endpoint** |  |  |  |  |  |  |
| Arrhythmia | 5 | 1 107.2 | 4.52 | 10 | 933.6 | 10.71 |
| Abdominal pain | 4 | 1 125.5 | 3.55 | 2 | 936.0 | 2.14 |
| Constipation | 11 | 1 124.3 | 9.78 | 16 | 928.2 | 17.24 |
| Headache | 14 | 1 122.1 | 12.48 | 11 | 932.9 | 11.79 |
| Hypertension | 1 | 1 112.4 | 0.90 | 5 | 937.0 | 5.34 |
| Nausea vomiting | 25 | 1 119.3 | 22.33 | 14 | 935.0 | 14.97 |
| Seizure | 18 | 1 070.6 | 16.81 | 23 | 918.7 | 25.04 |
| Traumatic injury | 5 | 1 125.5 | 4.44 | 4 | 937.6 | 4.27 |
| Tremor | 14 | 1 087.1 | 12.88 | 13 | 926.5 | 14.03 |
| **Negative control outcome** | 11 | 1 109.1 | 9.92 | 5 | 936.9 | 5.34 |
| SSRI: selective serotonin reuptake inhibitor; MPH: methylphenidate; §Incidence rate was calculated as case per 1 000 person–years; Negative control outcome indicates respiratory tract infection. | | | | | | |

Table S3. Incidence of outcome events between the fluoxetine and escitalopram groups

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Fluoxetine group (n = 1,820)** | | | **Escitalopram group (n = 1,820)** | | |
| **Number of events** | **Person–years** | **Incidence rate**§ | **Number of events** | **Person–years** | **Incidence rate**§ |
| **Primary endpoint** | | | | | | |
| Mania | 15 | 706.0 | 21.25 | 14 | 655.8 | 21.35 |
| Psychosis | 28 | 693.5 | 40.38 | 21 | 649.3 | 32.34 |
| Sleep disorder | 45 | 668.5 | 67.32 | 40 | 629.3 | 63.56 |
| Suicide | 1 | 718.1 | 1.39 | 0 | 667.8 | 0.00 |
| Tic disorder | 22 | 687.4 | 32.00 | 48 | 632.9 | 75.84 |
| Hospitalization | 9 | 712.4 | 12.63 | 15 | 667.1 | 22.49 |
| **Secondary endpoint** |  |  |  |  |  |  |
| Arrhythmia | 1 | 716.4 | 1.40 | 3 | 668.4 | 4.49 |
| Abdominal pain | 4 | 716.4 | 5.58 | 1 | 671.0 | 1.49 |
| Constipation | 7 | 715.3 | 9.79 | 8 | 670.0 | 11.94 |
| Headache | 14 | 712.7 | 19.64 | 11 | 667.0 | 16.49 |
| Hypertension | 0 | 721.1 | 0.00 | 2 | 668.8 | 2.99 |
| Nausea vomiting | 12 | 712.2 | 16.85 | 14 | 668.3 | 20.95 |
| Seizure | 15 | 703.3 | 21.33 | 15 | 656.4 | 22.85 |
| Traumatic injury | 3 | 714.0 | 4.20 | 1 | 670.7 | 1.49 |
| Tremor | 7 | 713.1 | 9.82 | 13 | 660.0 | 19.70 |
| **Negative control outcome** | 4 | 716.4 | 5.58 | 2 | 669.2 | 2.99 |
| §Incidence rate was calculated as case per 1 000 person–years; Negative control outcome indicates respiratory tract infection. | | | | | | |

Table S4. Risk of outcome events between the SSRI and MPH alone groups in the subgroup analysis by sex

