# Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

# eAppendix 1

## Expanded discussion of assessment of acetaminophen use during pregnancy and comparison with the literature

We identified use of acetaminophen during pregnancy between 1995 and 2019 from the Medical Birth Register, which contains detailed pregnancy and delivery information on virtually all deliveries in Sweden.[1] Early drug exposure information was prospectively collected during the first antenatal visit (typically occurring at 8-10 weeks of gestation), where midwives conducted structured interviews and examinations, recording use of over-the-counter (OTC) or prescription medications. Based on our team's clinical experience, the antenatal interview is intended to capture regular use of medications to advise the patient regarding treatment and side effects and is less focused on capturing sporadic use. Later medication use in pregnancy is also prospectively documented by the midwife and doctor within antenatal records in a separate data field, although records of later use were available for only 17 of the 25 birth cohorts in our data. These data are later translated into Anatomical Therapeutic Chemical (ATC) codes by the National Board of Health and Welfare. For the 17 birth cohorts with available first antenatal visit and later medication use data, we observed that of the individuals classified as ever-users of acetaminophen based only on Medical Birth Register data, 81.7% reported acetaminophen use only at the first antenatal visit; 12.7% reported use at both the first antenatal visit and a later visit; and 5.6% reported use only later in pregnancy. From 1 July 2005, we supplement the Medical Birth Register data with Prescribed Drug Register data covering all prescription dispensations in Sweden. We previously examined how antenatal records of drug use in the Medical Birth Register compare with dispensation information in the Prescribed Drug Register for pregnant women.[2] Of women who reported N02B analgesic use (which includes acetaminophen) in the Medical Birth Register at the first antenatal visit, only 6.6% had a dispensation for an N02B analgesic in the past 180 days. These data support that for our sample, compared with prescription records, antenatal records offers better detection of the use of OTC medications like acetaminophen.[3]

Our finding that 7.5% of Swedish pregnant individuals used acetaminophen during pregnancy is lower than found in some studies but is concordant with other studies. Over 60% of U.S. pregnant persons used acetaminophen during pregnancy.[4] The Danish National Birth Cohort found that 50% of Danish persons reported use during pregnancy in 1996-2003.[5] In contrast, Taagaard et al. found in the Copenhagen Pregnancy Cohort a 6.2% use prevalence in the first trimester in 2013-2019.[20] A study of a 2003 birth cohort in western Sweden found 7.7% of persons reported use of acetaminophen during pregnancy.[6] Another study in western Sweden found a 59.2% prevalence of acetaminophen use,[7] although this higher prevalence may have been due to significant self-selection bias for multiple characteristics, including enrichment for asthma/allergy in participants as compared to non-participants.[8] Asthma patients are often advised to use acetaminophen for fear of adverse reaction to NSAIDs. Two related factors may contribute to the lower use of acetaminophen in Sweden. First, pregnant persons who need medication may have refrained from use. In a survey of 850 pregnant Swedish persons, more than 60% considered medication use during early pregnancy to be "probably harmful" or "harmful".[9] In the same study, 45% of persons in need of medication for chronic pain and 37% of those in need for headache refrained from use, while 25% of persons in need of acetaminophen medication refrained. Notably, Taagaard et al. also found in the Copenhagen Pregnancy Cohort a 36.9% use prevalence in the 3 months prior to pregnancy that dropped to 6.2% in the first trimester. This observation that over 80% of persons discontinued acetaminophen use from before pregnancy to the first trimester demonstrates that pregnancy

discontinuation of use of acetaminophen is not uncommon in Scandinavia. Second, some messaging from Swedish authorities during the study period appeared to promote this culture of avoidance. For example, a 2014 commentary in *Läkartidningen,* the journal of the Swedish Medical Association, argues for a restrictive *primum non nocere* approach to acetaminophen.[10] The author also cites public health advice given on the 1177 website – a national Swedish healthcare resource and the principal source of medical advice for Swedish residents – stating that "You [as a pregnant person] should avoid painkillers if you can…"

While biomarkers may offer more in-depth characterization of exposure, biomarker studies are not necessarily the gold standard. A plasma drug screening study of 200 pregnant individuals in Sweden found that 6.5% had detectable acetaminophen concentrations at gestational week 10-12 (at the first antenatal visit), and 10% at gestational week 25, which is concordant with our estimates.[11] However, because the half-life of acetaminophen is only several hours long, it is impossible to extrapolate anything about acetaminophen use beyond those single points in time. This is especially problematic for studies assessing acetaminophen biomarkers and associations with health outcomes. For example, a study of cord plasma acetaminophen reported that higher acetaminophen levels were associated with higher risk of ASD, ADHD, and developmental disabilities.[12] These levels likely reflect events occurring around the delivery that would spur acetaminophen use, and do not say anything about acetaminophen use throughout the pregnancy.

# eAppendix 2

## Sibling analysis

A statistical association between acetaminophen use during pregnancy and child neurodevelopmental disorders may be due to unobserved confounding from genetics or environment. As an example, one plausible unobserved confounder might be birthing parent's autistic traits. Autistic traits are associated with both a higher degree of pain during pregnancy[13] that would increase probability of acetaminophen use, and birthing parent's autistic traits are also associated with child autistic traits.[14] Because autistic traits are not recorded in our data and thus are unobserved (although we adjust for birthing parent's autism diagnosis), standard statistical analyses cannot control for such confounding. However, sibling control analyses can control for an unobserved confounder like parental autistic traits, since full siblings share the same birthing parent, up to half of their genetic makeup, and early life environment. In a sibling analysis, outcomes in exposed siblings are compared against outcomes of their unexposed siblings. We use stratified Cox regression with cluster robust standard errors, conditioned on the family, to explicitly account for the matched nature of these analyses. If results from the sibling control analysis were qualitatively attenuated from standard analyses, this would suggest that standard analyses were influenced by familial confounding.

There are three potential issues with sibling analyses in the present manuscript that merit further consideration. First, because sibling sets with discordant exposures are a selected subsample of the general population, analyses within this group may have limited generalizability. Second, sibling analyses assume that exposure and outcome of one sibling do not affect the exposures and outcomes of their siblings. If this assumption is violated – in other words, if carryover effects were present – this can lead to biased estimates.[15] Third, measurement error in acetaminophen exposure is a possibility. If a person reports having taken acetaminophen but did not actually take it, or vice versa, if a person did not report having taken acetaminophen but did actually take it, this can attenuate estimates in models with sibling control.[16] Thus, the nullification of associations going from models without sibling control to models with sibling control may be the result of bias attributable to measurement error.

To address the first issue, we conduct a sensitivity analysis where we estimate the standard or conventional statistical models from the main article in the sibling cohort but without accounting for the matched sibling pairs (**eTable 7**). In this sensitivity analysis, we do not observe meaningful differences between results from the conventional statistical models in the main article and results from the conventional statistical models in the sibling cohort. This indicates that generalizability from analyses conducted in the sibling sample is likely to hold. To address the second issue, we conduct a stratified analysis of the sibling sample, examining the subgroup where the first child was exposed and the second child unexposed; and then separately examining the subgroup where the first child was unexposed, and the second child was exposed. We present the results only for acetaminophen in **eTable 8** because 1) the group of acetaminophen users is the largest of all the drugs examined in the present study and thus has the most power to support such a stratified analysis; 2) the presence of carryover effects for at least some drugs is likely, especially for aspirin, since low-dose aspirin is used to prophylactically treat women at high risk of pre-eclampsia. In this sensitivity analysis, for autism and intellectual disability we do not find meaningful differences between the strata where the first child was exposed and the second child unexposed, and the strata where the first child was unexposed and the second child exposed. This supports that carryover effects are not likely to bias the acetaminophen results of those sibling analyses. However, for ADHD, the statistically

significant difference between strata by child ordering indicates that we cannot rule out carryover effects as a possible influence, although a more likely explanation for the difference may be the calendar trends in ADHD in the population which differentially affects each strata. In strata where the first child is exposed and the second child is unexposed, the exposure is by design biased toward earlier calendar trends in the outcome incidence. Conversely, in strata where the first child is unexposed and the second child is exposed, the exposure is biased towards later calendar trends in outcome incidence. Hence, the explanation for why the exposure is associated with a lower risk of ADHD in the first child and a higher risk in the second child is the increase in ADHD incidence (as a more liberal approach to diagnosing ADHD has become the norm in Sweden across the study period).

To address the third issue, we perform a simulation analysis where in a cohort of sibling pairs, we examine how the association between acetaminophen exposure (yes vs. no) and neurodevelopmental disorder varies in different situations of exposure measurement error. A similar sensitivity analysis was performed by Gustavson et al.[17] Parameters in the simulation included the:

- number of sibling pairs: set to 1,000,000, to minimize random sampling variability
- observed exposure prevalence: set to 7.5% as observed
- tetrachoric correlation in exposure between siblings: set to 0.41 as observed
- exposure sensitivity and specificity: see below
- outcome prevalence in the unexposed persons: set to 0.027 (autism); 0.058 (ADHD); or 0.01 (intellectual disability)
- true exposure-outcome association: odds ratio set to 1.50, 2.00, 2.50, 3.00, and 5.00

Sensitivity is the proportion of true acetaminophen-exposed pregnancies that are recorded as acetaminophen-exposed. Specificity is the proportion of pregnancies that were true unexposed to acetaminophen that are recorded as acetaminophen-unexposed. Thus, if exposure assessment were perfect (i.e., no measurement error), sensitivity and specificity would both be 1. We examine different combinations of sensitivity and specificity based on the literature. First, van Gelder et al., in a study of 726 Dutch persons who completed medication diaries (the gold standard) in either pregnancy weeks 19-24 or 26-31 and a web-based medication questionnaire in week 34, found that sensitivity of the questionnaire for acetaminophen was 0.57.[18] The study did not report specificity but indicated that an exploratory analysis and previous studies found specificities for all medications greater than or equal to 0.97. Second, Sundermann et al. studied 318 American persons who completed daily medication diaries before conception (the gold standard) and compared against first trimester interview.[19] Although acetaminophen was not specifically assessed, the study reported a sensitivity and specificity for first trimester interview assessment for NSAID use of 0.79 and 0.62, respectively. Third, we examine a middle ground between the sensitivities and specificities found by van Gelder et al. and Sundermann et al. by using the mean sensitivity and specificity. Finally, we examine an extreme case of measurement error, where we assume that ~50% of Swedish persons truly use acetaminophen during pregnancy and thus our exposure assessment method has a sensitivity of 0.15 (7.5%/50%). We also assume that overreporting is unlikely so we use the specificity found by van Gelder et al. of 0.97.

The code was modified from the R script provided by Frisell et al.[16] and was executed in R version 4.2.2. While the code by Frisell et al. also includes the capability of assessing the impact of unobserved confounding, we did not include any unobserved confounding in these simulations to better study the impact of potential measurement error.

**eTable 9** shows that the effect of acetaminophen measurement error in scenarios of varying realism had overall little impact on the sibling control analyses. In situations of imperfect sensitivity and specificity, measures of association regardless of sibling control or not were greatly attenuated. However, the level of attenuation was only slightly more for models with sibling control as compared with models without sibling control. For example, in the first row of the table: in a setting with sensitivity = 0.57 and specificity = 0.97 and a true acetaminophen-autism odds ratio of 1.50, the observed odds ratio in a model without sibling control was 1.07. Meanwhile, the observed odds ratio in a model with sibling control was 1.06. This same pattern of only modest differences between models with and without sibling control is evident throughout the table, regardless of neurodevelopmental disorder, true exposure-outcome association, or level of measurement error. In the last row and last 2 columns, even with only 0.15 sensitivity and a true odds ratio of 5.00, the acetaminophen-intellectual disability odds ratios without sibling control and with sibling control were 1.26 and 1.18, respectively. In short, these simulations indicate that the complete nullification of the acetaminophen-neurodevelopmental disorder associations going from the population-based to the sibling control models is unlikely to result from even extreme levels of measurement error.

