Supplementary Material

Original article

Prenatal opioid exposure and subsequent risk of neuropsychiatric disorders in children: a nationwide birth cohort study in South Korea

Running head: **Prenatal opioid exposure and neuropsychiatric disorders**

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Contents of supplementary appendix

Figure S1. Disposition and study subjects (brief version)

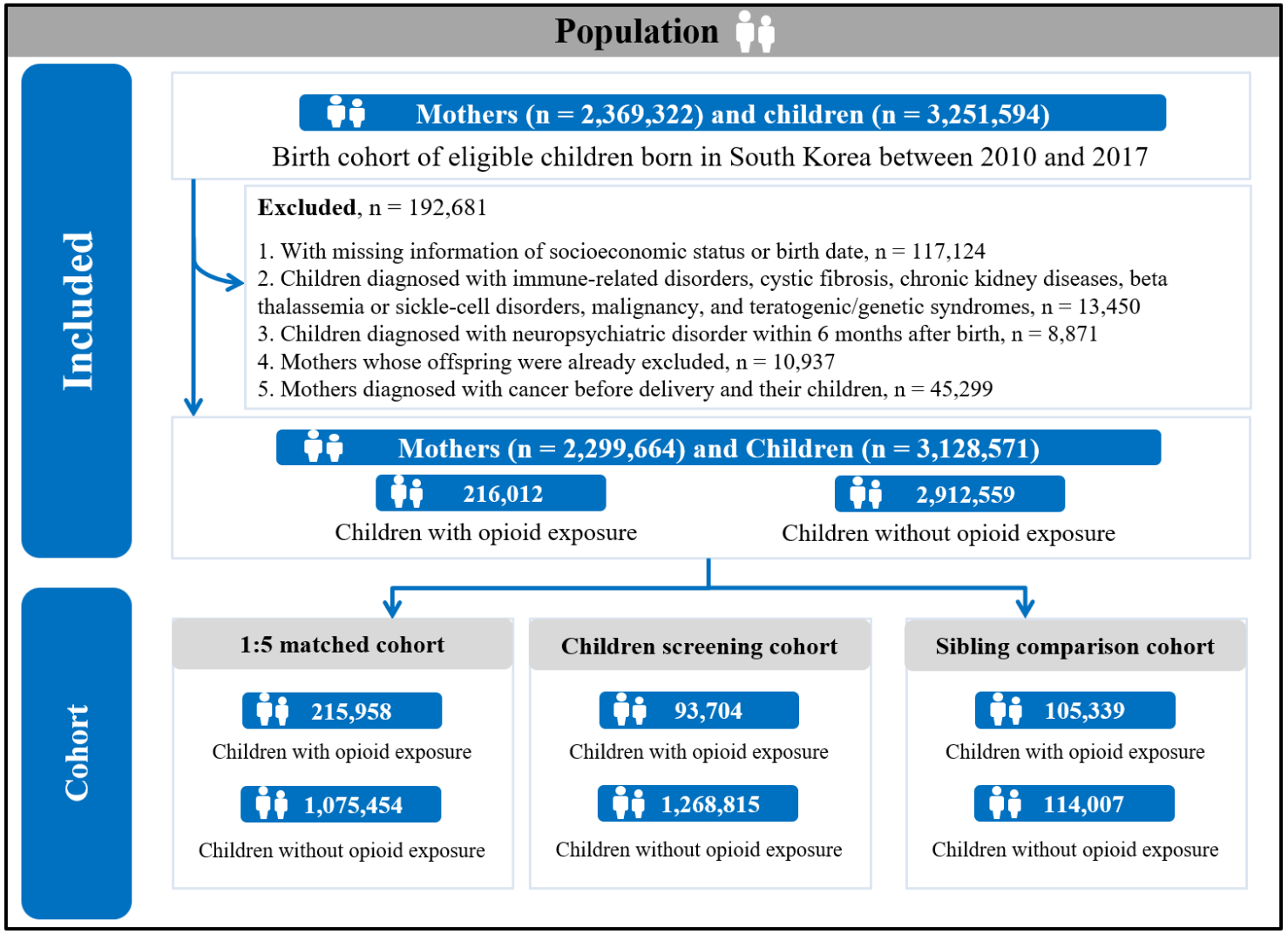


Figure S2. Study population and propensity score-matched cohort

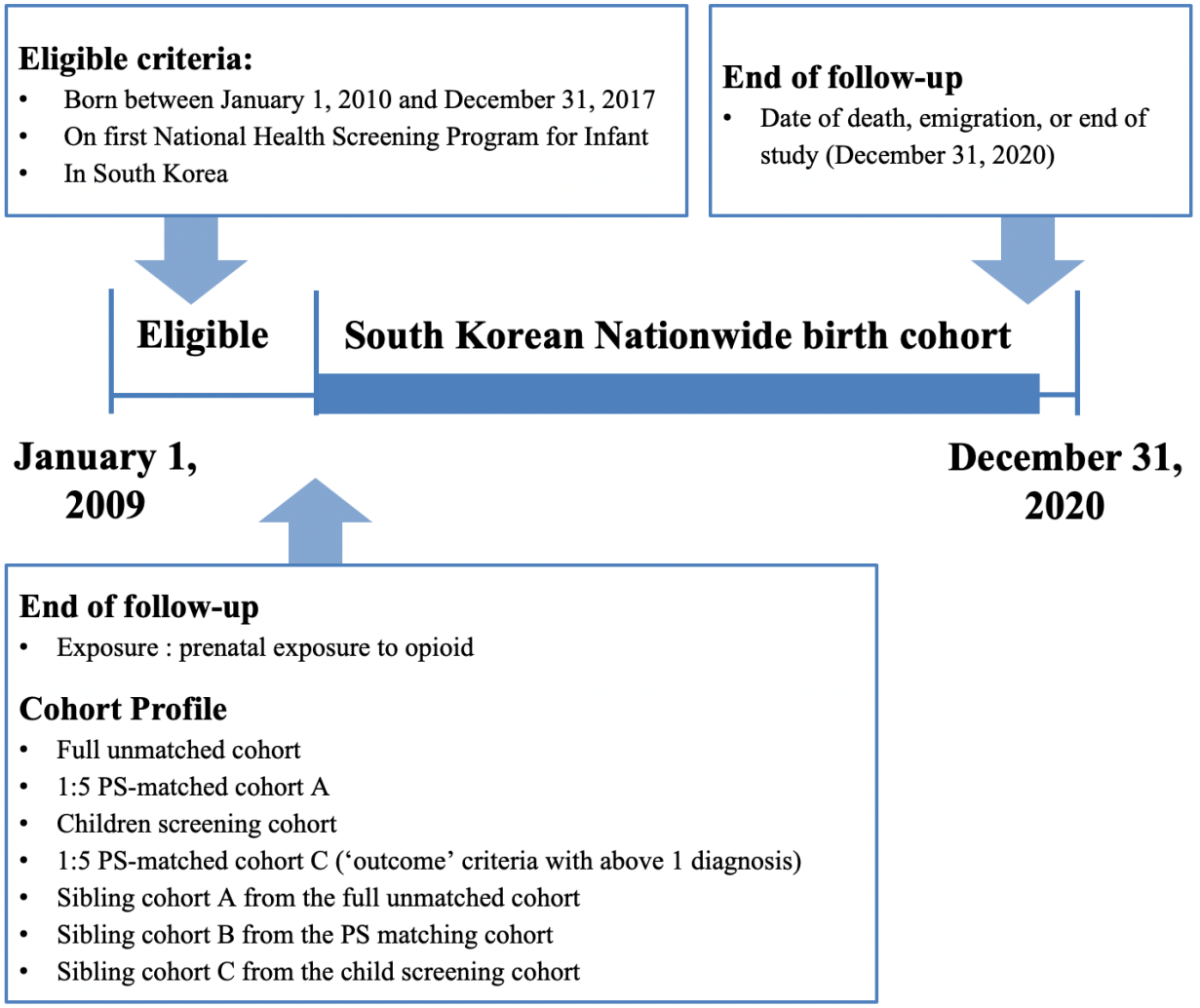


Figure S3. Study population and propensity score-matched cohort

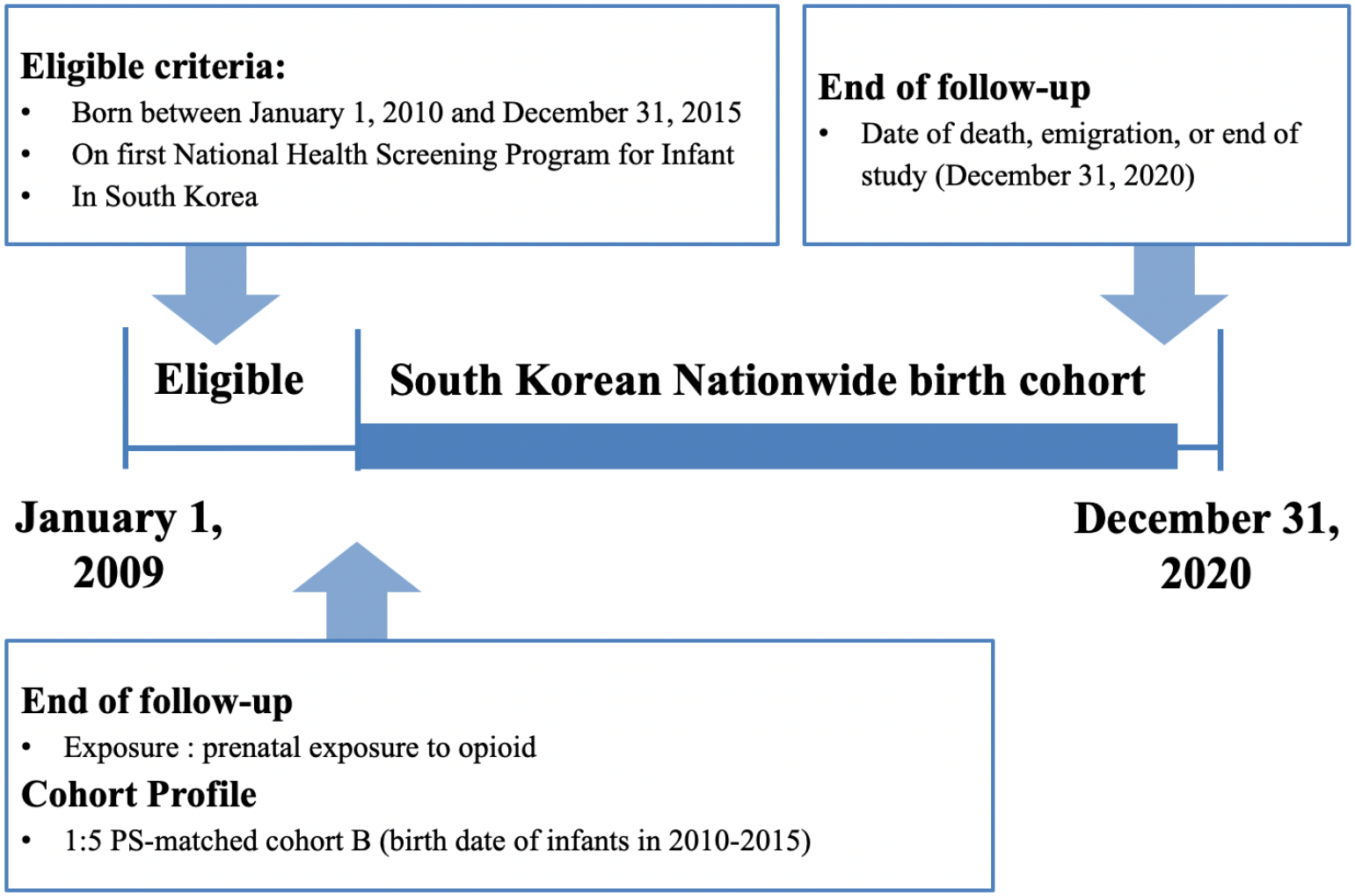
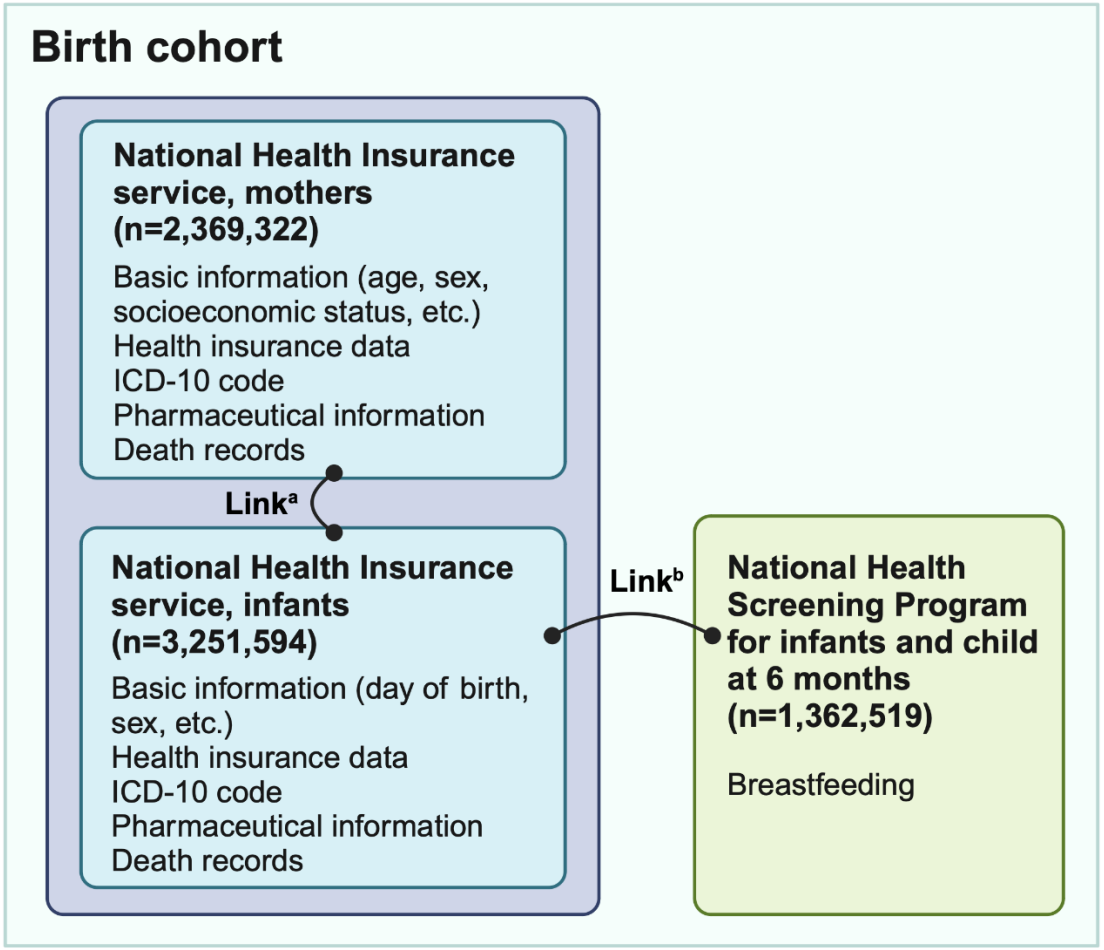
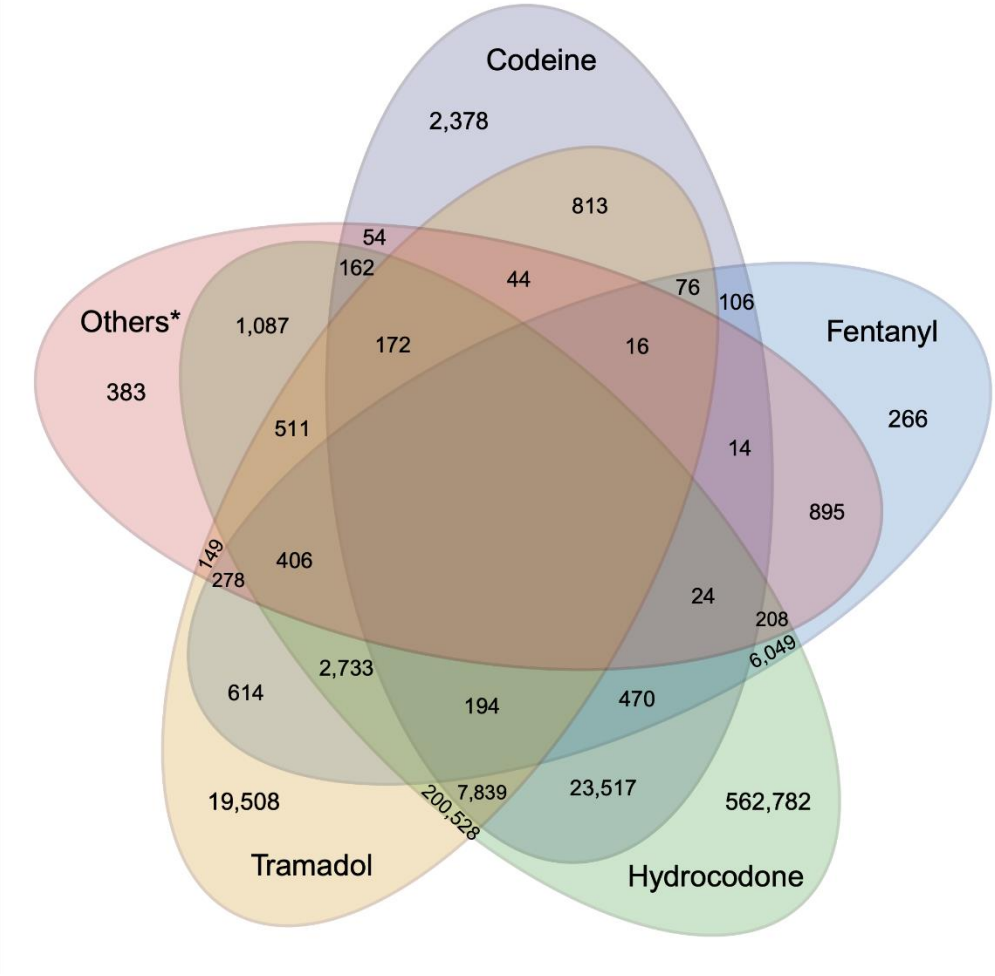


Figure S4. Data source and structure of birth cohort



Link[a] : linked by using family insurance identification number from the Korean government
Link[b] : linked by using individual identification number from the Korean government

Figure S5. Diagram for a specific prescription opioid and the number of prescriptions



*Butorphanol, hydromorphone, morphine, oxycodone, tapentadol

Figure S6. Density plot and box plot of 1:5 propensity scores of children with and without opioid exposure from 2010 to 2017

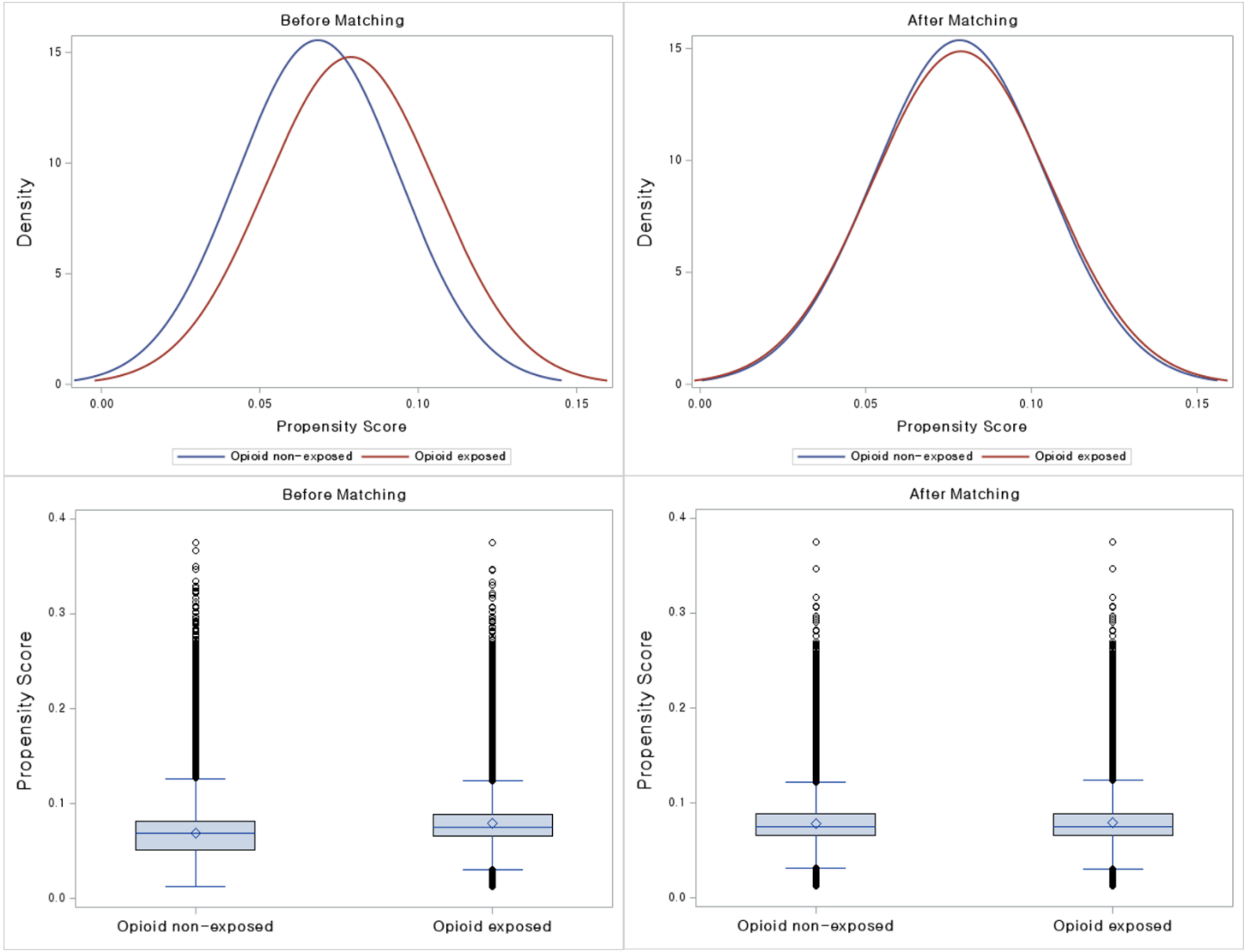


Figure S7. Density plot and box plot of 1:5 propensity scores of children with and without opioid exposure from 2010 to 2015