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Male subgroup** | | | **Female subgroup** | | |
| **Incidence Rate**§ | | **HR [95% CI]** | **Incidence Rate**§ | | **HR [95% CI]** |
| **SSRI**  **(n = 1,507)** | **MPH–only**  **(Reference, n = 1,507)** | **SSRI**  **(n = 1,081)** | **MPH–only**  **(Reference, n = 1,081)** |
| **Primary endpoint** | | | | | | |
| Mania | 24.75 | 14.73 | 1.70 [0.77–3.99] | 11.79 | 6.69 | 1.84 [0.40–12.91] |
| Psychosis | 23.28 | 35.18 | 0.68 [0.35–1.29] | 48.56 | 34.70 | 1.53 [0.73–3.42] |
| Sleep disorder | 37.97 | 36.38 | 1.02 [0.58–1.83] | 67.55 | 56.35 | 1.28 [0.70–2.43] |
| Suicide | 0.00 | 3.20 | NA | 0.00 | 0.00 | NA |
| Tic disorder | 60.49 | 62.65 | 0.97 [0.62–1.54] | 50.13 | 38.44 | 1.42 [0.69–3.07] |
| Hospitalization | 24.66 | 21.09 | 1.15 [0.56–2.42] | 19.09 | 3.33 | **6.14 [1.13–114.03]‡** |
| **Secondary endpoint** |  |  |  |  |  |  |
| Arrhythmia | 0.00 | 6.40 | NA | 9.15 | 20.19 | 0.52 [0.13–1.83] |
| Abdominal pain | 0.00 | 3.21 | NA | 2.38 | 0.00 | NA |
| Constipation | 7.18 | 12.92 | 0.55 [0.17–1.65] | 16.73 | 23.43 | 0.84 [0.29–2.45] |
| Headache | 11.52 | 14.49 | 0.81 [0.30–2.12] | 9.53 | 6.67 | 1.74 [0.34–12.56] |
| Hypertension | 1.44 | 4.80 | 0.31 [0.02–2.40] | 0.00 | 6.69 | NA |
| Nausea vomiting | 8.63 | 17.68 | 0.50 [0.17–1.31] | 35.96 | 10.00 | **4.4 [1.45–19.01]‡** |
| Seizure | 17.94 | 21.27 | 0.84 [0.38–1.86] | 16.89 | 30.70 | 0.61 [0.22–1.66] |
| Traumatic injury | 2.87 | 4.80 | 0.64 [0.08–3.89] | 7.14 | 3.33 | 2.31 [0.29–46.83] |
| Tremor | 10.30 | 12.93 | 0.78 [0.27–2.18] | 28.35 | 10.10 | 2.75 [0.87–12.11] |
| §Incidence rate was calculated as case per 1 000 person–years; MPH: methylphenidate; SSRI: selective serotonin reuptake inhibitor; ‡ statistically significant | | | | | | |

Table S5. Risk of outcome events between the fluoxetine and escitalopram groups in the subgroup analysis by sex

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Male subgroup** | | | **Female subgroup** | | |
| **Incidence Rate**§ | | **HR [95% CI]** | **Incidence Rate**§ | | **HR [95% CI]** |
| **Fluoxetine**  **(n = 825)** | **Escitalopram**  **(Reference, n = 825)** | **Fluoxetine**  **(n = 891)** | **Escitalopram**  **(Reference, n = 891)** |
| **Primary endpoints** | | | | | | |
| Mania | 33.61 | 14.61 | 2.41 [0.89–7.58] | 6.58 | 25.09 | 0.27 [0.04–1.12] |
| Psychosis | 34.29 | 24.23 | 1.5 [0.62–3.82] | 36.52 | 39.08 | 0.99 [0.42–2.31] |
| Sleep disorder | 40.75 | 45.28 | 0.89 [0.42–1.85] | 72.85 | 95.72 | 0.77 [0.43–1.36] |
| Suicide | 2.72 | 0.00 | NA | 3.23 | 0.00 | NA |
| Tic disorder | 34.19 | 103.89 | **0.35 [0.17–0.65]‡** | 29.98 | 42.42 | 0.73 [0.30–1.72] |
| Hospitalization | 11.01 | 23.37 | 0.48 [0.13–1.51] | 16.33 | 31.08 | 0.54 [0.17–1.58] |
| **Secondary endpoints** |  |  |  |  |  |  |
| Arrhythmia | 0.00 | 0.00 | NA | 3.29 | 3.45 | 0.93 [0.04–23.41] |
| Abdominal pain | 0.00 | 2.91 | 0.14 [NA–6.94] | 12.99 | 3.44 | 4.00 [0.59–78.21] |
| Constipation | 5.48 | 5.82 | 1.01 [0.12–8.39] | 19.56 | 20.70 | 0.98 [0.31–3.13] |
| Headache | 16.50 | 5.82 | 3.04 [0.70–20.78] | 16.21 | 13.81 | 1.21 [0.32–4.90] |
| Hypertension | 2.72 | 0.00 | NA | 0.00 | 3.46 | NA |
| Nausea vomiting | 13.71 | 17.47 | 0.85 [0.24–2.82] | 19.64 | 38.08 | 0.54 [0.19–1.43] |
| Seizure | 22.81 | 18.18 | 1.29 [0.45–3.92] | 16.60 | 21.02 | 0.81 [0.23–2.71] |
| Traumatic injury | 8.27 | 0.00 | NA | 0.00 | 10.34 | NA |
| Tremor | 8.23 | 8.76 | 0.99 [0.18–5.35] | 9.91 | 28.25 | 0.37 [0.08–1.27] |
| §Incidence rate was calculated as case per 1 000 person–years; MPH: methylphenidate; SSRI: selective serotonin reuptake inhibitor; FLX: fluoxetine; ECP: escitalopram; ‡ Statistically significant | | | | | | |

