**Table S1**. Characteristic of women with singleton pregnancies with conception from 1 November 2007 to 1 February 2014. Exposed with oneor more redeemed prescription of antidepressants, unexposed and former use

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Exposed  (n= 11 459) | Unexposed  (n= 346 227) | Former use  (n= 6 326) |
| Age at conception, years, mean (sd) | 29.6 (5.6) | 29.7 (5.1) | 28.7 (5.7) |
| Parity, n (%) |  |  |  |
| 0 | 4739 (41.4) | 146 935 (42.4) | 2809 (44.4) |
| >0 | 5653 (49.3) | 177 103 (51.2) | 2993 (47.3) |
| BMI, kg/m2, n (%), |  |  |  |
| <25 | 5434 (47.4) | 204 278 (59.0) | 3156 (49.9) |
| 25–29.9 | 2349 (20.5) | 64 727 (18.7) | 1331 (21.0) |
| > 30 | 2645 (23.1) | 57 112 (16.5) | 1347 (21.3) |
| Smoking in pregnancy, n (%) | 2518 (22.0) | 33 076 (9.6) | 1402 (22.2) |
| Civil status, living with partner, n (%) | 9617 (83.9) | 312 987 (90.4) | 5357 (84.7) |
| Ethnicities, n (%) |  |  |  |
| Afro-Caribbean | 45 (0.4) | 3483 (1.0) | 38 (0.6) |
| Asian | 192 (1.7) | 11 023 (3.2) | 120 (1.9) |
| Caucasian | 9773 (85.3) | 292 754 (84.6) | 5405 (85.4) |
| Other | 111 (1.0) | 5,732 (1.7) | 100 (1.6) |
| Depression diagnosis\*, n (%) | 4738 (41.4) | 10 208 (3,0) | 1457 (23.0) |
| Diabetes\*\*, n (%) | 299 (2.6) | 5624 (1.6) | 127 (2.0) |
| Use of antihypertensive\*\*\*, n (%) | 175 (1.5) | 1849 (0.5) | 51(0.8) |
| Use of known teratogen | 245 (2.1) | 2901 (0.8) | 80 (1.3) |
| Use of other psychotropic medication\*\*\*, n (%) |  |  |  |
| Antiepileptics | 457 (4.0) | 1370 (0.4) | 82 (1.3) |
| Antipsychotics | 687 (6.0) | 476 (0.1) | 87 (1.4) |
| Anxiolytics, hypnosis, and sedatives | 40 (0.3) | 47 (0.0) | 6 (0.1) |
| Missing, n (%): Exposed/ Unexposed/ Former use: Parity: 1067 (9.3)/ 22 189 (6.4)/ 524 (8.3), BMI: 1031 (9.0)/ 20 110 (5.8)/ 492 (7.8), smoking: 830 (7.2)/ 16 227 (4.7)/ 399 (6.3), civil status 39 (0.3)/ 478 (0.1)/ 20 (0.3), ethnicity: 1338 (11.7)/ 33 235 (9.6)/ 663 (10.5)  \* Diagnoses within two years prior to conception date  \*\* Diagnoses within two years prior to conception date and/or antidiabetic agents one month prior to conception date throughout first trimester  \*\*\* Use of other medication one month prior to conception date throughout first trimester | | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | Exposed  versus  unexposed |  | Exposed  versus  former use |  |  |
|  | |  | Crude  PR (95% CI) |  | Crude  PR (95% CI) |  | Cases / Unexposed  Cases / Former use |
| Unexposed | |  | 1.0 |  | - |  | 890/338 591\* |
|  | 1.0 |  | - |  | 897/341 788\* |
| Former use | |  | - |  | 1.0 |  | 18 /5370 |
|  | - |  | 1.0 |  | 21/6093 |
|  | |  |  |  |  |  | Cases / Exposed |
| Antidepressant^ (N06A**)** | |  | 1.62 (0.94*−* 2.79) |  | 1.27 (0.62*−* 2.58) |  | 13/3060\*\* |
|  | 1.74 (1.06*−* 2.85) |  | 1.33 (0.69*−* 2.54) |  | 16/3503\*\* |
|  | SSRI^^(N06AB) |  | 1.55 (0.80*−* 2.98) |  | 1.21 (0.55*−* 2.69) |  | 9/2216 |
|  |  | 1.71 (0.94*−* 3.09) |  | 1.30 (0.63*−* 2.69) |  | 11/2457 |