## eTable 1. ICD/ATC codes for each condition and therapeutic

| Variable | Code Type | Codes |
|---|---|---|
| Autism | ICD-10 | F84 |
| | ICD-9 | 299 |
| ADHD | ICD-10 | F90 |
| | ICD-9 | 314 |
| | ATC | N06BA09, N06BA04 |
| Intellectual disability | ICD-10 | F70-F79 |
| | ICD-9 | 317-319 |
| History of any psychiatric conditions | ICD-10 | F00-F99 |
| | ICD-9 | 29.0-29.9, 30.0-30.9, 31.0-31.9 |
| Migraine | ICD-10 | G43 |
| | ICD-9 | 346 |
| Diagnosed headache | ICD-10 | R51 |
| | ICD-9 | 784A |
| Chronic pain | ICD-10 | M70.0-M79.9, R52.0-R52.9, G35.0-G35.9, G50.0-G59.9, F45.0-F45.9 |
| | ICD-9 | 350.0-359.9, 723.0-723.9, 724.0-724.9 |
| Infection | ICD-10 | A00-A09, A15-A28, A30-A33, A4, A50-A59, A60-A69, A7, A70-A84, A8-A9, B00-B09, B15-B29, B30-B45, B50-B89, B95-B99, E060, E321, G00-G07, H000-H050, H100-H109, H162-H169, H32-H669, H70, I00-I02, I30-I33, I400, J00-J06, J10-J22, J32-J340, J36-J42, J850-J853, J86, K035, K046-K047, K052, K113, K122, K140, K35, K57, K61, K630, K650, K750, K810, K85, M0, M463, M465, M600, M651, M711, N10-N12, N136-N151, N159, N300-N303, N308-N309, N340-N341, N61-N76, O070-O075, O080, O353, O411, O753, O85-O86, O910-O911, O980-O989, P230-P239, P36-P39, T802, T814, T826-T827, T835-T847, T857, T880, Z21-Z29 |
| | ICD-9 | 001-009, 01-03, 040-041, 080-083, 087-089, 09, 100-104, 320-324, 360A, 371, 372A-372D, 373B, 375D-376A, 380B-382X, 383, 390-392, 421-422, 460-465, 480-487, 490, 491B, 510, 511B, 513, 522E-522H, 526E-528D, 540A-540B, 562-567, 569F-575A, 595A-595D, 595X, 595C-595D, 614A-614F, 614W-614X, 615A-615X, 616, 634A-639A, 640-648, 650-657, 658E, 659D, 670, 711A-711H, 728A, 729E, 730-730X, 771A-771D, 771F-771H, 771W, 790H-790W, 996G, 998F, 999D |
| Fever | ICD-10 | R50 |
| | ICD-9 | 790G |
| Rheumatoid arthritis | ICD-10 | M05 & M06 |
| | ICD-9 | 714 |

| | | |
|---|---|---|
| Asthma | ICD-10 | J45 & J46 |
| | ICD-9 | 493 |
| Acetaminophen | ATC | N02BE |
| Anti-migraine medications | ATC | N02C |
| Opioid medications | ATC | N02A |
| Non-aspirin NSAIDs | ATC | M01A & M02A |
| Aspirin | ATC | B01AC & N02BA |
| Psycholeptics medications | ATC | N05 |
| Antidepressant medications | ATC | N06A |
| Antiseizure medications | ATC | N03 |

## eTable 2. Descriptive characteristics of the full sibling cohort (N=1,773,747).

| | Acetaminophen exposed, N (%) | Acetaminophen unexposed, N (%) |
|---|---|---|
| | N=132,681 | N=1,641,066 |
| **CHILD CHARACTERSTICS** | | |
| **Birth sex** | | |
| Female | 64,402 (48.5) | 795,495 (48.5) |
| Male | 68,279 (51.5) | 845,571 (51.5) |
| **Neurodevelopmental diagnoses[a]** | | |
| Autism | 3,988 (3.0) | 41,968 (2.6) |
| ADHD | 8,593 (6.5) | 88,672 (5.4) |
| Intellectual disability | 1,382 (1.0) | 14,528 (0.9) |
| **Season of birth** | | |
| Dec-Feb | 29,532 (22.3) | 378,294 (23.1) |
| Mar-May | 35,044 (26.4) | 444,453 (27.1) |
| Jun-Aug | 35,532 (26.8) | 435,225 (26.5) |
| Sep-Nov | 32,573 (24.5) | 383,094 (23.3) |
| | | |
| **BIRTHING PARENT'S CHARACTERISTICS** | | |
| **Age at delivery** | | |
| <25 | 15,027 (11.3) | 191,527 (11.7) |
| 25-29 | 41,315 (31.1) | 514,739 (31.4) |
| 30-34 | 47,664 (35.9) | 601,806 (36.7) |
| 35-39 | 23,711 (17.9) | 281,352 (17.1) |
| >40 | 4,964 (3.7) | 51,642 (3.1) |
| **Swedish-born** | | |
| Yes | 100,900 (76.0) | 1,305,980 (79.6) |
| No | 31,781 (24.0) | 335,086 (20.4) |
| **Highest household education** | | |
| Secondary schooling level (mandatory) | 7,980 (6.0) | 69,114 (4.2) |
| Upper secondary level | 56,338 (42.5) | 615,379 (37.5) |
| University level | 68,363 (51.5) | 956,573 (58.3) |
| **Household disposable income, Quintiles** | | |
| Q1 (lowest) | 25,527 (19.2) | 262,272 (16.0) |
| Q2 | 29,464 (22.2) | 316,074 (19.3) |
| Q3 | 28,661 (21.6) | 346,953 (21.1) |
| Q4 | 26,572 (20.0) | 353,878 (21.6) |
| Q5 (highest) | 22,457 (16.9) | 361,889 (22.1) |
| **Residential region** | | |
| Middle Sweden | 31,121 (23.5) | 310,365 (18.9) |
| Stockholm | 26,478 (20.0) | 417,956 (25.5) |
| West Sweden | 24,579 (18.5) | 336,513 (20.5) |
| Southern Sweden | 22,348 (16.8) | 268,458 (16.4) |
| Southeast Sweden | 16,644 (12.5) | 168,391 (10.3) |
| Northern Sweden | 11,511 (8.7) | 139,383 (8.5) |
| **Co-habiting at delivery** | | |
| Yes | 122,738 (92.5) | 1,535,114 (93.5) |
| No | 9,943 (7.5) | 105,952 (6.5) |
| **Parity** | | |
| Nulliparous | 45,163 (34.0) | 637,118 (38.8) |
| 1 | 53,628 (40.4) | 686,221 (41.8) |
| 2 | 21,586 (16.3) | 221,229 (13.5) |
| 3 | 7,324 (5.5) | 60,497 (3.7) |

| | | |
|---|---|---|
| 4+ | 4,980 (3.8) | 36,001 (2.2) |
| **Early-pregnancy BMI category** | | |
| Underweight | 2,339 (1.8) | 36,663 (2.2) |
| Normal weight | 64,842 (48.9) | 918,211 (56.0) |
| Overweight | 35,594 (26.8) | 362,862 (22.1) |
| Obese | 21,490 (16.2) | 164,759 (10.0) |
| Missing category | 8,416 (6.3) | 158,571 (9.7) |
| **Smoking status** | | |
| No smoking | 110,303 (83.1) | 1,386,957 (84.5) |
| Smoked during pregnancy | 12,140 (9.1) | 103,384 (6.3) |
| Only smoked before pregnancy | 8,430 (6.4) | 84,877 (5.2) |
| Missing category | 1,808 (1.4) | 65,848 (4.0) |
| **Psychiatric conditions[a]** | | |
| Autism[b] | 673 (0.5) | 5,546 (0.3) |
| ADHD[b] | 4,017 (3.0) | 31,449 (1.9) |
| Intellectual disability[b] | 413 (0.3) | 2,638 (0.2) |
| History of any psychiatric conditions[c] | 16,345 (12.3) | 138,175 (8.4) |
| **Diagnoses [a,d]** | | |
| Infection | 8,507 (6.4) | 68,399 (4.2) |
| Diagnosed headache | 3,302 (2.5) | 15,630 (1.0) |
| Chronic pain | 2,119 (1.6) | 12,880 (0.8) |
| Asthma | 1,655 (1.2) | 12,254 (0.7) |
| Rheumatoid arthritis | 814 (0.6) | 1,727 (0.1) |
| Migraine | 510 (0.4) | 2,603 (0.2) |
| Fever | 440 (0.3) | 2,708 (0.2) |
| **Drug use in pregnancy[a]** | | |
| Opioid medications | 18,201 (13.7) | 37,769 (2.3) |
| Non-aspirin NSAIDs | 13,448 (10.1) | 29,807 (1.8) |
| Aspirin | 3,679 (2.8) | 23,315 (1.4) |
| Anti-migraine medications | 3,102 (2.3) | 10,203 (0.6) |
| Antidepressant medications | 6,191 (4.7) | 42,610 (2.6) |
| Psycholeptics medications | 4,028 (3.0) | 12,572 (0.8) |
| Antiseizure medications | 1,061 (0.8) | 6,212 (0.4) |
| **Health care visits in the year before pregnancy** | | |
| 0-3 | 116,860 (88.1) | 1,527,770 (93.1) |
| 4-10 | 13,800 (10.4) | 103,681 (6.3) |
| 11+ | 2,021 (1.5) | 9,615 (0.6) |
| **Number of antenatal visits** | | |
| ≥4 | 127,242 (95.9) | 1,494,147 (91.0) |
| < 4 | 3,348 (2.5) | 48,493 (3.0) |
| Missing category | 2,091 (1.6) | 98,426 (6.0) |

[a]Not mutually exclusive . [b]Diagnosed any time in life. [c]Diagnosed any time before pregnancy. [d]Diagnosed from one year before pregnancy until the day of delivery.

## eTable 3. Comparison at baseline of the first child in the full sibling analysis of birthing parents who were discordant for acetaminophen use across pregnancies vs. those concordant for acetaminophen use (N=781,746).

| | Persons with concordant acetaminophen use across pregnancies, N (%) | Persons with discordant acetaminophen use across pregnancies, N (%) |
|---|---|---|
| | N=680,124 | N=101,622 |
| **CHILD CHARACTERISTICS** | | |
| **Birth sex** | | |
| Female | 328557 (48.3) | 49128 (48.3) |
| Male | 351567 (51.7) | 52494 (51.7) |
| **Neurodevelopmental diagnoses[a]** | | |
| Autism | 21274 (3.1) | 3779 (3.7) |
| ADHD | 41051 (6.0) | 7569 (7.4) |
| Intellectual disability | 6429 (0.9) | 1231 (1.2) |
| **Season of birth** | | |
| Dec-Feb | 160973 (23.7) | 23916 (23.5) |
| Mar-May | 180268 (26.5) | 26586 (26.2) |
| Jun-Aug | 178289 (26.2) | 26696 (26.3) |
| Sep-Nov | 160594 (23.6) | 24424 (24.0) |
| **BIRTHING PARENT'S CHARACTERISTICS** | | |
| **Age at delivery** | | |
| <25 | 125957 (18.5) | 24422 (24.0) |
| 25-29 | 268134 (39.4) | 40454 (39.8) |
| 30-34 | 221502 (32.6) | 28683 (28.2) |
| 35-39 | 59293 (8.7) | 7396 (7.3) |
| >40 | 5238 (0.8) | 667 (0.7) |
| **Swedish-born** | | |
| Yes | 551082 (81.0) | 77291 (76.1) |
| No | 129042 (19.0) | 24331 (23.9) |
| **Highest household education** | | |
| Secondary schooling level (mandatory) | 26664 (3.9) | 6703 (6.6) |
| Upper secondary level | 256446 (37.7) | 43276 (42.6) |
| University level | 397014 (58.4) | 51643 (50.8) |
| **Household disposable income, Quintiles** | | |
| Q1 (lowest) | 90147 (13.3) | 18341 (18.0) |
| Q2 | 86029 (12.6) | 15388 (15.1) |
| Q3 | 115874 (17.0) | 18049 (17.8) |
| Q4 | 174817 (25.7) | 25000 (24.6) |
| Q5 (highest) | 213257 (31.4) | 24844 (24.4) |
| **Residential region** | | |
| Middle Sweden | 125445 (18.4) | 22963 (22.6) |
| Stockholm | 178831 (26.3) | 21671 (21.3) |
| West Sweden | 140395 (20.6) | 19049 (18.7) |
| Southern Sweden | 110603 (16.3) | 16883 (16.6) |
| Southeast Sweden | 67530 (9.9) | 12362 (12.2) |
| Northern Sweden | 57320 (8.4) | 8694 (8.6) |
| **Co-habiting at delivery** | | |
| Yes | 625167 (91.9) | 92248 (90.8) |
| No | 54957 (8.1) | 9374 (9.2) |

| | | |
|---|---|---|
| **Parity** | | |
| Nulliparous | 596000 (87.6) | 86445 (85.1) |
| 1 | 54677 (8.0) | 9160 (9.0) |
| 2 | 19715 (2.9) | 3794 (3.7) |
| 3 | 6060 (0.9) | 1312 (1.3) |
| 4+ | 3672 (0.5) | 911 (0.9) |
| **Early-pregnancy BMI category** | | |
| Underweight | 17666 (2.6) | 2390 (2.4) |
| Normal weight | 405144 (59.6) | 55240 (54.4) |
| Overweight | 133435 (19.6) | 23228 (22.9) |
| Obese | 51461 (7.6) | 11171 (11.0) |
| Missing category | 72418 (10.6) | 9593 (9.4) |
| **Smoking status** | | |
| No smoking | 556403 (81.8) | 80722 (79.4) |
| Smoked during pregnancy | 47352 (7.0) | 9952 (9.8) |
| Only smoked before pregnancy | 47888 (7.0) | 8156 (8.0) |
| Missing category | 28481 (4.2) | 2792 (2.7) |
| **Psychiatric conditions[a]** | | |
| Autism[b] | 2237 (0.3) | 474 (0.5) |
| ADHD[b] | 12853 (1.9) | 2803 (2.8) |
| Intellectual disability[b] | 1036 (0.2) | 259 (0.3) |
| History of any psychiatric conditions[c] | 49355 (7.3) | 9051 (8.9) |
| **Diagnoses [a,d]** | | |
| Migraine | 819 (0.1) | 249 (0.2) |
| Diagnosed headache | 5095 (0.7) | 1510 (1.5) |
| Chronic pain | 4854 (0.7) | 1122 (1.1) |
| Infection | 26623 (3.9) | 5153 (5.1) |
| Fever | 848 (0.1) | 192 (0.2) |
| Rheumatoid arthritis | 659 (0.1) | 228 (0.2) |
| Asthma | 5056 (0.7) | 956 (0.9) |
| **Drug use in pregnancy[a]** | | |
| Anti-migraine medications | 3800 (0.6) | 1327 (1.3) |
| Opioid medications | 13282 (2.0) | 6299 (6.2) |
| Non-aspirin NSAIDs | 13369 (2.0) | 5741 (5.6) |
| Aspirin | 6211 (0.9) | 1889 (1.9) |
| Psycholeptics medications | 5183 (0.8) | 1817 (1.8) |
| Antidepressant medications | 15123 (2.2) | 2682 (2.6) |
| Antiseizure medications | 2538 (0.4) | 426 (0.4) |
| **Health care visits in the year before pregnancy** | | |
| 0-3 | 640517 (94.2) | 93946 (92.4) |
| 4-10 | 35248 (5.2) | 6795 (6.7) |
| 11+ | 4359 (0.6) | 881 (0.9) |
| **Number of antenatal visits** | | |
| ³4 | 603133 (88.7) | 93153 (91.7) |
| < 4 | 19813 (2.9) | 2669 (2.6) |
| Missing category | 57178 (8.4) | 5800 (5.7) |

[a]Not mutually exclusive. [b]Diagnosed any time in life. [c]Diagnosed any time before pregnancy. [d]Diagnosed from one year before pregnancy until the day of delivery.