Table S6. Comparisons of baseline characteristics, comorbidities, and concomitant drugs between the SSRI and MPH-only groups after propensity score matching in sensitivity analyses

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **As-treated 1:n** | | | | | **As-treated Stratification** | | | | | **ITT 1:1** | | | | | **ITT 1:n** | | | | | | | **ITT Stratification** | | | | | |
| **SSRI (n=2,650)** | | **MPH-only (n=2,858)** | | **aSMD** | **SSRI (n=6,270)** | | **MPH-only (n=2,916)** | | **aSMD** | **SSRI (n=1,993)** | | **MPH-only (n=1,993)** | | **aSMD** | | **SSRI (n=1,993)** | | **MPH-only (n=2,166)** | | **aSMD** | | | **SSRI (n=5,141)** | | **MPH-only (n=2,206)** | | **aSMD** | |
| **Socio-demographics, n (%)** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Male | 1,500 (56.6) | 1,691 (57.9) | | 0.03 | | 3,007 (51.6) | 1,739 (52) | | 0.01 | | 1187 (59.6) | 1176 (59) | | 0.01 | | 1,187 (59.6) | | 1,321 (59.1) | | 0.01 | | 2,430 (51.7) | | | 1,358 (50.7) | | 0.02 | |
| 10–14 years | 1,161 (43.8) | 1,345 (44.9) | | 0.02 | | 2,226 (39.1) | 1,380 (38.5) | | 0.01 | | 930 (46.7) | 928 (46.6) | | 0.00 | | 930 (46.7) | | 1,049 (46.6) | | 0.00 | | 1,836 (39.3) | | | 1,072 (38.1) | | 0.02 | |
| 15–19 years | 1,489 (56.2) | 1,513 (55.1) | | 0.02 | | 4,044 (60.9) | 1,536 (61.5) | | 0.01 | | 1,063 (53.3) | 1,065 (53.4) | | 0.00 | | 1,063 (53.3) | | 1,117 (53.4) | | 0.00 | | 3,305 (60.7) | | | 1,134 (61.9) | | 0.02 | |
| Race, Korean | 2,650 (100.0) | 2,858 (100.0) | | 0.00 | | 6,270 (100.0) | 2,916 (100.0) | | 0.00 | | 1,993 (100.0) | 1,993 (100.0) | | 0.00 | | 1,993 (100.0) | | 2,166 (100.0) | | 0.00 | | 5,141 (100.0) | | | 2,206 (100.0) | | 0.00 | |
| **Index year, n (%)** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 2017 | 511 (19.3) | 545 (19.4) | | 0.00 | | 1,143 (18.7) | 554 (18.1) | | 0.01 | | 532 (26.7) | 511 (25.6) | | 0.02 | | 532 (26.7) | | 547 (25.4) | | 0.03 | | 1,205 (24.2) | | | 554 (23.4) | | 0.02 | |
| 2018 | 583 (22.0) | 659 (23.4) | | 0.03 | | 1,684 (25.7) | 674 (24.2) | | 0.03 | | 598 (30.0) | 611 (30.7) | | 0.01 | | 598 (30.0) | | 661 (31.1) | | 0.02 | | 1,797 (33.4) | | | 675 (32.3) | | 0.02 | |
| 2019 | 778 (29.4) | 855 (29.5) | | 0.00 | | 1,793 (28.8) | 872 (29.8) | | 0.02 | | 771 (38.7) | 782 (39.2) | | 0.01 | | 771 (38.7) | | 856 (39.1) | | 0.01 | | 1,951 (38.6) | | | 872 (40.1) | | 0.03 | |