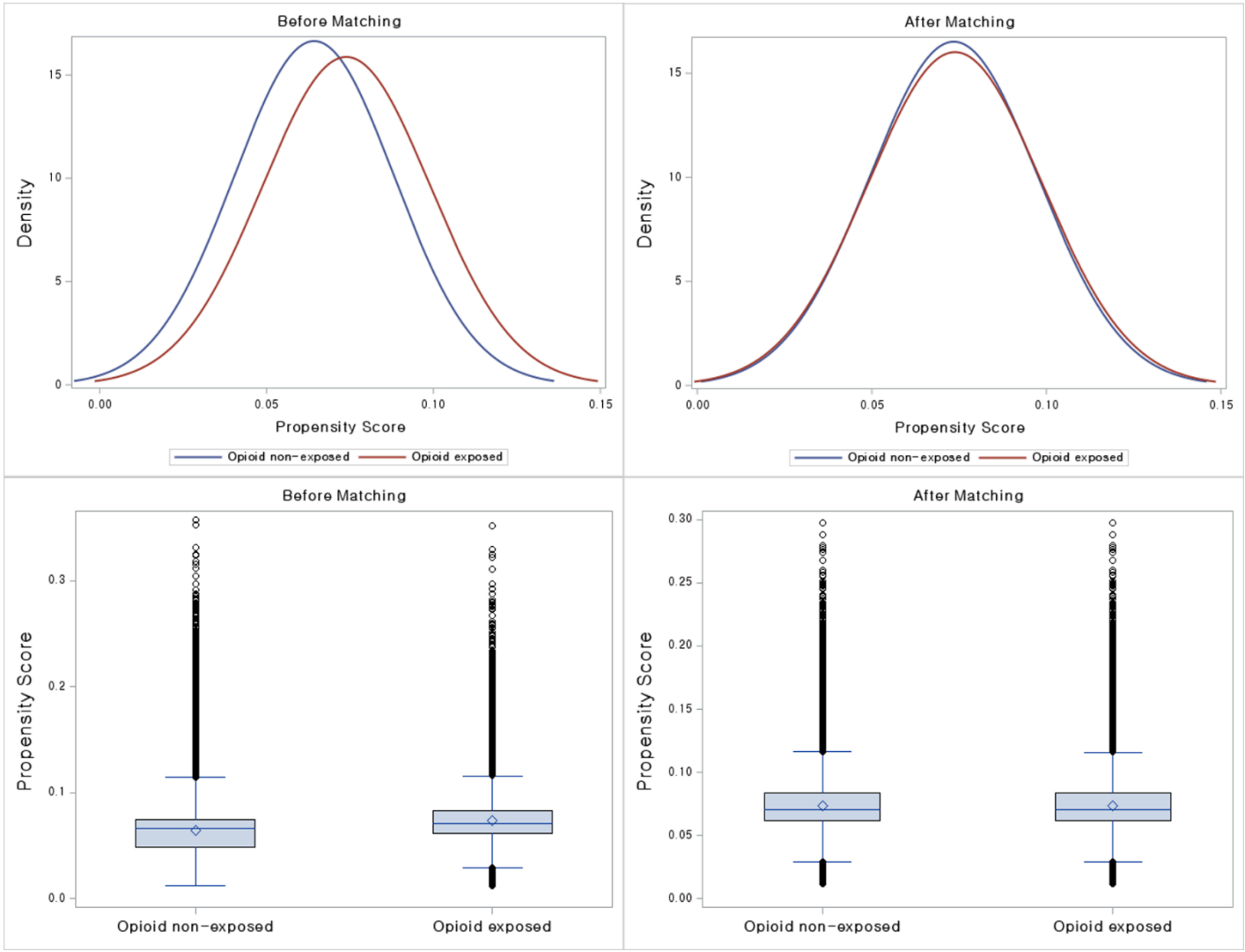


Table S1. The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data

	Item No.	STROBE items	RECORD items	Location in manuscript where items are reported
Title and abstract				
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title Page
Introduction				
Background	2	Explain the scientific background and rationale		Introduction

rationale		for the investigation being reported		
Objectives	3	State specific objectives, including any prespecified hypotheses		Introduction
Methods				
Study Design	4	Present key elements of study design early in the paper		- Nationwide cohort in South Korea
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		- Nationwide cohort in South Korea
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	- Nationwide cohort in South Korea

		(b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	-Outcomes -Covariates
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		- Nationwide cohort in South Korea
Bias	9	Describe any efforts to address potential sources of bias		- Propensity score matching

				- Child screening cohort - Sibling comparison cohort
Study size	10	Explain how the study size was arrived at		- Nationwide cohort in South Korea
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		- Nationwide cohort in South Korea
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling		Statistical analysis

		strategy (e) Describe any sensitivity analyses		
Data access and cleaning methods		..	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Statistical analysis
Linkage		..	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Statistical analysis
Results				
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed)	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or	Results

		(b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)		Results
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures		Results
Main results	16	(a) Give unadjusted estimates and, if applicable,		Results

		confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses		Results
Discussion				
Key results	18	Summarise key results with reference to study objectives		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding,	Limitations

			missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		Possible mechanisms in neuropsychiatric outcomes and prenatal opioid exposure.
Generalisability	21	Discuss the generalisability (external validity) of the study results		Comparisons with previous research
Other Information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		Funding
Accessibility of protocol, raw data, and programming code	23	..	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	NA

RECORD, the reporting of studies conducted using observational routinely-collected health data; STROBE, the strengthening the reporting of observational studies in epidemiology

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Medicine 2015; in press.

Table S2. Variable sources and codes used to define exclusion criteria, exposure, outcome of interest, and covariates

Variables	Source	Codes
Exclusion criteria		
Immune mechanism disorders	ICD-10 code	D80-D84, D89
Cystic fibrosis	ICD-10 code	E84
Chronic kidney disease	ICD-10 code	N18
Beta-thalassemia or sickle-cell disorders	ICD-10 code	D56.1, D57
Cancer	ICD-10 code	C00-C99
Teratogenic/genetic syndromes, microdeletions, chromosomal, abnormalities, and malformation syndromes with known causes	ICD-10 code	D821, P350-P351, P371, Q447, Q619, Q751, Q754, Q771-Q772, Q780, Q796, Q85-Q87, Q90-Q93, Q95-Q99
Exposure		
Opioid	Pharmaceutical information	NHIS-NHID procedure codes
Outcomes of interest		
Neuropsychiatric disorders	ICD-10 code	F00-F99
Severe neuropsychiatric disorder	ICD-10 code	F20-25, F28-31, F32.3, F33.3
Alcohol or drug misuse	ICD-10 code	F10-F19
Mood disorders except those with psychotic symptoms	ICD-10 code	F32-34, F38-39 (exclude F32.3, F33.3)
Anxiety and stress-related disorders	ICD-10 code	F40-48
Eating disorders	ICD-10 code	F50
Compulsive disorders	ICD-10 code	F42
ADHD	ICD-10 code	F90
ASD	ICD-10 code	F84.0, F84.1, F84.5, F84.8, F84.9
Intellectual disability	ICD-10 code	F70-F79
Maternal health indications related to opioid prescriptions		
Infectious and parasitic diseases	ICD-10 code	A00-A99, B00-B99
Neoplasm (benign), Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	ICD-10 code	D00-D99
Endocrine, nutritional and metabolic diseases	ICD-10 code	E00-E99
Neuropsychiatric disorders	ICD-10 code	F00-F99
Diseases of the nervous system	ICD-10 code	G00-G99

Diseases of the ear and mastoid process	ICD-10 code	H00-H95
Diseases of the circulatory system	ICD-10 code	I00-I99
Diseases of the respiratory system	ICD-10 code	J00-J99
Diseases of digestive system	ICD-10 code	K00-K99
Diseases of the skin and subcutaneous tissue	ICD-10 code	L00-L99
Diseases of musculoskeletal system and connective tissue	ICD-10 code	M00-M99
Diseases of the genitourinary system	ICD-10 code	N00-N99
Other	ICD-10 code	O00-O99, P00-P99, Q00-Q99, R00-R99, S00-S99, T00-T99, Z00-Z99
Maternal neuropsychiatric conditions		
Neuropsychiatric disorders	ICD-10 code	Common: F00-F99 Severe: F20-25, F28-31, F32.3, F33.3
Alcohol or drug misuse	ICD-10 code	F10-F19
Mood disorders except those with psychotic symptoms	ICD-10 code	F32-34, F38-39, excluding F32.3 and F33.3
Anxiety and stress-related disorders	ICD-10 code	F40-48
Sleep disorders	ICD-10 code	Insomnia: F51.0, G47.0 Hypersomnia: F51.1, G47.1 Disorder of sleep-wake schedule (circadian rhythm): F51.2, G47.2 Sleepwalking: F51.3 Night terrors: F51.4 Nightmares: F51.5 Other specified sleep disorders: F51.8, G47.8 Other sleep disorders, unspecified: F51.9, G47.9 Restless legs syndrome: G25.8 Sleep apnea: G47.3 Narcolepsy and cataplexy: G47.4
Epilepsy	ICD-10 code	G40, F44.4
Other neuropsychiatry disorders	ICD-10 code	Eating disorders: F50 Compulsive disorders: F42 ADHD: F90 ASD: F84.0, F84.1, F84.5, F84.8, F84.9 Intellectual disability: F70-F79
Concomitant drugs		
NSAID	Pharmaceutical information	NHIS-NHID procedure codes
Acetaminophen	Pharmaceutical information	NHIS-NHID procedure codes

Maternal characteristics		
Maternal age	Basic information	-
Region of residence	Basic information	-
Income	Basic information	-
Parity	Health insurance data	NHIS-NHID procedure codes
Severe maternal morbidity	ICD-10 code	Pre-existing hypertensive heart disease: O10.1 Pre-existing hypertensive heart and renal disease: O10.3 Eclampsia: O15 Cerebral venous thrombosis in pregnancy: O22.5 Cerebral venous thrombosis in the puerperium: O87.3 Pulmonary, cardiac, and central nervous system complications of anesthesia during pregnancy, labor and delivery, and the puerperium: O29.0, O29.1, O29.2, O89.0, O89.1, O89.2, O74.0, O74.1, O74.2, O74.3 Placental abruption with coagulation defect: O45.0 Antepartum hemorrhage with coagulation defect: O46.0 Intrapartum hemorrhage with coagulation defect: O67.0 Rupture of uterus before onset of labor: O71.0 Rupture of uterus during labor: O71.1 Obstetric shock: O75.1, R57, T80.5, T88.6 Septicemia during labor: O75.3 Puerperal sepsis: O85 Obstetric embolism: O88 Cardiomyopathy in the puerperium: O90.3 , I42, I43 Acute renal failure: O90.4, N17, N19, N99.0 Death, obstetric, cause unspecified: O95 Death, obstetric, after 42 days but 1 year after delivery: O96 Death from sequelae of direct obstetric causes: O97 Sudden death, death from unspecified cause: R96-R99 HIV disease: B20-B24, Z21 Cardiac arrest, cardiac failure, myocardial infarction, or pulmonary edema: O89.1, O74.2, O75.4, I21-I22, I46, I50, J81 Cerebrovascular diseases: subarachnoid and intracranial hemorrhage, cerebral infarction, stroke: I60-I64 Adult respiratory distress syndrome: J80 Acute abdomen: K35, K37, K65, N73.3, N73.5 Hepatic failure: K71-K72 Acute psychosis: F53.1, F23

		Cerebral edema or coma: G93.6, R40.2 Disseminated intravascular coagulation: D65 Sickle cell anemia with crisis: D57.0 Status asthmaticus: J45.01, J45.11, J45.81,J45.91 Status epilepticus: G41
Delivery type	ICD-10 code	Cesarean section: O82
Hospital admissions	Health insurance data	NHIS-NHID procedure codes
Outpatient contacts	Health insurance data	NHIS-NHID procedure codes
Infant characteristics		
Sex	Basic information	-
Birth season	Basic information	-
Year of delivery	Basic information	-
Preterm birth	ICD-10 code	P07.2-P07.3
Low birth weight	ICD-10 code	P07.0-P07.1
Breastfeeding	National Health Screening Program for infants and children at 6 months after birth	Questionnaire with personal medical interview

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ICD-10, international classification of diseases 10th revision; NHIS-NHID, national health insurance service-national health information database; NSAID, nonsteroidal anti-inflammatory drug

*Reference: Joseph KS, Liu S, Rouleau J, Kirby RS, Kramer MS, Sauve R, Fraser WD, Young DC, Liston RM. Severe maternal morbidity in Canada, 2003 to 2007: surveillance using routine hospitalization data and ICD-10CA codes. J Obstet Gynaecol Can. 2010 Sep;32(9):837-846. doi: 10.1016/S1701-2163(16)34655-2. PMID: 21050516.

Table S3. Study design and participants with excluded criteria

	Infant-linked mothers	**Mothers-linked infant**
Total N	**2,369,322**	**3,251,594**
Excluded criteria		
Inadequate socioeconomic status	12	54
Missing birth dates of infant	41,030	76,028
Infant with immune mechanism disorders	485	936
Infant with cystic fibrosis	9	18
Infant with chronic kidney diseases	180	338
Infant with beta-thalassemia or sickle-cell disorders	12	27
Infant with malignancy	2,101	4,116
Infant with teratogenic/genetic syndromes, chromosomal abnormalities, and malformation syndromes	2,758	6,871
Neuropsychiatric disorders within 6 months after birth of infants	18,679	26,620
Mothers with cancer	4,392	8,015
Included n	**2,299,664**	**3,128,571**

Table S4. Specific prescription opioid considered and number of prescriptions (n=832,276)

Specific opioid	**Number of prescriptions (%)**
Codeine	17,014 (2.0)
Fentanyl	4,518 (0.5)
Hydrocodone	717,906 (86.3)
Tramadol	90,313 (10.9)
Others*	2,525 (0.3)

*Butorphanol, hydromorphone, morphine, oxycodone, tapentadol

Table S5. Maternal health conditions among individuals with opioid prescriptions (total n=216,012)

Specific disease	**Number of mothers (%)**	
	Full unmatched cohort (n=216,012)	**PS-matched cohort (n=215,930)**
Infectious and parasitic diseases	2,549 (1.2)	2,546 (1.2)
Neoplasm (benign), Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	428 (0.2)	428 (0.2)
Endocrine, nutritional and metabolic diseases	1,442 (0.7)	1,441 (0.7)
Neuropsychiatric disorders	322 (0.1)	321 (0.2)
Diseases of the nervous system	1,025 (0.5)	1,021 (0.5)
Diseases of the ear and mastoid process	4,300 (2.0)	4,298 (2.0)
Diseases of the circulatory system	412 (0.2)	412 (0.2)
Diseases of the respiratory system	66,676 (30.9)	66,654 (30.9)
Diseases of digestive system	32,400 (15.0)	32,388 (15.0)
Diseases of the skin and subcutaneous tissue	3,233 (1.5)	3,231 (1.5)
Diseases of musculoskeletal system and connective tissue	16,559 (7.7)	16,546 (7.7)
Diseases of the genitourinary system	2,729 (1.3)	2,729 (1.3)
Other	83,937 (38.9)	83,915 (38.9)

Table S6. List of references of validation of ICD-10 code for neuropsychiatric disorders

Variables	ICD-10 code	Code validation and reference	Justification
Severe neuropsychiatric disorder	F20-24, F28-29, F25, F30-31, F32.3, and F33.3	All patients aged between 10 and 17 years who had presented to SLaM services were screened for ICD-10 diagnoses within clinician-recorded structured or unstructured free text fields. Those with structured data recorded were included if they had at least 1 psychosis diagnosis (ICD-10 codes F20-F29, F30-31, F32.3, F33.3, F1x.5). A random sample of 100 records revealed this identification process provided a 0.98 positive predictive value for psychotic disorder diagnosis. Reference: Downs JM, Lechler S, Dean H, Sears N, Patel R, Shetty H, Simonoff E, Hotopf M, Ford TJ, Diaz-Caneja CM, Arango C, MacCabe JH, Hayes RD, Pina-Camacho L. The Association Between Comorbid Autism Spectrum Disorders and Antipsychotic Treatment Failure in Early-Onset Psychosis: A Historical Cohort Study Using Electronic Health Records. J Clin Psychiatry. 2017 Nov/Dec;78(9):e1233-e1241. doi: 10.4088/JCP.16m11422. PMID: 29125721; PMCID: PMC6037287.	ICD-10 code for severe neuropsychiatric disorder (F20-F29, F30-31, F32.3, F33.3, F1x.5) were validated by previous research.
Alcohol or drug misuse	F10-19	They validated ICD-10 substance use codes for opioids (F11), stimulants (F15), cocaine (F14) and multiple substances (F19). All substance use codes shared the similar patter with high positive predictive value, ranging 78.8 – 92.0 %. Reference: Campanile Y, Silverman M. Sensitivity, specificity and predictive values of	ICD-10 code for alcohol or drug misuse (F10-19) were partially validated by previous research.

		ICD-10 substance use codes in a cohort of substance use-related endocarditis patients. Am J Drug Alcohol Abuse. 2022 Sep 3;48(5):538-547. doi: 10.1080/00952990.2022.2047713. Epub 2022 May 17. PMID: 35579599.	
Mood disorders except those with psychotic symptoms	F32-34, F38-39, excluding F32.3 and F33.3	Based on the ICD-10 diagnostic criteria, mood disorders showed 91.1% positive predictive value. Reference: Fiest KM, Jette N, Quan H, St Germaine-Smith C, Metcalfe A, Patten SB, Beck CA. Systematic review and assessment of validated case definitions for depression in administrative data. BMC Psychiatry. 2014 Oct 17;14:289. doi: 10.1186/s12888-014-0289-5. PMID: 25322690; PMCID: PMC4201696.	ICD-10 code for mood disorders were validated by previous research.
Anxiety and stress-related disorders	F40-48	NA	While the ICD-10 codes for anxiety and stress-related disorders have not been validated, it is likely to be relatively accurate, in the Korea context, given the challenges of securing insurances if they had an F-code diagnosis.
Eating disorders	F50	Based on the ICD-10 diagnostic criteria, eating disorders were categorized into three subtypes, including anorexia nervosa, bulimia nervosa, and unspecified eating disorders.	ICD-10 code for eating disorders were validated by previous

		Birgegård et al. showed 74.7-83.6% predictive values of ICD-10 codes. Reference: Birgegård A, Forsén Mantilla E, Dinkler L, Hedlund E, Savva A, Larsson H, Bulik CM. Validity of eating disorder diagnoses in the Swedish national patient register. J Psychiatr Res. 2022 Jun;150:227-230. doi: 10.1016/j.jpsychires.2022.03.064. Epub 2022 Apr 4. PMID: 35398665.	research.
Obsessive-compulsive disorders	F42	Based on the ICD-10 diagnostic criteria, obsessive-compulsive disorder (F42) were diagnosed with high validity (91-96% predictive values). Cases were identified in the obsessive-compulsive disorder between 1969 and 2009. Diagnosis at one point in time suffered for inclusion. Reference: Rück C, Larsson KJ, Lind K, Perez-Vigil A, Isomura K, Sariaslan A, Lichtenstein P, Mataix-Cols D. Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. BMJ Open. 2015 Jun 22;5(6):e007520. doi: 10.1136/bmjopen-2014-007520. PMID: 26100027; PMCID: PMC4480012.	ICD-10 code for obsessive-compulsive disorder was validated by previous research.
ADHD	F90	Based on the ICD-10 diagnostic criteria, 86.8% of the ADHD diagnoses (F90) could be confirmed. With an agreement rate of 96% (k-0.83), the inter-rater agreement was also substantial. Cases were identified in ADHD between 1994 and 2005. Diagnosis at one point in time suffered for inclusion. https://www.sciencedirect.com/science/article/abs/pii/S092493381602441X	ICD-10 code for ADHD was validated by previous research.

ASD	F84.0, F84.1, F84.5, F84.8, F84.9	NA	While the ICD-10 codes for ASD have not been validated, it is likely to be relatively accurate, in the Korea context, given the challenges of securing insurances if they had an F-code diagnosis.
Intellectual disability	F70-F79	Case was identified using up to 9 years of data from 1 July 2010 until 30 June 2019 via the presence of one or more diagnostic ICD-10 codes across any of the four data sets. Based on the ICD-10 diagnostic criteria, intellectual disability (F70-F79) were diagnosed with high 91% specificity. Reference: Mohr-Jensen C, Vinkel Koch S, Briciet Lauritsen M, Steinhausen HC. The validity and reliability of the diagnosis of hyperkinetic disorders in the Danish Psychiatric Central Research Registry. Eur Psychiatry. 2016 May;35:16-24. doi: 10.1016/j.eurpsy.2016.01.2427. Epub 2016 Apr 7. PMID: 27061373.	ICD-10 code for intellectual disability were validated by previous research.

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ICD-10, the international classification of disease, 10th edition

Table S7. The representativeness of the participants in the study

Category	
Disease	Neuropsychiatric disorders encompass conditions such as alcohol or drug misuse, mood disorders (excluding those with psychotic symptoms), anxiety and stress-related disorders, eating disorders, compulsive disorders, ADHD, ASD, and intellectual disability.
Special considerations related to	
Sex	While males are more prone to neurodevelopmental disorders such as ASD and ADHD, females are more susceptible to anxiety disorders and major depressive disorders.
Age	The vast majority of neuropsychiatric disorders begin in childhood, especially in the age range 5 to 15.
Socioeconomic status	Children and adolescents with low socioeconomic status showed higher risk of neuropsychiatric disorders.
Environment	Environmental factors including pollution, noise, and secondhand smoke may have a various impact on overall neuropsychiatric disorders.
Other considerations	Neuropsychiatric disorders vary broadly within and among countries throughout the world. They are associated with major comorbidities, including Alzheimer's disease, family history, maternal smoking during pregnancy and maternal obesity.