## eTable 4. Sample sizes[a] for sibling analyses of acetaminophen (N=1,773,747)

| Outcome pattern | Exposure pattern | Autism | ADHD | Intellectual disability |
|---|---|---|---|---|
| Concordant, all affected | Concordant, all unexposed | 4,237 | 15,705 | 785 |
| Concordant, all affected | Concordant, all exposed | 157 | 419 | 18 |
| Concordant, all affected | Discordant | 819 | 3,113 | 133 |
| Concordant, all unaffected | Concordant, all unexposed | 1,421,687 | 1,345,929 | 1,472,048 |
| Concordant, all unaffected | Concordant, all exposed | 21,968 | 20,538 | 22,932 |
| Concordant, all unaffected | Discordant | 232,074 | 214,891 | 242,085 |
| Discordant | Concordant, all unexposed | 75,208 | 139,498 | 28,299 |
| Discordant | Concordant, all exposed | 1,330 | 2,498 | 505 |
| Discordant | Discordant | 16,267 | 31,156 | 6,942 |

[a]All counts refer to the number of individual siblings from families with the respective outcome-exposure pattern.

**eTable 5. Associations between acetaminophen, aspirin, non-aspirin NSAIDs, opioids, and anti-migraine drugs during pregnancy and child neurodevelopmental disorders.**

| | Crude 1[a] | | | Model 1[b] | | | Model 2[c] | | | Model 3[d] | | | Sibling Analysis[e] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value | Exposed cases (% of outcome discordant) | HR | 95% CI | P-value |
| **Acetaminophen** | | | | | | | | | | | | | | | | |
| Autism | 1.26 | 1.22-1.29 | <0.001 | 1.11 | 1.08-1.14 | <0.001 | 1.10 | 1.07-1.14 | <0.001 | 1.05 | 1.02-1.08 | <0.001 | 3431 (3.65%) | 0.98 | 0.93-1.04 | 0.59 |
| ADHD | 1.29 | 1.27-1.32 | <0.001 | 1.13 | 1.11-1.15 | <0.001 | 1.12 | 1.10-1.14 | <0.001 | 1.07 | 1.05-1.10 | <0.001 | 6689 (3.82%) | 0.98 | 0.94-1.02 | 0.30 |
| Intellectual disability | 1.21 | 1.16-1.27 | <0.001 | 1.18 | 1.12-1.23 | <0.001 | 1.17 | 1.12-1.22 | <0.001 | 1.05 | 1.00-1.10 | 0.05 | 1294 (3.51%) | 1.01 | 0.92-1.10 | 0.87 |
| **Aspirin** | | | | | | | | | | | | | | | | |
| Autism | 1.23 | 1.15-1.31 | <0.001 | 1.13 | 1.06-1.20 | <0.001 | 1.12 | 1.05-1.20 | <0.001 | 1.07 | 1.00-1.14 | 0.04 | 561 (0.6%) | 0.87 | 0.76-0.99 | 0.04 |
| ADHD | 1.19 | 1.14-1.25 | <0.001 | 1.11 | 1.06-1.16 | <0.001 | 1.10 | 1.05-1.15 | <0.001 | 1.05 | 1.00-1.09 | 0.04 | 1030 (0.59%) | 0.92 | 0.83-1.01 | 0.09 |
| Intellectual disability | 1.11 | 0.99-1.24 | 0.08 | 1.07 | 0.96-1.19 | 0.25 | 1.06 | 0.95-1.18 | 0.29 | 1.04 | 0.93-1.16 | 0.50 | 187 (0.51%) | 0.71 | 0.57-0.88 | 0.001 |
| **Non-aspirin NSAIDs** | | | | | | | | | | | | | | | | |
| Autism | 1.47 | 1.40-1.53 | <0.001 | 1.19 | 1.14-1.25 | <0.001 | 1.18 | 1.13-1.23 | <0.001 | 1.07 | 1.02-1.12 | 0.002 | 1217 (1.29%) | 1.01 | 0.92-1.11 | 0.88 |
| ADHD | 1.55 | 1.51-1.60 | <0.001 | 1.23 | 1.20-1.27 | <0.001 | 1.22 | 1.18-1.26 | <0.001 | 1.10 | 1.07-1.14 | <0.001 | 2356 (1.35%) | 0.98 | 0.92-1.05 | 0.63 |
| Intellectual disability | 1.21 | 1.12-1.31 | <0.001 | 1.11 | 1.03-1.20 | 0.01 | 1.10 | 1.02-1.19 | 0.02 | 1.00 | 0.92-1.08 | 0.93 | 396 (1.07%) | 0.98 | 0.85-1.14 | 0.83 |
| **Opioids** | | | | | | | | | | | | | | | | |
| Autism | 2.11 | 2.02-2.19 | <0.001 | 1.52 | 1.46-1.59 | <0.001 | 1.46 | 1.40-1.52 | <0.001 | 1.15 | 1.11-1.20 | <0.001 | 1464 (1.56%) | 1.06 | 0.97-1.16 | 0.21 |
| ADHD | 2.40 | 2.34-2.47 | <0.001 | 1.73 | 1.68-1.78 | <0.001 | 1.65 | 1.60-1.69 | <0.001 | 1.23 | 1.19-1.26 | <0.001 | 2834 (1.62%) | 1.04 | 0.98-1.11 | 0.22 |
| Intellectual disability | 1.38 | 1.28-1.49 | <0.001 | 1.19 | 1.10-1.28 | <0.001 | 1.15 | 1.07-1.25 | <0.001 | 0.98 | 0.90-1.05 | 0.53 | 475 (1.29%) | 0.98 | 0.84-1.14 | 0.80 |
| **Anti-migraine** | | | | | | | | | | | | | | | | |
| Autism | 1.69 | 1.56-1.84 | <0.001 | 1.24 | 1.14-1.35 | <0.001 | 1.22 | 1.12-1.33 | <0.001 | 1.17 | 1.07-1.27 | <0.001 | 314 (0.33%) | 1.17 | 0.96-1.43 | 0.13 |
| ADHD | 1.55 | 1.46-1.65 | <0.001 | 1.11 | 1.04-1.18 | 0.001 | 1.09 | 1.02-1.16 | 0.007 | 1.12 | 1.05-1.19 | 0.001 | 527 (0.3%) | 0.91 | 0.79-1.06 | 0.23 |
| Intellectual disability | 1.13 | 0.96-1.32 | 0.15 | 0.98 | 0.83-1.15 | 0.78 | 0.97 | 0.83-1.14 | 0.73 | 1.03 | 0.88-1.21 | 0.73 | 95 (0.26%) | 0.94 | 0.68-1.32 | 0.73 |

[a]Crude model: All analgesics in separate models, without control for any covariates.

[b]Model 1: Adjusting for birth cohort and child sex, while jointly modeling all analgesics.

[c]Model 2: Model 1 + birthing parent's diagnosis of migraine, chronic pain, infections, fevers, rheumatoid arthritis, and headaches.

[d]Model 3: Model 2 + calendar period of delivery, parity, birthing parent'sl age at delivery (linear and cubic term), country of birth, residential region, cohabitation at delivery, early-pregnancy body mass index, smoking status, autism, ADHD, intellectual disability, history of psychiatric conditions, and prescription use of psycholeptics, antidepressants, and antiseizure medication, and health care visits in the year before pregnancy, and an inadequate number of antenatal visits, and the highest household education and disposable income.

[e]Sibling analysis: Model 3 covariates, excluding those with perfect balance between full siblings (i.e., birthing parent's birth country, psychiatric history, autism, ADHD, and intellectual disability).