|  | Venlafaxine (N06AX16) |  | 2.72 (1.02*−* 7.24) |  | 2.13 (0.73*−* 6.29) |  | <5/559 |
|  |  | 2.80 (1.17*−* 6.73) |  | 2.13 (0.81*−* 5.64) |  | 5/680 |
|  | Other ^^^ |  | - |  | - |  | 0/298 |
|  |  | - |  | - |  | 0/439 |
| # Severe cardiac malformations  ^ AD: Imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), doxepin (N06AA12), dosulepin (N06AA16), fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10), isocarboxazid (N06AF01), nialamide (N06AG02), mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22)  ^^ SSRI: Fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10)  ^^^ Other: TCA (N06AA), isocarboxazid (N06AF01), nialamide (N06AG02), mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), duloxetine (N06AX21), agomelatine (N06AX22)  \* No former use, no pregnancies with only one redeemed prescription  \*\* The sum of the cases in the subcategories of antidepressants does not add up to the total because cases may contribute to multiple categories | | | | | | | |

**Table S2.** Exposed restricted tono use of other psychiatric drugs or teratogens (first line; two years prior to conception date, second line; one month prior to conception date throughout first trimester). SCM# in first trimester exposed (> 2 prescriptions) compared with unexposed and former use.

**Table S3.**  Exposed restricted tono use of other psychiatric drugs or teratogens (first line; two years prior to conception date, second line; one month prior to conception date throughout first trimester). Non-SCM# in first trimester exposed (> 2 prescriptions) compared with unexposed and former use.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | |  | Exposed  versus  unexposed | |  | Exposed  versus  former use | |  |  |
|  | | |  | Crude  PR (95% CI) | Minimally adjusted ¤  PR (95% CI) |  | Crude  PR (95% CI) | Minimally adjusted ¤¤  PR (95% CI) |  | Cases / Unexposed  Cases / Former use |
| Unexposed | | |  | 1.0 | 1.0 |  | - | - |  | 3014/338 588\* |
|  | 1.0 | 1.0 |  | - | - |  | 3447/342 185\* |
| Former use | | |  | - | - |  | 1.0 | 1.0 |  | 58 /5370 |
|  | - | - |  | 1.0 | 1.0 |  | 64/6093 |
|  | | |  |  |  |  |  |  |  | Cases / Exposed |
| Antidepressant^ (N06A**)** | | |  | 1.69 (1.26*−* 2.25) | 1.66 (1.22*−* 2.24) |  | 1.39 (0.95*−* 2.04) | 1.42 (0.97*−* 2.09) |  | 46/3060\*\* |
|  | 1.79 (1.38*−* 2.33) | 1.72 (1.31*−* 2.27) |  | 1.52 (1.07*−* 2.17) | 1.64 (1.13*−* 2.36) |  | 56/3106\*\* |
|  | TCA^^ (N06AA) | |  | - | - |  | - | - |  | <5/131 |
|  |  | - | - |  | - | - |  | <5/178 |
|  | SSRI^^^(N06AB) | |  | 1.52 (1.06*−* 2.17) | 1.48 (1.03*−* 2.14) |  | 1.25 (0.55*−* 2.69) | 1.28 (0.83*−* 1.99) |  | 30/2216 |
|  |  | 1.60 (1.15*−* 2.22) | 1.53 (1.09*−* 2.15) |  | 1.36 (0.90*−* 2.04) | 1.45 (0.95*−* 2.20) |  | 35/2457 |
|  | | Fluoxetine (N06AB03) |  | 2.86 (1.44 *−* 5.67) | 2.76 (1.38*−* 5.50) |  | 2.36 (1.14*−* 4.90) | 2.44 (1.18*−* 5.08) |  | 8/314 |