Overall representativeness of this study	We analyzed a large-scale population-based study consisted of 3.1 million Korean children with elaborated statistical techniques to support the key findings. We observed the expected rates of neuropsychiatric disorders for most of the factors above and considered those factors as confounding variables, investigating the impact of early-life opioid exposure on neuropsychiatric disorders.

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder

Table S8. Summary of dataset and cohort

#	Cohort	Sample size	Time frame	Structure of cohort	Methods
1	Full unmatched cohort	216,012 children with opioid exposure and 2,912,559 children without opioid exposure	Birth date of infants in 2010-2017, with follow-up from the date of birth until the date of death or December 31, 2020	Birth cohort	- Cox proportional hazards model - Unmatched
2	PS-matched cohort A	215,958 children with opioid exposure and 1,075,454 children without opioid exposure	Birth date of infants in 2010-2017, with follow-up from the date of birth until the date of death or December 31, 2020	Birth cohort	- Cox proportional hazards model - 1:5 PS-matched (univariate logistic regression model)
3	Child screening cohort	93,704 children with opioid exposure and 1,263,815 children without opioid exposure	Birth date of infants in 2010-2017, with follow-up from the date of birth until the date of death or December 31, 2020	Birth cohort linked with the National Health Screening Program for infants and children	- Cox proportional hazards model - Unmatched
4	PS-matched cohort B (birth date of infants in 2010-2015)	146,789 children with opioid exposure and 731,115 children without opioid exposure	Birth date of infants in 2010-2015, with follow-up from the date of birth until the date of death or December 31, 2020	Birth cohort	- Cox proportional hazards model - 1:5 PS-matched (univariate logistic regression model)
5	PS-matched cohort C (‘outcome’ criteria with above 1 diagnosis)	215,958 children with opioid exposure and 1,075,454 children without opioid exposure	Birth date of infants in 2010-2017, with follow-up from the date of birth until the date of death or December 31, 2020	Birth cohort	- Cox proportional hazards model - 1:5 PS-matched (univariate logistic regression model)
6	Sibling cohort A from the full unmatched cohort	105,339 children with opioid exposure and 114,007 children without opioid exposure	Birth date of infants in 2010-2017, with follow-up from the date of birth until	Birth cohort	- Cox proportional hazards model - Unmatched

			the date of death or December 31, 2020		- Sibling matched with different exposure statuses
7	Sibling cohort B from the PS-matched cohort	46,034 children with opioid exposure and 47,294 children without opioid exposure	Birth date of infants in 2010-2017, with follow-up from the date of birth until the date of death or December 31, 2020	Birth cohort	- Cox proportional hazards model - 1:5 PS-matched (univariate logistic regression model) - Sibling matched with different exposure statuses
8	Sibling cohort C from the child screening cohort	20,699 children with opioid exposure and 21,221 children without opioid exposure	Birth date of infants in 2010-2017, with follow-up from the date of birth until the date of death or December 31, 2020	Birth cohort linked with the National Health Screening Program for infants and children	- Cox proportional hazards model - Unmatched - Sibling matched with different exposure statuses

ICD-10, International Classification of Diseases, 10th edition; PS, propensity score

Table S9. National Health Screening Program for infants and children at 6 months after birth

Infant and Toddler Checkup Questionnaire (6 months)					
Infant's name		Social security number		Parent Contact	
Parent's name		Relationship to examinee		E-mail	

The purpose of National Health Screening Program for infants and children is to check for normal growth and development in infants and child, not to detect specific conditions. Do you understand this?

☐ Yes ☐ No

Do you consent to the examination of infant genitals during the physical examination?

☐ Yes ☐ No

1. Date of birth: _____year ____month ____day
2. Birth weight: ☐.☐☐ kg
3. Was the child born prematurely?

   ☐ Yes (estimated date of delivery? _____year ____month ____day or gestational age _____weeks ____day)

   ☐ No

Nutrition education	Yes	No	N/A
1. If you are exclusively breastfeeding, your child may be deficient in iron during weaning. Are you giving your child iron supplments or iron-rich complementary foods (baby food)?			
2. Do you know that breastfeeding can be continued beyond 24 months of age in combination with complementary foods (baby food or baby meals)?			
3. Do you know that expressed breast milk can only be stored at room temperature for up to 4 hours?			
4. Do you know that breastfeeding moms do not need to stop breastfeeding if they take pain relievers, cold medicines, antibiotics, etc. unless there is a special need?			

5. How long have you been exclusively breastfeeding? (This refers to breastfeeding without the use of formula.)

   ☐ Less than 1 month ☐ 2 months ☐ 3 months ☐ 4 months

Sleep education	Yes	No
1. Do you put your child to bed on their back?		
2. Does your child play on his/her stomach when awake to prevent flat head and promote development?		
3. Does your child sleep with you in the same sleeping arrangement (bed, bassinet,		

etc.)?		
4. Do you put your child to bed after he/she has fallen asleep by holding or rocking him/her with a bottle of milk or formula?		
5. Do you engage in routine behaviors before putting your child to bed, such as bathing, massage, lullabies, or reading a book?		
6. If my child wakes up, do you put him/her to sleep with a latch on a breast or bottle of formula?		
Electronic media exposure training	Yes	No
1. ※ Experts recommend limiting exposure to electronic media (e.g., smartphones, TVs, tablet PCs, etc.) before the age of 2 years. Do you show your child electronic media?		
2. Do you use electronic media when you are with your child?		
3. Do you watch it with them, when you show your child electronic media?		
4. How much time does your child spend with electronic media on an average day? ☐ Not at all ☐ Less than 1 hour ☐ Less than 2 hours ☐ More than 2 hours		
Hip joint related	Yes	No
1. Has your child ever had a hip ultrasound examination for a developmental dysplasia of the hip?		
2. Has your child ever been diagnosed with a developmental dysplasia of the hip?		
Safety prevention education	Yes	No
1. Do you always use an age- and weight-appropriate car seat when traveling by car?		
2. Have you ever left your child unattended, even briefly, on an adult bed or couch?		
3. Are you aware that your child could be seriously injured while using a walker?		
4. Do you know that it is not good to shake your child vigorously when holding and soothing them?		
5. Have you ever left your child unattended in a bathtub, tub, or toilet, even for short time?		
6. Have you ever had a hot drink while holding your child?		
7. Have you ever put your child to sleep on an electric blanket or heating mat?		
Vision related	Yes	No
1. Does your child make good eye contact?		
2. Does the pupil of your child have a strange position (crowded inward or outward without focus)?		
3. Is your child’s black eye (pupil) cloudy?		

Hearing related	Yes	No
1. Does your child make a variety of sounds (“ah”, “ooh’, “ee”), or can your child make sounds when laughing?		
2. Has your child been in the neonatal intensive care unit (NICU) for more than 5 days after birth?		
3. Did your child have a newborn hearing screening (audiogram) within 1 month of birth (or within 1 month of birth if premature)?		
4. Has your child ever been diagnosed as ‘refer’ in one or both ears from newborn hearing screening test? ☐ Yes ☐ No ☐ N/A		
5. Has your child ever been diagnosed as ‘hearing loss’ in one or both ears?		
Personal hygiene related	Yes	No
1. Do you always wash your hands before and after wiping your child’s eyes, nose, and mouth?		

Table S10. Baseline characteristics of the study subjects in the child screening cohort from 2010 to 2017

	Total	**Children with prenatal opioid exposure**	**Children without prenatal exposure**
Total, n	1,362,519	93,704	1,268,815
Maternal characteristics			
Maternal age at delivery year, mean (SD)	31.8 (4.0)	32.2 (4.0)	31.8 (4.0)
Maternal age at delivery year, n (%)			
≤ 19	2,552 (0.2)	193 (0.2)	2,359 (0.2)
20-24	50,417 (3.7)	3,113 (3.3)	47,304 (3.7)
25-29	307,669 (22.6)	18,496 (19.7)	289,173 (22.8)
30-34	679,184 (49.9)	46,152 (49.3)	633,032 (49.9)
≥ 35	322,697 (23.7)	25,750 (27.5)	296,947 (23.4)
Region of residence, n (%)			
Rural	593,353 (43.6)	39,268 (41.9)	554,085 (43.7)
Urban	769,166 (56.5)	54,436 (58.1)	714,730 (56.3)
Income level, n (%)			
1st quartile	293,449 (21.5)	21,349 (22.8)	272,100 (21.5)
2nd quartile	354,967 (26.1)	24,456 (26.1)	330,511 (26.1)
3rd quartile	352,571 (25.9)	24,076 (25.7)	328,495 (25.9)
4th quartile	361,532 (26.5)	23,823 (25.4)	337,709 (26.6)
Parity, n (%)			
1	1,008,581 (74.0)	76,738 (81.9)	931,843 (73.4)
≥ 2	353,938 (26.0)	16,966 (18.1)	336,972 (26.6)
Maternal medical conditions, n (%)			
No mental illness	1,155,369 (84.8)	73,757 (78.7)	1,081,612 (85.3)
Common	188,896 (13.9)	18,024 (19.2)	170,872 (13.5)
Severe	18,254 (1.3)	1,923 (2.1)	16,331 (1.3)
Alcohol or drug misuse, n (%)	1,769 (0.1)	215 (0.2)	1,554 (0.1)
Mood disorders except those with psychotic symptoms, n (%)	35,796 (2.6)	3,984 (4.3)	31,812 (2.5)
Anxiety and stress-related disorders, n (%)	64,286 (4.7)	6,885 (7.4)	57,401 (4.5)
Sleep disorders, n (%)	29,065 (2.1)	3,542 (3.8)	25,523 (2.0)
Epilepsy, n (%)	4,119 (0.3)	378 (0.4)	3,741 (0.3)
Other neuropsychiatry disorders, n (%)	3,172 (0.2)	307 (0.3)	2,865 (0.2)
Severe maternal morbidity, n (%)			
0	1,275,572 (93.6)	85,941 (91.7)	1,189,631 (93.8)

1	84,661 (6.2)	7,496 (8.0)	77,165 (6.1)
≥ 2	2,286 (0.2)	267 (0.3)	2,019 (0.2)
Delivery type, n (%)			
Vaginal delivery	790,232 (58.0)	50,272 (53.7)	739,960 (58.3)
Cesarean section	572,287 (42.0)	43,432 (46.4)	528,855 (41.7)
Number of hospital admissions in a year before pregnancy, n (%)			
0	1,154,236 (84.7)	74,784 (79.8)	1,079,452 (85.1)
1	172,545 (12.7)	15,119 (16.1)	157,426 (12.4)
≥ 2	35,738 (2.6)	3,801 (4.1)	31,937 (2.5)
Number of outpatient contacts in a year before pregnancy, n (%)			
0	68,612 (5.0)	1,619 (1.7)	66,993 (5.3)
1	69,974 (5.1)	2,033 (2.2)	67,941 (5.4)
≥ 2	1,223,933 (89.8)	90,052 (96.1)	1,133,881 (89.4)
Use of NSAID during pregnancy, n (%)	254,058 (18.7)	44,693 (47.7)	209,365 (16.5)
Use of acetaminophen during pregnancy, n (%)	406,196 (29.8)	64,088 (68.4)	342,108 (27.0)
Infant characteristics			
Infant sex, n (%)			
Male	702,204 (51.5)	48,107 (51.3)	654,097 (51.6)
Female	660,315 (48.5)	45,597 (48.7)	614,718 (48.5)
Birth season, n (%)			
Spring	310,765 (22.8)	19,679 (21.0)	291,086 (22.9)
Summer	331,734 (24.4)	25,338 (27.0)	306,396 (24.2)
Autumn	375,799 (27.6)	26,062 (27.8)	349,737 (27.6)
Winter	344,221 (25.3)	22,625 (24.2)	321,596 (25.4)
Year of delivery, n (%)			
2010 to 2012	496,610 (36.5)	29,185 (31.2)	467,425 (36.8)
2013 to 2015	545,019 (40.0)	38,726 (41.3)	506,293 (39.9)
2016 to 2017	320,890 (23.6)	25,793 (27.5)	295,097 (23.3)
At-risk newborn, n (%)			
Preterm birth	41,862 (3.1)	3,994 (4.3)	37,868 (3.0)
Low birth weight	33,200 (2.4)	2,802 (3.0)	30,398 (2.4)
Breastfeeding, n (%)			
No	628,014 (46.1)	47,267 (50.4)	580,748 (45.8)
Yes	734,504 (53.9)	46,437 (49.6)	580,748 (45.8)

NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation

Table S11. Baseline characteristics of study subjects (PS-matched cohort B, birth date of infants in 2010-2015)

		Full unmatched cohort (n=2,264,056)[a]		PS-matched cohort A (n=877,904)[b]		SMD*
		Children with prenatal opioid exposure	Children without prenatal exposure	Children with prenatal opioid exposure	Children without prenatal exposure	
	Total, n	146,858	2,117,198	146,789	731,115	
Matching variables	**Maternal characteristics**					
	Maternal age at delivery year, mean (SD)	32.0 (4.1)	31.7 (4.1)	32.0 (4.1)	32.0 (4.1)	0.01
	Maternal age at delivery year, n (%)					<0.01
	≤ 19	379 (0.3)	5,797 (0.3)	376 (0.3)	1,819 (0.3)	
	20-24	5,802 (4.0)	96,272 (4.6)	5,796 (4.0)	28,514 (3.9)	
	25-29	29,773 (20.3)	483,644 (22.8)	29,761 (20.3)	148,318 (20.3)	
	30-34	73,035 (49.7)	1,044,582 (49.3)	73,013 (49.7)	364,033 (49.8)	
	≥ 35	37,869 (25.8)	486,903 (23.0)	37,843 (25.8)	188,431 (25.8)	
	Region of residence, n (%)					<0.01
	Rural	60,859 (41.4)	920,131 (43.5)	60,835 (41.4)	302,952 (41.4)	
	Urban	85,999 (58.6)	1,197,067 (56.5)	85,954 (58.6)	428,163 (58.6)	
	Income level, n (%)					<0.01
	1st quartile	34,981 (23.8)	476,057 (22.5)	34,952 (23.8)	173,176 (23.7)	
	2nd quartile	38,672 (26.3)	551,432 (26.1)	38,655 (26.3)	192,737 (26.4)	
	3rd quartile	36,509 (24.9)	530,381 (25.1)	36,492 (24.9)	182,018 (24.9)	
	4th quartile	36,696 (25.0)	559,328 (26.4)	36,690 (25.0)	183,184 (25.1)	

	Parity, n (%)					<0.01
	1	124,459 (84.8)	1,643,964 (77.7)	124,401 (84.8)	620,036 (84.8)	
	≥ 2	22,399 (15.3)	473,234 (22.4)	22,388 (15.3)	111,079 (15.2)	
	Maternal medical conditions, n (%)					0.01
	No mental illness	113,537 (77.3)	1,789,943 (84.5)	113,532 (77.3)	567,701 (77.6)	
	Common	29,840 (20.3)	296,659 (14.0)	29,741 (20.3)	150,164 (20.5)	
	Severe	3,481 (2.4)	30,596 (1.5)	3,516 (2.4)	13,250 (1.8)	
	Severe maternal morbidity, n (%)					<0.01
	0	134,654 (91.7)	1,986,819 (93.8)	134,642 (91.7)	671,936 (91.9)	
	1	11,724 (8.0)	126,887 (6.0)	11,698 (8.0)	57,279 (7.8)	
	≥ 2	480 (0.3)	3,492 (0.2)	449 (0.3)	1,900 (0.3)	
	Number of hospital admissions in a year before pregnancy, n (%)					<0.01
	0	118,207 (80.5)	1,808,567 (85.4)	118,195 (80.5)	590,517 (80.8)	
	1	23,027 (15.7)	260,020 (12.3)	23,004 (15.7)	114,000 (15.6)	
	≥ 2	5,624 (3.8)	48,611 (2.3)	5,590 (3.8)	26,598 (3.6)	
	Number of outpatient contacts in a year before pregnancy, n (%)					<0.01
	0	3,337 (2.3)	144,636 (6.8)	3,331 (2.3)	16,590 (2.3)	
	1	3,622 (2.5)	125,198 (5.9)	3,620 (2.5)	18,054 (2.5)	

	≥ 2	139,899 (95.3)	1,847,364 (87.3)	139,838 (95.3)	696,471 (95.3)	
	Alcohol or drug misuse, n (%)	294 (0.2)	2,194 (0.1)	280 (0.2)	943 (0.1)	0.02
	Mood disorders except those with psychotic symptoms, n (%)	5,208 (3.6)	42,490 (2.0)	5,171 (3.5)	24,317 (3.3)	0.01
	Anxiety and stress-related disorders, n (%)	9,160 (6.2)	76,743 (3.6)	9,116 (6.2)	43,631 (6.0)	0.01
	Sleep disorders, n (%)	506 (0.3)	5,451 (0.3)	4,419 (3.0)	20,365 (2.8)	0.01
	Epilepsy, n (%)	384 (0.3)	3,535 (0.2)	491 (0.3)	2,019 (0.3)	0.01
	Other neuropsychiatry disorders, n (%)	4,467 (3.0)	32,980 (1.6)	379 (0.3)	1,417 (0.2)	0.01
Unmatching variables	Delivery type, n (%)					0.15
	Vaginal delivery	81,215 (55.3)	1,275,479 (60.2)	81,185 (55.3)	459,279 (62.8)	
	Cesarean section	65,643 (44.7)	841,719 (39.8)	65,604 (44.7)	271,836 (37.2)	
	Use of NSAID during pregnancy, n (%)	71,593 (48.8)	347,854 (16.4)	71,553 (48.8)	140,166 (19.2)	0.66
	Use of acetaminophen during pregnancy, n (%)	124,822 (85.0)	695,710 (32.9)	124,757 (85.0)	273,122 (37.4)	1.12
	Infant characteristics					
	Infant sex, n (%)					<0.01
	Male	75,203 (51.2)	1,087,053 (51.3)	75,166 (51.2)	375,366 (51.3)	
	Female	71,655 (48.8)	1,030,145 (48.7)	71,623 (48.8)	355,749 (48.7)	
	Birth season, n (%)					0.08
	Spring	35,866 (24.4)	545,587 (25.8)	35,851 (24.4)	186,955 (25.6)	
	Summer	39,916 (27.2)	513,192 (24.2)	39,890 (27.2)	177,840 (24.3)	

	Autumn	35,515 (24.2)	529,822 (25.0)	35,497 (24.2)	186,827 (25.6)	
	Winter	35,561 (24.2)	528,597 (25.0)	35,551 (24.2)	179,493 (24.6)	
	Year of delivery, n (%)					0.08
	2010 to 2012	69,885 (47.6)	1,119,845 (52.9)	69,862 (47.6)	378,391 (51.8)	
	2013 to 2015	76,973 (52.4)	997,353 (47.1)	76,927 (52.4)	352,724 (48.2)	
	At-risk newborn, n (%)					0.07
	Preterm birth	6,727 (4.6)	68,824 (3.3)	138,864 (94.6)	701,930 (96.0)	
	Low birth weight	4,976 (3.4)	55,422 (2.6)	7,925 (5.4)	29,185 (4.0)	

NSAID, nonsteroidal anti-inflammatory drug; PS, propensity score; SD, standard deviation; SMD, standardized mean difference

[a] PS-matched cohort B consists of infants born between 2010 and 2015, with the exposed and unexposed groups matched in a 1:5 ratio (Cohort 4 in Figure 1 and Table S8).

* SMD <0.1 corresponds to no major imbalance

Table S12. Interaction analysis of maternal health condition with opioid prescriptions and opioid prescriptions during pregnancy in PS-matched cohort A from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Maternal health condition with opioid prescriptions X Opioid prescriptions during pregnancy (p-value)					P<0.001	P<0.001	P=0.001
Maternal health condition with opioid prescriptions							
No	1,373,510 (86.4)	34,499 (3.2)	6,376,813	5.4	1 (reference)	1 (reference)	1 (reference)
Pain to related [a]	62,815 (4.0)	2,424 (3.9)	372,087	6.5	**1.21 (1.16 to 1.26)**	**1.18 (1.14 to 1.23)**	**1.16 (1.11 to 1.20)**
Antitussive-related [b]	69,200 (4.4)	2,376 (3.4)	416,509	5.7	**1.05 (1.01 to 1.10)**	1.05 (1.00 to 1.09)	1.04 (1.00 to 1.09)
Other	83,915 (5.3)	2,596 (3.1)	483,308	5.4	1.00 (0.96 to 1.04)	1.01 (0.97 to 1.05)	1.01 (0.97 to 1.05)

CI, confidence interval; PS, propensity score; SMM, severe maternal morbidity

[a] Pain-related condition includes medical conditions such as neoplasm (benign), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, endocrine, nutritional and metabolic diseases, neuropsychiatric disorders, diseases of the nervous system, diseases of the ear and mastoid process, diseases of the circulatory system, diseases of digestive system, diseases of the skin and subcutaneous tissue, diseases of musculoskeletal system and connective tissue, and diseases of the genitourinary system

[b] Antitussive-related condition includes medical conditions such as infectious and parasitic diseases and diseases of the respiratory system

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S13. Interaction analysis of opioid prescriptions in a year before pregnancy and opioid prescriptions during pregnancy

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid prescriptions in a year before pregnancy X Opioid prescriptions during pregnancy (p-value)					p=0.001	P=0.003	P=0.040
PS-matched cohort A							
Opioid prescriptions in a year before pregnancy							
No	340,154 (26.3)	1,953 (3.33)	354,785	5.5	**1.08 (1.03 to 1.13)**	1.04 (0.99 to 1.10)	1.05 (1.00 to 1.10)
Yes	951,258 (73.7)	5,451 (3.46)	917,168	5.9	**1.07 (1.03 to 1.10)**	**1.08 (1.04 to 1.11)**	**1.07 (1.04 to 1.10)**
Child screening cohort							
Opioid prescriptions in a year before pregnancy							
No	655,754 (48.1)	827 (3.3)	154,111	5.4	1.01 (0.95 to 1.09)	1.03 (0.96 to 1.11)	1.02 (0.95 to 1.10)
Yes	706,765 (51.9)	2,269 (3.3)	396,326	5.7	**1.06 (1.02 to 1.11)**	**1.09 (1.04 to 1.14)**	**1.06 (1.02 to 1.11)**

CI, confidence interval; PS, propensity score; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer,

autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S14. Interaction analysis and ratio of hazard ratio of delivery type and opioid prescriptions during pregnancy in PS-matched cohort A

	Hazard ratio (95% CI)		
	Crude	**Adjusted†**	**Fully adjusted††**
Delivery type X Opioid prescriptions during pregnancy (p-value)	P=0.002	P=0.003	P=0.009
Delivery type			
Vaginal delivery	1.03 (1.00 to 1.07)	1.04 (1.00 to 1.08)	1.04 (1.00 to 1.08)
Cesarean section	**1.09 (1.05 to 1.13)**	**1.13 (1.09 to 1.17)**	**1.12 (1.08 to 1.17)**
Ratio of hazard ratio (Cesarean section vs. Vaginal delivery)	1.06 (1.00 to 1.11)	**1.09 (1.04 to 1.14)**	**1.08 (1.03 to 1.14)**

CI, confidence interval; PS, propensity score

PS-matched cohort A, derived from the full unmatched cohort, involves a 1:5 matching ratio and pairs the exposed and unexposed groups in a 1:5 ratio using PS (Cohort 2 in Figure 1 and Table S8).