| 2020 | 778 (29.4) | 799 (27.7) | | 0.04 | | 1,650 (26.9) | 816 (27.9) | | 0.02 | | 92 (4.6) | 89 (4.5) | | 0.01 | | 92 (4.6) | | 102 (4.4) | | 0.01 | | 188 (3.9) | | | 105 (4.2) | | 0.01 | |
| **Medical history, n (%)** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Anxiety disorder | 758 (28.6) | 839 (28.1) | | 0.01 | | 1,858 (29.6) | 864 (28.5) | | 0.02 | | 537 (26.9) | 523 (26.2) | | 0.02 | | 537 (26.9) | | 607 (26.5) | | 0.01 | | 1522 (29) | | | 621 (27.7) | | 0.03 | |
| Autism spectrum disorder | 69 (2.6) | 76 (2.5) | | 0.00 | | 136 (2.3) | 78 (2.5) | | 0.01 | | 56 (2.8) | 46 (2.3) | | 0.03 | | 56 (2.8) | | 62 (2.5) | | 0.02 | | 100 (2.2) | | | 66 (2.5) | | 0.02 | |
| Conduct disorder | 241 (9.1) | 263 (8.4) | | 0.02 | | 418 (7.5) | 279 (7.8) | | 0.01 | | 193 (9.7) | 193 (9.7) | | 0.00 | | 193 (9.7) | | 229 (9.8) | | 0.00 | | 368 (8.1) | | | 242 (8.1) | | 0.00 | |
| Intellectual disability | 128 (4.8) | 148 (4.6) | | 0.01 | | 201 (3.8) | 155 (3.8) | | 0.00 | | 105 (5.3) | 106 (5.3) | | 0.00 | | 105 (5.3) | | 118 (5.2) | | 0.00 | | 174 (4.0) | | | 122 (4.0) | | 0.00 | |
| **Medication use, n (%)** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Anticholinergics | 702 (26.5) | 790 (27.8) | | 0.03 | | 2,530 (36.0) | 822 (36.2) | | 0.00 | | 510 (25.6) | 548 (27.5) | | 0.04 | | 510 (25.6) | | 596 (27.7) | | 0.05 | | 353 (6.6) | | | 144 (6.4) | | 0.01 | |
| Antiepileptics | 134 (5.1) | 156 (4.9) | | 0.01 | | 403 (6.1) | 178 (6.4) | | 0.01 | | 102 (5.1) | 105 (5.3) | | 0.01 | | 102 (5.1) | | 124 (5.2) | | 0.00 | | 1332 (24.8) | | | 521 (25.7) | | 0.02 | |
| Antipsychotics | 581 (21.9) | 662 (23) | | 0.03 | | 1,654 (25.1) | 692 (25.7) | | 0.01 | | 428 (21.5) | 454 (22.8) | | 0.03 | | 428 (21.5) | | 500 (22.9) | | 0.04 | | 1174 (18.3) | | | 182 (19.3) | | 0.03 | |
| Anxiolytics | 225 (8.5) | 241 (8.8) | | 0.01 | | 1321 (17) | 249 (17.1) | | 0.00 | | 1187 (59.6) | 1176 (59.0) | | 0.01 | | 140 (7) | | 178 (8.5) | | 0.06 | | 2133 (37.0) | | | 618 (38.1) | | 0.02 | |
| ADHD: attention-deficit/hyperactivity disorder; PS: propensity score; MPH: methylphenidate; SSRI: selective serotonin reuptake inhibitor; aSMD: absolute standardized mean difference; | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Table S7. Comparisons of baseline characteristics, comorbidities, and concomitant drugs between the Fluoxetine and Escitalopram groups after propensity score matching in sensitivity analyses