|  | |  | 2.47 (1.24*−* 4.91) | 2.33 (1.17*−* 4.66) |  | 2.10 (1.01*−* 4.77) | 2.29 (1.10*−* 4.77) |  | 8/363 |
|  | | Citalopram (N06AB04) |  | 0.95 (0.49*−* 1.81) | 0.93 (0.48*−* 1.78) |  | 0.78 (0.39*−* 1.57) | 0.79 (0.39*−* 1.60) |  | 9/1068 |
|  | |  | 1.17 (0.67*−* 2.06) | 1.13 (0.64*−* 1.99) |  | 0.99 (0.54*−* 1.83) | 1.09 (0.59*−* 2.02) |  | 12/1150 |
|  | | Sertraline (N06AB06) |  | 1.79 (0.94*−* 3.43) | 1.75 (0.91*−* 3.38) |  | 1.48 (0.74*−* 2.97) | 1.49 (0.74*−* 2.99) |  | 9/564 |
|  | |  | 1.89 (1.05*−* 3.40) | 1.82 (1.01*−* 3.30) |  | 1.61 (0.85*−* 3.03) | 1.91 (1.00*−* 3.63) |  | 11/652 |
|  | | Escitalopram (N06AB10) |  | 2.32 (0.97*−* 5.52) | 2.35 (0.98*−* 5.62) |  | 1.91 (0.77*−* 4.73) | 2.01 (0.81*−* 4.95) |  | 5/242 |
|  | |  | 2.12 (0.89*−* 5.06) | 2.10 (0.87*−* 5.02) |  | 1.80 (0.73*−* 4.44) | 2.11 (0.85*−* 5.21) |  | 5/264 |
|  | Other AD^^^^ (N06AX) | |  | 2.17 (1.32*−* 3.59) | 2.13 (1.27*−* 3.54) |  | 1.79 (1.02*−* 3.15) | 1.77 (1.00*−* 3.11) |  | 15/774 |
|  |  | 2.27 (1.45*−* 3.54) | 2.16 (1.37*−* 3.42) |  | 1.93 (1.16*−* 3.20) | 2.24 (1.32*−* 3.79) |  | 19/939 |
|  | | Venlafaxine (N06AX16) |  | 2.00 (1.08*−* 3.71) | 1.93 (1.03*−* 3.60) |  | 1.66 (0.85*−* 3.22) | 1.63 (0.84*−* 3.17) |  | 10/559 |
|  | |  | 1.98 (1.13*−* 3.47) | 1.86 (1.05*−* 3.30) |  | 1.68 (0.91*−* 3.10) | 2.00 (1.06*−* 3.76) |  | 12/680 |
| # Severe cardiac malformations  ^ AD: ATCs below + isocarboxazid (N06AF01), nialamide (N06AG02)  ^^ TCA: Imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), doxepin (N06AA12), dosulepin (N06AA16)  ^^^ SSRI: Fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10)  ^^^^ Other AD: Mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22)  ¤ Adjusted for age, smoking, and depression diagnosis  ¤¤ Adjusted for age and smoking  \* No former use, no pregnancies with only one redeemed prescription  \*\* The sum of the cases in the subcategories of antidepressants does not add up to the total because cases may contribute to multiple categories | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | |  | Exposed  versus  unexposed |  | Exposed  versus  former use |  |  |
|  | | |  | Crude  PR (95% CI) |  | Crude  PR (95% CI) |  | Cases / Unexposed  Cases / Former use |
| Unexposed  Former use | | |  | 1.0  - |  | -  1.0 |  | 936 /352 553\*  21 /6326 |
|  | | |  |  |  |  |  | Cases / Exposed |
| Antidepressant^ (N06A**)** | | |  | 1.18 (0.84*−* 1.65) |  | 0.95 (0.55*−* 1.62) |  | 36/11 459\*\* |
|  | SSRI^^(N06AB) | |  | 1.10 (0.75*−* 1.63) |  | 0.88 (0.50*−* 1.56) |  | 26/8887 |
|  | | Fluoxetine (N06AB03) |  | 1.78 (0.80*−* 3.97) |  | 1.42 (0.58*−* 3.52) |  | 6/1269 |
|  | | Citalopram (N06AB04) |  | 1.05 (0.59*−* 1.85) |  | 0.83 (0.41*−* 1.70) |  | 12/4312 |
|  | | Escitalopram (N06AB10) |  | 2.23 (0.93*−* 5.35) |  | 1.78 (0.67*−* 4.71) |  | 5/846 |
|  | Other AD (N06AX) | |  | 1.43 (0.77*−* 2.67) |  | 1.14 (0.54*−* 2.43) |  | 10/2632 |
|  | | Venlafaxine (N06AX16) |  | 1.39 (0.62*−* 3.10) |  | 1.11 (0.45*−* 2.75) |  | 6/1627 |