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S15. Summary of main outcome in each cohort

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Full unmatched cohort							
Opioid exposure during pregnancy							
No	2,912,559 (93.1)	98,022 (3.4)	18,203,128	5.4	1 (reference)	1 (reference)	1 (reference)
Yes	216,012 (6.9)	7,404 (3.4)	1,272,208	5.8	**1.10 (1.07 to 1.12)**	**1.12 (1.09 to 1.15)**	**1.09 (1.07 to 1.12)**
PS to matched cohort A							
Opioid exposure during pregnancy							
No	1,075,454 (83.3)	36,648 (3.4)	6,650,015	5.5	1 (reference)	1 (reference)	1 (reference)
Yes	215,958 (16.7)	7,398 (3.4)	1,271,953	5.8	**1.07 (1.04 to 1.10)**	**1.08 (1.05 to 1.11)**	**1.07 (1.05 to 1.10)**
Child screening cohort							
Opioid exposure during pregnancy							
No	1,268,815 (93.1)	42,691 (3.4)	7,888,143	5.4	1 (reference)	1 (reference)	1 (reference)
Yes	93,704 (6.9)	3,096 (3.3)	550,437	5.6	**1.06 (1.02 to 1.10)**	**1.08 (1.04 to 1.12)**	**1.05 (1.01 to 1.09)**
PS to matched cohort B (birth date of infants in 2010-2015)							
Opioid exposure during pregnancy							
No	731,115 (83.3)	31,530 (4.3)	5,393,061	5.8	1 (reference)	1 (reference)	1 (reference)

Yes	146,789 (16.7)	6,608 (4.5)	1,060,207	6.2	**1.07 (1.05 to 1.10)**	**1.08 (1.05 to 1.11)**	**1.08 (1.05 to 1.10)**
PS-matched cohort C ('outcome' criteria with above 1 diagnosis)							
Opioid exposure during pregnancy							
No	1,075,454 (83.3)	64,239 (6.0)	6,551,602	9.8	1 (reference)	1 (reference)	1 (reference)
Yes	215,958 (16.7)	12,838 (5.9)	1,253,736	10.2	**1.05 (1.03 to 1.07)**	**1.05 (1.03 to 1.07)**	**1.05 (1.03 to 1.07)**
Sibling cohort A from the full unmatched cohort							
Opioid exposure during pregnancy							
No	114,007 (52.0)	5,008 (4.4)	760,040	6.6	1 (reference)	1 (reference)	1 (reference)
Yes	105,339 (48.0)	2,754 (2.6)	566,329	4.9	**0.78 (0.73 to 0.82)**	1.00 (0.93 to 1.07)	1.00 (0.93 to 1.07)
Sibling cohort B from the PS-matched cohort							
Opioid exposure during pregnancy							
No	47,294 (50.7)	2,049 (4.3)	303,650	6.9	1 (reference)	1 (reference)	1 (reference)
Yes	46,034 (49.3)	1,391 (3.0)	255,035	5.7	**0.89 (0.82 to 0.97)**	1.04 (0.93 to 1.16)	1.03 (0.92 to 1.16)
Sibling cohort C from the child screening cohort							
Opioid exposure during pregnancy							

No	21,221 (50.6)	1,066 (5.0)	152,981	7.0	1 (reference)	1 (reference)	1 (reference)
Yes	20,699 (49.4)	585 (2.8)	121,848	4.8	**0.72 (0.63 to 0.80)**	0.95 (0.82 to 1.12)	0.95 (0.81 to 1.11)

CI, confidence interval; PS, propensity-score; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S16. Hazard ratio models of the association between prenatal opioid exposure during pregnancy and neuropsychiatric disorders in children with the 1:5 PS-matched cohort B (birth date of infants in 2010-2015)

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid exposure during pregnancy							
No	731,115 (83.3)	31,530 (4.3)	5,393,061	5.8	1 (reference)	1 (reference)	1 (reference)
Yes	146,789 (16.7)	6,608 (4.5)	1,060,207	6.2	**1.07 (1.05 to 1.10)**	**1.08 (1.05 to 1.11)**	**1.08 (1.05 to 1.10)**
Timing of opioid exposure							
No opioid exposure	731,115 (83.3)	31,530 (4.3)	5,393,061	5.8	1 (reference)	1 (reference)	1 (reference)
First trimester only	61,802 (7.0)	2,980 (4.8)	454,469	6.6	**1.13 (1.09 to 1.17)**	**1.10 (1.06 to 1.15)**	**1.10 (1.06 to 1.14)**
Second trimester only	33,552 (3.8)	1,414 (4.2)	238,224	5.9	1.03 (0.97 to 1.08)	1.04 (0.99 to 1.10)	1.04 (0.99 to 1.10)
Third trimester only	40,710 (4.6)	1,663 (4.1)	291,804	5.7	0.98 (0.93 to 1.02)	1.02 (0.97 to 1.07)	1.02 (0.97 to 1.07)
More than one trimester	10,725 (1.2)	551 (5.1)	75,710	7.3	**1.26 (1.16 to 1.37)**	**1.29 (1.19 to 1.41)**	**1.25 (1.15 to 1.36)**
Dose-dependent association, MME							
None	731,115 (83.3)	31,530 (4.3)	5,393,061	5.8	1 (reference)	1 (reference)	1 (reference)
Low-dose user	120,776 (13.8)	5,203 (4.3)	868,733	6.0	1.03 (1.00 to 1.06)	**1.04 (1.01 to 1.08)**	**1.05 (1.02 to 1.08)**
High to dose user	26,013 (3.0)	1,405 (5.4)	191,474	7.3	**1.26 (1.19 to 1.33)**	**1.23 (1.17 to 1.30)**	**1.20 (1.13 to 1.26)**
Opioid prescriptions, days							
0	731,115 (83.3)	31,530 (4.3)	5,393,061	5.8	1 (reference)	1 (reference)	1 (reference)
1-29	144,926 (16.5)	6,489 (4.5)	1,047,344	6.2	**1.07 (1.04 to 1.10)**	**1.07 (1.04 to 1.10)**	**1.07 (1.04 to 1.10)**
30-59	1,702 (0.2)	100 (5.9)	11,789	8.5	**1.47 (1.21 to 1.79)**	**1.52 (1.25 to 1.84)**	**1.42 (1.17 to 1.73)**
≥60	161 (0.0)	19 (11.8)	1,074	17.7	**3.14 (2.00 to 4.92)**	**3.12 (1.99 to 4.88)**	**2.40 (1.53 to 3.76)**

Number of opioid prescriptions							
0-1	731,115 (83.3)	31,530 (4.3)	5,393,061	5.8	1 (reference)	1 (reference)	1 (reference)
2	72,363 (8.2)	3,105 (4.3)	526,608	5.9	1.01 (0.98 to 1.05)	1.01 (0.97 to 1.05)	1.02 (0.98 to 1.05)
≥ 3	74,426 (8.5)	3,503 (4.7)	533,599	6.6	**1.13 (1.09 to 1.17)**	**1.15 (1.11 to 1.19)**	**1.13 (1.10 to 1.17)**

CI, confidence interval; MME, morphine milligram equivalent; PS, propensity-score; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S17. Hazard ratio models of the association between prenatal opioid exposure during pregnancy and neuropsychiatric disorders in children with the 1:5 PS-matched cohort C from 2010 to 2017 ('outcome' criteria with above 1 diagnosis)

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid exposure during pregnancy							
No	1,075,454 (83.3)	64,239 (6.0)	6,551,602	9.8	1 (reference)	1 (reference)	1 (reference)
Yes	215,958 (16.7)	12,838 (5.9)	1,253,736	10.2	**1.05 (1.03 to 1.07)**	**1.05 (1.03 to 1.07)**	**1.05 (1.03 to 1.07)**
Timing of opioid exposure							
No opioid exposure	1,075,454 (83.3)	64,239 (6.0)	6,551,602	9.8	1 (reference)	1 (reference)	1 (reference)
First trimester only	87,567 (6.8)	5,650 (6.5)	524,839	10.8	**1.11 (1.08 to 1.14)**	**1.08 (1.06 to 1.11)**	**1.08 (1.05 to 1.11)**
Second trimester only	50,765 (3.9)	2,898 (5.7)	286,792	10.1	1.04 (1.00 to 1.08)	**1.04 (1.01 to 1.08)**	**1.05 (1.01 to 1.08)**
Third trimester only	61,122 (4.7)	3,297 (5.4)	349,889	9.4	0.96 (0.93 to 0.99)	0.99 (0.96 to 1.03)	0.99 (0.96 to 1.03)
More than one trimester	16,504 (1.3)	993 (6.0)	92,216	10.8	**1.11 (1.04 to 1.18)**	**1.13 (1.06 to 1.20)**	**1.10 (1.03 to 1.17)**
Dose-dependent association, MME							
None	1,075,454 (83.3)	64,239 (6.0)	6,551,602	9.8	1 (reference)	1 (reference)	1 (reference)
Low-dose user	161,695 (12.5)	9,892 (6.1)	986,154	10.0	1.02 (1.00 to 1.05)	**1.03 (1.01 to 1.05)**	**1.03 (1.01 to 1.05)**
High-dose user	54,263 (4.2)	2,946 (5.4)	267,582	11.0	**1.16 (1.12 to 1.21)**	**1.14 (1.10 to 1.18)**	**1.12 (1.08 to 1.16)**
Opioid prescriptions, days							
0	1,075,454 (83.3)	64,239 (6.0)	6,551,602	9.8	1 (reference)	1 (reference)	1 (reference)
1-29	212,839 (16.5)	12,634 (5.9)	1,237,295	10.2	**1.05 (1.03 to 1.07)**	**1.05 (1.03 to 1.07)**	**1.05 (1.03 to 1.07)**
30-59	2,824 (0.2)	178 (6.3)	14,995	11.9	**1.23 (1.06 to 1.43)**	**1.26 (1.08 to 1.45)**	**1.19 (1.02 to 1.37)**
≥60	295 (0.0)	26 (8.8)	1,446	18.0	**1.91 (1.30 to 2.80)**	**1.87 (1.27 to 2.74)**	**1.51 (1.03 to 2.22)**

Number of opioid prescriptions							
0-1	1,075,454 (83.3)	64,239 (6.0)	6,551,602	9.8	1 (reference)	1 (reference)	1 (reference)
2	104,991 (8.1)	6,164 (5.9)	617,476	10.0	1.02 (1.00 to 1.05)	1.02 (0.99 to 1.04)	1.02 (1.00 to 1.05)
≥ 3	110,967 (8.6)	6,674 (6.0)	636,260	10.5	**1.08 (1.05 to 1.11)**	**1.09 (1.06 to 1.11)**	**1.08 (1.05 to 1.10)**

CI, confidence interval; MME, morphine milligram equivalent; PS, propensity-score; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S18. Hazard ratio model of the association between prenatal opioid exposure during pregnancy and specific neuropsychiatric disorders in children within the 1:5 PS-matched cohort A from 2010 to 2017

	n (%)	**Neuropsychiatric disorder events (%)**	**Crude hazard ratio (95% CI)**
Alcohol or drug misuse			
No opioid exposure	1,075,454 (83.3)	94 (0.0)	1 (reference)
Opioid exposure	215,958 (16.7)	15 (0.0)	0.80 (0.47 to 1.38)
Mood disorders, excluding those with psychotic symptoms			
No opioid exposure	1,075,454 (83.3)	2,594 (0.2)	1 (reference)
Opioid exposure	215,958 (16.7)	535 (0.3)	**1.13 (1.03 to 1.24)**
Anxiety and stress-related disorders			
No opioid exposure	1,075,454 (83.3)	4,772 (0.4)	1 (reference)
Opioid exposure	215,958 (16.7)	932 (0.4)	1.06 (0.98 to 1.13)
Eating disorders			
No opioid exposure	1,075,454 (83.3)	157 (0.0)	1 (reference)
Opioid exposure	215,958 (16.7)	21 (0.0)	0.68 (0.43 to 1.08)
Compulsive disorders			
No opioid exposure	1,075,454 (83.3)	379 (0.0)	1 (reference)
Opioid exposure	215,958 (16.7)	56 (0.0)	0.81 (0.62 to 1.08)
ADHD			
No opioid exposure	1,075,454 (83.3)	12,170 (1.1)	1 (reference)
Opioid exposure	215,958 (16.7)	2,452 (1.1)	**1.10 (1.05 to 1.15)**
ASD			

No opioid exposure	1,075,454 (83.3)	5,533 (0.5)	1 (reference)
Opioid exposure	215,958 (16.7)	1,072 (0.5)	0.99 (0.93 to 1.06)
Intellectual disability			
No opioid exposure	1,075,454 (83.3)	3,554 (0.3)	1 (reference)
Opioid exposure	215,958 (16.7)	864 (0.4)	**1.27 (1.18 to 1.37)**
Common neuropsychiatric disorder			
No opioid exposure	1,075,454 (83.3)	35,294 (3.3)	1 (reference)
Opioid exposure	215,958 (16.7)	7,080 (3.3)	**1.06 (1.04 to 1.09)**
Severe neuropsychiatric disorder			
No opioid exposure	1,075,454 (83.3)	1,354 (0.1)	1 (reference)
Opioid exposure	215,958 (16.7)	318 (0.2)	**1.26 (1.12 to 1.42)**

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; PS, propensity score

Numbers in bold indicate significant differences ($P < 0.05$)

Table S19. Hazard ratio models of the association between prenatal opioid exposure during pregnancy and neuropsychiatric disorders in children with the full unmatched cohort from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid exposure during pregnancy							
No	2,912,559 (93.1)	98,022 (3.4)	18,203,128	5.5	1 (reference)	1 (reference)	1 (reference)
Yes	216,012 (6.9)	7,404 (3.4)	1,272,208	5.8	**1.10 (1.07 to 1.12)**	**1.12 (1.09 to 1.15)**	**1.09 (1.07 to 1.12)**
Timing of opioid exposure							
No opioid exposure	2,912,559 (93.1)	98,022 (3.4)	18,203,128	5.5	1 (reference)	1 (reference)	1 (reference)
First trimester only	87,596 (2.8)	3,331 (3.8)	533,104	6.3	**1.18 (1.14 to 1.22)**	**1.16 (1.12 to 1.21)**	**1.13 (1.10 to 1.17)**
Second trimester only	50,779 (1.6)	1,600 (3.2)	291,047	5.5	1.04 (0.99 to 1.10)	**1.07 (1.02 to 1.13)**	1.05 (1.00 to 1.11)
Third trimester only	61,129 (2.0)	1,863 (3.1)	354,619	5.3	0.98 (0.94 to 1.03)	1.04 (1.00 to 1.09**)**	1.03 (0.98 to 1.08)
More than one trimester	16,508 (0.5)	610 (3.7)	93,438	6.5	**1.24 (1.15 to 1.34)**	**1.30 (1.20 to 1.40)**	**1.22 (1.13 to 1.32)**
Dose-dependent association, MME							
None	2,912,559 (93.1)	98,022 (3.4)	18,203,128	5.4	1 (reference)	1 (reference)	1 (reference)
Low-dose user	161,724 (5.2)	5,733 (3.5)	1,000,669	5.7	**1.07 (1.04 to 1.10)**	**1.16 (1.12 to 1.21)**	**1.08 (1.05 to 1.10)**
High-dose user	54,288 (1.7)	1,671 (3.1)	271,539	6.2	**1.21 (1.15 to 1.27)**	**1.07 (1.02 to 1.13)**	**1.16 (1.11 to 1.22)**
Opioid prescriptions, days							
0	2,912,559 (93.1)	98,022 (3.4)	18,203,128	5.4	1 (reference)	1 (reference)	1 (reference)
1-29	212,892 (6.8)	7,272 (3.4)	1,255,536	5.8	**1.09 (1.07 to 1.12)**	**1.11 (1.09 to 1.14)**	**1.09 (1.06 to 1.12)**
30-59	2,825 (0.1)	113 (4.0)	15,199	7.4	**1.43 (1.19 to 1.72)**	**1.50 (1.24 to 1.80)**	**1.36 (1.13 to 1.64)**
≥60	295 (0.0)	19 (6.4)	1,473	12.9	**2.59 (1.66 to 4.05)**	**2.59 (1.66 to 4.05)**	**1.92 (1.22 to 3.00)**

Number of opioid prescriptions							
0-1	2,912,559 (93.1)	98,022 (3.4)	18,203,128	5.4	1 (reference)	1 (reference)	1 (reference)
2	105,007 (3.4)	3,510 (3.3)	626,670	5.6	**1.05 (1.02 to 1.09)**	**1.07 (1.03 to 1.10)**	**1.05 (1.02 to 1.09)**
≥ 3	111,005 (3.6)	3,894 (3.5)	645,538	6.0	**1.14 (1.10 to 1.18)**	**1.17 (1.14 to 1.21)**	**1.14 (1.10 to 1.17)**

CI, confidence interval; MME, morphine milligram equivalent; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S20. Stratification analysis for hazard ratio models of the association between opioid exposure during pregnancy and neuropsychiatric disorders in children with the full unmatched cohort from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Maternal parameters							
Maternal medical conditions							
No mental illness	168,482 (6.4)	4,437 (2.6)	989,760	4.5	1.02 (0.99 to 1.05)	**1.05 (1.02 to 1.08)**	**1.05 (1.02 to 1.08)**
Mental illness	47,530 (9.8)	2,967 (6.2)	282,448	10.5	1.01 (0.98 to 1.05)	**1.05 (1.01 to 1.09)**	**1.05 (1.01 to 1.09)**
Delivery type							
Vaginal delivery	115,193 (6.4)	3,723 (3.2)	695,853	5.4	**1.08 (1.04 to 1.11)**	**1.08 (1.04 to 1.11)**	**1.06 (1.02 to 1.09)**
Cesarean section	100,819 (7.6)	3,681 (3.7)	576,355	6.4	**1.10 (1.06 to 1.14)**	**1.19 (1.15 to 1.23)**	**1.16 (1.12 to 1.20)**
Alcohol or drug misuse							
No	215,454 (6.9)	7,344 (3.4)	1,269,636	5.8	**1.09 (1.07 to 1.12)**	**1.12 (1.09 to 1.14)**	**1.09 (1.06 to 1.12)**
Yes	558 (12.5)	60 (10.8)	2,572	23.3	**2.15 (1.61 to 2.86)**	**2.06 (1.54 to 2.75)**	**2.03 (1.52 to 2.72)**
Mood disorders except those with psychotic symptoms							
No	206,313 (6.8)	6,861 (3.3)	1,224,798	5.6	**1.08 (1.05 to 1.10)**	**1.10 (1.08 to 1.13)**	**1.09 (1.06 to 1.12)**
Yes	9,699 (11.6)	543 (5.6)	47,410	11.5	**1.14 (1.04 to 1.25)**	**1.16 (1.06 to 1.27)**	**1.14 (1.05 to 1.25)**
Anxiety and stress-related disorders							
No	199,817 (6.7)	6,648 (3.3)	1,190,217	5.6	**1.07 (1.05 to 1.10)**	**1.10 (1.07 to 1.13)**	**1.09 (1.06 to 1.12)**
Yes	16,195 (11.1)	756 (4.7)	81,991	9.2	**1.12 (1.04 to 1.21)**	**1.14 (1.06 to 1.23)**	**1.11 (1.03 to 1.20)**
Sleep disorders							
No	215,128 (6.9)	7,338 (3.4)	1,267,784	5.8	**1.09 (1.07 to 1.12)**	**1.12 (1.09 to 1.14)**	**1.09 (1.07 to 1.12)**

