國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Association of Prenatal Opioid Exposure with the Disorders in Children

Chiu-Wen Chang
2nd Year, PhD in Public Health
Advisor: Professor Pei-Chen Lee
2025.03.19

https://www.healthday.com/healthpro-news/child-health/prenatal-opioid-exposure-ups-risk-of-childhood-adhd-2656951317.html

Women and Children affected By Opioid Use

- The global opioid crisis has generated widespread attention because of its extensive effect on public health. According to the United Nations Office on Drugs and Crime report, over 280 million people aged between 15 and 64 used at least one illicit drug in the past year, accounting for 5% of the population.
- During pregnancy, the need for pain management in some instances has led to an observable reliance on analgesics, including opioids. The prevalence of substance use before or during pregnancy may range from 1% to as high as 21%.
- Prenatal exposure to alcohol, tobacco, and some medications has been associated with an array of developmental, cognitive, and behavioral deficits in the child. The effect of opioid exposure during the prenatal period is a topic of substantial importance but requires more in-depth examination.

JAMA Network Open

Original Investigation | Pediatrics

Association of Timing and Duration of Prenatal Analgesic Opioid Exposure With Attention-Deficit/Hyperactivity Disorder in Children

Johanne Naper Trønnes, MScPharm; Angela Lupattelli, PhD; Marte Handal, MD, PhD; Svetlana Skurtveit, PhD; Eivind Ystrom, PhD; Hedvig Nordeng, PhD

JAMA Netw Open. 2021;4(9):e2124324. doi:10.1001/jamanetworkopen.2021.24324

2023 JOURNAL IMPACT FACTOR

22.3

View calculation

JOURNAL IMPACT FACTOR WITHOUT SELF CITATIONS

21.7

View calculation

MEDICINE, GENERAL & INTERNAL

7/329

JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
2023	7/329	Q1	98.0

Rank by JIF before 2023 for MEDICINE, GENERAL & INTERNAL

EDITION

Science Citation Index Expanded (SCIE)

JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
2022	7/169	Q1	96.2
2021	7/172	Q1	96.22
2020	8/167	Q1	95.51
2019	7/165	Q1	96.06

Introduction

- In recent years, consumption of prescribed opioid analgesics has increased, a trend also affecting women of childbearing age. Prevalence estimates among pregnant women range
  - 1% to 3% in Norway
  - 14% to 28% in the United States
- One of the most common behavioral disorders in childhood is attention-deficit/hyperactivity disorder (ADHD), which affects approximately 2% to 7% of children worldwide. The median age of first diagnosis is estimated to be around 7 to 9 years.
- Azuine et al reported an odds ratio of 2.55 (95% CI, 1.42-4.57) for ADHD after opioid exposure when children with exposure were compared with those without.

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Knowledge Gaps

Available Knowledge

Opioid use during pregnancy → Outcomes of neonatal, fetal brain function

Limited Knowledge

Prenatal Analgesic Opioid → Behavioral disorders in childhood

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Study Design

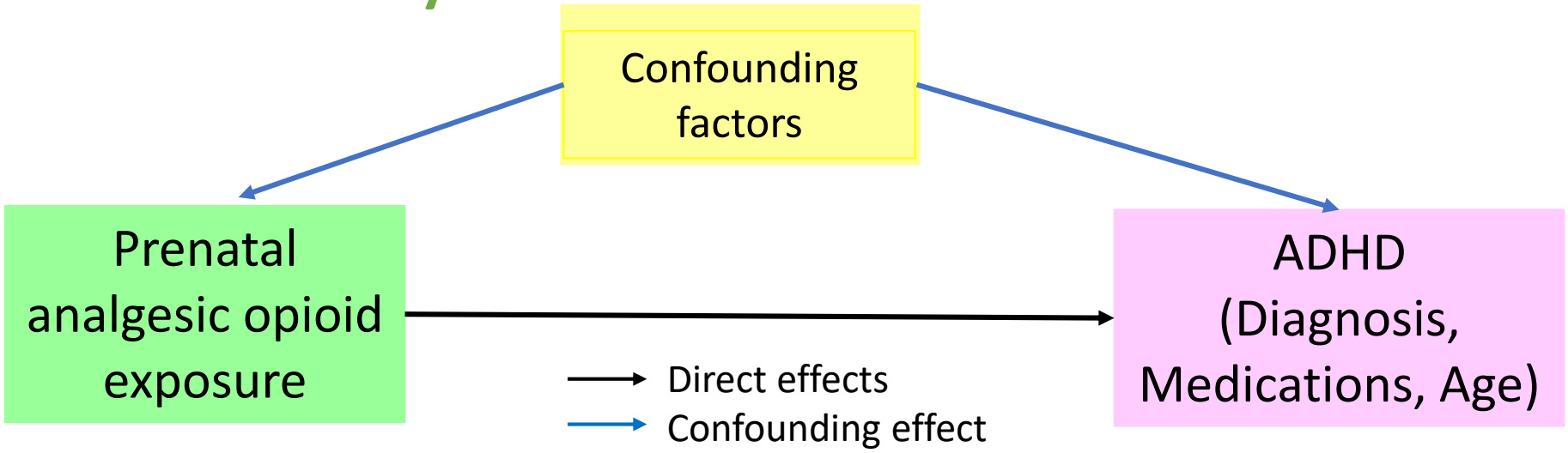
Research Question

Is prenatal analgesic opioid exposure associated with ADHD in children?