## eTable 6. Hazard ratios and 95% CI for each variable in final models

| | Autism[a] | | ADHD[a] | | Intellectual disability[a] | |
|---|---|---|---|---|---|---|
| | **Population** | **Siblings** | **Population** | **Siblings** | **Population** | **Siblings** |
| **CHILD VARIABLES** | | | | | | |
| **Birth sex** | | | | | | |
| Male | 1.92 (1.89-1.95) | 2.30 (2.23-2.37) | 1.67 (1.65-1.69) | 2.15 (2.11-2.20) | 1.57 (1.53-1.61) | 1.59 (1.52-1.67) |
| **Season of birth** | | | | | | |
| Dec-Feb | | | | | | |
| Mar-May | 0.96 (0.94-0.98) | 0.97 (0.93-1.01) | 0.95 (0.94-0.97) | 0.97 (0.94-1.00) | 0.98 (0.94-1.01) | 1.01 (0.94-1.07) |
| Jun-Aug | 1.04 (1.02-1.06) | 1.08 (1.03-1.12) | 1.08 (1.07-1.10) | 1.10 (1.07-1.14) | 1.03 (1.00-1.07) | 1.04 (0.98-1.11) |
| Sep-Nov | 1.12 (1.10-1.15) | 1.15 (1.11-1.21) | 1.21 (1.19-1.22) | 1.25 (1.22-1.29) | 1.08 (1.04-1.12) | 1.08 (1.01-1.15) |
| **BIRTHING PARENT'S VARIABLES** | | | | | | |
| **Age at delivery** | | | | | | |
| Years | 0.98 (0.97-0.99) | 1.23 (1.19-1.27) | 0.95 (0.95-0.96) | 1.12 (1.09-1.14) | 0.99 (0.98-1.00) | 1.06 (1.02-1.11) |
| Years$^2$ | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| **Swedish-born** | | | | | | |
| Yes | 1.10 (1.08-1.13) | | 1.62 (1.59-1.64) | | 0.77 (0.75-0.80) | |
| **Highest household education** | | | | | | |
| Secondary schooling level | | | | | | |
| Upper secondary level | 1.00 (0.97-1.03) | 1.11 (0.92-1.34) | 0.93 (0.92-0.95) | 0.97 (0.85-1.10) | 0.75 (0.72-0.79) | 1.05 (0.84-1.33) |
| University level | 0.93 (0.90-0.96) | 1.13 (0.90-1.43) | 0.67 (0.65-0.69) | 0.98 (0.84-1.14) | 0.49 (0.47-0.52) | 1.02 (0.75-1.39) |
| **Household disposable income, Quintiles** | | | | | | |
| Q1 (lowest) | | | | | | |
| Q2 | 1.01 (0.98-1.03) | 0.96 (0.91-1.02) | 1.04 (1.02-1.06) | 0.95 (0.91-0.98) | 0.83 (0.80-0.86) | 0.88 (0.81-0.95) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Q3 | 0.85 (0.83-0.87) | 0.92 (0.86-0.98) | 0.96 (0.94-0.98) | 0.97 (0.92-1.01) | 0.67 (0.64-0.70) | 0.78 (0.71-0.86) |
| Q4 | 0.73 (0.71-0.75) | 0.93 (0.87-1.01) | 0.86 (0.85-0.88) | 1.00 (0.95-1.05) | 0.56 (0.54-0.59) | 0.67 (0.59-0.75) |
| Q5 (Highest) | 0.61 (0.59-0.63) | 0.91 (0.83-0.99) | 0.74 (0.73-0.76) | 1.04 (0.97-1.10) | 0.46 (0.44-0.49) | 0.61 (0.53-0.70) |
| **Residential region** | | | | | | |
| Northern Sweden | | | | | | |
| Middle Sweden | 1.20 (1.16-1.24) | 0.95 (0.75-1.20) | 1.16 (1.13-1.18) | 0.98 (0.82-1.16) | 0.91 (0.87-0.96) | 0.93 (0.65-1.33) |
| Stockholm | 1.63 (1.58-1.68) | 0.93 (0.74-1.18) | 1.70 (1.67-1.74) | 1.02 (0.86-1.21) | 0.87 (0.82-0.91) | 0.96 (0.67-1.38) |
| Southeast Sweden | 1.06 (1.02-1.10) | 0.96 (0.73-1.27) | 0.86 (0.84-0.88) | 0.94 (0.76-1.16) | 1.00 (0.95-1.06) | 0.96 (0.63-1.46) |
| West Sweden | 1.13 (1.09-1.17) | 0.89 (0.68-1.15) | 1.07 (1.05-1.10) | 0.96 (0.79-1.16) | 0.83 (0.79-0.88) | 1.00 (0.67-1.51) |
| Southern Sweden | 0.99 (0.96-1.03) | 0.97 (0.73-1.28) | 0.76 (0.74-0.78) | 1.14 (0.92-1.41) | 0.90 (0.85-0.94) | 0.90 (0.59-1.38) |
| **Co-habiting at delivery** | | | | | | |
| Yes | 0.79 (0.78-0.81) | 0.97 (0.90-1.04) | 0.74 (0.73-0.75) | 0.97 (0.92-1.02) | 0.75 (0.72-0.77) | 0.90 (0.81-1.00) |
| **Parity** | | | | | | |
| Nulliparous | | | | | | |
| 1 | 0.73 (0.71-0.74) | 0.66 (0.63-0.69) | 0.98 (0.97-1.00) | 1.15 (1.11-1.19) | 0.86 (0.83-0.89) | 0.95 (0.89-1.01) |
| 2 | 0.69 (0.68-0.71) | 0.50 (0.46-0.55) | 1.02 (1.00-1.04) | 1.30 (1.22-1.39) | 0.83 (0.80-0.87) | 0.84 (0.74-0.95) |
| 3 | 0.76 (0.73-0.79) | 0.45 (0.40-0.52) | 1.12 (1.09-1.15) | 1.43 (1.30-1.58) | 0.90 (0.85-0.96) | 0.89 (0.74-1.06) |
| 4+ | 0.72 (0.68-0.76) | 0.35 (0.29-0.42) | 1.13 (1.09-1.17) | 1.65 (1.44-1.89) | 0.93 (0.87-1.00) | 0.99 (0.77-1.27) |
| **Early-pregnancy BMI category** | | | | | | |
| Underweight | | | | | | |
| Normal weight | 0.89 (0.85-0.94) | 0.98 (0.86-1.13) | 1.00 (0.97-1.04) | 0.95 (0.86-1.05) | 0.81 (0.75-0.88) | 1.06 (0.87-1.30) |
| Overweight | 1.10 (1.04-1.16) | 0.99 (0.86-1.15) | 1.18 (1.14-1.23) | 0.93 (0.83-1.03) | 1.01 (0.93-1.09) | 1.07 (0.86-1.34) |
| Obese | 1.48 (1.41-1.57) | 1.04 (0.89-1.22) | 1.55 (1.49-1.60) | 0.96 (0.86-1.08) | 1.37 (1.26-1.49) | 1.04 (0.82-1.31) |
| Missing category | 1.04 (0.98-1.10) | 1.05 (0.91-1.21) | 1.12 (1.08-1.16) | 0.97 (0.87-1.08) | 0.94 (0.86-1.02) | 1.02 (0.82-1.27) |
| **Smoking status** | | | | | | |
| No smoking | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Smoked during pregnancy | 1.26 (1.23-1.29) | 0.95 (0.87-1.03) | 1.54 (1.51-1.56) | 0.99 (0.93-1.04) | 1.20 (1.16-1.25) | 0.95 (0.83-1.08) |
| Only smoked before pregnancy | 1.04 (1.01-1.07) | 1.02 (0.95-1.11) | 1.25 (1.22-1.28) | 1.02 (0.96-1.07) | 0.89 (0.84-0.95) | 0.92 (0.81-1.05) |
| Missing category | 1.06 (1.01-1.11) | 0.97 (0.88-1.07) | 1.13 (1.09-1.16) | 0.98 (0.92-1.05) | 1.14 (1.05-1.23) | 1.10 (0.95-1.29) |
| **Psychiatric conditions** [a] | | | | | | |
| Autism[b] | 3.13 (2.98-3.28) | | 1.24 (1.19-1.29) | | 1.73 (1.54-1.94) | |
| ADHD[b] | 2.29 (2.22-2.37) | | 3.51 (3.44-3.58) | | 1.14 (1.06-1.22) | |
| Intellectual disability[b] | 1.41 (1.29-1.54) | | 1.36 (1.28-1.44) | | 5.03 (4.59-5.50) | |
| History of any psychiatric conditions[c] | 1.29 (1.26-1.33) | | 1.23 (1.21-1.26) | | 1.27 (1.22-1.33) | |
| **Diagnoses** [a,d] | | | | | | |
| Migraine | 1.08 (0.91-1.29) | 1.16 (0.81-1.65) | 1.06 (0.93-1.20) | 1.14 (0.88-1.48) | 0.96 (0.69-1.34) | 1.34 (0.74-2.41) |
| Diagnosed headache | 1.14 (1.06-1.22) | 1.16 (0.99-1.35) | 1.17 (1.11-1.23) | 1.07 (0.96-1.20) | 0.86 (0.74-0.98) | 0.84 (0.64-1.10) |
| Chronic pain | 1.08 (1.00-1.17) | 0.97 (0.84-1.13) | 1.16 (1.10-1.22) | 0.94 (0.84-1.05) | 1.07 (0.94-1.23) | 1.15 (0.90-1.47) |
| Infection | 1.12 (1.09-1.16) | 1.04 (0.97-1.12) | 1.14 (1.11-1.17) | 1.02 (0.96-1.07) | 1.15 (1.08-1.22) | 1.05 (0.94-1.18) |
| Fever | 0.97 (0.80-1.18) | 0.86 (0.57-1.28) | 1.00 (0.87-1.14) | 0.97 (0.73-1.30) | 0.99 (0.72-1.37) | 1.10 (0.59-2.03) |
| Rheumatoid arthritis | 1.19 (0.98-1.44) | 1.44 (0.80-2.60) | 1.06 (0.92-1.23) | 0.90 (0.60-1.36) | 1.30 (0.93-1.81) | 1.53 (0.59-3.94) |
| Asthma | 1.24 (1.15-1.33) | 0.97 (0.82-1.16) | 1.26 (1.20-1.32) | 0.95 (0.83-1.08) | 1.20 (1.06-1.37) | 0.98 (0.72-1.33) |
| **Drug use in pregnancy** [a] | | | | | | |
| Acetaminophen | 1.05 (1.02-1.08) | 0.98 (0.93-1.04) | 1.07 (1.05-1.10) | 0.98 (0.94-1.02) | 1.05 (1.00-1.10) | 1.01 (0.92-1.10) |
| Aspirin | 1.07 (1.00-1.14) | 0.87 (0.76-0.99) | 1.05 (1.00-1.09) | 0.92 (0.83-1.01) | 1.04 (0.93-1.16) | 0.71 (0.57-0.88) |
| Non-aspirin NSAIDs | 1.07 (1.02-1.12) | 1.01 (0.92-1.11) | 1.10 (1.07-1.14) | 0.98 (0.92-1.05) | 1.00 (0.92-1.08) | 0.98 (0.85-1.14) |
| Opioids | 1.15 (1.11-1.20) | 1.06 (0.97-1.16) | 1.23 (1.19-1.26) | 1.04 (0.98-1.11) | 0.98 (0.90-1.05) | 0.98 (0.84-1.14) |
| Anti-migraine | 1.17 (1.07-1.27) | 1.17 (0.96-1.43) | 1.12 (1.05-1.19) | 0.91 (0.79-1.06) | 1.03 (0.88-1.21) | 0.94 (0.68-1.32) |
| Psycholeptics medications | 1.05 (0.99-1.11) | 1.08 (0.93-1.25) | 1.02 (0.97-1.06) | 1.05 (0.94-1.17) | 1.01 (0.91-1.13) | 1.06 (0.83-1.34) |
| Antidepressant medications | 1.35 (1.30-1.41) | 1.18 (1.06-1.30) | 1.19 (1.16-1.23) | 1.05 (0.97-1.13) | 1.03 (0.96-1.11) | 1.27 (1.05-1.53) |
| **Antiseizure medication** | 1.25 (1.15-1.36) | 1.06 (0.77-1.46) | 1.10 (1.03-1.17) | 1.02 (0.81-1.28) | 1.87 (1.65-2.12) | 0.96 (0.59-1.56) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Health care visits in the year before pregnancy** | | | | | | |
| **0-3** | | | | | | |
| **4-10** | 1.16 (1.13-1.20) | 1.12 (1.05-1.20) | 1.17 (1.14-1.19) | 1.04 (0.99-1.09) | 1.05 (1.00-1.11) | 0.88 (0.80-0.98) |
| **11+** | 1.21 (1.11-1.31) | 1.16 (0.97-1.40) | 1.17 (1.10-1.25) | 1.16 (1.01-1.35) | 1.15 (1.00-1.34) | 0.92 (0.68-1.25) |
| **Number of antenatal visits** | | | | | | |
| **≥ 4** | | | | | | |
| **< 4** | 1.18 (1.13-1.23) | 1.17 (1.07-1.28) | 1.08 (1.05-1.12) | 1.11 (1.04-1.19) | 1.46 (1.37-1.56) | 1.39 (1.23-1.58) |
| **Missing category** | 0.99 (0.95-1.02) | 1.02 (0.94-1.10) | 0.98 (0.95-1.00) | 0.99 (0.94-1.05) | 1.12 (1.06-1.19) | 1.12 (1.00-1.26) |
| **Birthyear** | | | | | | |
| **1995-1996** | | | | | | |
| **1997-1999** | 1.25 (1.21-1.30) | 1.17 (1.08-1.27) | 1.31 (1.28-1.34) | 1.12 (1.05-1.18) | 1.05 (0.99-1.10) | 1.00 (0.88-1.13) |
| **2000-2002** | 1.59 (1.53-1.64) | 1.25 (1.10-1.41) | 1.71 (1.67-1.75) | 1.19 (1.09-1.30) | 1.07 (1.01-1.13) | 0.93 (0.77-1.13) |
| **2003-2005** | 1.99 (1.92-2.06) | 1.29 (1.09-1.52) | 2.23 (2.17-2.28) | 1.21 (1.07-1.37) | 1.07 (1.01-1.13) | 0.87 (0.67-1.14) |
| **2006-2008** | 2.47 (2.38-2.56) | 1.27 (1.02-1.58) | 2.93 (2.86-3.01) | 1.19 (1.02-1.39) | 1.18 (1.12-1.25) | 0.85 (0.60-1.19) |
| **2009-2011** | 3.00 (2.88-3.12) | 1.15 (0.88-1.51) | 3.52 (3.43-3.61) | 1.00 (0.82-1.21) | 1.37 (1.29-1.45) | 0.83 (0.55-1.27) |
| **2012-2014** | 3.61 (3.45-3.78) | 0.90 (0.65-1.24) | 4.19 (4.05-4.33) | 0.80 (0.64-1.01) | 1.55 (1.45-1.65) | 0.72 (0.44-1.20) |
| **2015-2017** | 4.67 (4.44-4.92) | 0.66 (0.46-0.97) | 4.01 (3.76-4.28) | 0.49 (0.37-0.66) | 1.37 (1.27-1.48) | 0.54 (0.30-0.97) |
| **2018-2019** | 5.31 (4.79-5.88) | 0.43 (0.27-0.69) | 3.37 (2.40-4.73) | 0.35 (0.16-0.79) | 0.92 (0.78-1.08) | 0.44 (0.21-0.91) |

[a]Not mutually exclusive. [b]Diagnosed any time in life. [c]Diagnosed any time before pregnancy. [d]Diagnosed from one year before pregnancy until the day of delivery.

