**Maternal opioid prescription from preconception through pregnancy and the odds of autism spectrum disorder and autism features in children**

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**Supplement 1. Brand and generic names of opioids listed on maternal medical records prescribed to mothers in the Study to Explore Early Development from three months pre-pregnancy to one day prior to childbirth, 2003 to 2012**

Contains codeine: Codeine / Phenergan with codeine / Tylenol with codeine / Acetaminophen with codeine / Brontex / Guaifenesin with codeine

Contains morphine: Morphine / Duramorph / Avinza

Contains oxycodone: Oxycodone / Oxycontin / Endocet / Tylox / Percocet

Contains hydrocodone: Hydrocodone / Hydrocodone with acetaminophen / Vicodin / Hycodan / Lortab / Norco / Vicoprofen

Contains propoxyphene: Propoxyphene / Darvocet

Contains meperidine: Meperidine / Demerol

Contains hydromorphone: Hydromorphone / Dilaudid

Contains fentanyl: Fentanyl / Ropivacaine with fentanyl

Methadone

Contains nalbuphrene: Nubain

Contains butorphanol: Stadol

Contains bupropenphren: Subutex

Contains tramadol: Ultram

**Supplement 2. Fully adjusted odds ratios and 95% confidence intervals for the association between maternal opioid prescriptions in the peri-pregnancy period and child neurodevelopmental outcomes for children born from 2003 to 2012 enrolled in the Study to Explore Early Development**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Autism spectrum disorder** | | |  | **DD-only** | | |  | **ASD/DD with autism featuresa** | | |
|  | N=1352 | | |  | N=918 | | |  | N= 1820 | | |
| **Time of use** | **N** | **aORb** | **95% CI** |  | **N** | **aOR** | **95% CI** |  | **N** | **aOR** | **95% CI** |
| **Peri-pregnancy c** | 126 | 1.27 | 0.95, 1.70 |  | 66 | 0.98 | 0.69, 1.38 |  | 174 | 1.28 | 0.97, 1.69 |
| **Preconceptiond** | 17 | 2.17 | 0.87, 5.43 |  | 8 | 1.69 | 0.58, 4.88 |  | 23 | 2.20 | 0.92, 5.30 |
| **Trimester 1** | 29 | 1.55 | 0.82, 2.91 |  | 12 | 1.02 | 0.47, 2.22 |  | 36 | 1.44 | 0.78, 2.65 |
| **Trimester 2** | 25 | 1.23 | 0.66, 2.32 |  | 21 | 1.49 | 0.77, 2.85 |  | 38 | 1.30 | 0.72, 2.34 |
| **Trimester 3** | 47 | 1.04 | 0.68, 1.61 |  | 24 | 0.79 | 0.47, 1.31 |  | 63 | 0.98 | 0.65, 1.48 |

ASD: Autism spectrum disorder

DD-only: Developmental delay/disorder without features of ASD

OR: Odds ratio

aOR: Adjusted odds ratio

CI: confidence interval

a ASD/DD with autism features group includes children with autism spectrum disorder or non-ASD developmental delay/disorders with autism features

b Exposure for case groups were compared to exposure for population controls at each time of use

cThree months preconception to one day prior to childbirth

d Three months preconception to conception

e Adjusted for maternal education, race/ethnicity, smoking during pregnancy, psychiatric condition prior to childbirth, and SEED study period (2003 to 2006 or 2007 to 2012). Ns are smaller due to missing covariate data.

**Supplement 3. Change in estimate approach to improve model precision using any opioid prescription during peri-pregnancy as an exposure and autism spectrum disorder as an outcome using data from the Study to Explore Early Development**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **ln(OR)** | **% Change** | **Variance** | **% Change in variance** |
| **Full model** | 0.24 | - | 0.0227 |  |
| **Drop BMI** | 0.24 | 0.0 | 0.0226 | -0.13 |
| **Drop age** | 0.25 | 4.2 | 0.0225 | -0.80 |
| **Drop alcohol** | 0.25 | 4.2 | 0.0223 | -1.59 |
| **Drop site** | 0.23 | 3.7 | 0.0218 | -3.69 |
| **Drop psychiatric condition** | 0.27 | 12.5 | 0.0214 | -5.37 |
| **Drop smoking** | 0.30 | 25.0 | 0.0213 | -6.02 |

Full model adjusted for study site, SEED study period, maternal race/ethnicity, education, maternal psychiatric condition prior to childbirth, smoking during pregnancy, alcohol use during pregnancy, maternal age at childbirth (cubic splines at 22 and 44 years), and pre-pregnancy body mass index

ln(OR):natural log of the odds ratio;

BMI: pre-pregnancy body mass index;

Order of exclusion based on strength of associations between covariate and exposure and covariate and outcome with the covariate with the weakest associations being dropped first