Aims

To examine the association of timing and duration of prenatal analgesic opioid exposure with ADHD in children.

Hypothesized Pathways



Methods ~1/5

Study Type :

A cohort study

Participants

- Norwegian Mother, Father and Child Cohort study (1999-2008)
- A nationwide birth cohort study linked to national health registries, with a mean (SD) follow-up of 10.8 years.

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Methods ~2/5

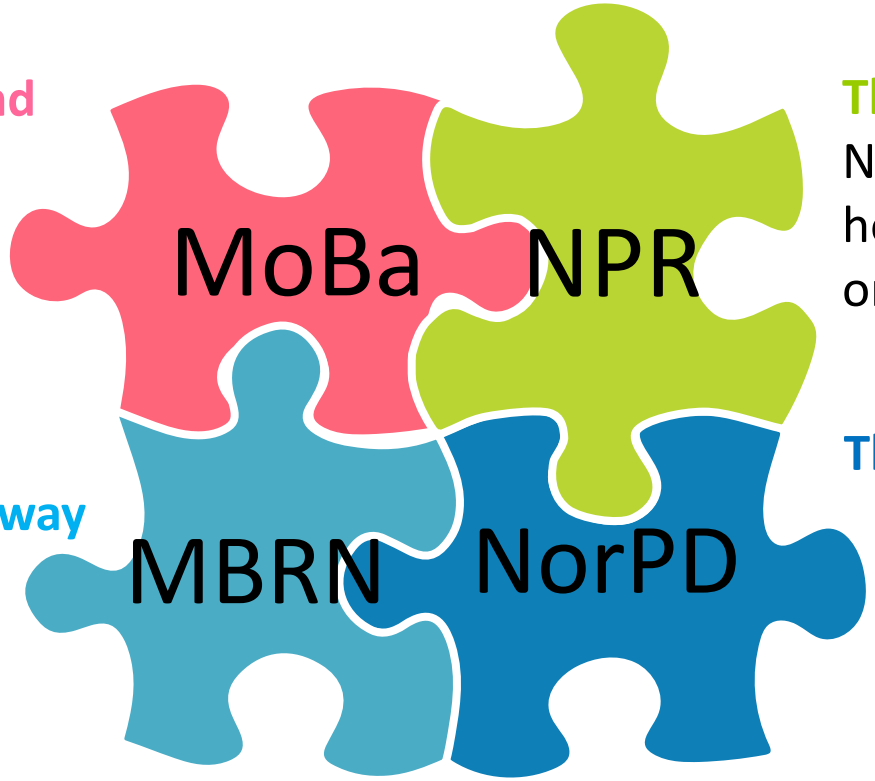
Data Collection

The Norwegian Mother, Father and Child Cohort study

MoBa is a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health.

The Medical Birth Registry of Norway

MBRN includes information on pregnancy, delivery, and neonatal health for all births from gestational week (GW) 12 in Norway.



The Norwegian Patient Registry

NPR contains records on admission to hospitals and specialist health care on an individual level since 2008.

The Norwegian Prescription Database

NorPD contains information about all prescribed medications to individuals in ambulatory care since 2004. All pharmacies in Norway register prescriptions electronically, and the information is sent in monthly.

Linking data via the woman's personal identification number and pregnancy sequence

Norsk NIPH

Norwegian Mother, Father and Child Cohort Study (MoBa)

moba

- MoBa is a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health.
- Pregnant women from all over Norway were recruited between 1999 and 2008 through a postal invitation in connection with their routine ultrasonography examination in GW 17 or 18.
- The initial participation rate was 41%, and the cohort now includes 114,500 children, 95,200 mothers, and 75,200 fathers.
- Mothers were followed up by paper-based questionnaires during pregnancy (in GW 17 [Q1] and 30 [Q3]) and after the child was born (at 6 months [Q4], 18 months, 3 years, 5 years [Q–5 years], 7 years, 8 years, 13 years, 14 years, and 16 to 17 years).

Source: https://www.fhi.no/moba-en

Methods ~3/5

Analgesic Opioid Exposure

- The exposed group included children of women who reported use of analgesic opioids in pregnancy, defined as reporting of ATC code N02A
- Two comparison groups
  - A broad group consisting of children of women who did not report use of analgesic opioids (unexposed group)
  - A narrower comparison group consisting of children of women who used analgesic opioids prior to pregnancy only (pre-pregnancy users only).