|  | Other ^^^^ | |  | - |  | - |  | <5/658 |
|  |  | |  |  |  |  |  |  |
| # Severe cardiac malformations  ^ AD: Imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), doxepin (N06AA12), dosulepin (N06AA16), fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10), isocarboxazid (N06AF01), nialamide (N06AG02), mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22)  ^^ SSRI: Fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10)  ^^^ Other AD: Mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22)  ^^^^ Other: TCA (N06AA), isocarboxazid (N06AF01), nialamide (N06AG02)  \* No former use  \*\* The sum of the cases in the subcategories of antidepressants does not add up to the total because cases may contribute to multiple categories | | | | | | | | |

**Table S4.** SCM# in first trimester exposed (> 1 prescription) compared to unexposed and former use.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | |  | Exposed  versus  unexposed | |  | Exposed  versus  former use | |  |  |
|  | | |  | Crude  PR (95% CI) | Minimally adjusted ¤  PR (95% CI) |  | Crude  PR (95% CI) | Minimally adjusted ¤¤  PR (95% CI) |  | Cases / Unexposed  Cases / Former use |
| Unexposed | | |  | 1.0 | 1.0 |  | - | - |  | 3184 /352 553\* |
| Former use | | |  | - | - |  | 1.0 | 1.0 |  | 65/6326 |
|  | | |  |  |  |  |  |  |  | Cases / Exposed |
| Antidepressant^ (N06A**)** | | |  | 1.71 (1.47*−* 1.99) | 1.69 (1.43*−* 1.99) |  | 1.50 (1.13*−* 1.99) | 1.51 (1.14*−* 2.00) |  | 177/11 459\*\* |
|  | TCA^^ (N06AA) | |  | 2.71 (1.67*−* 4.40) | 2.63 (1.61*−* 4.31) |  | 2.38 (1.39*−* 4.09) | 2.24 (1.30*−* 3.85) |  | 16/654 |
|  | | Nortriptyline (N06AA10) |  | 3.76 (2.10*−* 6.73) | 3.63 (2.01*−* 6.57) |  | 3.30 (1.76*−* 6.20) | 3.09 (1.64*−* 5.81) |  | 11/324 |
|  | SSRI^^^(N06AB) | |  | 1.63 (1.37*−* 1.94) | 1.60 (1.33*−* 1.92) |  | 1.43 (1.07*−* 1.93) | 1.44 (1.07*−* 1.94) |  | 131/8887 |
|  | | Fluoxetine (N06AB03) |  | 2.44 (1.69*−* 3.53) | 2.36 (1.62*−* 3.43) |  | 2.15 (1.38*−* 3.33) | 2.15 (1.38*−* 3.33) |  | 28/1269 |
|  | | Citalopram (N06AB04) |  | 1.41 (1.08*−* 1.84) | 1.37 (1.04*−* 1.79) |  | 1.24 (0.87*−* 1.77) | 1.23 (0.86*−* 1.76) |  | 55/4312 |
|  | | Paroxetine (N06AB05) |  | 3.26 (1.71*−* 6.20) | 3.27 (1.71*−* 6.23) |  | 2.86 (1.44*−* 5.69) | 2.73 (1.36*−* 5.47) |  | 9/306 |
|  | | Sertraline (N06AB06) |  | 1.65 (1.21*−* 2.24) | 1.60 (1.16*−* 2.20) |  | 1.45 (0.98*−* 2.14) | 1.45 (0.98*−* 2.14) |  | 40/2692 |
|  | | Escitalopram (N06AB10) |  | 1.70 (0.99*−* 2.92) | 1.66 (0.96*−* 2.86) |  | 1.50 (0.83*−* 2.70) | 1.48 (0.82*−* 2.67) |  | 13/846 |
|  | Other AD^^^^ (N06AX) | |  | 1.94 (1.45*−* 2.58) | 1.88 (1.39*−* 2.54) |  | 1.70 (1.17*−* 2.47) | 1.68 (1.16*−* 2.46) |  | 46/2632 |
|  | | Mirtazapine (N06AX11) |  | 2.44 (1.39*−* 4.28) | 2.41 (1.37*−* 4.23) |  | 2.15 (1.17*−* 3.95) | 2.08 (1.13*−* 3.84) |  | 12/544 |
|  | | Venlafaxine (N06AX16) |  | 1.91 (1.32*−* 2.76) | 1.81 (1.24*−* 2.65) |  | 1.67 (1.08*−* 2.60) | 1.63 (1.05*−* 2.54) |  | 28/1627 |