## eTable 7. The crude age-10 absolute risk and adjusted risk differences of autism, ADHD, and intellectual disability in relation to pregnancy drug exposure.

| | Crude Risk (%) at age 10 (95% CI) | Adjusted Risk Difference (%) at age 10 (95% CI) | |
|---|---|---|---|
| | Entire population | Population analysis[a] | Sibling analysis[b] |
| **Autism** | | | |
| *Unexposed* | 1.33 (1.32-1.35) | Ref. | Ref. |
| *Acetaminophen* | 1.53 (1.48-1.57) | 0.09 (-0.01, 0.20) | 0.02 (-0.14, 0.18) |
| *Aspirin* | 1.55 (1.46-1.65) | 0.12 (-0.12, 0.38) | -0.24 (-0.54, 0.12) |
| *Non-aspirin NSAIDs* | 1.72 (1.65-1.80) | 0.12 (-0.06, 0.31 | 0.00 (-0.23, 0.28) |
| *Opioids* | 2.55 (2.45-2.66) | 0.25 (0.08, 0.44) | 0.01 (-0.22, 0.25 |
| *Anti-migraine* | 1.84 (1.69-2.00) | 0.26 (-0.06, 0.67) | 0.11 (-0.41, 0.84) |
| **ADHD** | | | |
| *Unexposed* | 2.46 (2.44-2.48) | Ref. | Ref. |
| *Acetaminophen* | 2.87 (2.82-2.93) | 0.21 (0.08, 0.34) | -0.02 (-0.21, 0.15) |
| *Aspirin* | 2.75 (2.63-2.88) | 0.14 (-0.16, 0.45) | -0.17 (-0.64, 0.35) |
| *Non-aspirin NSAIDs* | 3.31 (3.21-3.41) | 0.30 (0.07, 0.51) | 0.05 (-0.24, 0.39) |
| *Opioids* | 5.30 (5.16-5.45) | 0.64 (0.39, 0.87) | 0.02 (-0.30, 0.33) |
| *Anti-migraine* | 3.01 (2.83-3.20) | 0.32 (-0.10, 0.78) | -0.28 (-0.84, 0.44) |
| **Intellectual Disability** | | | |
| *Unexposed* | 0.70 (0.69-0.72) | Ref. | Ref. |
| *Acetaminophen* | 0.82 (0.79-0.86) | 0.04 (-0.04, 0.12) | 0.00 (-0.10, 0.13) |
| *Aspirin* | 0.76 (0.68-0.84) | 0.03 (-0.16, 0.22) | -0.26 (-0.42, -0.04) |
| *Non-aspirin NSAIDs* | 0.80 (0.74-0.86) | 0.00 (-0.13, 0.13) | -0.02 (-0.18, 0.17) |
| *Opioids* | 0.91 (0.85-0.98) | -0.02 (-0.14, 0.11) | 0.00 (-0.16, 0.21) |
| *Anti-migraine* | 0.72 (0.61-0.84) | 0.01 (-0.23, 0.30) | -0.02 (-0.36, 0.56) |

[a]Population analysis: Adjusting for birth cohort and child sex, while jointly modeling all analgesics + birthing parent's diagnosis of migraine, chronic pain, infections, fevers, rheumatoid arthritis, and headaches, and calendar period of delivery, parity, age at delivery (linear and cubic term), country of birth, residential region, cohabitation at delivery, early-pregnancy body mass index, smoking status, autism, ADHD, intellectual disability, history of psychiatric conditions, and prescription use of psycholeptics, antidepressants, and antiseizure medication, and health care visits in the year before pregnancy, and an inadequate number of antenatal visits, and the highest household education and disposable income.
[b]Sibling analysis: All covariates above, excluding those with perfect balance between full siblings (i.e., birthing parent's birth country, psychiatric history, autism, ADHD, and intellectual disability).

## eTable 8. Replication of conventional analysis in the full sibling cohort (N=1,773,747).

| | Model 1[a] | | | Model 1[a] in full sibling cohort | | | Model 3[b] (as reported in main article) | | | Model 3[b] in full sibling cohort | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value |
| **Acetaminophen** | | | | | | | | | | | | |
| Autism | 1.11 | 1.08-1.14 | <.001 | 1.11 | 1.08-1.15 | <.001 | 1.05 | 1.02-1.08 | <.001 | 1.06 | 1.02-1.10 | .001 |
| ADHD | 1.13 | 1.11-1.15 | <.001 | 1.13 | 1.10-1.15 | <.001 | 1.07 | 1.05-1.10 | <.001 | 1.08 | 1.05-1.10 | <.001 |
| Intellectual disability | 1.18 | 1.12-1.23 | <.001 | 1.18 | 1.11-1.25 | <.001 | 1.05 | 1.00-1.10 | .05 | 1.04 | 0.99-1.11 | .15 |
| **Aspirin** | | | | | | | | | | | | |
| Autism | 1.13 | 1.06-1.20 | <.001 | 1.17 | 1.08-1.27 | <.001 | 1.07 | 1.00-1.14 | .037 | 1.10 | 1.01-1.19 | .02 |
| ADHD | 1.11 | 1.06-1.16 | <.001 | 1.18 | 1.12-1.25 | <.001 | 1.05 | 1.00-1.09 | .04 | 1.10 | 1.04-1.16 | .001 |
| Intellectual disability | 1.07 | 0.96-1.19 | .25 | 1.08 | 0.94-1.24 | .30 | 1.04 | 0.93-1.16 | .50 | 1.05 | 0.91-1.21 | .53 |
| **Non-aspirin NSAIDs** | | | | | | | | | | | | |
| Autism | 1.19 | 1.14-1.25 | <.001 | 1.21 | 1.15-1.28 | <.001 | 1.07 | 1.02-1.12 | .002 | 1.10 | 1.04-1.16 | .001 |
| ADHD | 1.23 | 1.20-1.27 | <.001 | 1.22 | 1.18-1.27 | <.001 | 1.10 | 1.07-1.14 | <.001 | 1.11 | 1.07-1.15 | <.001 |
| Intellectual disability | 1.11 | 1.03-1.20 | .01 | 1.09 | 0.99-1.21 | .08 | 1.00 | 0.92-1.08 | .93 | 0.99 | 0.89-1.09 | .83 |
| **Opioids** | | | | | | | | | | | | |
| Autism | 1.52 | 1.46-1.59 | <.001 | 1.56 | 1.48-1.64 | <.001 | 1.15 | 1.11-1.20 | <.001 | 1.18 | 1.12-1.24 | <.001 |
| ADHD | 1.73 | 1.68-1.78 | <.001 | 1.75 | 1.69-1.81 | <.001 | 1.23 | 1.19-1.26 | <.001 | 1.24 | 1.20-1.29 | <.001 |
| Intellectual disability | 1.19 | 1.10-1.28 | <.001 | 1.24 | 1.13-1.36 | <.001 | 0.98 | 0.90-1.05 | .53 | 1.02 | 0.93-1.12 | .67 |
| **Anti-migraine** | | | | | | | | | | | | |
| Autism | 1.24 | 1.14-1.35 | <.001 | 1.20 | 1.08-1.34 | .001 | 1.17 | 1.07-1.27 | <.001 | 1.12 | 1.01-1.26 | .04 |
| ADHD | 1.11 | 1.04-1.18 | .001 | 1.09 | 1.01-1.18 | .03 | 1.12 | 1.05-1.19 | .001 | 1.09 | 1.00-1.18 | .04 |
| Intellectual disability | 0.98 | 0.83-1.15 | .78 | 0.99 | 0.81-1.21 | .94 | 1.03 | 0.88-1.21 | .73 | 1.04 | 0.85-1.27 | .70 |

[a]Model 1: Adjusting for birth cohort and child sex, while jointly modeling all analgesics.

[b]Model 3: Model 1 + birthing parent's diagnosis of migraine, chronic pain, infections, fevers, rheumatoid arthritis, and headaches, and calendar period of delivery, parity, age at delivery (linear and cubic term), country of birth, residential region, cohabitation at delivery, early-pregnancy body mass index, smoking status, autism, ADHD, intellectual disability, history of psychiatric conditions, and prescription use of psycholeptics, antidepressants, and antiseizure medication, and health care visits in the year before pregnancy, and an inadequate number of antenatal visits, and the highest household education and disposable income.

## eTable 9. Sensitivity analysis addressing potential carry-over effects in sibling analysis.

| | As reported in main article | | | By pattern of exposure discordance[a] *When carry-over effects are present, the pattern of exposure discordance will yield different estimates* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sibling Analysis[a] | | | First child exposed, second child unexposed | | | First child unexposed, second child exposed | | | Difference in ORs by discordance patterns |
| | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value | P-value of difference |
| **Acetaminophen** | | | | | | | | | | |
| *Autism* | 0.98 | 0.93-1.04 | 0.59 | 0.98 | 0.89-1.09 | 0.73 | 0.98 | 0.90-1.08 | 0.69 | 0.99 |
| *ADHD* | 0.98 | 0.94-1.02 | 0.30 | 0.83 | 0.77-0.89 | <0.001 | 1.12 | 1.05-1.20 | <0.001 | <0.001 |
| *Intellectual disability* | 1.01 | 0.92-1.10 | 0.87 | 0.97 | 0.82-1.14 | 0.69 | 1.05 | 0.91-1.21 | 0.50 | 0.46 |

[a]Adjusting for birth cohort and child sex, other analgesics (opioids, aspirin, anti-migraine, non-aspirin NSAIDs), birthing parent's diagnosis of migraine, chronic pain, infections, fevers, rheumatoid arthritis, and headaches, and calendar period of delivery, parity, age at delivery (linear and cubic term), residential region, cohabitation at delivery, early-pregnancy body mass index, smoking status, and prescription use of psycholeptics, antidepressants, and antiseizure medication, and health care visits in the year before pregnancy, and an inadequate number of antenatal visits, and the highest household education and disposable income

## eTable 10: Simulations for acetaminophen and neurodevelopmental disorders under measurement error.

| | | | Autism | | ADHD | | Intellectual disability | |
|---|---|---|---|---|---|---|---|---|
| **Sensitivity** | **Specificity** | **True OR** | **Observed OR in model without sibling control** | **Observed OR in model with sibling control** | **Observed OR in model without sibling control** | **Observed OR in model with sibling control** | **Observed OR in model without sibling control** | **Observed OR in model with sibling control** |
| **From van Gelder et al., 2017** | | | | | | | | |
| 0.57 | 0.97 | 1.50 | 1.07 | 1.06 | 1.08 | 1.06 | 1.09 | 1.07 |
| | | 2.00 | 1.13 | 1.11 | 1.14 | 1.11 | 1.15 | 1.15 |
| | | 2.50 | 1.23 | 1.19 | 1.21 | 1.19 | 1.23 | 1.19 |
| | | 3.00 | 1.29 | 1.26 | 1.27 | 1.22 | 1.29 | 1.23 |
| | | 5.00 | 1.53 | 1.44 | 1.49 | 1.39 | 1.53 | 1.42 |
| **From Sunderman et al., 2016** | | | | | | | | |
| 0.79 | 0.62 | 1.50 | 1.08 | 1.07 | 1.07 | 1.04 | 1.09 | 1.06 |
| | | 2.00 | 1.13 | 1.10 | 1.15 | 1.11 | 1.13 | 1.14 |
| | | 2.50 | 1.22 | 1.20 | 1.20 | 1.17 | 1.21 | 1.18 |
| | | 3.00 | 1.30 | 1.23 | 1.28 | 1.23 | 1.25 | 1.17 |
| | | 5.00 | 1.50 | 1.41 | 1.47 | 1.38 | 1.57 | 1.47 |
| **Average of van Gelder et al. and Sunderman et al.** | | | | | | | | |
| 0.68 | 0.80 | 1.50 | 1.07 | 1.05 | 1.07 | 1.06 | 1.08 | 1.06 |
| | | 2.00 | 1.14 | 1.12 | 1.13 | 1.11 | 1.15 | 1.12 |
| | | 2.50 | 1.20 | 1.17 | 1.19 | 1.17 | 1.22 | 1.19 |
| | | 3.00 | 1.25 | 1.20 | 1.25 | 1.22 | 1.25 | 1.21 |
| | | 5.00 | 1.51 | 1.42 | 1.46 | 1.37 | 1.53 | 1.45 |
| **Assuming true prevalence of use is ~50% and specificity from van Gelder et al.** | | | | | | | | |
| 0.15 | 0.97 | 1.50 | 1.03 | 1.02 | 1.05 | 1.05 | 1.02 | 1.02 |
| | | 2.00 | 1.07 | 1.07 | 1.07 | 1.06 | 1.08 | 1.04 |
| | | 2.50 | 1.10 | 1.08 | 1.11 | 1.09 | 1.11 | 1.09 |
| | | 3.00 | 1.12 | 1.11 | 1.13 | 1.10 | 1.10 | 1.09 |
| | | 5.00 | 1.24 | 1.18 | 1.21 | 1.17 | 1.26 | 1.18 |