Outcomes

- Child ADHD diagnosis: at least 1 diagnosis of ADHD recorded in the NPR (ICD-10 code, F90) from 2008 to 2015 and/or at least 1 filled prescription for an ADHD medication in NorPD between 2004 and 2016.
- This was measured by 12 items from the Conners' Parent Rating Scale–Revised Short Form (CPRS-R) included in the MoBa questionnaire at Q–5 years.
- The sample with available outcome data at 5 years.

Methods~ 4/5

■ Potential Confounding Factors

1) Socioeconomic status and Lifestyle factors: maternal age, marital status, maternal education, maternal income, parity, pre-pregnancy BMI, folic acid intake, smoking habits, alcohol use, illicit drug use, symptoms of anxiety and depression, co-medications, episodes of pain, maternal chronic conditions, Adult ADHD Self-report Scale
2) Child characteristics: child gender, malformations, prematurity

■ Missing Data and Multiple Imputation

- Nearly 20% of the pregnancies had missing values in at least 1 of the sufficient confounders
- Under the assumption that data were missing at random, study imputed incomplete data via multiple imputation with chained equation (10 replications)

Methods~ 5/5

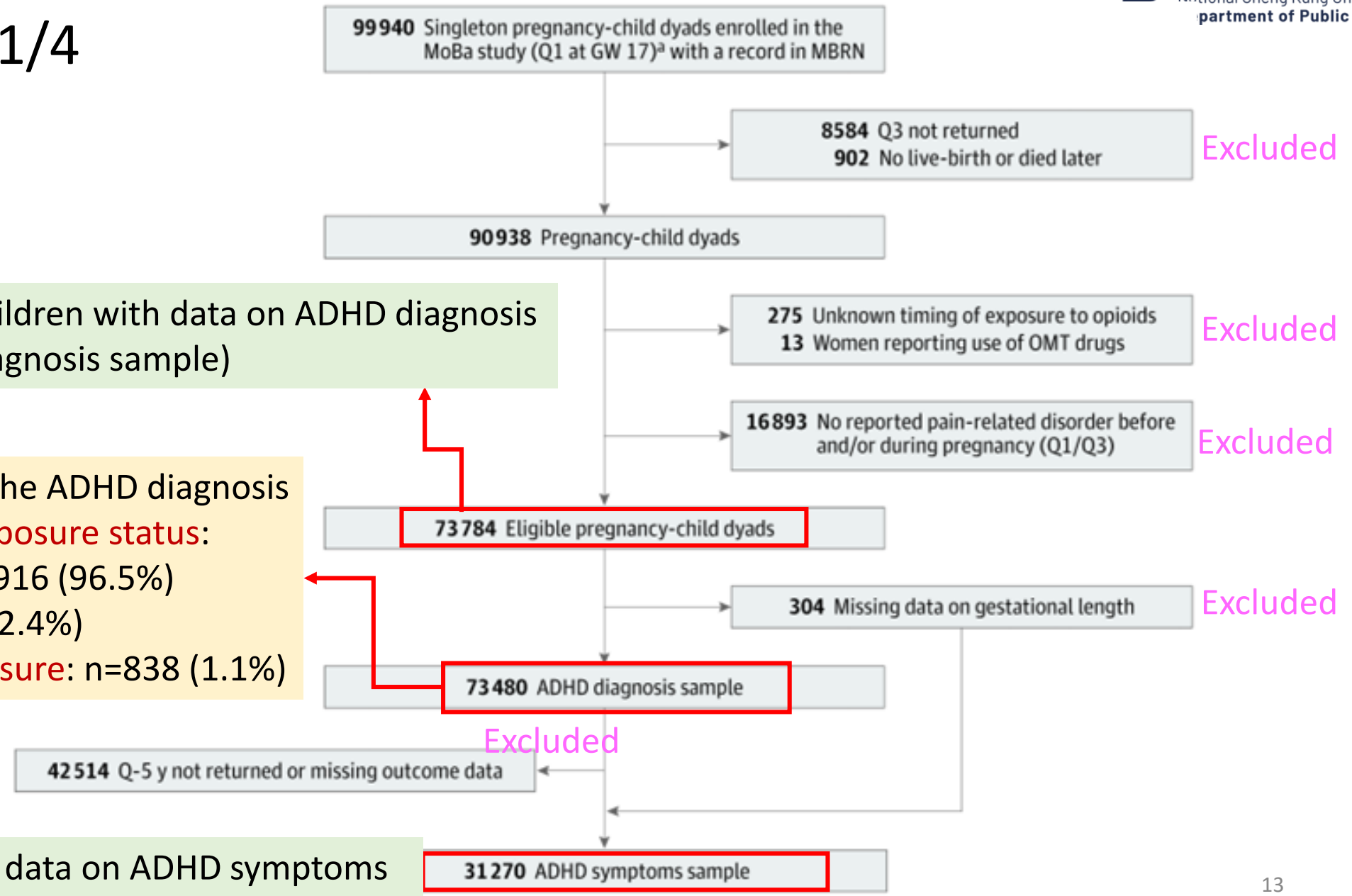
Statistical Analysis

1) Propensity score (PS)–based methods with inverse probability of treatment weights (IPTW)
2) Standardized mean differences
3) The hazard ratio (HR) for ADHD, performed crude and weighted Cox regression analysis with robust standard errors