Yes	884 (9.2)	66 (7.5)	4,424	14.9	**1.40 (1.09 to 1.81)**	**1.44 (1.11 to 1.86)**	**1.36 (1.05 to 1.76)**
Epilepsy							
No	215,198 (6.9)	7,337 (3.4)	1,268,593	5.8	**1.09 (1.07 to 1.12)**	**1.12 (1.09 to 1.14)**	**1.09 (1.07 to 1.12)**
Yes	814 (10.8)	67 (8.2)	3,615	18.5	**1.43 (1.10 to 1.84)**	**1.43 (1.10 to 1.85)**	**1.41 (1.09 to 1.83)**
Other neuropsychiatry disorders							
No	207,620 (6.8)	6,968 (3.4)	1,231,523	5.7	**1.08 (1.05 to 1.10)**	**1.10 (1.08 to 1.13)**	**1.09 (1.06 to 1.11)**
Yes	8,392 (12.4)	436 (5.2)	40,685	10.7	**1.22 (1.11 to 1.36)**	**1.22 (1.10 to 1.35)**	**1.20 (1.08 to 1.33)**
Use of NSAID during pregnancy							
No	112,100 (4.4)	3,420 (3.1)	652,079	5.2	1.02 (0.98 to 1.05)	**1.06 (1.02 to 1.10)**	**1.04 (1.01 to 1.08)**
Yes	103,912 (17.7)	3,984 (3.8)	620,129	6.4	**1.07 (1.03 to 1.10)**	**1.08 (1.05 to 1.12)**	**1.06 (1.03 to 1.10)**
Use of acetaminophen during pregnancy							
No	67,988 (3.1)	1,443 (2.1)	295,341	4.9	1.04 (0.98 to 1.09)	**1.08 (1.03 to 1.14)**	**1.06 (1.01 to 1.12)**
Yes	148,024 (15.8)	5,961 (4.0)	976,867	6.1	**1.05 (1.02 to 1.08)**	**1.07 (1.04 to 1.10)**	**1.05 (1.03 to 1.08)**
Infantal parameters							
Infant sex							
Male	110,511 (6.9)	5,144 (4.7)	647,888	7.9	**1.08 (1.05 to 1.11)**	**1.10 (1.07 to 1.14)**	**1.08 (1.05 to 1.11)**
Female	105,501 (6.9)	2,260 (2.1)	624,320	3.6	**1.14 (1.09 to 1.19)**	**1.16 (1.11 to 1.21)**	**1.13 (1.08 to 1.18)**
Birth season							
Spring	53,228 (6.6)	1,731 (3.3)	308,353	5.6	**1.12 (1.06 to 1.17)**	**1.15 (1.10 to 1.21)**	**1.12 (1.07 to 1.18)**
Summer	58,458 (7.6)	2,066 (3.5)	346,044	6.0	**1.11 (1.06 to 1.16)**	**1.13 (1.08 to 1.18)**	**1.10 (1.06 to 1.15)**
Autumn	51,697 (6.7)	1,839 (3.6)	307,273	6.0	**1.07 (1.02 to 1.12)**	**1.09 (1.04 to 1.14)**	**1.06 (1.01 to 1.11)**
Winter	52,629 (6.7)	1,768 (3.4)	310,538	5.7	**1.09 (1.04 to 1.15)**	**1.12 (1.06 to 1.17)**	**1.09 (1.04 to 1.15)**

Year of delivery							
2010-2012	69,885 (5.9)	4,318 (6.2)	605,044	7.1	**1.16 (1.12 to 1.19)**	**1.15 (1.12 to 1.19)**	**1.13 (1.10 to 1.17)**
2013-2015	76,973 (7.2)	2,303 (3.0)	455,601	5.1	**1.06 (1.02 to 1.11)**	**1.08 (1.04 to 1.13)**	**1.05 (1.01 to 1.10)**
2016-2017	69,154 (8.0)	783 (1.1)	211,563	3.7	1.02 (0.94 to 1.09)	1.07 (0.99 to 1.15)	1.03 (0.96 to 1.11)
Medical condition of infant							
None	203,225 (6.8)	6,695 (3.3)	1,202,495	5.6	**1.08 (1.05 to 1.11)**	**1.10 (1.08 to 1.13)**	**1.08 (1.05 to 1.11)**
At-risk newborn	12,787 (8.9)	709 (5.5)	69,713	10.2	**1.15 (1.06 to 1.24)**	**1.17 (1.09 to 1.27)**	**1.14 (1.05 to 1.23)**

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; MME, morphine milligram equivalent; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S21. Adjusted hazard ratio models of the dose-dependence between prenatal opioid exposure during pregnancy and specific neuropsychiatric disorders in children within the full unmatched cohort from 2010 to 2017

	Overall			**Low-dose users (<25.5 MME)**			**High-dose users (≥25.5 MME)**		
	Events, n (%)	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**	**Events, n (%)**	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**	**Events, n (%)**	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**
Alcohol or drug misuse									
No opioid exposure	242/2,912,559 (0.0)	1 (reference)	1 (reference)	242/2,912,559 (0.0)	1 (reference)	1 (reference)	242/2,912,559 (0.0)	1 (reference)	1 (reference)
Opioid exposure	15/216,012 (0.0)	0.85 (0.50 to 1.44)	0.83 (0.49 to 1.41)	14/161,724 (0.0)	1.04 (0.61 to 1.79)	1.03 (0.60 to 1.76)	1/54,288 (0.0)	0.24 (0.03 to 1.69)	0.23 (0.03 to 1.65)
Mood disorders, excluding those with psychotic symptoms									
No opioid exposure	6,526/2,912,559 (0.2)	1 (reference)	1 (reference)	6,526/2,912,559 (0.2)	1 (reference)	1 (reference)	6,526/2,912,559 (0.2)	1 (reference)	1 (reference)
Opioid exposure	535/216,012 (0.2)	**1.28 (1.18 to 1.40)**	**1.24 (1.13 to 1.35)**	418/161,724 (0.3)	**1.25 (1.13 to 1.38)**	**1.21 (1.10 to 1.34)**	117/54,288 (0.2)	**1.43 (1.19 to 1.72)**	**1.33 (1.11 to 1.60)**
Anxiety and stress-related disorders									
No opioid exposure	12,495/2,912,559 (0.4)	1 (reference)	1 (reference)	12,495/2,912,559 (0.4)	1 (reference)	1 (reference)	12,495/2,912,559 (0.4)	1 (reference)	1 (reference)

Opioid exposure	934/216,012 (0.4)	**1.13 (1.06 to 1.21)**	**1.09 (1.02 to 1.17)**	734/161,724 (0.5)	**1.12 (1.04 to 1.20)**	**1.09 (1.01 to 1.17)**	200/54,288 (0.4)	**1.22 (1.06 to 1.40)**	1.13 (0.98 to 1.30)
Eating disorders									
No opioid exposure	430/2,912,559 (0.0)	1 (reference)	1 (reference)	430/2,912,559 (0.0)	1 (reference)	1 (reference)	430/2,912,559 (0.0)	1 (reference)	1 (reference)
Opioid exposure	21/216,012 (0.0)	0.75 (0.48 to 1.16)	0.73 (0.47 to 1.13)	16/161,724 (0.0)	0.72 (0.44 to 1.18)	0.70 (0.43 to 1.16)	5/54,288 (0.0)	0.88 (0.36 to 2.13)	0.82 (0.34 to 1.99)
Compulsive disorders									
No opioid exposure	948/2,912,559 (0.0)	1 (reference)	1 (reference)	948/2,912,559 (0.0)	1 (reference)	1 (reference)	948/2,912,559 (0.0)	1 (reference)	1 (reference)
Opioid exposure	56/216,012 (0.0)	0.93 (0.71 to 1.22)	0.90 (0.69 to 1.18)	42/161,724 (0.0)	0.86 (0.63 to 1.18)	0.84 (0.62 to 1.15)	14/54,288 (0.0)	1.22 (0.72 to 2.06)	1.14 (0.67 to 1.93)
ADHD									
No opioid exposure	31,573/2,912,559 (1.1)	1 (reference)	1 (reference)	31,573/2,912,559 (1.1)	1 (reference)	1 (reference)	31,573/2,912,559 (1.1)	1 (reference)	1 (reference)
Opioid exposure	2,455/216,012 (1.1)	**1.20 (1.15 to 1.25)**	**1.17 (1.12 to 1.22)**	1,954/161,724 (1.2)	**1.19 (1.14 to 1.24)**	**1.16 (1.11 to 1.22)**	501/54,288 (0.9)	**1.27 (1.16 to 1.38)**	**1.20 (1.09 to 1.31)**
ASD									
No opioid exposure	15,329/2,912,559 (0.5)	1 (reference)	1 (reference)	15,329/2,912,559 (0.5)	1 (reference)	1 (reference)	15,329/2,912,559 (0.5)	1 (reference)	1 (reference)
Opioid exposure	1,073/216,012 (0.5)	1.02 (0.96 to 1.08)	1.00 (0.94 to 1.06)	818/161,724 (0.5)	0.99 (0.92 to 1.06)	0.98 (0.91 to 1.05)	255/54,288 (0.5)	1.12 (0.99 to 1.27)	1.09 (0.96 to 1.23)
Intellectual disability									

No opioid exposure	9,514/2,912,559 (0.3)	1 (reference)	1 (reference)	9,514/2,912,559 (0.3)	1 (reference)	1 (reference)	9,514/2,912,559 (0.3)	1 (reference)	1 (reference)
Opioid exposure	865/216,012 (0.4)	**1.35 (1.26 to 1.45)**	**1.32 (1.23 to 1.42)**	651/161,724 (0.4)	**1.27 (1.18 to 1.38)**	**1.25 (1.16 to 1.36)**	214/54,288 (0.4)	**1.68 (1.47 to 1.93)**	**1.61 (1.40 to 1.84)**
Common neuropsychiatric disorder									
No opioid exposure	94,544/2,909,081 (3.2)	1 (reference)	1 (reference)	94,544/2,909,081 (3.2)	1 (reference)	1 (reference)	94,544/2,909,081 (3.2)	1 (reference)	1 (reference)
Opioid exposure	7,085/215,693 (3.3)	**1.11 (1.08 to 1.14)**	**1.09 (1.06 to 1.11)**	5,479/161,470 (3.4)	**1.08 (1.05 to 1.11)**	**1.07 (1.04 to 1.10)**	1,606/54,223 (3.0)	**1.22 (1.16 to 1.28)**	**1.16 (1.10 to 1.22)**
Severe neuropsychiatric disorder									
No opioid exposure	3,478/2,818,015 (0.1)	1 (reference)	1 (reference)	3,478/2,818,015 (0.0012)	1 (reference)	1 (reference)	3,478/2,818,015 (0.1)	1 (reference)	1 (reference)
Opioid exposure	319/208,927 (0.2)	**1.40 (1.25 to 1.57)**	**1.35 (1.21 to 1.52)**	254/156,245 (0.0016)	**1.39 (1.22 to 1.58)**	**1.35 (1.19 to 1.54)**	65/52,682 (0.1)	**1.46 (1.14 to 1.87)**	**1.37 (1.07 to 1.75)**

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio; MME, morphine milligram equivalents; SMM, severe maternal morbidity

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer,

autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S22. Hazard ratio model of the association between prenatal opioid exposure during pregnancy and specific neuropsychiatric disorders in children within the full unmatched cohort from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Crude hazard ratio (95% CI)
Alcohol or drug misuse			
No opioid exposure	2,912,559 (93.1)	242 (0.0)	1 (reference)
Opioid exposure	216,012 (6.9)	15 (0.0)	0.85 (0.50 to 1.43)
Mood disorders, excluding those with psychotic symptoms			
No opioid exposure	2,912,559 (93.1)	6,526 (0.2)	1 (reference)
Opioid exposure	216,012 (6.9)	535 (0.2)	**1.25 (1.14 to 1.36)**
Anxiety and stress-related disorders			
No opioid exposure	2,912,559 (93.1)	12,495 (0.4)	1 (reference)
Opioid exposure	216,012 (6.9)	934 (0.4)	**1.11 (1.04 to 1.19)**
Eating disorders			
No opioid exposure	2,912,559 (93.1)	430 (0.0)	1 (reference)
Opioid exposure	216,012 (6.9)	21 (0.0)	0.68 (0.44 to 1.05)
Compulsive disorders			
No opioid exposure	2,912,559 (93.1)	948 (0.0)	1 (reference)
Opioid exposure	216,012 (6.9)	56 (0.0)	0.91 (0.69 to 1.19)
ADHD			
No opioid exposure	2,912,559 (93.1)	31,573 (1.1)	1 (reference)
Opioid exposure	216,012 (6.9)	2,455 (1.1)	**1.17 (1.13 to 1.22)**
ASD			
No opioid exposure	2,912,559 (93.1)	15,329 (0.5)	1 (reference)

Opioid exposure	216,012 (6.9)	1,073 (0.5)	0.97 (0.91 to 1.03)
Intellectual disability			
No opioid exposure	2,912,559 (93.1)	9,514 (0.3)	1 (reference)
Opioid exposure	216,012 (6.9)	865 (0.4)	**1.29 (1.21 to 1.39)**
Common neuropsychiatric disorder			
No opioid exposure	2,912,559 (93.1)	94,544 (3.2)	1 (reference)
Opioid exposure	216,012 (6.9)	7,085 (3.3)	**1.09 (1.06 to 1.12)**
Severe neuropsychiatric disorder			
No opioid exposure	2,912,559 (93.1)	3,478 (0.1)	1 (reference)
Opioid exposure	216,012 (6.9)	319 (0.2)	**1.35 (1.21 to 1.52)**

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval

Numbers in bold indicate significant differences ($P < 0.05$)

Table S23. Hazard ratio models of the association between prenatal opioid exposure during pregnancy and neuropsychiatric disorders in children with the child screening cohort from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid exposure during pregnancy							
No	1,268,815 (93.1)	42,691 (3.4)	7,888,143	5.4	1 (reference)	1 (reference)	1 (reference)
Yes	93,704 (6.9)	3,096 (3.3)	550,437	5.6	**1.06 (1.02 to 1.10)**	**1.08 (1.04 to 1.12)**	**1.05 (1.01 to 1.09)**
Timing of opioid exposure							
No opioid exposure	1,268,815 (93.1)	42,691 (3.4)	7,888,143	5.4	1 (reference)	1 (reference)	1 (reference)
First trimester only	38,456 (2.8)	1,378 (3.6)	229,509	6.0	**1.13 (1.07 to 1.19)**	**1.12 (1.06 to 1.18)**	**1.09 (1.03 to 1.15)**
Second trimester only	22,141 (1.6)	685 (3.1)	128,347	5.3	1.00 (0.93 to 1.08)	1.02 (0.95 to 1.10)	1.01 (0.93 to 1.09)
Third trimester only	26,058 (1.9)	783 (3.0)	152,491	5.1	0.95 (0.89 to 1.02)	1.01 (0.94 to 1.09)	1.00 (0.93 to 1.07)
More than one trimester	7,049 (0.5)	250 (3.6)	40,090	6.2	**1.18 (1.04 to 1.33)**	**1.23 (1.08 to 1.39)**	**1.16 (1.03 to 1.32)**
Dose-dependent association, MME							
None	1,268,815 (93.1)	42,691 (3.4)	7,888,143	5.4	1 (reference)	1 (reference)	1 (reference)
Low-dose user	69,123 (5.1)	2,446 (3.5)	436,461	5.6	1.03 (0.99 to 1.08)	**1.05 (1.01 to 1.10)**	1.04 (0.99 to 1.08)
High-dose user	24,581 (1.8)	650 (2.6)	113,976	5.7	**1.15 (1.06 to 1.24)**	**1.17 (1.08 to 1.26)**	**1.12 (1.03 to 1.21)**
Opioid prescriptions, days							
0	1,268,815 (93.1)	42,691 (3.5)	7,888,143	5.4	1 (reference)	1 (reference)	1 (reference)
1-29	92,447 (6.8)	3,049 (3.3)	543,644	5.6	**1.05 (1.02 to 1.09)**	**1.07 (1.03 to 1.11)**	**1.05 (1.01 to 1.09)**
30-59	1,145 (0.1)	41 (3.6)	6,229	6.6	1.26 (0.93 to 1.71)	1.32 (0.97 to 1.79)	1.19 (0.88 to 1.62)
≥60	112 (0.0)	6 (5.4)	564	10.6	2.11 (0.95 to 4.69)	2.12 (0.95 to 4.72)	1.69 (0.76 to 3.76)
Number of opioid prescriptions							

0-1	1,268,815 (93.1)	42,691 (3.4)	7,888,143	5.4	1 (reference)	1 (reference)	1 (reference)
2	45,821 (3.4)	1,460 (3.2)	272,449	5.5	1.00 (0.95 to 1.06)	1.01 (0.96 to 1.07)	1.00 (0.95 to 1.05)
≥ 3	47,883 (3.5)	1,636 (3.4)	277,988	5.9	**1.11 (1.05 to 1.16)**	**1.14 (1.08 to 1.20)**	**1.10 (1.05 to 1.16)**

CI, confidence interval; MME, morphine milligram equivalent; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S24. Stratification analysis for hazard ratio models of the association between opioid exposure during pregnancy and neuropsychiatric disorders in children with the child screening cohort from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Maternal parameters							
Maternal medical conditions							
No mental illness	73,757 (6.4)	1,893 (2.6)	432,479	4.4	0.99 (0.95 to 1.04)	1.02 (0.97 to 1.07)	1.02 (0.97 to 1.07)
Mental illness	19,947 (9.6)	1,203 (6.0)	117,958	10.2	0.96 (0.90 to 1.02)	0.99 (0.93 to 1.05)	0.99 (0.93 to 1.05)
Delivery type							
Vaginal delivery	50,272 (6.4)	1,595 (3.2)	305,211	5.2	1.04 (0.99 to 1.09)	1.03 (0.98 to 1.09)	1.02 (0.96 to 1.07)
Cesarean section	43,432 (7.6)	1,501 (3.5)	245,226	6.1	**1.06 (1.01 to 1.12)**	**1.15 (1.09 to 1.21)**	**1.12 (1.06 to 1.18)**
Alcohol or drug misuse							
No	93,489 (6.9)	3,077 (3.3)	549,461	5.6	**1.05 (1.02 to 1.09)**	**1.07 (1.03 to 1.11)**	**1.05 (1.01 to 1.09)**
Yes	215 (12.2)	19 (8.8)	976	19.5	**2.02 (1.23 to 3.34)**	**1.97 (1.19 to 3.28)**	**2.01 (1.21 to 3.35)**
Mood disorders except those with psychotic symptoms							
No	89,720 (6.8)	2,884 (3.2)	531,154	5.4	1.04 (1.00 to 1.08)	**1.06 (1.02 to 1.10)**	**1.05 (1.01 to 1.09)**
Yes	3,984 (11.1)	212 (5.3)	19,283	11.0	1.07 (0.92 to 1.23)	1.11 (0.96 to 1.28)	1.10 (0.95 to 1.27)
Anxiety and stress-related disorders							
No	86,819 (6.7)	2,800 (3.2)	515,652	5.4	1.04 (1.00 to 1.08)	**1.06 (1.02 to 1.11)**	**1.05 (1.01 to 1.09)**
Yes	6,885 (10.7)	296 (4.3)	34,785	8.5	1.02 (0.91 to 1.16)	1.04 (0.92 to 1.18)	1.03 (0.91 to 1.16)
Sleep disorders							
No	93,397 (6.9)	3,075 (3.3)	549,154	5.6	**1.06 (1.02 to 1.09)**	**1.07 (1.03 to 1.11)**	**1.05 (1.01 to 1.09)**

Yes	307 (9.7)	21 (6.8)	1,283	16.4	1.35 (0.86 to 2.12)	1.30 (0.82 to 2.07)	1.29 (0.81 to 2.05)
Epilepsy							
No	90,162 (6.8)	2,917 (3.2)	533,415	5.5	1.04 (1.00 to 1.08)	**1.06 (1.02 to 1.10)**	**1.05 (1.01 to 1.09)**
Yes	3,542 (12.2)	179 (5.1)	17,022	10.5	1.14 (0.97 to 1.33)	1.15 (0.98 to 1.34)	1.14 (0.98 to 1.34)
Other neuropsychiatry disorders							
No	93,326 (6.9)	3,070 (3.3)	548,603	5.6	**1.05 (1.02 to 1.09)**	**1.07 (1.03 to 1.11)**	**1.05 (1.01 to 1.09)**
Yes	378 (9.2)	26 (6.9)	1,834	14.2	1.39 (0.93 to 2.09)	1.44 (0.95 to 2.18)	1.35 (0.89 to 2.05)
Use of NSAID during pregnancy							
No	49,011 (4.4)	1,500 (3.1)	287,307	5.2	1.00 (0.95 to 1.05)	1.04 (0.98 to 1.09)	1.02 (0.97 to 1.08)
Yes	44,693 (17.6)	1,596 (3.6)	263,130	6.1	1.02 (0.97 to 1.08)	1.04 (0.98 to 1.09)	1.02 (0.96 to 1.07)
Use of acetaminophen during pregnancy							
No	29,616 (3.1)	537 (1.8)	118,857	4.5	0.99 (0.91 to 1.08)	1.03 (0.94 to 1.12)	1.01 (0.93 to 1.10)
Yes	64,088 (15.8)	2,559 (4.0)	431,580	5.9	1.00 (0.96 to 1.05)	1.03 (0.98 to 1.07)	1.01 (0.97 to 1.06)
Infantal parameters							
Infant sex	48,107 (6.9)	2,149 (4.5)	281,305	7.6	1.03 (0.99 to 1.08)	1.05 (1.00 to 1.10)	1.03 (0.98 to 1.07)
Male	45,597 (6.9)	947 (2.1)	269,132	3.5	**1.12 (1.05 to 1.20)**	**1.14 (1.07 to 1.22)**	**1.11 (1.04 to 1.18)**
Female							
Birth season	19,679 (6.3)	653 (3.3)	120,467	5.4	1.05 (0.97 to 1.14)	1.09 (1.00 to 1.18)	1.06 (0.98 to 1.15)
Spring	25,338 (7.6)	843 (3.3)	146,686	5.8	1.06 (0.99 to 1.14)	**1.09 (1.02 to 1.17)**	1.07 (0.99 to 1.15)
Summer	26,062 (6.9)	846 (3.3)	148,570	5.7	1.03 (0.96 to 1.11)	1.05 (0.98 to 1.12)	1.02 (0.95 to 1.10)
Autumn	22,625 (6.6)	754 (3.3)	134,714	5.6	1.07 (0.99 to 1.15)	**1.08 (1.01 to 1.17)**	1.06 (0.99 to 1.14)
Winter							