**eTable 11. Analyses using either only the Medical Birth Register (MBR) or only the Prescribed Drug Register (PDR) to ascertain exposure status.**

| | | Model 1[a] | | | Model 2[b] | | | Model 3[c] | | | Sibling Analysis[d] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Source | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value |
| **Acetaminophen** | | | | | | | | | | | | | |
| Autism | MBR | 1.07 | 1.04-1.11 | <.001 | 1.07 | 1.04-1.10 | <.001 | 1.05 | 1.02-1.08 | .002 | 0.99 | 0.93-1.06 | .73 |
| | PDR | 1.32 | 1.24-1.39 | <.001 | 1.28 | 1.21-1.36 | <.001 | 1.08 | 1.02-1.14 | .01 | 0.91 | 0.79-1.05 | .21 |
| ADHD | MBR | 1.09 | 1.07-1.12 | <.001 | 1.09 | 1.07-1.11 | <.001 | 1.06 | 1.04-1.08 | <.001 | 0.96 | 0.92-1.00 | .07 |
| | PDR | 1.38 | 1.32-1.43 | <.001 | 1.33 | 1.27-1.38 | <.001 | 1.20 | 1.14-1.25 | <.001 | 1.02 | 0.91-1.14 | .77 |
| Intellectual disability | MBR | 1.11 | 1.05-1.17 | <.001 | 1.11 | 1.05-1.17 | <.001 | 1.05 | 1.00-1.11 | .06 | 1.08 | 0.97-1.19 | .15 |
| | PDR | 1.46 | 1.33-1.60 | <.001 | 1.43 | 1.30-1.56 | <.001 | 1.05 | 0.96-1.15 | .31 | 0.94 | 0.76-1.15 | .52 |
| **Aspirin** | | | | | | | | | | | | | |
| Autism | MBR | 1.14 | 1.06-1.22 | <.001 | 1.13 | 1.05-1.21 | .001 | 1.07 | 0.99-1.15 | .07 | 0.90 | 0.77-1.04 | .16 |
| | PDR | 1.15 | 1.04-1.27 | .008 | 1.13 | 1.02-1.25 | .02 | 1.11 | 1.00-1.23 | .05 | 0.79 | 0.61-1.04 | .09 |
| ADHD | MBR | 1.10 | 1.05-1.16 | <.001 | 1.09 | 1.04-1.15 | <.001 | 1.03 | 0.97-1.08 | .33 | 0.95 | 0.85-1.06 | .36 |
| | PDR | 1.14 | 1.05-1.24 | .001 | 1.12 | 1.03-1.22 | .005 | 1.13 | 1.04-1.23 | <.001 | 0.86 | 0.68-1.10 | .24 |
| Intellectual disability | MBR | 1.02 | 0.90-1.16 | .73 | 1.02 | 0.90-1.15 | .79 | 1.00 | 0.88-1.14 | .96 | 0.71 | 0.56-0.91 | .008 |
| | PDR | 1.10 | 0.93-1.30 | .28 | 1.09 | 0.92-1.29 | .34 | 1.06 | 0.89-1.26 | .49 | 0.56 | 0.39-0.81 | .002 |
| **Opioids** | | | | | | | | | | | | | |
| Autism | MBR | 1.18 | 1.11-1.25 | <.001 | 1.17 | 1.11-1.24 | <.001 | 1.10 | 1.04-1.16 | .001 | 1.02 | 0.91-1.15 | .70 |
| | PDR | 1.18 | 1.11-1.27 | <.001 | 1.16 | 1.09-1.25 | <.001 | 1.04 | 0.97-1.12 | .23 | 0.91 | 0.77-1.07 | .25 |
| ADHD | MBR | 1.20 | 1.16-1.25 | <.001 | 1.20 | 1.16-1.25 | <.001 | 1.10 | 1.06-1.14 | <.001 | 1.01 | 0.93-1.10 | .80 |
| | PDR | 1.24 | 1.18-1.30 | <.001 | 1.21 | 1.16-1.27 | <.001 | 1.10 | 1.05-1.16 | <.001 | 0.93 | 0.82-1.05 | .23 |
| Intellectual disability | MBR | 0.95 | 0.85-1.06 | .39 | 0.95 | 0.85-1.06 | .37 | 0.92 | 0.82-1.03 | .15 | 1.04 | 0.84-1.29 | .69 |
| | PDR | 1.26 | 1.13-1.41 | <.001 | 1.24 | 1.11-1.39 | <.001 | 1.08 | 0.97-1.21 | .16 | 0.98 | 0.77-1.24 | .86 |
| **Anti-migraine** | | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Autism | MBR | 1.58 | 1.46-1.70 | <.001 | 1.52 | 1.40-1.64 | <.001 | 1.14 | 1.06-1.24 | .001 | 0.99 | 0.83-1.17 | .87 |
| | PDR | 1.45 | 1.38-1.52 | <.001 | 1.40 | 1.33-1.47 | <.001 | 1.18 | 1.13-1.24 | <.001 | 1.03 | 0.91-1.17 | .64 |
| ADHD | MBR | 1.89 | 1.79-1.99 | <.001 | 1.81 | 1.71-1.90 | <.001 | 1.27 | 1.21-1.35 | <.001 | 1.06 | 0.95-1.19 | .31 |
| | PDR | 1.62 | 1.57-1.68 | <.001 | 1.55 | 1.49-1.60 | <.001 | 1.20 | 1.15-1.24 | <.001 | 0.99 | 0.90-1.08 | .75 |
| Intellectual disability | MBR | 1.45 | 1.26-1.67 | <.001 | 1.41 | 1.23-1.62 | <.001 | 1.09 | 0.95-1.26 | .22 | 1.00 | 0.75-1.33 | .98 |
| | PDR | 1.05 | 0.96-1.15 | .29 | 1.03 | 0.94-1.12 | .57 | 0.96 | 0.88-1.05 | .40 | 0.97 | 0.79-1.20 | .81 |
| **non-aspirin NSAIDs** | | | | | | | | | | | | | |
| Autism | MBR | 1.22 | 1.07-1.40 | .003 | 1.21 | 1.06-1.38 | .005 | 1.19 | 1.04-1.36 | .01 | 1.02 | 0.75-1.38 | .89 |
| | PDR | 1.27 | 1.14-1.40 | <.001 | 1.24 | 1.12-1.37 | <.001 | 1.19 | 1.08-1.32 | .001 | 1.23 | 0.92-1.65 | .17 |
| ADHD | MBR | 1.11 | 1.01-1.22 | .025 | 1.10 | 1.00-1.20 | .05 | 1.15 | 1.05-1.27 | .003 | 0.79 | 0.64-0.98 | .05 |
| | PDR | 1.08 | 1.00-1.17 | .06 | 1.06 | 0.98-1.15 | .16 | 1.07 | 0.99-1.17 | .10 | 1.20 | 0.94-1.54 | .15 |
| Intellectual disability | MBR | 1.20 | 0.96-1.50 | .11 | 1.20 | 0.96-1.50 | .12 | 1.29 | 1.03-1.61 | .03 | 1.42 | 0.89-2.24 | .14 |
| | PDR | 0.93 | 0.76-1.13 | .45 | 0.91 | 0.75-1.12 | .38 | 0.98 | 0.80-1.19 | .81 | 0.93 | 0.57-1.50 | .76 |

[a]Model 1: Adjusting for birth cohort and child sex, while jointly modeling all analgesics.

[b]Model 2: Model 1 + birthing parent's diagnosis of migraine, chronic pain, infections, fevers, rheumatoid arthritis, and headaches.

[c]Model 3: Model 2 + calendar period of delivery, parity, birthing parent's age at delivery (linear and cubic term), country of birth, residential region, cohabitation at delivery, early-pregnancy body mass index, smoking status, autism, ADHD, intellectual disability, history of psychiatric conditions, and prescription use of psycholeptics, antidepressants, and antiseizure medication, and health care visits in the year before pregnancy, and an inadequate number of antenatal visits, and the highest household education and disposable income.

[d]Sibling analysis: Model 3 covariates, excluding those with perfect balance between full siblings (i.e., birthing parent's birth country, psychiatric history, autism, ADHD, and intellectual disability).

## eTable 12. Analyses stratified by birth cohort

| | Pre-2006 | | | | | | Post-2005 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Model 3[a] in population | | | Sibling Analysis[b] | | | Model 3[a] in population | | | Sibling Analysis[b] | | |
| | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value |
| **Acetaminophen** | | | | | | | | | | | | |
| Autism | 1.06 | 1.02-1.10 | 0.005 | 0.96 | 0.88-1.05 | 0.35 | 1.06 | 1.01-1.10 | 0.01 | 0.91 | 0.82-1.02 | 0.11 |
| ADHD | 1.05 | 1.03-1.08 | <0.001 | 0.93 | 0.88-0.98 | 0.01 | 1.12 | 1.09-1.15 | <0.001 | 1.03 | 0.95-1.12 | 0.44 |
| Intellectual disability | 1.05 | 0.98-1.12 | 0.016 | 1.04 | 0.90-1.19 | 0.62 | 1.04 | 0.97-1.12 | 0.23 | 0.99 | 0.85-1.16 | 0.93 |
| **Aspirin** | | | | | | | | | | | | |
| Autism | 1.04 | 0.95-1.13 | 0.38 | 0.90 | 0.74-1.10 | 0.30 | 1.09 | 1.00-1.20 | 0.06 | 0.87 | 0.68-1.13 | 0.31 |
| ADHD | 1.01 | 0.95-1.07 | 0.68 | 0.92 | 0.81-1.05 | 0.23 | 1.10 | 1.02-1.18 | 0.01 | 0.90 | 0.72-1.13 | 0.37 |
| Intellectual disability | 1.03 | 0.88-1.20 | 0.73 | 0.77 | 0.55-1.09 | 0.14 | 1.02 | 0.87-1.20 | 0.77 | 0.61 | 0.43-0.87 | 0.007 |
| **Non-aspirin NSAIDs** | | | | | | | | | | | | |
| Autism | 1.11 | 1.03-1.18 | 0.003 | 1.10 | 0.95-1.28 | 0.20 | 1.04 | 0.98-1.10 | 0.24 | 0.92 | 0.79-1.07 | 0.26 |
| ADHD | 1.12 | 1.07-1.17 | <0.001 | 0.98 | 0.89-1.09 | 0.75 | 1.09 | 1.05-1.14 | <0.001 | 0.94 | 0.83-1.05 | 0.26 |
| Intellectual disability | 0.94 | 0.82-1.07 | 0.35 | 1.04 | 0.79-1.38 | 0.78 | 1.04 | 0.94-1.15 | 0.49 | 0.98 | 0.78-1.23 | 0.86 |
| **Opioids** | | | | | | | | | | | | |
| Autism | 1.21 | 1.10-1.34 | <0.001 | 0.99 | 0.79-1.25 | 0.95 | 1.18 | 1.12-1.24 | <0.001 | 1.04 | 0.91-1.18 | 0.55 |
| ADHD | 1.34 | 1.26-1.43 | <0.001 | 1.10 | 0.94-1.28 | 0.22 | 1.21 | 1.16-1.25 | <0.001 | 0.99 | 0.90-1.09 | 0.91 |
| Intellectual disability | 1.21 | 1.01-1.44 | 0.04 | 0.97 | 0.66-1.42 | 0.88 | 0.96 | 0.88-1.05 | 0.37 | 0.98 | 0.80-1.21 | 0.85 |
| **Anti-migraine** | | | | | | | | | | | | |
| Autism | 1.14 | 0.96-1.35 | 0.14 | 0.94 | 0.63-1.41 | 0.77 | 1.21 | 1.09-1.34 | <0.001 | 1.20 | 0.89-1.61 | 0.23 |
| ADHD | 1.24 | 1.11-1.38 | <0.001 | 0.73 | 0.56-0.96 | 0.03 | 1.07 | 0.99-1.16 | 0.09 | 1.20 | 0.93-1.54 | 0.16 |
| Intellectual disability | 1.06 | 0.78-1.45 | 0.71 | 1.17 | 0.58-2.37 | 0.66 | 1.02 | 0.85-1.24 | 0.82 | 0.77 | 0.46-1.29 | 0.33 |

[a]Model 3: Adjusting for birth cohort and child sex, while jointly modeling all analgesics + birthing parent's diagnosis of migraine, chronic pain, infections, fevers, rheumatoid arthritis, and headaches, and calendar period of delivery, parity, age at delivery (linear and cubic term), country of birth, residential region, cohabitation at delivery, early-pregnancy body mass index, smoking status, autism, ADHD, intellectual disability, history of psychiatric conditions, and prescription use of psycholeptics, antidepressants, and antiseizure medication, and health care visits in the year before pregnancy, and an inadequate number of antenatal visits, and the highest household education and disposable income.

[b]Sibling analysis: Model 3 covariates, excluding those with perfect balance between full siblings (i.e., birthing parent's birth country, psychiatric history, autism, ADHD, and intellectual disability).

## eTable 13. Sensitivity analysis to assess impact of missing data handling strategy.

| | Missing-as-indicator[a] (as reported in main article) N=2,480,797 | | | Complete case analysis[b] (excluding those missing data) N=2,142,519 | | | Inverse-probability weighting[c] (correct for missing patterns) N=2,142,519 | | |
|---|---|---|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | **P-value** | **HR** | **95% CI** | **P-value** | **HR** | **95% CI** | **P-value** |
| **Acetaminophen** | | | | | | | | | |
| Autism | 1.05 | 1.02-1.08 | <0.001 | 1.05 | 1.02-1.08 | 0.003 | 1.05 | 1.01-1.08 | 0.004 |
| ADHD | 1.07 | 1.05-1.10 | <0.001 | 1.07 | 1.05-1.10 | <0.001 | 1.07 | 1.05-1.09 | <0.001 |
| Intellectual disability | 1.05 | 1.00-1.10 | 0.05 | 1.04 | 0.99-1.10 | 0.10 | 1.04 | 0.99-1.09 | 0.12 |
| **Aspirin** | | | | | | | | | |
| Autism | 1.07 | 1.00-1.14 | 0.04 | 1.07 | 1.00-1.15 | 0.05 | 1.07 | 1.00-1.15 | 0.05 |
| ADHD | 1.05 | 1.00-1.10 | 0.05 | 1.03 | 0.98-1.08 | 0.24 | 1.03 | 0.98-1.08 | 0.23 |
| Intellectual disability | 1.04 | 0.93-1.16 | 0.50 | 1.01 | 0.90-1.14 | 0.81 | 1.01 | 0.90-1.14 | 0.83 |
| **Non-aspirin NSAIDs** | | | | | | | | | |
| Autism | 1.07 | 1.02-1.12 | 0.003 | 1.07 | 1.02-1.13 | 0.003 | 1.08 | 1.02-1.13 | 0.003 |
| ADHD | 1.10 | 1.07-1.14 | <0.001 | 1.10 | 1.07-1.14 | <0.001 | 1.10 | 1.07-1.14 | <0.001 |
| Intellectual disability | 1.00 | 0.92-1.08 | 0.93 | 0.98 | 0.90-1.07 | 0.63 | 0.97 | 0.89-1.06 | 0.54 |
| **Opioids** | | | | | | | | | |
| Autism | 1.15 | 1.10-1.20 | <0.001 | 1.16 | 1.11-1.22 | <0.001 | 1.16 | 1.11-1.21 | <0.001 |
| ADHD | 1.23 | 1.19-1.27 | <0.001 | 1.23 | 1.19-1.27 | <0.001 | 1.23 | 1.19-1.27 | <0.001 |
| Intellectual disability | 0.98 | 0.90-1.06 | 0.54 | 0.99 | 0.91-1.07 | 0.73 | 0.99 | 0.91-1.07 | 0.80 |
| **Anti-migraine** | | | | | | | | | |
| Autism | 1.17 | 1.07-1.27 | <0.001 | 1.17 | 1.07-1.29 | <0.001 | 1.17 | 1.07-1.28 | 0.001 |
| ADHD | 1.12 | 1.04-1.19 | 0.001 | 1.08 | 1.00-1.16 | 0.04 | 1.08 | 1.01-1.16 | 0.04 |
| Intellectual disability | 1.03 | 0.88-1.21 | 0.73 | 1.02 | 0.86-1.21 | 0.86 | 1.01 | 0.85-1.21 | 0.87 |

[a]Referred to as Model 3 in main article (fully adjusted cohort model).