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **As-treated 1:n** | | | **As-treated Stratification** | | | **ITT 1:1** | | | **ITT 1:n** | | | **ITT Stratification** | | |
| **Fluoxetine (n=1,820)** | **Escitalopram (n=2,926)** | **aSMD** | **Fluoxetine (n=2,182)** | **Escitalopram (n=3,128)** | **aSMD** | **Fluoxetine (n=1,468)** | **Escitalopram (n=1,468)** | **aSMD** | **Fluoxetine (n=1,468)** | **Escitalopram (n=2,327)** | **aSMD** | **Fluoxetine (n=1,839)** | **Escitalopram (n=2,532)** | **aSMD** |
| **Socio-demographics, n (%)** | | | | | | | | | | | | | | | |
| Male | 860 (47.3) | 1,411 (47.7) | 0.01 | 1,016 (47.2) | 1,520 (48.1) | 0.02 | 697 (47.5) | 714 (48.6) | 0.02 | 697 (47.5) | 1102 (47.8) | 0.01 | 858 (46.4) | 1,208 (47.6) | 0.02 |
| 10–14 years | 638 (35.1) | 1,039 (34.9) | 0.00 | 761 (35.7) | 1,120 (35.7) | 0.00 | 504 (34.3) | 517 (35.2) | 0.02 | 504 (34.3) | 840 (35.0) | 0.01 | 638 (36.1) | 919 (35.6) | 0.01 |
| 15–19 years | 1182 (64.9) | 1,887 (65.1) | 0.00 | 1,421 (64.3) | 2,008 (64.3) | 0.00 | 964 (65.7) | 951 (64.8) | 0.02 | 964 (65.7) | 1487 (65.0) | 0.01 | 1,201 (63.9) | 1,613 (64.4) | 0.01 |
| Race, Korean | 1,820 (100.0) | 2,926 (100.0) | 0.00 | 2,182 (100.0) | 3,128 (100.0) | 0.00 | 1,468 (100.0) | 1,468 (100.0) | 0.00 | 1,468 (100.0) | 2,327 (100.0) | 0.00 | 1,839 (100.0) | 2,532 (100.0) | 0.00 |
| **Index year, n (%)** | | | | | | | | | | | | | | | |
| 2017 | 344 (18.9) | 529 (19.6) | 0.02 | 428 (18.4) | 549 (18.6) | 0.00 | 358 (24.4) | 369 (25.1) | 0.02 | 358 (24.4) | 541 (25.2) | 0.02 | 457 (23.6) | 579 (23.9) | 0.01 |
| 2018 | 483 (26.5) | 762 (26.4) | 0.00 | 591 (26.7) | 823 (26.4) | 0.01 | 503 (34.3) | 517 (35.2) | 0.02 | 503 (34.3) | 804 (34.8) | 0.01 | 643 (35.1) | 874 (34.5) | 0.01 |
| 2019 | 530 (29.1) | 854 (28.8) | 0.01 | 620 (28.4) | 905 (28.7) | 0.01 | 556 (37.9) | 530 (36.1) | 0.04 | 556 (37.9) | 897 (36.6) | 0.03 | 678 (38.1) | 986 (38.1) | 0.00 |