| # Severe cardiac malformations  ^ AD: ATCs below + isocarboxazid (N06AF01), nialamide (N06AG02)  ^^ TCA: Imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), doxepin (N06AA12), dosulepin (N06AA16)  ^^^ SSRI: Fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10)  ^^^^ Other AD: Mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22)  ¤ Adjusted for age, smoking, and depression diagnosis  ¤¤ Adjusted for age and smoking  \* No former use  \*\* The sum of the cases in the subcategories of antidepressants does not add up to the total because cases may contribute to multiple categories | | | | | | | | | | |

**Table S5.** Non-SCM# in first trimester exposed (> 1 prescription) compared with unexposed and former use.

**Table S6.** SCM# of children born alive, first trimester exposed (> 2 prescriptions) compared with unexposed (born alive).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | |  | Exposed  versus  unexposed |  |  |  |
|  | |  | Crude  PR (95% CI) |  |  | Cases / Unexposed |
| Unexposed | |  | 1.0 |  |  | 695/346 227\* |
|  | |  |  |  |  | Cases / Exposed |
| Antidepressant^ (N06A**)** | |  | 1.39 (0.77*−* 2.52) |  |  | 11/4105\*\* |
|  | SSRI^^(N06AB) |  | 1.87 (1.00*−* 3.48) |  |  | 10/2767 |
|  | Venlafaxine (N06AX16) |  | 0.62 (0.09*−* 4.40) |  |  | <5/847 |
|  | Other^^^ |  | - |  |  | 0/629 |
| # Severe cardiac malformations  ^ AD: Imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), doxepin (N06AA12), dosulepin (N06AA16), fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10), isocarboxazid (N06AF01), nialamide (N06AG02), mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), venlafaxine (N06AX16), reboxetine (N06AX18), duloxetine (N06AX21), agomelatine (N06AX22)  ^^ SSRI: Fluoxetine (N06AB03), citalopram (N06AB04), paroxetine (N06AB05), sertraline (N06AB06), fluvoxamine (N06AB08), escitalopram (N06AB10)  ^^^ Other: TCA (N06AA), isocarboxazid (N06AF01), nialamide (N06AG02), mianserin (N06AX03), mirtazapine (N06AX11), bupropion (N06AX12), duloxetine (N06AX21), agomelatine (N06AX22)  \* No former use, no pregnancies with only one redeemed prescription  \*\* The sum of the cases in the subcategories of antidepressants does not add up to the total because cases may contribute to multiple categories | | | | | | |

**Table S7.** SCM and HLHS in the former use group (> 2 prescriptions) compared with unexposed.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | |  | Former use  versus  unexposed |  |  |  |
|  | |  | Crude  PR (95% CI) |  |  | Cases / Unexposed “severe”  Cases / Unexposed HLHS |
| Unexposed “severe”  Unexposed HLHS | |  | 1.0  1.0 |  |  | 915/346 227\*  90/346 581\* |
|  | |  |  |  |  | Cases / Former use |
| SCM | |  | 1.26 (0.8*−* 1.9) |  |  | 21/6326 |
|  | HLHS |  | 0.58 (0.1*−* 4.2) |  |  | <5/6326 |
|  |  |  |  |  |  |  |
| # Severe cardiac malformations  HRHS: Hypoplastic right heart syndrome  \* No former use, no pregnancies with only one redeemed prescription | | | | | | |