Sensitivity Analyses

- Study conducted separate models for all exposure definitions that considered additional parental and child factors under alternate model specifications
- Stratified analysis by child sex
- Multiple sensitivity analyses

Results ~1/4



73,784 children with data on ADHD diagnosis (ADHD diagnosis sample)

73,480 Pregnancies in the ADHD diagnosis sample according to exposure status:

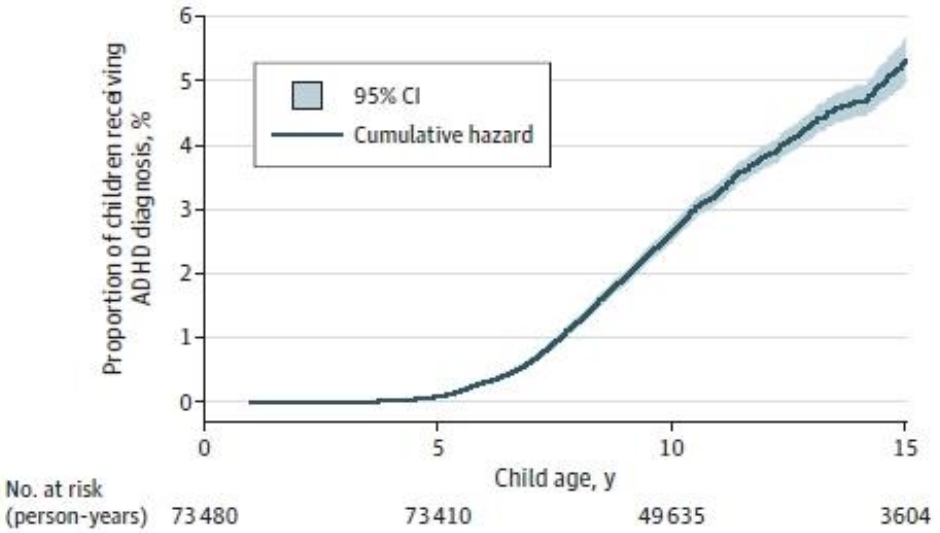
- ✓ No exposure: n=70,916 (96.5%)
- ✓ Exposure: n=1,726 (2.4%)
- ✓ Pre-pregnancy exposure: n=838 (1.1%)

31,270 children with data on ADHD symptoms

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Results ~ Child with ADHD cumulative hazard

Figure 2. Nelson-Aalen Cumulative Hazard Estimate and the Estimated Proportion of Children Receiving a Diagnosis for Attention-Deficit/Hyperactivity (ADHD) by Child Age



- In total, 2,211 children (3.0%) had ADHD, and its cumulative hazard.
- Fewer than 5 children were diagnosed before the age of 3 years. The incidence rate was highest at age 7 to 11 years, and the mean (SD) follow-up time was 10.8 (2.2) years.

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Results ~ADHD Symptoms

Table 2. Association Between Timing of Prenatal Analgesic Opioid Exposure and ADHD Diagnosis and ADHD Symptoms in Children Aged 5 Years

Exposure window	No.	Events, No.	IR per 1000 person-years	Crude HR (95% CI)	Weighted HR (95% CI)
ADHD diagnosis sample					
Exposure vs no exposure					
No opioids in early pregnancy	72 675	2166	2.8	1 [Reference]	1 [Reference]
Opioids in early pregnancy	805	45	5.0	1.76 (1.30 to 2.36)	1.34 (0.90 to 2.02)
No opioids in middle or late pregnancy	72 244	2145	2.8	1 [Reference]	1 [Reference]
Opioids in middle and/or late pregnancy	1236	66	4.9	1.76 (1.38 to 2.25)	1.32 (0.92 to 1.89)
Exposure vs prepregnancy exposure only					
Opioid use in prepregnancy only	838	39	4.2	1 [Reference]	1 [Reference]
Opioids in early pregnancy	805	45	5.0	1.17 (0.76 to 1.80)	1.13 (0.71 to 1.79)
Opioids in middle and/or late pregnancy	1236	66	4.9	1.16 (0.78 to 1.72)	1.08 (0.70 to 1.68)
ADHD symptoms sample					
Exposure window	**No.**	**Mean**	**SD**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Exposure vs no exposure					
No opioids in early pregnancy	30 973	1.38	0.39	[Reference]	[Reference]
Opioids in early pregnancy	297	1.41	0.42	0.09 (−0.03 to 0.22)	0.08 (−0.08 to 0.24)
No opioids in middle or late pregnancy	30 779	1.38	0.39	[Reference]	[Reference]
Opioids in middle and/or late pregnancy	491	1.40	0.38	0.05 (−0.04 to 0.14)	−0.02 (−0.13 to 0.08)
Exposure vs prepregnancy exposure only					
Opioids prepregnancy only	334	1.43	0.40	[Reference]	[Reference]
Opioids in early pregnancy	297	1.41	0.42	−0.04 (−0.20 to 0.13)	0.05 (−0.14 to 0.24)
Opioids in middle and/or late pregnancy	491	1.40	0.38	−0.08 (−0.22 to 0.07)	−0.02 (−0.19 to 0.16)