| 2020 | 463 (25.4) | 781 (25.3) | 0.00 | 543 (26.6) | 851 (26.2) | 0.01 | 51 (3.5) | 52 (3.5) | 0.00 | 51 (3.5) | 85 (3.5) | 0.00 | 61 (3.2) | 93 (3.4) | 0.01 |
| **Medical history, n (%)** | | | | | | | | | | | | | | | |
| Anxiety disorder | 447 (24.6) | 889 (23.8) | 0.02 | 537 (30.8) | 984 (27.9) | 0.06 | 369 (25.1) | 364 (24.8) | 0.01 | 369 (25.1) | 698 (24.2) | 0.02 | 457 (29.9) | 798 (27.9) | 0.05 |
| Autism spectrum disorder | 36 (2) | 59 (2.3) | 0.02 | 49 (1.9) | 66 (2.2) | 0.02 | 28 (1.9) | 29 (2.0) | 0.00 | 28 (1.9) | 43 (1.9) | 0.00 | 39 (1.8) | 47 (2.1) | 0.02 |
| Conduct disorder | 119 (6.5) | 191 (6.9) | 0.02 | 168 (6.9) | 197 (7.2) | 0.01 | 103 (7.0) | 104 (7.1) | 0.00 | 103 (7.0) | 167 (7.6) | 0.02 | 144 (7.1) | 176 (7.6) | 0.02 |
| Intellectual disability | 66 (3.6) | 80 (3.3) | 0.02 | 86 (3.2) | 80 (3.2) | 0.00 | 45 (3.1) | 45 (3.1) | 0.00 | 45 (3.1) | 63 (3.2) | 0.01 | 75 (3.2) | 67 (3.4) | 0.01 |
| **Medication use, n (%)** | | | | | | | | | | | | | | | |
| Anticholinergics | 594 (32.6) | 1220 (30.5) | 0.05 | 733 (40.8) | 1378 (38) | 0.06 | 512 (34.9) | 457 (31.1) | 0.08 | 512 (34.9) | 997 (32) | 0.06 | 635 (41.9) | 1157 (38.9) | 0.06 |
| Antiepileptics | 81 (4.5) | 187 (4.8) | 0.02 | 112 (6.4) | 226 (6.1) | 0.01 | 89 (6.1) | 86 (5.9) | 0.01 | 89 (6.1) | 159 (5.8) | 0.01 | 115 (6.7) | 182 (6.7) | 0.00 |
| Antipsychotics | 398 (21.9) | 769 (21.4) | 0.01 | 525 (25.9) | 852 (24.7) | 0.03 | 327 (22.3) | 291 (19.8) | 0.06 | 327 (22.3) | 611 (20.8) | 0.04 | 436 (25.5) | 690 (24) | 0.03 |
| Anxiolytics | 289 (15.9) | 674 (14.0) | 0.05 | 335 (22.2) | 774 (19.8) | 0.06 | 267 (18.2) | 235 (16.0) | 0.06 | 267 (18.2) | 564 (16.3) | 0.05 | 319 (23.8) | 660 (21.1) | 0.06 |
| ADHD: attention-deficit/hyperactivity disorder; PS: propensity score; MPH: methylphenidate; SSRI: selective serotonin reuptake inhibitor; aSMD: absolute standardized mean difference; | | | | | | | | | | | | | | | |