Year of delivery	29,185 (5.9)	1,670 (5.7)	244,091	6.8	**1.10 (1.05 to 1.15)**	**1.10 (1.04 to 1.15)**	**1.08 (1.02 to 1.13)**
2010-2012	38,726 (7.1)	1,285 (3.3)	246,139	5.2	1.06 (1.00 to 1.12)	**1.08 (1.02 to 1.14)**	1.05 (0.99 to 1.11)
2013-2015	25,793 (8.0)	141 (0.6)	60,207	2.3	0.83 (0.70 to 0.98)	0.87 (0.73 to 1.03)	0.84 (0.71 to 1.00)
2016-2017	48,107 (6.9)	2,149 (4.5)	281,305	7.6	1.03 (0.99 to 1.08)	1.05 (1.00 to 1.10)	1.03 (0.98 to 1.07)
Medical condition of infant							
None	88,927 (6.8)	2,879 (3.2)	524,939	5.5	**1.05 (1.01 to 1.09)**	**1.07 (1.03 to 1.11)**	**1.05 (1.01 to 1.09)**
At-risk newborn	4,777 (8.9)	217 (4.5)	25,498	8.5	1.06 (0.92 to 1.22)	1.09 (0.95 to 1.25)	1.05 (0.91 to 1.21)
Breastfeeding							
No	47,267 (7.5)	1,567 (3.3)	252,732	6.2	1.05 (0.99 to 1.10)	**1.07 (1.02 to 1.13)**	1.04 (0.99 to 1.10)
Yes	46,437 (6.3)	1,529 (3.3)	297,705	5.1	1.05 (0.99 to 1.10)	**1.07 (1.01 to 1.12)**	1.05 (0.99 to 1.10)

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; MME, morphine milligram equivalent; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S25. Adjusted hazard ratio models of the dose-dependence between prenatal opioid exposure during pregnancy and specific neuropsychiatric disorders in children within the child screening cohort from 2010 to 2017

	Overall			**Low-dose users (<25.5 MME)**			**High-dose users (≥25.5 MME)**		
	Events, n (%)	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**	**Events, n (%)**	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**	**Events, n (%)**	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**
Alcohol or drug misuse									
No opioid exposure	111/1,268,815 (0.0)	1 (reference)	1 (reference)	111/1,268,815 (0.0)	1 (reference)	1 (reference)	111/1,268,815 (0.0)	1 (reference)	1 (reference)
Opioid exposure	4/93,704 (0.0)	0.51 (0.19 to 1.37)	0.50 (0.18 to 1.35)	4/69,123 (0.0)	0.67 (0.25 to 1.82)	0.66 (0.24 to 1.79)	0/24,581 (0.0)	NA	NA
Mood disorders, excluding those with psychotic symptoms									
No opioid exposure	2,867/1,268,815 (0.2)	1 (reference)	1 (reference)	2,867/1,268,815 (0.2)	1 (reference)	1 (reference)	2,867/1,268,815 (0.2)	1 (reference)	1 (reference)
Opioid exposure	243/93,704 (0.3)	**1.32 (1.16 to 1.51)**	**1.27 (1.12 to 1.45)**	185/69,123 (0.3)	**1.23 (1.06 to 1.42)**	**1.19 (1.03 to 1.39)**	58/24,581 (0.2)	**1.74 (1.34 to 2.26)**	**1.62 (1.25 to 2.11)**
Anxiety and stress-related disorders									
No opioid exposure	5,437/1,268,815 (0.4)	1 (reference)	1 (reference)	5,437/1,268,815 (0.4)	1 (reference)	1 (reference)	5,437/1,268,815 (0.4)	1 (reference)	1 (reference)
Opioid exposure	428/93,704 (0.5)	**1.20 (1.08 to 1.32)**	**1.16 (1.05 to 1.28)**	348/69,123 (0.5)	**1.19 (1.07 to 1.33)**	**1.17 (1.05 to 1.30)**	80/24,581 (0.3)	1.21 (0.97 to 1.51)	1.14 (0.91 to 1.42)
Eating disorders									
No opioid exposure	178/1,268,815 (0.0)	1 (reference)	1 (reference)	178/1,268,815 (0.0)	1 (reference)	1 (reference)	178/1,268,815 (0.0)	1 (reference)	1 (reference)
Opioid exposure	6/93,704 (0.0)	0.51 (0.23 to 1.15)	0.50 (0.22 to 1.12)	4/69,123 (0.0)	0.42 (0.16 to 1.13)	0.41 (0.15 to 1.11)	2/24,581 (0.0)	0.90 (0.22 to 3.63)	0.85 (0.21 to 3.43)

Compulsive disorders									
No opioid exposure	441/1,268,815 (0.0)	1 (reference)	1 (reference)	441/1,268,815 (0.0)	1 (reference)	1 (reference)	441/1,268,815 (0.0)	1 (reference)	1 (reference)
Opioid exposure	29/93,704 (0.0)	1.04 (0.71 to 1.52)	1.00 (0.68 to 1.45)	24/69,123 (0.0)	1.05 (0.69 to 1.58)	1.01 (0.67 to 1.53)	5/24,581 (0.0)	1.01 (0.42 to 2.44)	0.93 (0.39 to 2.26)
ADHD									
No opioid exposure	14,629/1,268,815 (1.2)	1 (reference)	1 (reference)	14,629/1,268,815 (1.2)	1 (reference)	1 (reference)	14,629/1,268,815 (1.2)	1 (reference)	1 (reference)
Opioid exposure	1,115/93,704 (1.2)	**1.16 (1.10 to 1.24)**	**1.13 (1.07 to 1.21)**	904/69,123 (1.3)	**1.15 (1.07 to 1.23)**	**1.13 (1.05 to 1.20)**	211/24,581 (0.9)	**1.24 (1.08 to 1.42)**	**1.17 (1.02 to 1.34)**
ASD									
No opioid exposure	6,328/1,268,815 (0.5)	1 (reference)	1 (reference)	6,328/1,268,815 (0.5)	1 (reference)	1 (reference)	6,328/1,268,815 (0.5)	1 (reference)	1 (reference)
Opioid exposure	414/93,704 (0.4)	0.96 (0.87 to 1.06)	0.95 (0.86 to 1.04)	324/69,123 (0.5)	0.94 (0.84 to 1.05)	0.93 (0.83 to 1.04)	90/24,581 (0.4)	1.04 (0.85 to 1.29)	1.01 (0.82 to 1.25)
Intellectual disability									
No opioid exposure	3,778/1,268,815 (0.3)	1 (reference)	1 (reference)	3,778/1,268,815 (0.3)	1 (reference)	1 (reference)	3,778/1,268,815 (0.3)	1 (reference)	1 (reference)
Opioid exposure	334/93,704 (0.4)	**1.31 (1.17 to 1.47)**	**1.29 (1.15 to 1.44)**	251/69,123 (0.4)	**1.20 (1.06 to 1.37)**	**1.19 (1.05 to 1.35)**	83/24,581 (0.3)	**1.80 (1.45 to 2.24)**	**1.74 (1.40 to 2.16)**
Common neuropsychiatric disorder									
No opioid exposure	41,204/1,267,328 (3.3)	1 (reference)	1 (reference)	41,204/1,267,328 (3.3)	1 (reference)	1 (reference)	41,204/1,267,328 (3.3)	1 (reference)	1 (reference)
Opioid exposure	2,976/93,584 (3.2)	**1.07 (1.03 to 1.11)**	**1.05 (1.01 to 1.09)**	2,354/69,031 (3.4)	**1.05 (1.01 to 1.10)**	1.03 (0.99 to 1.08)	622/24,553 (2.5)	**1.16 (1.07 to 1.25)**	**1.10 (1.02 to 1.20)**
Severe neuropsychiatric disorder									
No opioid exposure	1,487/1,227,611 (0.1)	1 (reference)	1 (reference)	1,487/1,227,611 (0.1)	1 (reference)	1 (reference)	1,487/1,227,611 (0.1)	1 (reference)	1 (reference)

Opioid exposure	120/90,728 (0.1)	**1.21 (1.01 to 1.46)**	1.18 (0.98 to 1.42)	92/66,769 (0.1)	1.13 (0.92)	1.11 (0.90 to 1.37)	28/23,959 (0.1)	**1.58 (1.09 to 2.30)**	**1.49 (1.02 to 2.16)**

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio; MME, morphine milligram equivalents; SMM, severe maternal morbidity

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Table S26. Hazard ratio model of the association between prenatal opioid exposure during pregnancy and specific neuropsychiatric disorders in children within the child screening cohort from 2010 to 2017

	n (%)	**Neuropsychiatric disorder events (%)**	**Crude hazard ratio (95% CI)**
Alcohol or drug misuse			
No opioid exposure	1,268,815 (93.1)	111 (0.0)	1 (reference)
Opioid exposure	93,704 (6.9)	4 (0.0)	0.49 (0.18 to 1.34)
Mood disorders, excluding those with psychotic symptoms			
No opioid exposure	1,268,815 (93.1)	2,867 (0.2)	1 (reference)
Opioid exposure	93,704 (6.9)	243 (0.3)	**1.28 (1.12 to 1.46)**
Anxiety and stress-related disorders			
No opioid exposure	1,268,815 (93.1)	5,437 (0.4)	1 (reference)
Opioid exposure	93,704 (6.9)	428 (0.5)	**1.17 (1.06 to 1.29)**
Eating disorders			
No opioid exposure	1,268,815 (93.1)	178 (0.0)	1 (reference)
Opioid exposure	93,704 (6.9)	06 (0.0)	0.47 (0.21 to 1.06)
Compulsive disorders			
No opioid exposure	1,268,815 (93.1)	441 (0.0)	1 (reference)
Opioid exposure	93,704 (6.9)	29 (0.0)	1.01 (0.70 to 1.47)
ADHD			
No opioid exposure	1,268,815 (93.1)	14,629 (1.2)	1 (reference)
Opioid exposure	93,704 (6.9)	1,115 (1.2)	**1.14 (1.07 to 1.21)**
ASD			
No opioid exposure	1,268,815 (93.1)	6,328 (0.5)	1 (reference)

Opioid exposure	93,704 (6.9)	414 (0.4)	0.92 (0.83 to 1.01)
Intellectual disability			
No opioid exposure	1,268,815 (93.1)	3,778 (0.3)	1 (reference)
Opioid exposure	93,704 (6.9)	334 (0.4)	**1.26 (1.13 to 1.41)**
Common neuropsychiatric disorder			
No opioid exposure	1,268,815 (93.1)	41,204 (3.3)	1 (reference)
Opioid exposure	93,704 (6.9)	2,976 (3.2)	**1.05 (1.01 to 1.09)**
Severe neuropsychiatric disorder			
No opioid exposure	1,268,815 (93.1)	1,487 (0.1)	1 (reference)
Opioid exposure	93,704 (6.9)	120 (0.1)	1.18 (0.98 to 1.42)

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

Numbers in bold indicate significant differences ($P < 0.05$)

Table S27. Results of a systematic rapid review reporting trend of prenatal opioid exposure in the study periods (published, 2020-2023)

Author, year	Country	Samples	Subject	Data source	Results	References
Odsbu et al., 2023	Denmark, Norway, and Sweden	14,764	Infants and paired mothers	Nationwide claims cohort	There are no association between prenatal exposure to opioids and risk of childhood asthma (Norway/Sweden: aHR, 1.07 [95% CI, 0.60-1.92]; Denmark: aHR, 1.25 [95% CI, 0.87-1.81]).	Odsbu I, Handal M, Hjellvik V, Hernandez-Diaz S, Kieler H, Nørgaard M, Skurtveit S, Esen BÖ, Mahic M. Prenatal opioid exposure and risk of asthma in childhood: a population-based study from Denmark, Norway, and Sweden. Front Pharmacol. 2023 May 4;14:1056192. doi: 10.3389/fphar.2023.1056192. PMID: 37214456; PMCID: PMC10192698.
Grossarth et al., 2023	United States	390,075	Infants and paired mothers (mean age, 24.5 years)	Tennessee Medicaid claims cohort	Maternal excessive opioid use had an increased postneonatal infant mortality (aHR, 1.54 [95% CI, 1.07-2.21]).	Grossarth S, Osmundson SS, Wiese AD, Phillips SE, Pham A, Leech AA, Patrick SW, Spieker AJ, Grijalva CG, Adgent MA. Maternal Opioid Use Disorder and the Risk of Postneonatal Infant Mortality. JAMA Pediatr. 2023 Jul 1;177(7):675-683. doi: 10.1001/jamapediatrics.2023.1047. PMID: 37155175; PMCID: PMC10167598.

Bierce et al., 2023	United States	85	Infants and paired mothers	Electronic medical record	Prenatal opioid exposure was not significantly related to any developmental outcomes.	Bierce L, Tabachnick AR, Eiden RD, Dozier M, Labella MH. A 12-month follow-up of infant neurodevelopmental outcomes of prenatal opioid exposure and polysubstance use. Neurotoxicol Teratol. 2023 May-Jun;97:107176. doi: 10.1016/j.ntt.2023.107176. Epub 2023 Apr 11. PMID: 37054901; PMCID: PMC10198960.
Zipursky et al., 2023	Ontario, Canada	865,691	Infants and paired mothers	Population based cohort	There are no association between maternal opioid use and adverse outcomes in infant (aHR, 0.98 [95% CI, 0.93-1.03]).	Zipursky JS, Gomes T, Everett K, Calzavara A, Paterson JM, Austin PC, Mamdani MM, Ray JG, Juurlink DN. Maternal opioid treatment after delivery and risk of adverse infant outcomes: population based cohort study. BMJ. 2023 Mar 15;380:e074005. doi: 10.1136/bmj-2022-074005. PMID: 36921977; PMCID: PMC10015218.
Yen et al., 2023	United States	54	Opioid-exposed and non-exposed	Electronic medical record	Prenatal opioid exposure induced white matter injury and altered reward signaling through a	Yen E, Madan N, Tarui T, Kaneko-Tarui T, Breeze JL, Davis JM, Maron JL. Sex-specific inflammatory and white matter effects of

			infants		proinflammatory process.	prenatal opioid exposure: a pilot study. Pediatr Res. 2023 Feb;93(3):604-611. doi: 10.1038/s41390-022-02357-5. Epub 2022 Oct 24. PMID: 36280708; PMCID: PMC9998341.
Vishnubhotla et al., 2022	United States	29	Opioid-exposed and non-exposed infants	Electronic medical record	Prenatal opioid exposure induced significant differences in fiber count in two structural connections in brain.	Vishnubhotla RV, Zhao Y, Wen Q, Dietrich J, Sokol GM, Sadhasivam S, Radhakrishnan R. Brain structural connectome in neonates with prenatal opioid exposure. Front Neurosci. 2022 Sep 16;16:952322. doi: 10.3389/fnins.2022.952322. PMID: 36188457; PMCID: PMC9523134.
Borrelli et al., 2022	United States	39	19 opioid-exposed and 20 unexposed control full-term pregnancies	Electronic medical record	Prenatal opioid use resulted in placental dysfunction, leading to abnormal fetal brain development	Borrelli KN, Wachman EM, Beierle JA, Taglauer ES, Jain M, Bryant CD, Zhang H. Effect of Prenatal Opioid Exposure on the Human Placental Methylome. Biomedicines. 2022 May 17;10(5):1150. doi: 10.3390/biomedicines10051150. PMID: 35625888; PMCID: PMC9138340.
Radhakrishnan et	United	39	Opioid-	Electronic	Prenatal opioid exposure was	Radhakrishnan R, Vishnubhotla RV, Guckien

al., 2022	States		exposed and non-exposed infants	medical record	associated with thalamocortical functional connectivity in infants.	Z, Zhao Y, Sokol GM, Haas DM, Sadhasivam S. Thalamocortical functional connectivity in infants with prenatal opioid exposure correlates with severity of neonatal opioid withdrawal syndrome. Neuroradiology. 2022 Aug;64(8):1649-1659. doi: 10.1007/s00234-022-02939-4. Epub 2022 Apr 12. PMID: 35410397.
Wen et al., 2021	United States	24,910	Infants and paired mothers	Medicare advantage health insurance claims data	There are no association between maternal opioid use and risk of neurodevelopmental disorders in the child (aHR, 1.10 [95% CI, 0.92-1.32]).	Wen X, Lawal OD, Belviso N, Matson KL, Wang S, Quilliam BJ, Meador KJ. Association Between Prenatal Opioid Exposure and Neurodevelopmental Outcomes in Early Childhood: A Retrospective Cohort Study. Drug Saf. 2021 Aug;44(8):863-875. doi: 10.1007/s40264-021-01080-0. Epub 2021 Jun 7. PMID: 34100263; PMCID: PMC8830246.
Bateman et al., 2021	United States	1,602,580	Infants and paired mothers	Population based cohort	There are no association prescription opioid used in early pregnancy and risk of congenital	Bateman BT, Hernandez-Diaz S, Straub L, Zhu Y, Gray KJ, Desai RJ, Mogun H, Gautam N, Huybrechts KF. Association of first trimester

					malformations in the offspring.	prescription opioid use with congenital malformations in the offspring: population based cohort study. BMJ. 2021 Feb 10;372:n102. doi: 10.1136/bmj.n102. PMID: 33568363; PMCID: PMC7873721.

aHR, adjusted hazard ratio; CI, confidence intervals

Supplementary Material

The supplementary data 1-11 presented in this supplementary section are results from before the round 3 revision. Following the reviewer's comments, we revised the matching covariates as shown in the table below, and the methodology and results of the original version are attached.

PS-matching covariates (original version)	PS-matching covariates (revised version)
maternal age at delivery, infant sex, region of residence, household income level, birth season, year of delivery, parity, delivery type, preterm birth, low birth weight, maternal mental illness, SMM score, and hospital admission and outpatient visit in the year before pregnancy	maternal age at delivery, region of residence, household income level, parity, maternal mental illness, SMM score, hospital admission and outpatient visit in the year before pregnancy and history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders

Supplementary Methods for Supplementary Data

Propensity score-matched cohort

To mitigate potential confounding and to achieve a demographic covariate balance between the opioid-exposed and unexposed groups, we created a PS-matched cohort informed by opioid exposure. PS was derived using an univariate logistic regression model, incorporating variables such as maternal age at delivery, infant sex, region of residence, household income level, birth season, year of delivery, parity, delivery type, preterm birth, low birth weight, maternal mental illness, SMM score, and hospital admission and outpatient visit in the year before pregnancy. Individuals were matched in 1:5 ratio matching between the opioid-exposed (matched n=254,131) and unexposed groups (matched n=1,174,429) within the entire cohort. Using the “greedy nearest-neighbor” algorithm, we randomly matched the two

groups based on PS values within the specified caliper (0.001), ensuring minimal differences. The appropriateness of PS-matched was evaluated using standardized mean differences (SMDs). We considered no substantial imbalance between the two groups when the SMD was less than 0.1 (Figure S6 and S7).