- In crude analysis, ever exposure to analgesic opioids during pregnancy was associated with a higher risk of ADHD (HR, 1.76; 95% CI, 1.38-2.25) compared with no exposure.
- After weighting, the association was attenuated (weighted HR, 1.32; 95% CI, 0.98-1.76).

- Exposure in early and middle and/or late pregnancy was associated with a moderate increased risk of ADHD in crude analysis when compared with no exposure in the same time window.

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Results ~ADHD Symptoms

Table 3. Association Between Duration of Prenatal Analgesic Opioid Exposure and ADHD Diagnosis and ADHD Symptoms in Children Aged 5 Years

Length of exposure	No.	Events, No.	IR per 1000 person-years	Crude HR (95% CI)	Weighted HR (95% CI)
ADHD diagnosis sample					
Exposed in ≤4 weeks	1084	48	4.0	1 [Reference]	1 [Reference]
Exposed ≥5 weeks	642	43	6.2	1.60 (1.06 to 2.41)	1.60 (1.04 to 2.47)
ADHD symptoms sample					
Length of exposure	No.	Mean	SD	Crude β (95% CI)	Weighted β (95% CI)
Exposed in ≤4 weeks	423	1.41	0.40	[Reference]	[Reference]
Exposed ≥5 weeks	244	1.40	0.40	−0.01 (−0.18 to 0.15)	−0.05 (−0.25 to 0.15)

- Exposure for 5 weeks or more of pregnancy was associated with increased risk of ADHD (weighted HR, 1.60; 95% CI, 1.04-2.47) compared with exposure for 4 or fewer weeks
- No associations were found in analyses of timing or duration (≥5 weeks vs ≤4 weeks: weighted β = −0.05; 95% CI: −0.25 to 0.15)

Discussion

- Study results may indicate that the increased risk of ADHD could be driven by longer duration of use.
- Heterogeneity of pain-related disorders
  - Study included a second comparator group consisting of women who used analgesic opioids prior to pregnancy only.
  - The group with pre-pregnancy opioid use only may be a fairer comparison group, with a more similar confounder structure as women using opioid analgesics in pregnancy because both groups have a history of analgesic opioid exposure.
- Opioid exposure with combined product of codeine and paracetamol
  - Using the combined product in a sensitivity analysis, study found no associations with ADHD or symptoms among children with vs without exposure.
  - Causal or due to bias is a debated topic
- ADHD and its symptoms are highly heritable, study cannot exclude the role of unmeasured genetic factors.

Limitations

- Selection bias
  - The MoBa study has a moderate participation rate (41%), with a possibility of self-selection of the healthiest women into the cohort.
- Outcome nondifferential misclassification
  - The ADHD symptoms were parent reported
- Residual confounding is possible
  - Study did not have information regarding dosage or duration of use of opioids in MoBa.
  - The lack of information on lifestyle and behavioral factors

thebmj

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

Jiseung Kang,[1,2,3] Hyeon Jin Kim,[4,5] Tae Kim,[1] Hyeri Lee,[4,5] Minji Kim,[4,5] Seung Won Lee,[6] Min Seo Kim,[7] Ai Koyanagi,[8] Lee Smith,[9] Guillaume Fond,[10] Laurent Boyer,[10] Masoud Rahmati,[10,11,12] Guillermo F López Sánchez,[13] Elena Dragioti,[14,15] Samuele Cortese,[16,17,18,19,20] Jae Il Shin,[21,22] Dong Keon Yon,[4,5,23] Marco Solmi[24,25,26,27]

BMJ 2024 ; 385 doi: https://doi.org/10.1136/bmj-2023-077664 (Published 24 April 2024)
Cite this as: *BMJ* 2024;385:e077664

BMJ

Key facts

- **ISSN:** 1756 1833
- **Impact factor:** 107.7
- **Frequency:** Weekly issues, published continuously online
- **First published:** 1840
- **Ranked 4**/167 in General and Internal Medicine
- **Editor-in-Chief:** Fiona Godlee, MD
- **Website:** bmj.com