Graphical user interface, application

Description automatically generated

Figure S3. Scatter plots between before and after the propensity score adjustment between the SSRI and MPH–only groups

Graphical user interface, application, map

Description automatically generated

Figure S4. Scatter plots between before and after the propensity score adjustment between the fluoxetine and escitalopram groups

Table S8. Results of sensitivity analyses between the SSRI and MPH–only groups

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Analysis description** | Abdominal pain | ADHD hospitalization | Arrhythmia | Constipation | Headache | Hypertension | Mania | Nausea vomiting | Psychosis | Seizure | Sleep disorder | Suicide | Tic disorder | Traumatic injury | Tremor | **NC** |
| **Main setting** | 1.79  [0.35–12.88] | 1.85  [0.95–3.80] | 0.43  [0.13–1.21] | 0.60  [0.27–1.28] | 1.11  [0.51–2.51] | 0.17  [0.01–1.07] | 1.71  [0.85–3.67] | 1.60  [0.85–3.17] | 1.04  [0.66–1.65] | 0.69  [0.37–1.28] | 1.41  [0.96–2.12] | 0.41  [0.02–4.28] | 1.13  [0.77–1.67] | 1.11  [0.29–4.48] | 0.92  [0.43–1.99] | 1.69  [0.65–4.85] |
| **AT PS matched (1: n)** | 1.93  [0.38–13.96] | 1.74  [0.92–3.43] | 0.43  [0.14–1.18] | 0.62 [0.28–1.30] | 1.21  [0.55–2.73] | 0.19  [0.01–1.17] | 1.48  [0.76–2.96] | 1.52  [0.82–2.9] | 1.04  [0.66–1.64] | 0.75  [0.40–1.39] | **1.48  [1.01–2.21]‡** | 0.45  [0.02–4.75] | 1.14  [0.78–1.66] | 1.22  [0.32–4.94] | 1.01  [0.47–2.19] | 1.40  [0.58–3.57] |
| **AT PS stratified** | 1.90  [0.44–13.21] | 1.52  [0.90–2.70] | 0.47  [0.18–1.19] | 0.80  [0.44–1.50] | 1.56  [0.82–3.17] | 0.30  [0.09–1.11] | 1.29  [0.72–2.45] | 1.66  [0.97–3.02] | 1.01  [0.68–1.54] | 0.83  [0.49–1.42] | 1.33  [0.94–1.91] | 0.53  [0.06–4.86] | 1.13  [0.81–1.61] | 0.98  [0.31–3.75] | 1.08  [0.57–2.16] | 1.00  [0.45–2.41] |
| **ITT PS matched (1: 1)** | 1.50  [0.25–11.39] | **1.82  [1.10–3.12]‡** | 0.45  [0.14–1.25] | 0.94  [0.46–1.90] | 0.75  [0.35–1.58] | 0.50  [0.07–2.56] | 1.38  [0.82–2.36] | 1.22  [0.60–2.50] | 1.13  [0.76–1.69] | 1.07  [0.64–1.78] | 1.06  [0.76–1.46] | NA | 0.97  [0.68–1.38] | 1.00  [0.24–4.23] | 1.12  [0.58–2.17] | 1.00  [0.39–2.56] |
| **ITT PS matched (1: n)** | 1.63  [0.27–12.37] | **1.74  [1.07–2.91]‡** | 0.49  [0.16–1.36] | 1.02  [0.50–2.07] | 0.81  [0.38–1.71] | 0.54  [0.08–2.78] | 1.38  [0.83–2.33] | 1.09  [0.55–2.14] | 1.15  [0.78–1.70] | 1.06 [0.64–1.73] | 1.07  [0.77–1.46] | NA | 1.02  [0.72–1.45] | 1.09  [0.26–4.60] | 1.22  [0.63–2.36] | 0.98  [0.39–2.43] |
| **ITT PS stratified** | 1.87  [0.46–12.78] | **1.63  [1.05–2.62]‡** | 0.77  [0.36–1.76] | 0.97  [0.53–1.84] | 1.12  [0.64–2.06] | 0.91  [0.28–3.59] | 1.22  [0.78–1.98] | 1.27  [0.75–2.29] | 1.17  [0.85–1.65] | 1.07  [0.70–1.67] | 0.98  [0.75–1.29] | 0.54  [0.02–15.88] | 0.98  [0.72–1.34] | 1.06  [0.35–3.96] | 1.23  [0.71–2.24] | 1.12  [0.54–2.44] |
| **30–days gap** | 2.48  [0.54–17.33] | 1.78  [0.94–3.52] | 0.76  [0.27–2.05] | 1.00  [0.49–2.00] | 1.63  [0.78–3.56] | NA | 1.56  [0.78–3.21] | 1.56  [0.77–3.31] | 1.20  [0.74–1.98] | 1.01  [0.51–1.99] | 1.27  [0.83–1.97] | NA | 1.09  [0.73–1.64] | 1.02  [0.24–4.31] | 1.19  [0.55–2.62] | 1.28  [0.48–3.59] |
| **All ADHD drugs** | 2.06  [0.57–9.57] | 1.49  [0.99–2.30] | 0.55  [0.23–1.26] | 0.76  [0.46–1.27] | 1.16  [0.64–2.14] | 1.05  [0.41–2.75] | 1.29  [0.78–2.16] | 1.10  [0.71–1.73] | 1.18  [0.86–1.62] | 0.70  [0.45–1.06] | 1.21  [0.91–1.62] | 1.64  [0.32–11.82] | 1.11  [0.87–1.43] | 0.87  [0.34–2.23] | 1.09  [0.64–1.87] | 1.19  [0.62–2.35] |
| SSRI: selective serotonin reuptake inhibitor; MPH: methylphenidate; ADHD: attention–deficit/hyperactivity disorder; NC: respiratory infectious disease as a negative control outcome; Main setting: As treated PS matched (1:1); AT: as treated; PS: propensity score; ITT: intention–to–treat; ‡: statistically significant. | | | | | | | | | | | | | | | | | |

Table S9. Results of sensitivity analyses between the fluoxetine and the escitalopram groups