[b]Same as above but excluding those with missing data on birthing parent's smoking, BMI, and antenatal visits.

[b]Same as above but using inverse-probability weights trimmed at the 90$^{th}$ percentile with all other factors as predictors of missingness (completely observed exposure, binary outcomes, and covariates) to correct for missing data patterns.

## eTable 14. Characteristics of the subset of the study population with coverage of the Prescribed Drug Registry (those born after 1st of July 2005).

| | Total | According to dispensed acetaminophen average daily dose | | | |
|---|---|---|---|---|---|
| | | No dispensation | Low dose (<166 mg) | Medium dose (166-429 mg) | High Dose (≥430mg) |
| | N=1,546,482 | N=1,484,323 | N=15,672 | N=30,956 | N=15,531 |
| **CHILD CHARACTERISTICS** | | | | | |
| **Birth sex** | | | | | |
| **Female** | 750,891 (48.6) | 720,544 (48.5) | 7,587 (48.4) | 15,114 (48.8) | 7,646 (49.2) |
| **Male** | 795,591 (51.4) | 763,779 (51.5) | 8,085 (51.6) | 15,842 (51.2) | 7,885 (50.8) |
| **Neurodevelopmental diagnoses** | | | | | |
| **Autism** | 29,951 (1.9) | 28,393 (1.9) | 375 (2.4) | 713 (2.3) | 470 (3.0) |
| **ADHD** | 57,581 (3.7) | 54,629 (3.7) | 776 (5.0) | 1,321 (4.3) | 855 (5.5) |
| **Intellectual disability** | 10,882 (0.7) | 10,300 (0.7) | 140 (0.9) | 259 (0.8) | 183 (1.2) |
| **Season of birth** | | | | | |
| **Dec-Feb** | 353,558 (22.9) | 338,834 (22.8) | 3,591 (22.9) | 7,352 (23.7) | 3,781 (24.3) |
| **Mar-May** | 396,219 (25.6) | 380,292 (25.6) | 4,114 (26.3) | 7,938 (25.6) | 3,875 (25.0) |
| **Jun-Aug** | 416,767 (26.9) | 400,393 (27.0) | 4,185 (26.7) | 8,063 (26.0) | 4,126 (26.6) |
| **Sep-Nov** | 379,938 (24.6) | 364,804 (24.6) | 3,782 (24.1) | 7,603 (24.6) | 3,749 (24.1) |
| **BIRTHING PARENT'S CHARACTERISTICS** **Age at delivery** | | | | | |
| **<25** | 178,542 (11.5) | 172,154 (11.6) | 1,968 (12.6) | 3,437 (11.1) | 983 (6.3) |
| **25-29** | 442,771 (28.6) | 425,988 (28.7) | 4,407 (28.1) | 8,700 (28.1) | 3,676 (23.7) |
| **30-34** | 545,572 (35.3) | 524,991 (35.4) | 5,163 (32.9) | 10,167 (32.8) | 5,251 (33.8) |
| **35-39** | 303,177 (19.6) | 289,406 (19.5) | 3,223 (20.6) | 6,469 (20.9) | 4,079 (26.3) |
| **>40** | 76,420 (4.9) | 71,784 (4.8) | 911 (5.8) | 2,183 (7.1) | 1,542 (9.9) |
| **Swedish-born** | | | | | |
| **Yes** | 1,157,736 (74.9) | 1,117,191 (75.3) | 9,533 (60.8) | 20,396 (65.9) | 10,616 (68.4) |
| **No** | 388,746 (25.1) | 367,132 (24.7) | 6,139 (39.2) | 10,560 (34.1) | 4,915 (31.6) |
| **Highest household education** | | | | | |
| **Secondary schooling level (mandatory)** | 81,583 (5.3) | 75,603 (5.1) | 1,714 (10.9) | 2,760 (8.9) | 1,506 (9.7) |
| **Upper secondary level** | 538,670 (34.8) | 512,129 (34.5) | 6,126 (39.1) | 13,167 (42.5) | 7,248 (46.7) |
| **University level** | 926,229 (59.9) | 896,591 (60.4) | 7,832 (50.0) | 15,029 (48.5) | 6,777 (43.6) |
| **Household disposable income, quintiles** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Q1 (lowest)** | 266,445 (17.2) | 251,548 (16.9) | 4,070 (26.0) | 6,941 (22.4) | 3,886 (25.0) |
| **Q2** | 301,283 (19.5) | 286,952 (19.3) | 3,318 (21.2) | 6,986 (22.6) | 4,027 (25.9) |
| **Q3** | 316,778 (20.5) | 304,627 (20.5) | 2,806 (17.9) | 6,233 (20.1) | 3,112 (20.0) |
| **Q4** | 325,324 (21.0) | 314,685 (21.2) | 2,658 (17.0) | 5,490 (17.7) | 2,491 (16.0) |
| **Q5 (highest)** | 336,652 (21.8) | 326,511 (22.0) | 2,820 (18.0) | 5,306 (17.1) | 2,015 (13.0) |
| **Residential region** | | | | | |
| **Middle Sweden** | 297,599 (19.2) | 284,610 (19.2) | 2,783 (17.8) | 6,697 (21.6) | 3,509 (22.6) |
| **Stockholm** | 398,584 (25.8) | 383,110 (25.8) | 4,302 (27.5) | 8,044 (26.0) | 3,128 (20.1) |
| **West Sweden** | 309,645 (20.0) | 298,508 (20.1) | 2,963 (18.9) | 5,484 (17.7) | 2,690 (17.3) |
| **Southern Sweden** | 259,388 (16.8) | 249,964 (16.8) | 3,071 (19.6) | 4,040 (13.1) | 2,313 (14.9) |
| **Southeast Sweden** | 155,530 (10.1) | 147,496 (9.9) | 1,492 (9.5) | 4,261 (13.8) | 2,281 (14.7) |
| **Northen Sweden** | 125,736 (8.1) | 120,635 (8.1) | 1,061 (6.8) | 2,430 (7.8) | 1,610 (10.4) |
| **Co-habitation at delivery** | | | | | |
| **Yes** | 1,386,150 (89.6) | 1,333,140 (89.8) | 13,290 (84.8) | 26,600 (85.9) | 13,120 (84.5) |
| **No** | 160,332 (10.4) | 151,183 (10.2) | 2,382 (15.2) | 4,356 (14.1) | 2,411 (15.5) |
| **Parity** | | | | | |
| **Null** | 678,057 (43.8) | 655,662 (44.2) | 6,212 (39.6) | 11,397 (36.8) | 4,786 (30.8) |
| **1** | 569,513 (36.8) | 548,782 (37.0) | 5,182 (33.1) | 10,618 (34.3) | 4,931 (31.7) |
| **2** | 207,598 (13.4) | 196,507 (13.2) | 2,570 (16.4) | 5,423 (17.5) | 3,098 (19.9) |
| **3** | 57,493 (3.7) | 52,946 (3.6) | 950 (6.1) | 2,102 (6.8) | 1,495 (9.6) |
| **4+** | 33,821 (2.2) | 30,426 (2.0) | 758 (4.8) | 1,416 (4.6) | 1,221 (7.9) |
| **Early BMI category** | | | | | |
| **Underweight** | 36,057 (2.3) | 34,968 (2.4) | 299 (1.9) | 585 (1.9) | 205 (1.3) |
| **Normal weight** | 847,251 (54.8) | 821,399 (55.3) | 7,265 (46.4) | 13,259 (42.8) | 5,328 (34.3) |
| **Overweight** | 367,570 (23.8) | 349,595 (23.6) | 4,370 (27.9) | 9,003 (29.1) | 4,602 (29.6) |
| **Obese** | 189,163 (12.2) | 175,655 (11.8) | 2,765 (17.6) | 6,306 (20.4) | 4,437 (28.6) |
| **Missing category** | 106,441 (6.9) | 102,706 (6.9) | 973 (6.2) | 1,803 (5.8) | 959 (6.2) |
| **Smoking status** | | | | | |
| **No smoking** | 1,290,013 (83.4) | 1,240,861 (83.6) | 12,632 (80.6) | 24,682 (79.7) | 11,838 (76.2) |
| **Smoke during pregnancy** | 95,230 (6.2) | 88,660 (6.0) | 1,414 (9.0) | 3,048 (9.8) | 2,108 (13.6) |
| **Only smoked before pregnancy** | 108,687 (7.0) | 103,987 (7.0) | 1,206 (7.7) | 2,378 (7.7) | 1,116 (7.2) |
| **Missing category** | 52,552 (3.4) | 50,815 (3.4) | 420 (2.7) | 848 (2.7) | 469 (3.0) |
| **Psychiatric conditions** | | | | | |
| **Autism** | 7,892 (0.5) | 7,259 (0.5) | 133 (0.8) | 283 (0.9) | 217 (1.4) |
| **ADHD** | 42,998 (2.8) | 39,398 (2.7) | 688 (4.4) | 1,720 (5.6) | 1,192 (7.7) |
| **Intellectual disability** | 4,166 (0.3) | 3,767 (0.3) | 83 (0.5) | 194 (0.6) | 122 (0.8) |

| | | | | | |
|---|---|---|---|---|---|
| **History of any psychiatric conditions** | 206,621 (13.4) | 191,246 (12.9) | 2,890 (18.4) | 7,381 (23.8) | 5,104 (32.9) |
| **Diagnoses** | | | | | |
| **Migraine** | 3,621 (0.2) | 3,170 (0.2) | 81 (0.5) | 214 (0.7) | 156 (1.0) |
| **Diagnosed headache** | 24,645 (1.6) | 21,497 (1.4) | 686 (4.4) | 1,494 (4.8) | 968 (6.2) |
| **Chronic pain** | 17,837 (1.2) | 15,827 (1.1) | 408 (2.6) | 945 (3.1) | 657 (4.2) |
| **Infection** | 85,559 (5.5) | 78,523 (5.3) | 1,700 (10.8) | 3,450 (11.1) | 1,886 (12.1) |
| **Fever** | 3,923 (0.3) | 3,460 (0.2) | 109 (0.7) | 212 (0.7) | 142 (0.9) |
| **Rheumatoid arthritis** | 3,069 (0.2) | 2,118 (0.1) | 102 (0.7) | 286 (0.9) | 563 (3.6) |
| **Asthma** | 16,740 (1.1) | 15,015 (1.0) | 324 (2.1) | 767 (2.5) | 634 (4.1) |
| **Drug use in pregnancy** | | | | | |
| **Anti-migraine medications** | 17,056 (1.1) | 14,251 (1.0) | 501 (3.2) | 1,179 (3.8) | 1,125 (7.2) |
| **Opioid medications** | 76,919 (5.0) | 57,273 (3.9) | 4,398 (28.1) | 8,661 (28.0) | 6,587 (42.4) |
| **Non-aspirin NSAIDs** | 45,665 (3.0) | 33,631 (2.3) | 2,750 (17.5) | 5,446 (17.6) | 3,838 (24.7) |
| **Aspirin** | 29,129 (1.9) | 27,007 (1.8) | 365 (2.3) | 1,022 (3.3) | 735 (4.7) |
| **Psycholeptics medications** | 22,529 (1.5) | 19,502 (1.3) | 491 (3.1) | 1,218 (3.9) | 1,318 (8.5) |
| **Antidepressant medications** | 71,634 (4.6) | 64,228 (4.3) | 1,201 (7.7) | 3,190 (10.3) | 3,015 (19.4) |
| **Antiseizure medications** | 9,815 (0.6) | 8,253 (0.6) | 193 (1.2) | 579 (1.9) | 790 (5.1) |
| **Health care visits in year before pregnancy** | | | | | |
| **0-3** | 1,375,935 (89.0) | 1,329,753 (89.6) | 12,576 (80.2) | 23,473 (75.8) | 10,133 (65.2) |
| **4-10** | 151,668 (9.8) | 138,434 (9.3) | 2,692 (17.2) | 6,297 (20.3) | 4,245 (27.3) |
| **11+** | 18,879 (1.2) | 16,136 (1.1) | 404 (2.6) | 1,186 (3.8) | 1,153 (7.4) |
| **Number of antenatal visits** | | | | | |
| **³4** | 1,428,705 (92.4) | 1,371,099 (92.4) | 14,669 (93.6) | 28,596 (92.4) | 14,341 (92.3) |
| **< 4** | 62,542 (4.0) | 59,751 (4.0) | 555 (3.5) | 1,515 (4.9) | 721 (4.6) |
| **Missing category** | 55,235 (3.6) | 53,473 (3.6) | 448 (2.9) | 845 (2.7) | 469 (3.0) |