Supplement data 1. Baseline characteristics of study subjects from 2010-2017

	Full unmatched cohort (n=3,128,571)[a]		PS-matched cohort A (n=1,289,440)[b]		SMD*
	Children with prenatal opioid exposure	Children without prenatal exposure	Children with prenatal opioid exposure	Children without prenatal exposure	
Total, n	216,012	2,912,559	215,930	1,073,510	
Maternal characteristics					
Maternal age at delivery year, mean (SD)	32.3 (4.2)	31.9 (4.2)	32.3 (4.2)	32.3 (4.1)	<0.01
Maternal age at delivery year, n (%)					<0.01
≤ 19	545 (0.3)	7,330 (0.3)	544 (0.3)	2,337 (0.2)	
20-24	7,992 (3.7)	128,697 (4.4)	7,990 (3.7)	38,521 (3.6)	
25-29	41,094 (19.0)	633,948 (21.8)	41,083 (19.0)	203,502 (19.0)	
30-34	102,874 (47.6)	1,393,988 (47.9)	102,849 (47.6)	512,798 (47.8)	
≥ 35	63,507 (29.4)	748,596 (25.7)	63,464 (29.4)	316,352 (29.5)	
Region of residence, n (%)					<0.01
Rural	90,163 (41.7)	1,262,028 (43.3)	90,135 (41.7)	448,142 (41.8)	
Urban	125,849 (58.3)	1,650,531 (56.7)	125,795 (58.3)	625,368 (58.3)	
Income level, n (%)					<0.01
1st quartile	50,684 (23.5)	649,207 (22.3)	50,639 (23.5)	250,953 (23.4)	
2nd quartile	55,788 (25.8)	750,159 (25.8)	55,769 (25.8)	276,620 (25.8)	
3rd quartile	54,441 (25.2)	733,069 (25.2)	54,426 (25.2)	270,519 (25.2)	
4th quartile	55,099 (25.5)	780,124 (26.8)	55,096 (25.5)	275,418 (25.7)	
Parity, n (%)					<0.01
1	181,261 (83.9)	2,217,878 (76.2)	181,179 (83.9)	903,334 (84.2)	
≥ 2	34,751 (16.1)	694,681 (23.9)	34,751 (16.1)	170,176 (15.9)	

Maternal medical conditions, n (%)					0.02
No mental illness	168,482 (78.0)	2,473,110 (84.9)	168,480 (78.0)	844,247 (78.6)	
Common	42,533 (19.7)	398,371 (13.7)	42,492 (19.7)	206,982 (19.3)	
Severe	4,997 (2.3)	41,078 (1.4)	4,958 (2.3)	22,281 (2.1)	
Severe maternal morbidity, n (%)					<0.01
0	198,017 (91.7)	2,731,862 (93.8)	197,996 (91.7)	988,414 (92.1)	
1	17,332 (8.0)	175,983 (6.0)	17,294 (8.0)	82,760 (7.7)	
≥ 2	663 (0.3)	4,714 (0.2)	640 (0.3)	2,336 (0.2)	
Delivery type, n (%)					<0.01
Vaginal delivery	115,193 (53.3)	1,693,716 (58.2)	115,192 (53.4)	576,083 (53.7)	
Cesarean section	100,819 (46.7)	1,218,843 (41.9)	100,738 (46.7)	497,427 (46.3)	
Number of hospital admissions in a year before pregnancy, n (%)					<0.01
0	171,976 (79.6)	2,468,433 (84.8)	171,967 (79.6)	858,185 (79.9)	
1	35,213 (16.3)	370,988 (12.7)	35,196 (16.3)	174,556 (16.3)	
≥ 2	8,823 (4.1)	73,138 (2.5)	8,767 (4.1)	40,769 (3.8)	
Number of outpatient contacts in a year before pregnancy, n (%)					<0.01
0	4,619 (2.1)	188,625 (6.5)	4,619 (2.1)	23,055 (2.2)	
1	4,890 (2.3)	162,503 (5.6)	4,890 (2.3)	24,291 (2.3)	
≥ 2	206,503 (95.6)	2,561,431 (87.9)	206,421 (95.6)	1,026,164 (95.6)	
Infant characteristics					
Infant sex, n (%)					<0.01
Male	110,511 (51.2)	1,495,374 (51.3)	110,468 (51.2)	549,630 (51.2)	

Female	105,501 (48.8)	1,417,185 (48.7)	105,462 (48.8)	523,880 (48.8)	
Birth season, n (%)					<0.01
Spring	53,228 (24.6)	756,304 (26.0)	53,222 (24.7)	265,508 (24.7)	
Summer	58,458 (27.1)	708,808 (24.3)	58,414 (27.1)	289,063 (26.9)	
Autumn	51,697 (23.9)	718,496 (24.7)	51,685 (23.9)	257,521 (24.0)	
Winter	52,629 (24.4)	728,951 (25.0)	52,609 (24.4)	261,418 (24.4)	
Year of delivery, n (%)					<0.01
2010 to 2012	69,885 (32.4)	1,119,845 (38.5)	69,884 (32.4)	347,978 (32.4)	
2013 to 2015	76,973 (35.6)	997,353 (34.2)	76,949 (35.6)	382,853 (35.7)	
2016 to 2017	69,154 (32.0)	795,361 (27.3)	69,097 (32.0)	342,679 (31.9)	
At-risk newborn, n (%)					0.02
Preterm birth	10,817 (5.0)	103,949 (3.6)	10,760 (5.0)	47,474 (4.4)	
Low birth weight	7,860 (3.6)	83,354 (2.9)	7,823 (3.6)	34,172 (3.2)	
Unmatching variables (maternal parameters)					
Alcohol or drug misuse, n (%)	558 (0.3)	3,920 (0.1)	550 (0.3)	2,211 (0.2)	
Mood disorders except those with psychotic symptoms, n (%)	9,699 (4.5)	74,053 (2.5)	9,651 (4.5)	41,468 (3.9)	
Anxiety and stress-related disorders, n (%)	16,195 (7.5)	129,873 (4.5)	16,150 (7.5)	72,171 (6.7)	
Sleep disorders, n (%)	8,392 (3.9)	59,394 (2.0)	8,359 (3.9)	30,223 (2.8)	
Epilepsy, n (%)	884 (0.4)	8,696 (0.3)	873 (0.4)	4,071 (0.4)	
Other neuropsychiatry disorders, n (%)	814 (0.4)	6,713 (0.2)	810 (0.4)	3,630 (0.3)	
Use of NSAID during pregnancy, n (%)	103,912 (48.1)	482,329 (16.6)	103,848 (48.1)	197,804 (18.4)	

Use of acetaminophen during pregnancy, n (%)	148,024 (68.5)	789,528 (27.1)	147,964 (68.5)	305,624 (28.5)	

NSAID, nonsteroidal anti-inflammatory drug; PS, propensity score; SD, standard deviation; SMD, standardized mean difference

* SMD <0.1 corresponds to no major imbalance

[a] Full unmatched cohort involves infants born between 2010 and 2017 (Cohort 1 in Figure 1 and Table S8).

[b] PS-matched cohort A, derived from the full unmatched cohort, involves a 1:5 matching ratio and pairs the exposed and unexposed groups in a 1:5 ratio using PS (Cohort 2 in Figure 1 and Table S8).

Supplement data 2. Hazard ratio models of the association between prenatal opioid exposure during pregnancy and neuropsychiatric disorders in children with the 1:5 PS-matched cohort A from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid exposure during pregnancy							
No	1,073,510 (83.3)	34,499 (3.2)	6,376,813	5.4	1 (reference)	1 (reference)	1 (reference)
Yes	215,930 (16.8)	7,396 (3.4)	1,271,904	5.8	**1.08 (1.05 to 1.11)**	**1.07 (1.05 to 1.10)**	**1.06 (1.04 to 1.09)**
Timing of opioid exposure							
No opioid exposure	1,073,510 (83.3)	34,499 (3.2)	6,376,813	5.4	1 (reference)	1 (reference)	1 (reference)
First trimester only	87,555 (6.8)	3,326 (3.8)	532,942	6.2	**1.16 (1.12 to 1.20)**	**1.11 (1.08 to 1.55)**	**1.10 (1.06 to 1.14)**
Second trimester only	50,764 (3.9)	1,600 (3.2)	290,994	5.5	1.03 (0.98 to 1.08)	1.03 (0.98 to 1.08)	1.03 (0.97 to 1.04)
Third trimester only	61,117 (4.7)	1,861 (3.0)	354,579	5.3	0.97 (0.92 to 1.01)	1.00 (0.95 to 1.05)	1.00 (0.95 to 1.05)
More than one trimester	16,494 (1.3)	609 (3.7)	93,389	6.5	**1.22 (1.13 to 1.32)**	**1.24 (1.15 to 1.35)**	**1.19 (1.10 to 1.29)**
Dose-dependent association, MME							
None	1,073,510 (83.3)	34,499 (3.2)	6,376,813	5.4	1 (reference)	1 (reference)	1 (reference)
Low-dose user	161,682 (12.5)	5,730 (3.5)	1,000,497	5.7	**1.05 (1.02 to 1.08)**	**1.05 (1.02 to 1.08)**	**1.04 (1.02 to 1.08)**
High-dose user	54,248 (4.2)	1,666 (3.07)	271,407	6.14	**1.19 (1.13 to 1.25)**	**1.17 (1.12 to 1.23)**	**1.14 (1.08 to 1.19)**
Opioid prescriptions, days							
0	1,073,510 (83.3)	34,499 (3.2)	6,376,813	5.4	1 (reference)	1 (reference)	1 (reference)
1-29	212,818 (16.5)	7,265 (3.4)	1,255,258	5.8	**1.07 (1.05 to 1.10)**	**1.07 (1.03 to 1.10)**	**1.06 (1.03 to 1.09)**
30-59	2,818 (0.2)	113 (4.0)	15,174	7.5	**1.41 (1.17 to 1.70)**	**1.43 (1.19 to 1.72)**	**1.34 (1.11 to 1.61)**

≥60	294 (0.0)	18 (6.1)	1,472	12.2	**2.41 (1.52 to 3.82)**	**2.33 (1.47 to 3.69)**	**1.79 (1.13 to 2.84)**
Number of opioid prescriptions							
0-1	1,073,510 (83.3)	34,499 (3.2)	6,376,813	5.4	1 (reference)	1 (reference)	1 (reference)
2	104,975 (8.1)	3,506 (3.3)	626,564	5.6	1.03 (1.00 to 1.07)	1.02 (0.99 to 1.06)	1.02 (0.99 to 1.06)
≥ 3	110,955 (8.6)	3,890 (3.5)	645,340	6.0	**1.12 (1.08 to 1.16)**	**1.13 (1.09 to 1.16)**	**1.11 (1.07 to 1.14)**

CI, confidence interval; MME, morphine milligram equivalent; PS, propensity-score; SMM, severe maternal morbidity

PS-matched cohort A, derived from the full unmatched cohort, involves a 1:5 matching ratio and pairs the exposed and unexposed groups in a 1:5 ratio using PS (Cohort 2 in Figure 1 and Table S8).

* Neuropsychiatric incidence rate is expressed per 1,000 person-years.

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$).

Supplement data 3. Stratification analysis for hazard ratio models of the association between opioid exposure during pregnancy and neuropsychiatric disorders in children with the 1:5 PS-matched cohort A from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Infant sex							
Male	660,098 (51.2)	5,138 (4.7)	647,727	7.9	**1.07 (1.04 to 1.10)**	**1.06 (1.03 to 2.00)**	**1.05 (1.02 to 1.09)**
Female	629,342 (48.8)	2,258 (2.1)	624,177	3.6	**1.10 (1.05 to 1.16)**	**1.10 (1.05 to 1.15)**	**1.08 (1.03 to 1.13)**
Birth season							
Spring	318,730 (24.7)	1,731 (3.3)	308,335	5.6	**1.09 (1.04 to 1.15)**	**1.09 (1.04 to 1.15)**	**1.08 (1.03 to 1.14)**
Summer	347,477 (27.0)	2,061 (3.5)	345,877	6.0	**1.10 (1.05 to 1.15)**	**1.09 (1.04 to 1.13)**	**1.08 (1.03 to 1.13)**
Autumn	309,206 (24.0)	1,838 (3.6)	307,223	6.0	1.05 (1.00 to 1.10)	1.042 (0.99 to 1.10)	1.03 (0.98 to 1.09)
Winter	314,027 (24.4)	1,766 (3.4)	310,469	5.7	**1.07 (1.02 to 1.13)**	**1.07 (1.02 to 1.13)**	**1.06 (1.01 to 1.12)**
Year of delivery							
2010-2012	417,862 (32.4)	4,317 (6.2)	605,042	7.1	**1.10 (1.07 to 1.14)**	**1.10 (1.06 to 1.14)**	**1.09 (1.05 to 1.13)**
2013-2015	459,802 (35.7)	2,300 (3.0)	455,473	5.1	1.04 (1.00 to 1.10)	1.04 (0.99 to 1.09)	1.03 (0.99 to 1.09)
2016-2017	411,776 (31.9)	779 (1.1)	211,389	3.7	1.04 (0.96 to 1.12)	1.04 (0.96 to 1.12)	1.03 (0.95 to 1.11)
Maternal medical conditions							
No mental illness	1,012,727 (78.5)	4,437 (2.6)	989,756	4.5	**1.07 (1.04 to 1.11)**	**1.07 (1.03 to 1.10)**	**1.07 (1.03 to 1.10)**
Mental illness	276,713 (21.5)	2,959 (6.2)	282,148	10.5	**1.08 (1.03 to 1.12)**	**1.07 (1.03 to 1.11)**	**1.07 (1.03 to 1.11)**
Delivery type							
Vaginal delivery	691,275 (53.6)	3,723 (3.2)	695,849	5.4	1.04 (1.00 to 1.07)	1.04 (1.00 to 1.07)	1.03 (0.99 to 1.07)
Cesarean section	598,165 (46.4)	3,673 (3.7)	576,055	6.4	**1.12 (1.08 to 1.16)**	**1.12 (1.08 to 1.16)**	**1.10 (1.06 to 1.14)**
Medical condition of infant							

None	1,220,768 (94.7)	6,691 (3.3)	1,202,399	5.6	**1.11 (1.02 to 1.20)**	**1.07 (1.04 to 1.10)**	**1.06 (1.03 to 1.09)**
At-risk newborn	68,672 (5.3)	705 (5.5)	69,505	10.1	1.00 (0.97 to 1.04)	1.09 (1.00 to 1.18)	1.07 (0.98 to 1.16)
Alcohol or drug misuse							
No	1,286,679 (99.8)	7,337 (3.4)	1,269,363	5.8	**1.08 (1.05 to 1.10)**	**1.07 (1.04 to 1.10)**	**1.09 (1.03 to 1.09)**
Yes	2,761 (0.2)	59 (10.7)	2,541	23.2	**2.12 (1.56 to 2.90)**	**2.12 (1.55 to 2.90)**	**2.07 (1.51 to 2.83)**
Mood disorders except those with psychotic symptoms							
No	1,238,321 (96.0)	6,858 (3.3)	1,224,673	5.6	**1.06 (1.04 to 1.09)**	**1.06 (1.03 to 1.09)**	**1.06 (1.03 to 1.08)**
Yes	51,119 (4.0)	538 (5.6)	47,231	11.4	**1.19 (1.08 to 1.30)**	**1.17 (1.06 to 1.29)**	**1.16 (1.05 to 1.27)**
Anxiety and stress-related disorders							
No	1,201,119 (93.2)	6,644 (3.3)	1,190,094	5.6	**1.06 (1.03 to 1.09)**	**1.06 (1.03 to 1.09)**	**1.06 (1.03 to 1.09)**
Yes	88,321 (6.9)	752 (4.7)	81,810	9.2	**1.18 (1.09 to 1.28)**	**1.15 (1.07 to 1.25)**	**1.13 (1.04 to 1.22)**
Sleep disorders							
No	1,250,858 (97.0)	6,963 (3.4)	1,231,349	5.7	**1.06 (1.03 to 1.09)**	**1.06 (1.03 to 1.09)**	**1.05 (1.03 to 1.08)**
Yes	38,582 (3.0)	433 (5.2)	40,555	10.7	**1.29 (1.15 to 1.43)**	**1.25 (1.12 to 1.40)**	**1.25 (1.12 to 1.39)**
Epilepsy							
No	1,284,496 (99.6)	7,333 (3.4)	1,267,523	5.8	**1.08 (1.05 to 1.10)**	**1.07 (1.05 to 1.10)**	**1.06 (1.04 to 1.09)**
Yes	4,944 (0.4)	63 (7.2)	4,381	14.4	1.29 (0.98 to 1.70)	**1.36 (1.03 to 1.80)**	**1.33 (1.01 to 1.76)**
Other neuropsychiatry disorders							
No	1,285,000 (99.7)	7,330 (3.4)	1,268,302	5.8	**1.08 (1.05 to 1.10)**	**1.07 (1.04 to 1.10)**	**1.06 (1.04 to 1.09)**
Yes	4,440 (0.3)	66 (8.2)	3,602	18.3	**1.37 (1.04 to 1.80)**	**1.34 (1.02 to 1.76)**	1.32 (1.00 to 1.75)
Use of NSAID during pregnancy							
No	987,788 (76.6)	3,418 (3.1)	652,020	5.2	1.04 (1.00 to 1.08)	1.02 (0.98 to 1.06)	1.02 (0.98 to 1.05)

Yes	301,652 (23.4)	3,978 (3.8)	619,884	6.4	1.03 (0.97 to 1.08)	1.03 (0.99 to 1.07)	1.03 (0.99 to 1.07)
Use of acetaminophen during pregnancy							
No	835,852 (64.8)	1,441 (2.1)	295,283	4.9	1.03 (0.97 to 1.08)	1.05 (0.99 to 1.11)	1.05 (0.99 to 1.10)
Yes	453,588 (35.2)	5,955 (4.0)	976,621	6.1	1.03 (1.00 to 1.06)	1.03 (1.00 to 1.06)	1.03 (0.99 to 1.06)

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; MME, morphine milligram equivalent; PS, propensity score; SMM, severe maternal morbidity

PS-matched cohort A, derived from the full unmatched cohort, involves a 1:5 matching ratio and pairs the exposed and unexposed groups in a 1:5 ratio using PS (Cohort 2 in Figure 1 and Table S8).

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$).

Supplement data 4. Adjusted hazard ratio models of the dose-dependence between prenatal opioid exposure during pregnancy and specific neuropsychiatric disorders in children within the 1:5 PS-matched cohort A from 2010 to 2017

	Overall			**Low-dose users (<25.5 MME)**			**High-dose users (≥25.5 MME)**		
	Events, n (%)	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**	**Events, n (%)**	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**	**Events, n (%)**	**Adjusted HR (95% CI)†**	**Fully adjusted HR (95% CI)††**
Alcohol or drug misuse									
No opioid exposure	84/1,073,510 (0.0)	1 (reference)	1 (reference)	84/1,073,510 (0.0)	1 (reference)	1 (reference)	84/1,073,510 (0.0)	1 (reference)	1 (reference)
Opioid exposure	15/215,930 (0.0)	0.89 (0.51 to 1.53)	0.88 (0.51 to 1.52)	14/161,682 (0.0)	1.07 (0.61 to 1.88)	1.06 (0.60 to 1.88)	1/54,248 (0.0)	0.27 (0.04 to 1.91)	0.26 (0.04 to 1.88)
Mood disorders, excluding those with psychotic symptoms									
No opioid exposure	2,281/1,073,510 (0.2)	1 (reference)	1 (reference)	2,281/1,073,510 (0.2)	1 (reference)	1 (reference)	2,281/1,073,510 (0.2)	1 (reference)	1 (reference)
Opioid exposure	535/215,930 (0.3)	**1.18 (1.08 to 1.30)**	**1.16 (1.06 to 1.28)**	418/161,682 (0.3)	**1.15 (1.03 to 1.27)**	**1.14 (1.03 to 1.26)**	117/54,248 (0.2)	**1.32 (1.10 to 1.59)**	**1.26 (1.05 to 1.52)**
Anxiety and stress-related disorders									
No opioid exposure	4,456/1,073,510 (0.4)	1 (reference)	1 (reference)	4,456/1,073,510 (0.4)	1 (reference)	1 (reference)	4,456/1,073,510 (0.4)	1 (reference)	1 (reference)

Opioid exposure	933/215,930 (0.4)	1.05 (0.98 to 1.13)	1.04 (0.97 to 1.11)	734/161,682 (0.5)	1.03 (0.96 to 1.12)	1.03 (0.95 to 1.11)	199/54,248 (0.4)	1.13 (0.98 to 1.30)	1.08 (0.94 to 1.25)
Eating disorders									
No opioid exposure	134/1,073,510 (0.0)	1 (reference)	1 (reference)	134/1,073,510 (0.0)	1 (reference)	1 (reference)	134/1,073,510 (0.0)	1 (reference)	1 (reference)
Opioid exposure	21/215,930 (0.0)	0.78 (0.49 to 1.24)	0.78 (0.49 to 1.23)	16/161,682 (0.0)	0.74 (0.44 to 1.25)	0.74 (0.44 to 1.25)	5/54,248 (0.0)	0.96 (0.39 to 2.34)	0.92 (0.38 to 2.25)
Compulsive disorders									
No opioid exposure	326/1,073,510 (0.0)	1 (reference)	1 (reference)	326/1,073,510 (0.0)	1 (reference)	1 (reference)	326/1,073,510 (0.0)	1 (reference)	1 (reference)
Opioid exposure	56/215,930 (0.0)	0.87 (0.65 to 1.15)	0.86 (0.65 to 1.14)	42/161,682 (0.0)	0.81 (0.59 to 1.11)	0.80 (0.58 to 1.11)	14/54,248 (0.0)	1.13 (0.66 to 1.93)	1.10 (0.64 to 1.88)
ADHD									
No opioid exposure	11,013/1,073,510 (1.0)	1 (reference)	1 (reference)	11,013/1,073,510 (1.0)	1 (reference)	1 (reference)	11,013/1,073,510 (1.0)	1 (reference)	1 (reference)
Opioid exposure	2,454/215,930 (1.1)	**1.12 (1.07 to 1.17)**	**1.11 (1.06 to 1.16)**	1,954/161,682 (1.2)	**1.11 (1.05 to 1.16)**	**1.10 (1.05 to 1.16)**	500/54,248 (0.9)	**1.18 (1.08 to 1.29)**	**1.13 (1.04 to 1.24)**
ASD									
No opioid exposure	5,472/1,073,510 (0.5)	1 (reference)	1 (reference)	5,472/1,073,510 (0.5)	1 (reference)	1 (reference)	5,472/1,073,510 (0.5)	1 (reference)	1 (reference)
Opioid exposure	1,072/215,930 (0.5)	0.98 (0.91 to 1.04)	0.97 (0.91 to 1.03)	818/161,682 (0.5)	0.95 (0.88 to 1.02)	0.95 (0.88 to 1.02)	254/54,248 (0.5)	1.08 (0.95 to 1.22)	1.05 (0.93 to 1.20)
Intellectual disability									

No opioid exposure	3,399/1,073,510 (0.3)	1 (reference)	1 (reference)	3,399/1,073,510 (0.3)	1 (reference)	1 (reference)	3,399/1,073,510 (0.3)	1 (reference)	1 (reference)
Opioid exposure	864/215,930 (0.4)	**1.27 (1.18 to 1.36)**	**1.26 (1.17 to 1.35)**	650/161,682 (0.4)	**1.19 (1.09 to 1.29)**	**1.19 (1.10 to 1.29)**	214/54,248 (0.4)	**1.58 (1.37 to 1.81)**	**1.54 (1.34 to 1.77)**
Common neuropsychiatric disorder									
No opioid exposure	33,282/1,072,293 (3.1)	1 (reference)	1 (reference)	33,282/1,072,293 (3.1)	1 (reference)	1 (reference)	33,282/1,072,293 (3.1)	1 (reference)	1 (reference)
Opioid exposure	7,077/215,611 (3.3)	**1.07 (1.04 to 1.09)**	**1.06 (1.03 to 1.08)**	5,476/161,428 (3.4)	**1.04 (1.01 to 1.07)**	**1.04 (1.01 to 1.07)**	1,601/54,183 (3.0)	**1.17 (1.11 to 1.23)**	**1.13 (1.08 to 1.19)**
Severe neuropsychiatric disorder									
No opioid exposure	1,217/1,040,228 (0.1)	1 (reference)	1 (reference)	1,217/1,040,228 (0.1)	1 (reference)	1 (reference)	1,217/1,040,228 (0.1)	1 (reference)	1 (reference)
Opioid exposure	319/208,853 (0.2)	**1.31 (1.16 to 1.49)**	**1.29 (1.14 to 1.46)**	254/156,206 (0.2)	**1.30 (1.14 to 1.49)**	**1.29 (1.13 to 1.48)**	65/52,647 (0.1)	**1.37 (1.06 to 1.75)**	**1.30 (1.01 to 1.67)**

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio; MME, morphine milligram equivalents; PS, propensity score; SMM, severe maternal morbidity

PS-matched cohort A, derived from the full unmatched cohort, involves a 1:5 matching ratio and pairs the exposed and unexposed groups in a 1:5 ratio using PS (Cohort 2 in Figure 1 and Table S8).