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Analysis description** | Abdominal pain | ADHD hospitalization | Arrhythmia | Constipation | Headache | Hypertension | Mania | Nausea vomiting | Psychosis | Seizure | Sleep disorder | Suicide | Tic disorder | Traumatic injury | Tremor | **NC** |
| **Main setting** | 4.03  [0.60–78.80] | 0.57  [0.24–1.28] | 0.32  [0.02–2.51] | 0.88  [0.31–2.44] | 1.28  [0.58–2.88] | NA | 1.04  [0.50–2.19] | 0.86  [0.39–1.86] | 1.33  [0.76–2.38] | 0.91  [0.44–1.89] | 1.07  [0.70–1.65] | NA | **0.43  [0.25–0.71]‡** | 3.05  [0.39–61.57] | 0.52  [0.2–1.28] | 1.60  [0.39–7.83] |
| **AT PS matched (1: n)** | 2.16  [0.48–10.94] | **0.40  [0.18–0.79]‡** | 0.19  [0.01–1.03] | 0.74  [0.28–1.75] | 0.85  [0.43–1.60] | NA | 1.16  [0.59–2.27] | **0.50  [0.25–0.94]‡** | 1.10  [0.67–1.77] | 1.07  [0.54–2.06] | 0.81  [0.56–1.16] | NA | **0.42  [0.25–0.66]‡** | 1.19  [0.23–5.38] | **0.40  [0.16–0.88]‡** | 0.86  [0.26–2.48] |
| **AT PS stratified** | 3.87  [0.98–16.57] | 0.51  [0.24–1.01] | 0.43  [0.06–1.80] | 0.88  [0.38–1.92] | 1.14  [0.58–2.19] | 1.37  [0.22–8.92] | 0.90  [0.44–1.80] | 0.80  [0.41–1.46] | 1.31  [0.81–2.12] | 0.97  [0.49–1.87] | 0.95  [0.66–1.36] | NA | **0.43  [0.27–0.67]‡** | 1.47  [0.29–6.01] | **0.41  [0.17–0.89]‡** | 0.87  [0.28–2.41] |
| **ITT PS matched (1: 1)** | 2.50  [0.54–17.47] | 0.72  [0.41–1.22] | 2.76  [0.94–9.94] | **2.81  [1.07–8.69]‡** | 1.46  [0.68–3.23] | NA | **2.06  [1.19–3.71]‡** | 1.07  [0.51–2.24] | **1.56  [1.02–2.43]‡** | 0.85  [0.44–1.62] | 0.99  [0.71–1.38] | NA | **0.52  [0.33–0.82]‡** | 1.00  [0.12–8.33] | 0.84  [0.43–1.64] | 0.67  [0.22–1.85] |
| **ITT PS matched (1: n)** | 1.32  [0.38–4.39] | 0.65  [0.39–1.04] | 2.49  [0.98–6.77] | 1.48  [0.71–3.09] | 0.91  [0.48–1.65] | 2.65  [0.65–12.9] | **2.27  [1.38–3.78]‡** | 0.61  [0.32–1.08] | 1.18  [0.82–1.68] | 0.75  [0.41–1.31] | 0.93  [0.68–1.25] | NA | **0.50  [0.32–0.76]‡** | 0.53  [0.08–2.29] | 0.84  [0.45–1.52] | 0.73  [0.26–1.85] |
| **ITT PS stratified** | 2.67  [0.82–8.34] | 0.75  [0.46–1.19] | 2.42  [0.95–6.47] | 1.58 [0.77–3.26] | 1.15  [0.61–2.11] | 2.80  [0.72–13.82] | **1.98  [1.19–3.31]‡** | 0.78  [0.42–1.38] | 1.28  [0.90–1.82] | 0.89  [0.52–1.50] | 1.03  [0.76–1.37] | NA | **0.54  [0.36–0.81]‡** | 0.56  [0.08–2.29] | 0.79  [0.42–1.44] | 0.77  [0.31–1.80] |
| **30–days gap** | 4.02  [0.59–78.55] | 0.57  [0.26–1.18] | 0.48  [0.07–2.48] | 1.00  [0.39–2.56] | 1.55  [0.74–3.42] | NA | 1.16  [0.52–2.65] | 0.88  [0.44–1.77] | 1.46  [0.83–2.61] | 1.02  [0.49–2.15] | 0.97  [0.66–1.42] | NA | **0.44  [0.27–0.69]‡** | 1.00  [0.18–5.39] | 0.52  [0.22–1.14] | 2.98  [0.69–20.32] |
| **All ADHD drugs** | 2.66  [0.77–12.12] | 0.58  [0.32–1.02] | **0.11  [0.01–0.59]‡** | 0.80  [0.41–1.54] | 1.09  [0.60–1.99] | 1.77  [0.61–5.76] | 0.83  [0.46–1.51] | 0.88  [0.49–1.58] | 1.23  [0.81–1.88] | 1.16  [0.65–2.10] | 0.89  [0.64–1.24] | 1.81  [0.17–39.05] | **0.66  [0.46–0.95]‡** | 2.99  [0.89–13.50] | **0.38  [0.17–0.79]‡** | 1.58  [0.55–5.15] |
| ADHD: attention–deficit/hyperactivity disorder; NC: respiratory tract infection disease as a negative control outcome; Main setting: As treated PS matched (1:1); AT: as treated; PS: propensity score; ITT: intention–to–treat; ‡: statistically significant. | | | | | | | | | | | | | | | | | |

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