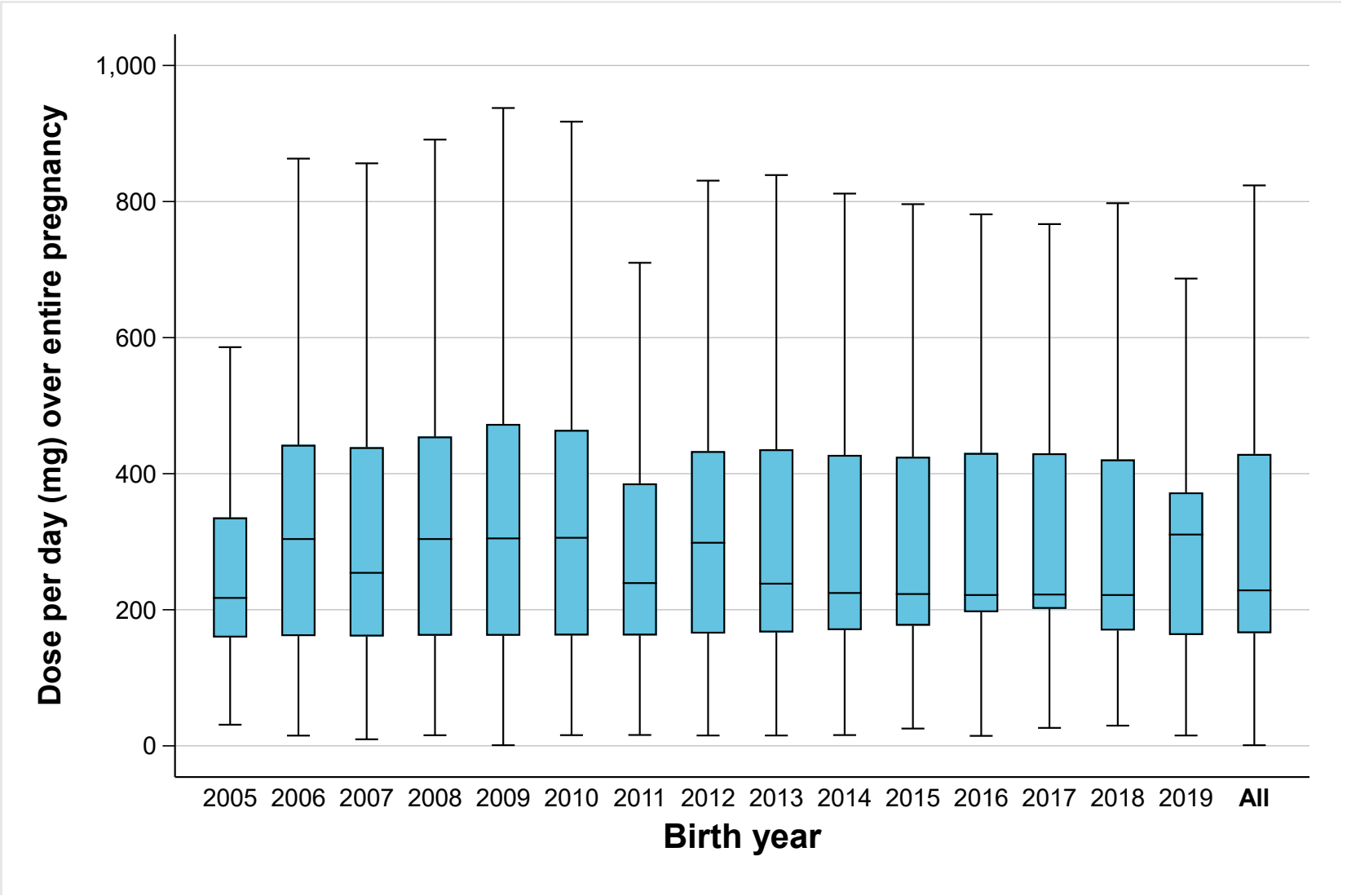
## eTable 15. Sensitivity analysis with different approaches to dealing with self-reported acetaminophen use in the Medical Birth Registry when analyzing dose data.

| | As reported in main article[a] (N=1,546,482) | | | Adjusting for OTC-use[b] (N=1,546,482) | | | Dropping OTC-users[b] (N=1,485,303) | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P-value | HR | 95% CI | P-value | HR | 95% CI | P-value |
| **Autism** | | | | | | | | | |
| No use | 1.00 | - | - | 1.00 | - | - | 1.00 | - | - |
| Low dose (<166 mg) | 1.01 | 0.91-1.12 | 0.89 | 1.01 | 0.91-1.12 | 0.84 | 1.01 | 0.91-1.12 | 0.90 |
| Medium Dose (166-429 mg) | 1.11 | 1.03-1.20 | 0.007 | 1.11 | 1.03-1.21 | 0.006 | 1.11 | 1.03-1.20 | 0.008 |
| High Dose (≥430mg) | 1.10 | 1.00-1.22 | 0.06 | 1.11 | 1.00-1.22 | 0.05 | 1.10 | 1.00-1.22 | 0.06 |
| **ADHD** | | | | | | | | | |
| No use | 1.00 | - | - | 1.00 | - | - | 1.00 | - | - |
| Low dose (<166 mg) | 1.14 | 1.06-1.23 | <0.001 | 1.15 | 1.06-1.24 | <0.001 | 1.15 | 1.06-1.23 | <0.001 |
| Medium Dose (166-429 mg) | 1.25 | 1.18-1.33 | <0.001 | 1.26 | 1.18-1.33 | <0.001 | 1.25 | 1.18-1.33 | <0.001 |
| High Dose (≥430mg) | 1.17 | 1.08-1.27 | <0.001 | 1.18 | 1.09-1.27 | <0.001 | 1.17 | 1.08-1.27 | <0.001 |
| **Intellectual Disability** | | | | | | | | | |
| No use | 1.00 | - | - | 1.00 | - | - | 1.00 | - | - |
| Low dose (<166 mg) | 0.98 | 0.83-1.16 | 0.84 | 0.99 | 0.83-1.17 | 0.87 | 0.99 | 0.84-1.17 | 0.91 |
| Medium Dose (166-429 mg) | 1.06 | 0.93-1.20 | 0.40 | 1.06 | 0.93-1.20 | 0.37 | 1.07 | 0.94-1.21 | 0.33 |
| High Dose (≥430mg) | 1.12 | 0.96-1.31 | 0.17 | 1.12 | 0.96-1.32 | 0.15 | 1.13 | 0.97-1.33 | 0.12 |

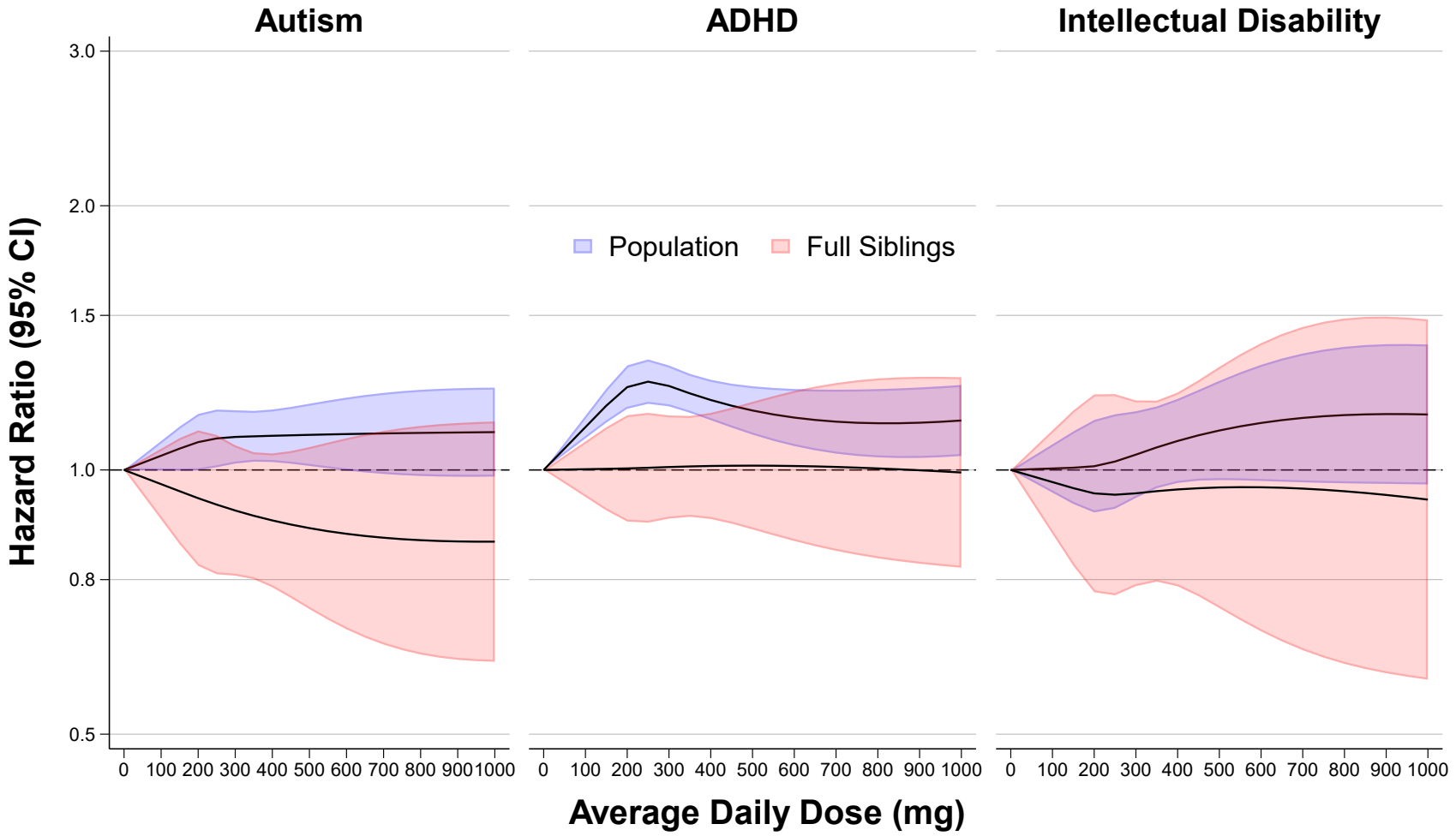
[a]Fully adjusted cohort model. Adjusting for birth cohort and child sex, while jointly modeling all analgesics + birthing parent's diagnosis of migraine, chronic pain, infections, fevers, rheumatoid arthritis, and headaches, and calendar period of delivery, parity, age at delivery (linear and cubic term), country of birth, residential region, cohabitation at delivery, early-pregnancy body mass index, smoking status, autism, ADHD, intellectual disability, history of psychiatric conditions, and prescription use of psycholeptics, antidepressants, and antiseizure medication, and health care visits in the year before pregnancy, and an inadequate number of antenatal visits, and the highest household education and disposable income.

[b]Defined as having a self-report/MBR record of acetaminophen but no available prescription dispensation (i.e., OTC use). Adjusted for the same covariates.

**eFigure 1. Box and whiskers plot of average dispensed prescription acetaminophen dose per day (mg) during pregnancy (2006-2019 birth cohorts).**



**eFigure 2: Plots of adjusted associations between dispensed acetaminophen dose and autism, ADHD, and intellectual disability, estimated using restricted cubic splines.**




Population model adjusts for birth cohort and child sex, while jointly modeling all analgesics + birthing parent's diagnosis of migraine, chronic pain, infections, fevers, rheumatoid arthritis, and headaches, and calendar period of delivery, parity, age at delivery (linear and cubic term), country of birth, residential region, cohabitation at delivery, early-pregnancy body mass index, smoking status, autism, ADHD, intellectual disability, history of psychiatric conditions, and prescription dispensations of psycholeptics, antidepressants, and antiseizure medication, and health care visits in the year before pregnancy, and an inadequate number of antenatal visits, and the highest household education and disposable income. Sibling model adjusts for all of the above except for birthing parent's birth country, psychiatric history, autism, ADHD, and intellectual disability.

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