2022 JOURNAL IMPACT FACTOR

107.7

View calculation

JOURNAL IMPACT FACTOR WITHOUT SELF CITATIONS

105.8

View calculation

CATEGORY

MEDICINE, GENERAL & INTERNAL

5/327

JCR YEAR	JCI RANK	JCI QUARTILE	JCI PERCENTILE
2022	5/327	Q1	98.62
2021	5/329	Q1	98.63
2020	6/315	Q1	98.25
2019	6/312	Q1	98.24
2018	7/304	Q1	97.86
2017	6/298	Q1	98.15

Introduction

- The global opioid crisis has generated widespread attention because of its extensive effect on public health.
- Prenatal and early life exposure to various substances, such as alcohol, tobacco, and some medications has been associated with long term neuropsychiatric and developmental outcomes in the child.
- Various neuropsychiatric disorders begin in childhood and result in established neuropsychiatric disorders later in life.
- Opioid exposure during the prenatal and infancy periods might be an emerging risk factor for neuropsychiatric outcomes.
- The effect of opioid exposure during the prenatal period is a topic of substantial importance but requires more in-depth examination.

Knowledge Gaps

Available Knowledge

Opioid use during pregnancy → Outcomes of neonatal, fetal brain function

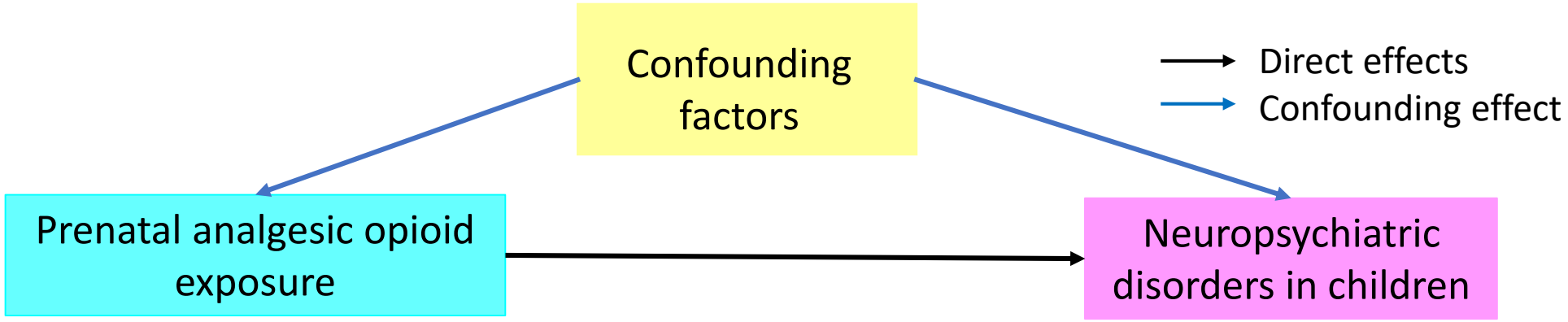
Limited Knowledge

Prenatal Opioid Exposure → Neuropsychiatric disorders in children

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Study Design

- **Research Question**
  - Is prenatal analgesic opioid exposure associated with neuropsychiatric disorders in children?
- **Study Aims**
  - To examine the association between maternal opioid exposure and the subsequent risk of neuropsychiatric disorders in children in South Korea.
  - To investigate the specific neuropsychiatric disorders potentially associated with fetal exposure to opioids.
- **Hypothesized Pathways**