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Supplement data 5. Crude and adjusted hazard ratio models of the association between opioid exposure during pregnancy and neuropsychiatric disorders in children with the sibling comparison cohort from full unmatched cohort, PS-matched cohort A, and child screening cohort from 2010 to 2017

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid exposure during pregnancy (Sibling cohort A from the full unmatched cohort)							
No	114,007 (52.0)	5,008 (4.4)	760,040	6.6	1 (reference)	1 (reference)	1 (reference)
Yes	105,339 (48.0)	2,754 (2.6)	566,329	4.9	**0.78 (0.73 to 0.82)**	1.00 (0.93 to 1.07)	1.00 (0.93 to 1.07)
Opioid exposure during pregnancy (Sibling cohort B from the PS-matched cohort A)							
No	42,646 (50.7)	1,814 (4.3)	264,230	6.9	1 (reference)	1 (reference)	1 (reference)
Yes	41,420 (49.3)	1,307 (3.2)	228,421	5.7	**0.90 (0.82 to 0.99)**	1.01 (0.91 to 1.12)	1.01 (0.91 to 1.12)
Opioid exposure during pregnancy (Sibling cohort C from the child screening cohort)							
No	21,221 (50.6)	1,066 (5.0)	152,981	7.0	1 (reference)	1 (reference)	1 (reference)
Yes	20,699 (49.4)	585 (2.8)	121,848	4.8	**0.72 (0.63 to 0.80)**	0.95 (0.82 to 1.12)	0.95 (0.81 to 1.11)

CI, confidence interval; MME, morphine milligram equivalents; PS, propensity score; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Supplement data 6. Baseline characteristics of study subjects (PS-matched cohort B, birth date of infants in 2010-2015)

	Full unmatched cohort (n=2,264,056)		PS-matched cohort B (n=877,470)[a]		
	Children with prenatal opioid exposure	**Children without prenatal exposure**	**Children with prenatal opioid exposure**	**Children without prenatal exposure**	**SMD***
Total, n	146,858	2,117,198	146,788	730,682	
Maternal characteristics					
Maternal age at delivery year, mean (SD)	32.0 (4.1)	31.7 (4.1)	32.0 (4.1)	32.0 (4.1)	<0.01
Maternal age at delivery year, n (%)					<0.01
≤ 19	379 (0.3)	5,797 (0.3)	377 (0.3)	1,616 (0.2)	
20-24	5,802 (4.0)	96,272 (4.6)	5,797 (4.0)	28,011 (3.8)	
25-29	29,773 (20.3)	483,644 (22.8)	29,766 (20.3)	147,198 (20.2)	
30-34	73,035 (49.7)	1,044,582 (49.3)	73,009 (49.7)	364,742 (49.9)	
≥ 35	37,869 (25.8)	486,903 (23.0)	37,839 (25.8)	189,115 (25.9)	
Region of residence, n (%)					<0.01
Rural	60,859 (41.4)	920,131 (43.5)	60,840 (41.5)	302,824 (41.4)	
Urban	85,999 (58.6)	1,197,067 (56.5)	85,948 (58.6)	427,858 (58.6)	
Income level, n (%)					<0.01
1st quartile	34,981 (23.8)	476,057 (22.5)	34,943 (23.8)	173,439 (23.7)	
2nd quartile	38,672 (26.3)	551,432 (26.1)	38,657 (26.3)	192,377 (26.3)	
3rd quartile	36,509 (24.9)	530,381 (25.1)	36,496 (24.9)	181,773 (24.9)	
4th quartile	36,696 (25.0)	559,328 (26.4)	36,692 (25.0)	183,093 (25.1)	
Parity, n (%)					<0.01
1	124,459 (84.8)	1,643,964 (77.7)	124,390 (84.7)	621,060 (85.0)	
≥ 2	22,399 (15.3)	473,234 (22.4)	22,398 (15.3)	109,622 (15.0)	

Maternal medical conditions, n (%)					0.06
No mental illness	113,537 (77.3)	1,789,943 (84.5)	113,536 (77.4)	568,946 (77.9)	
Common	29,840 (20.3)	296,659 (14.0)	29,794 (20.3)	145,951 (20.0)	
Severe	3,481 (2.4)	30,596 (1.5)	3,458 (2.4)	15,785 (2.2)	
Severe maternal morbidity, n (%)					<0.01
0	134,654 (91.7)	1,986,819 (93.8)	134,645 (91.7)	673,133 (92.1)	
1	11,724 (8.0)	126,887 (6.0)	11,690 (8.0)	55,897 (7.7)	
≥ 2	480 (0.3)	3,492 (0.2)	453 (0.3)	1,652 (0.2)	
Delivery type, n (%)					<0.01
Vaginal delivery	81,215 (55.3)	1,275,479 (60.2)	81,212 (55.3)	405,785 (55.5)	
Cesarean section	65,643 (44.7)	841,719 (39.8)	65,576 (44.7)	324,897 (44.5)	
Number of hospital admissions in a year before pregnancy, n (%)					<0.01
0	118,207 (80.5)	1,808,567 (85.4)	118,195 (80.5)	590,433 (80.8)	
1	23,027 (15.7)	260,020 (12.3)	23,016 (15.7)	114,543 (15.7)	
≥ 2	5,624 (3.8)	48,611 (2.3)	5,577 (3.8)	25,706 (3.5)	
Number of outpatient contacts in a year before pregnancy, n (%)					<0.01
0	3,337 (2.3)	144,636 (6.8)	3,336 (2.3)	16,570 (2.3)	
1	3,622 (2.5)	125,198 (5.9)	3,622 (2.5)	18,006 (2.5)	
≥ 2	139,899 (95.3)	1,847,364 (87.3)	139,830 (95.3)	696,106 (95.3)	
Infant characteristics					
Infant sex, n (%)					<0.01
Male	75,203 (51.2)	1,087,053 (51.3)	75,166 (51.2)	374,258 (51.2)	

Female	71,655 (48.8)	1,030,145 (48.7)	71,622 (48.8)	356,424 (48.8)	
Birth season, n (%)					0.02
Spring	35,866 (24.4)	545,587 (25.8)	35,858 (24.4)	179,102 (24.5)	
Summer	39,916 (27.2)	513,192 (24.2)	39,880 (27.2)	197,457 (27.0)	
Autumn	35,515 (24.2)	529,822 (25.0)	35,498 (24.2)	177,023 (24.2)	
Winter	35,561 (24.2)	528,597 (25.0)	35,552 (24.2)	177,100 (24.2)	
Year of delivery, n (%)					<0.01
2010 to 2012	69,885 (47.6)	1,119,845 (52.9)	69,871 (47.6)	347,759 (47.6)	
2013 to 2015	76,973 (52.4)	997,353 (47.1)	76,917 (52.4)	382,923 (52.4)	
At-risk newborn, n (%)					
Preterm birth	6,727 (4.6)	68,824 (3.3)	6,685 (4.6)	29,560 (4.1)	0.02
Low birth weight	4,976 (3.4)	55,422 (2.6)	4,948 (3.4)	21,380 (2.9)	0.02
Unmatching variables (maternal parameters)					
Alcohol or drug misuse, n (%)	294 (0.2)	2,194 (0.1)	289 (0.2)	1,405 (0.2)	
Mood disorders except those with psychotic symptoms, n (%)	5,208 (3.6)	42,490 (2.0)	5,181 (3.5)	26,869 (3.7)	
Anxiety and stress-related disorders, n (%)	9,160 (6.2)	76,743 (3.6)	9,129 (6.2)	48,704 (6.7)	
Sleep disorders, n (%)	506 (0.3)	5,451 (0.3)	499 (0.3)	2,475 (0.3)	
Epilepsy, n (%)	384 (0.3)	3,535 (0.2)	383 (0.3)	2,042 (0.3)	
Other neuropsychiatry disorders, n (%)	4,467 (3.0)	32,980 (1.6)	4,445 (3.0)	17,053 (2.3)	
Use of NSAID during pregnancy, n (%)	71,593 (48.8)	347,854 (16.4)	71,538 (48.7)	162,775 (22.3)	
Use of acetaminophen during pregnancy, n (%)	124,822 (85.0)	695,710 (32.9)	124,755 (85.0)	342,618 (46.9)	

NSAID, nonsteroidal anti-inflammatory drug; PS, propensity score; SD, standard deviation; SMD, standardized mean difference

[a] PS-matched cohort B consists of infants born between 2010 and 2015, with the exposed and unexposed groups matched in a 1:5 ratio (Cohort 4 in Figure 1 and Table S8).

* SMD <0.1 corresponds to no major imbalance

Supplement data 7. Interaction analysis of opioid prescriptions in a year before pregnancy and opioid prescriptions during pregnancy

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid prescriptions in a year before pregnancy X Opioid prescriptions during pregnancy (p-value)					p=0.001	P=0.003	P=0.036
PS-matched cohort A							
Opioid prescriptions in a year before pregnancy							
No	537,101 (41.9)	1,953 (3.3)	354,819	5.5	1.02 (0.98 to 1.07)	1.02 (0.98 to 1.07)	1.02 (0.98 to 1.07)
Yes	752,339 (58.1)	5,451 (3.5)	917,389	5.9	**1.09 (1.06 to 1.13)**	**1.09 (1.06 to 1.12)**	**1.08 (1.05 to 1.11)**
Child screening cohort							
Opioid prescriptions in a year before pregnancy							
No	655,754 (48.1)	827 (3.3)	154,111	5.4	1.01 (0.95 to 1.09)	1.03 (0.96 to 1.11)	1.02 (0.95 to 1.10)
Yes	706,765 (51.9)	2,269 (3.3)	396,326	5.7	**1.06 (1.02 to 1.11)**	**1.09 (1.04 to 1.14)**	**1.06 (1.02 to 1.11)**

CI, confidence interval; PS, propensity score; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer,

autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Supplement data 8. Interaction analysis and ratio of hazard ratio of delivery type and opioid prescriptions during pregnancy in PS-matched cohort A

	Hazard ratio (95% CI)		
	Crude	**Adjusted†**	**Fully adjusted††**
Delivery type X Opioid prescriptions during pregnancy (p-value)	P=0.002	P=0.003	P=0.009
Delivery type			
Vaginal delivery	**1.037 (1.001 to 1.074)**	1.035 (1.000 to 1.073)	1.030 (0.994 to 1.067)
Cesarean section	**1.121 (1.082 to 1.162)**	**1.117 (1.077 to 1.157)**	**1.101 (1.062 to 1.141)**
Ratio of hazard ratio (Cesarean section vs. Vaginal delivery)	**1.081 (1.028 to 1.137)**	**1.079 (1.026 to 1.135)**	**1.069 (1.016 to 1.124)**

CI, confidence interval; PS, propensity score

PS-matched cohort A, derived from the full unmatched cohort, involves a 1:5 matching ratio and pairs the exposed and unexposed groups in a 1:5 ratio using PS (Cohort 2 in Figure 1 and Table S8).

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Supplement data 9. Hazard ratio models of the association between prenatal opioid exposure during pregnancy and neuropsychiatric disorders in children with the 1:5 PS-matched cohort B (birth date of infants in 2010-2015)

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid exposure during pregnancy							
No	730,682 (83.3)	30,912 (4.2)	5,309,582	5.8	1 (reference)	1 (reference)	1 (reference)
Yes	146,788 (16.7)	6,612 (4.5)	1,060,222	6.2	**1.07 (1.04 to 1.10)**	**1.07 (1.04 to 1.10)**	**1.07 (1.04 to 1.10)**
Timing of opioid exposure							
No opioid exposure	730,682 (83.3)	30,912 (4.2)	5,309,582	5.8	1 (reference)	1 (reference)	1 (reference)
First trimester only	61,797 (7.0)	2,984 (4.8)	454,456	6.6	**1.13 (1.09 to 1.17)**	**1.09 (1.05 to 1.13)**	**1.09 (1.05 to 1.13)**
Second trimester only	33,559 (3.8)	1,414 (4.2)	238,266	5.9	1.02 (0.97 to 1.08)	1.03 (0.98 to 1.09)	1.03 (0.98 to 1.09)
Third trimester only	40,706 (4.6)	1,664 (4.1)	291,778	5.7	0.97 (0.93 to 1.02)	1.01 (0.96 to 1.06)	1.02 (0.97 to 1.07)
More than one trimester	10,726 (1.2)	550 (5.1)	75,722	7.3	**1.25 (1.15 to 1.36)**	**1.28 (1.17 to 1.39)**	**1.23 (1.13 to 1.34)**
Dose-dependent association, MME							
None	730,682 (83.3)	30,912 (4.2)	5,309,582	5.8	1 (reference)	1 (reference)	1 (reference)
Low-dose user	120,786 (13.8)	5,209 (4.3)	868,809	6.0	1.03 (1.00 to 1.06)	**1.04 (1.01 to 1.07)**	**1.04 (1.01 to 1.07)**
High-dose user	26,002 (3.0)	1,403 (5.4)	191,413	7.3	**1.26 (1.19 to 1.33)**	**1.21 (1.15 to 1.28)**	**1.18 (1.12 to 1.25)**
Opioid prescriptions, days							
0	730,682 (83.3)	30,912 (4.2)	5,309,582	5.8	1 (reference)	1 (reference)	1 (reference)
1-29	144,926 (16.5)	6,493 (4.5)	1,047,370	6.2	**1.07 (1.04 to 1.10)**	**1.06 (1.03 to 1.09)**	**1.06 (1.03 to 1.09)**
30-59	1,701 (0.2)	100 (5.9)	11,778	8.5	**1.47 (1.21 to 1.79)**	**1.49 (1.23 to 1.81)**	**1.40 (1.15 to 1.70)**
≥60	161 (0.0)	19 (11.8)	1,074	17.7	**3.13 (2.00 to 4.91)**	**3.02 (1.93 to 4.74)**	**2.34 (1.49 to 3.66)**

Number of opioid prescriptions							
0-1	730,682 (83.3)	30,912 (4.2)	5,309,582	5.8	1 (reference)	1 (reference)	1 (reference)
2	72,369 (8.3)	3,108 (4.3)	526,657	5.9	1.01 (0.98 to 1.05)	1.00 (0.97 to 1.04)	1.01 (0.97 to 1.05)
≥ 3	74,419 (8.5)	3,504 (4.7)	533,565	6.6	**1.13 (1.09 to 1.17)**	**1.14 (1.10 to 1.18)**	**1.13 (1.09 to 1.17)**

CI, confidence interval; MME, morphine milligram equivalent; PS, propensity-score; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Supplement data 10. Hazard ratio models of the association between prenatal opioid exposure during pregnancy and neuropsychiatric disorders in children with the 1:5 PS-matched cohort C from 2010 to 2017 ('outcome' criteria with above 1 diagnosis)

	n (%)	Neuropsychiatric disorder events (%)	Person-years	Neuropsychiatric incidence rate*	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted††
Opioid exposure during pregnancy							
No	1,073,510 (83.3)	60,742 (5.7)	5,225,294	11.6	1 (reference)	1 (reference)	1 (reference)
Yes	215,930 (16.8)	12,841 (6.0)	1,043,673	12.3	**1.06 (1.04 to 1.08)**	**1.06 (1.04 to 1.08)**	**1.05 (1.03 to 1.07)**
Timing of opioid exposure							
No opioid exposure	1,073,510 (83.3)	60,742 (5.7)	5,225,294	11.6	1 (reference)	1 (reference)	1 (reference)
First trimester only	87,555 (6.8)	5,651 (6.5)	446,948	12.6	**1.12 (1.09 to 1.15)**	**1.09 (1.06 to 1.12)**	**1.08 (1.05 to 1.11)**
Second trimester only	50,764 (3.9)	2,900 (5.7)	234,557	12.4	**1.04 (1.01 to 1.08)**	**1.05 (1.01 to 1.09)**	**1.04 (1.01 to 1.08)**
Third trimester only	61,117 (4.7)	3,296 (5.4)	287,529	11.5	0.97 (0.94 to 1.01)	0.99 (0.96 to 1.03)	0.99 (0.96 to 1.03)
More than one trimester	16,494 (1.3)	994 (6.0)	74,639	13.3	**1.11 (1.05 to 1.18)**	**1.13 (1.06 to 1.21)**	**1.10 (1.03 to 1.17)**
Dose-dependent association, MME							
None	1,073,510 (83.3)	60,742 (5.7)	5,225,294	11.6	1 (reference)	1 (reference)	1 (reference)
Low-dose user	161,682 (12.5)	9,893 (6.1)	855,514	11.6	**1.04 (1.02 to 1.06)**	**1.03 (1.01 to 1.06)**	**1.03 (1.01 to 1.05)**
High-dose user	54,248 (4.2)	2,948 (5.4)	188,159	15.7	**1.14 (1.10 to 1.18)**	**1.13 (1.09 to 1.18)**	**1.11 (1.07 to 1.15)**
Opioid prescriptions, days							
0	1,073,510 (83.3)	60,742 (5.7)	5,225,294	11.6	1 (reference)	1 (reference)	1 (reference)
1-29	212,818 (16.5)	12,637 (5.9)	1,031,018	12.3	**1.06 (1.04 to 1.08)**	**1.05 (1.03 to 1.07)**	**1.05 (1.03 to 1.07)**
30-59	2,818 (0.2)	179 (6.4)	11,601	15.4	**1.23 (1.06 to 1.43)**	**1.26 (1.09 to 1.46)**	**1.19 (1.02 to 1.37)**
≥60	294 (0.0)	25 (8.5)	1,054	23.7	**1.81 (1.23 to 2.67)**	**1.74 (1.17 to 2.57)**	1.42 (0.96 to 2.10)

Number of opioid prescriptions							
0-1	1,073,510 (83.3)	60,742 (5.7)	5,225,294	11.6	1 (reference)	1 (reference)	1 (reference)
2	104,975 (8.1)	6,164 (5.9)	518,373	11.9	**1.03 (1.01 to 1.06)**	1.02 (1.00 to 1.05)	1.02 (0.99 to 1.05)
≥ 3	110,955 (8.6)	6,677 (6.0)	525,300	12.7	**1.08 (1.06 to 1.11)**	**1.09 (1.06 to 1.12)**	**1.07 (1.05 to 1.10)**

CI, confidence interval; MME, morphine milligram equivalent; PS, propensity-score; SMM, severe maternal morbidity

* Neuropsychiatric incidence rate is expressed per 1,000 person-years

† The adjusted model was adjusted for the following variables: maternal age at delivery years (≤19, 20-24, 25-29, 30-34, and ≥35 years), infant sex, region of residence (urban and rural), household income level (1st, 2nd, 3rd, and 4th quartiles), birth season (spring, summer, autumn, and winter), parity (1 and ≥2), maternal mental illness, SMM score (0, 1, and ≥2), and hospital outpatient visit (0, 1, and ≥2), and admission contact (0, 1, and ≥2) in a year before pregnancy.

†† The fully adjusted model was adjusted for the following variables: covariates as in the adjusted model, history of maternal neuropsychiatric conditions (alcohol or drug misuse, mood disorders except those with psychotic symptoms, anxiety and stress-related disorders, sleep disorders, epilepsy, and other neuropsychiatry disorders), and use of NSAID and acetaminophen during pregnancy.

Numbers in bold indicate significant differences ($P < 0.05$)

Supplement data 11. Hazard ratio model of the association between prenatal opioid exposure during pregnancy and specific neuropsychiatric disorders in children within the 1:5 PS-matched cohort A from 2010 to 2017

	n (%)	**Neuropsychiatric disorder events (%)**	**Crude hazard ratio (95% CI)**
Alcohol or drug misuse			
No opioid exposure	1,073,510 (83.3)	84 (0.0)	1 (reference)
Opioid exposure	215,930 (16.8)	15 (0.0)	0.89 (0.51 to 1.54)
Mood disorders, excluding those with psychotic symptoms			
No opioid exposure	1,073,510 (83.3)	2,281 (0.2)	1 (reference)
Opioid exposure	215,930 (16.8)	535 (0.3)	**1.19 (1.08 to 1.30)**
Anxiety and stress-related disorders			
No opioid exposure	1,073,510 (83.3)	4,456 (0.4)	1 (reference)
Opioid exposure	215,930 (16.8)	933 (0.43	1.06 (0.99 to 1.13)
Eating disorders			
No opioid exposure	1,073,510 (83.3)	134 (0.0)	1 (reference)
Opioid exposure	215,930 (16.8)	21 (0.0)	0.78 (0.49 to 1.24)
Compulsive disorders			
No opioid exposure	1,073,510 (83.3)	326 (0.0)	1 (reference)
Opioid exposure	215,930 (16.8)	56 (0.0)	0.87 (0.66 to 1.16)
ADHD			
No opioid exposure	1,073,510 (83.3)	11,013 (1.0)	1 (reference)
Opioid exposure	215,930 (16.8)	2,454 (1.1)	**1.13 (1.08 to 1.18)**
ASD			

No opioid exposure	1,073,510 (83.3)	5,472 (0.5)	1 (reference)
Opioid exposure	215,930 (16.8)	1,072 (0.5)	0.98 (0.92 to 1.04)
Intellectual disability			
No opioid exposure	1,073,510 (83.3)	3,399 (0.3)	1 (reference)
Opioid exposure	215,930 (16.8)	864 (0.4)	**1.27 (1.18 to 1.37)**
Common neuropsychiatric disorder			
No opioid exposure	1,073,510 (83.3)	33,282 (3.1)	1 (reference)
Opioid exposure	215,930 (16.8)	7,077 (3.3)	**1.07 (1.04 to 1.10)**
Severe neuropsychiatric disorder			
No opioid exposure	1,073,510 (83.3)	1,217 (0.1)	1 (reference)
Opioid exposure	215,930 (16.8)	319 (0.2)	**1.32 (1.17 to 1.49)**

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; PS, propensity score

Numbers in bold indicate significant differences ($P < 0.05$)