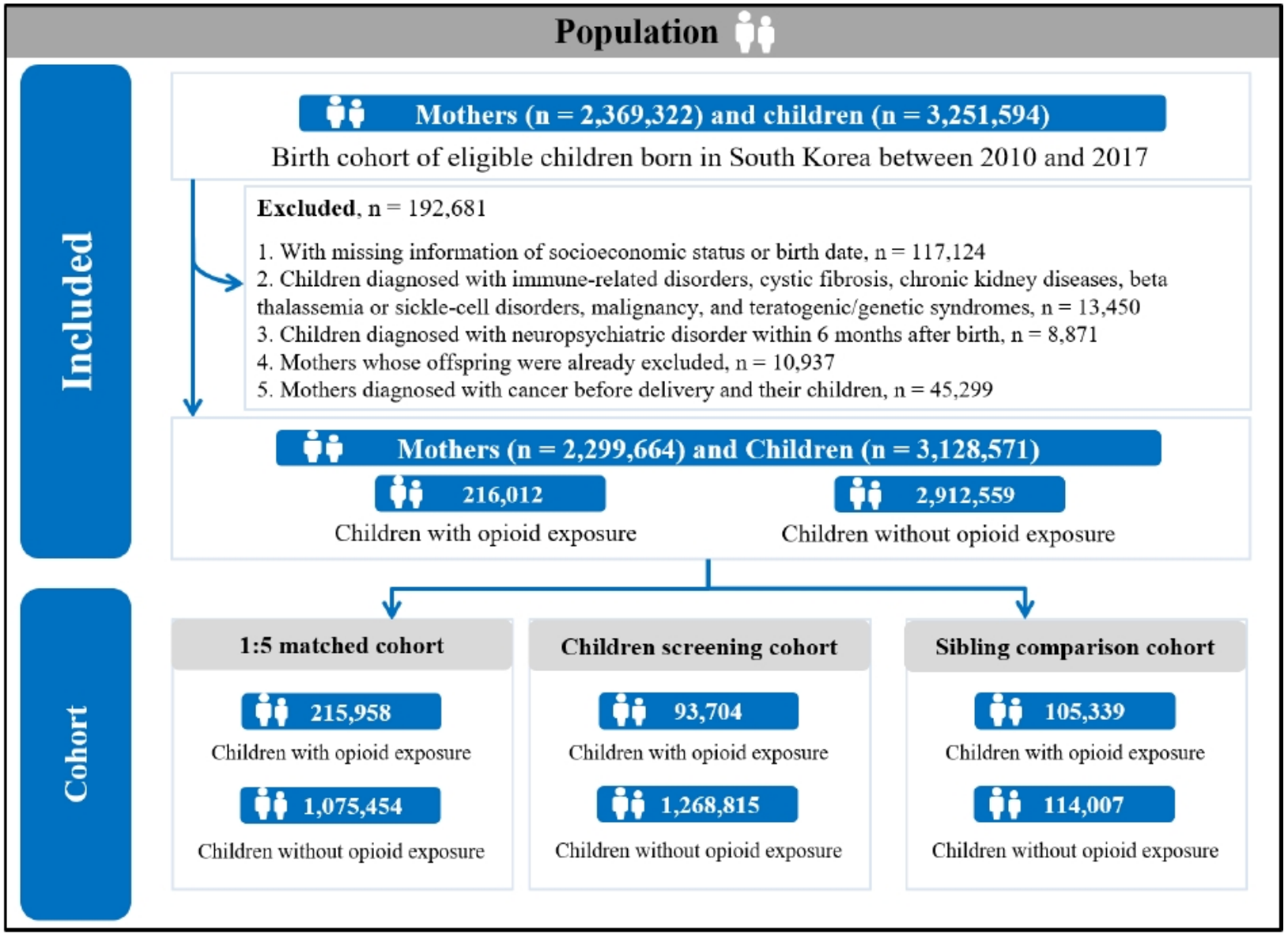


國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

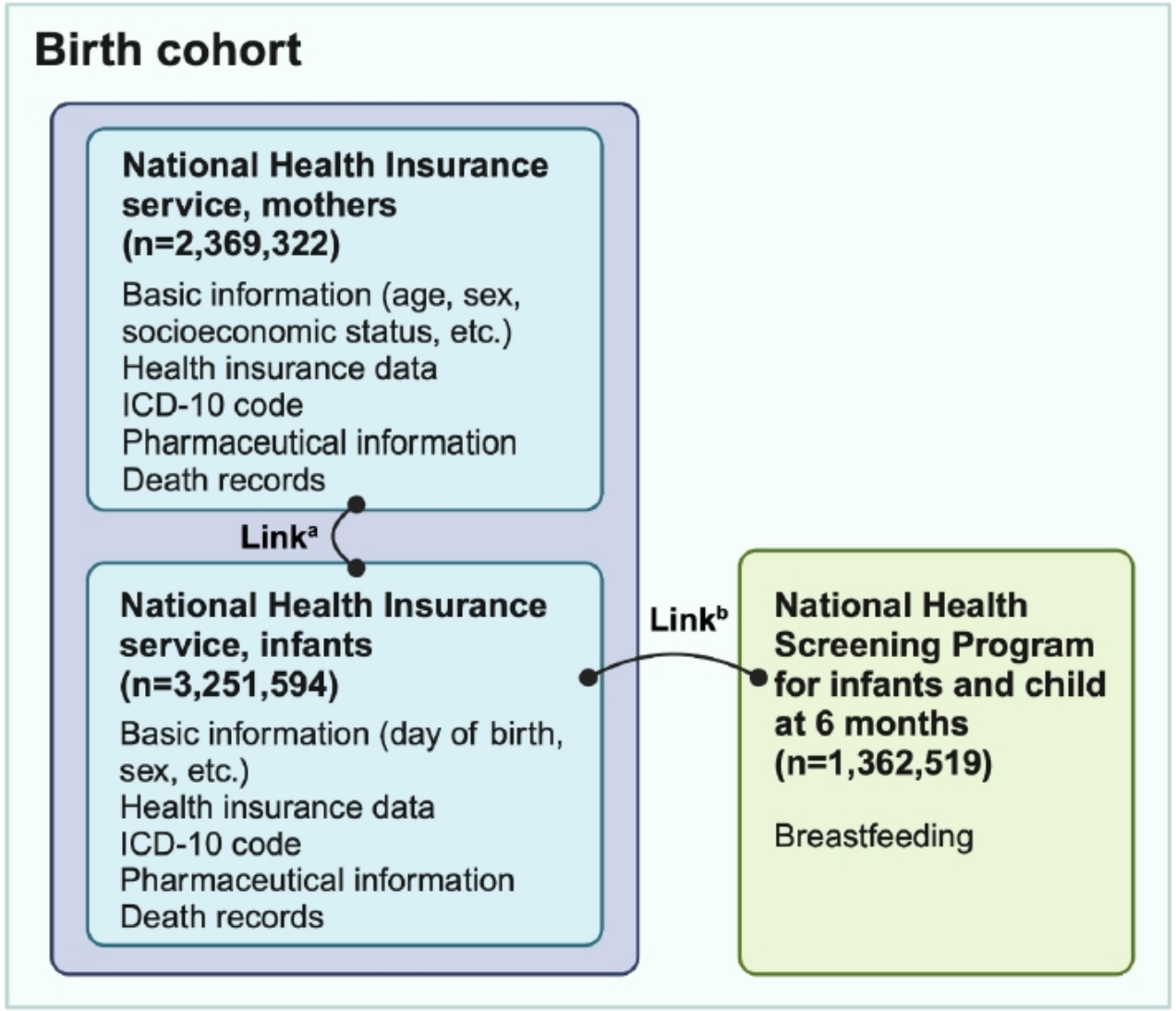
Methods

- **Study Type**
  - A Cohort Study
- **Data source**
  - The National Health Insurance Service (NHIS) of South Korea, which covers 98% of the South Korean population.
  - Data including baseline demographic details of individuals, outpatient and inpatient medical records, general health screening, and mortality information were collected through a universal health coverage system that provides comprehensive insurance services.
- **Participants**
  - Children born between 1 January 2010 and 31 December 2017.
  - The children were paired with their mothers using the unique family insurance identification numbers in the NHIS data

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health



國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health



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

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Methods~ Exposures

- Opioid exposure was defined on the basis of mothers receiving two or more opioid prescriptions within each trimester.
- Prenatal opioid exposure was classified into three categories:

Trimesters pregnancy: Opioid use in the first, second, and third trimesters, and more than one trimester

Opioid Intake: Morphine milligram equivalents and categorized into non-user, user of low dose, and user of high dose by using the 75th percentile as the cutoff (25.5 mg)

Opioid Prescriptions: Number of opioid prescriptions received (0-1, 2, or ≥3) and exposure duration (<30, 30-59, or ≥60 days) over whole pregnancy

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Methods ~ Outcomes

- The primary outcome
  - ➢ Neuropsychiatric disorders in children
  - ➢ Defined as having received at least two diagnoses of F00-99 in ICD-10 codes.
  - ➢ The infants with psychotic features were categorized as having severe neuropsychiatric disorders, and the other cases were classified as common neuropsychiatric disorders
- The psychiatric diagnoses
  - ➢diagnose psychiatric conditions and assign the F-code in ICD-10 codes.
- The specific diagnoses for children with neuropsychiatric disorders were categorized as follows : alcohol or drug misuse; mood disorders, excluding those with psychotic symptoms; anxiety and stress-related disorders; eating disorders; compulsive disorders; attention deficit hyperactivity disorder; autism spectrum disorder; and intellectual disability

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Methods~ Cohort (1/2)

A full unmatched cohort involving infants born between 2010 and 2017

Cohort 1
Full unmatched

Cohort 2
1:5 PS matched
Cohort A

Derived from the full unmatched cohort, pairing the exposed and unexposed groups in a 1:5 ratio using propensity score

Based on the full unmatched cohort, consisted of children from the NHS Program for Infants and Children at six months after birth

Cohort 3
Child screening cohort

Cohort 4
1:5 PS matched
Cohort B

1:5 propensity score matched cohort B consisting of study infants, with the exposed and unexposed groups matched

Cohort C, children who received at least one diagnosis based on the outcome criteria

Cohort 5
1:5 PS matched
Cohort C

Cohort 6
Sibling cohort A

Sibling pairs with differing exposure statuses: sibling cohort A is formed from the full unmatched cohort

Sibling cohort B is derived from the propensity score matched cohort A

Cohort 7
Sibling cohort B

Cohort 8
Sibling cohort C

Sibling cohort C is based on the child screening cohort

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Methods~ Cohort (2/2)

Propensity score matched cohort

- Individuals were matched in 1:5 ratio matching between the opioid exposed and unexposed groups within the entire cohort.
- Using the greedy nearest-neighbor algorithm, randomly matched the two groups based on propensity score values, ensuring minimal differences.

Child screening cohort

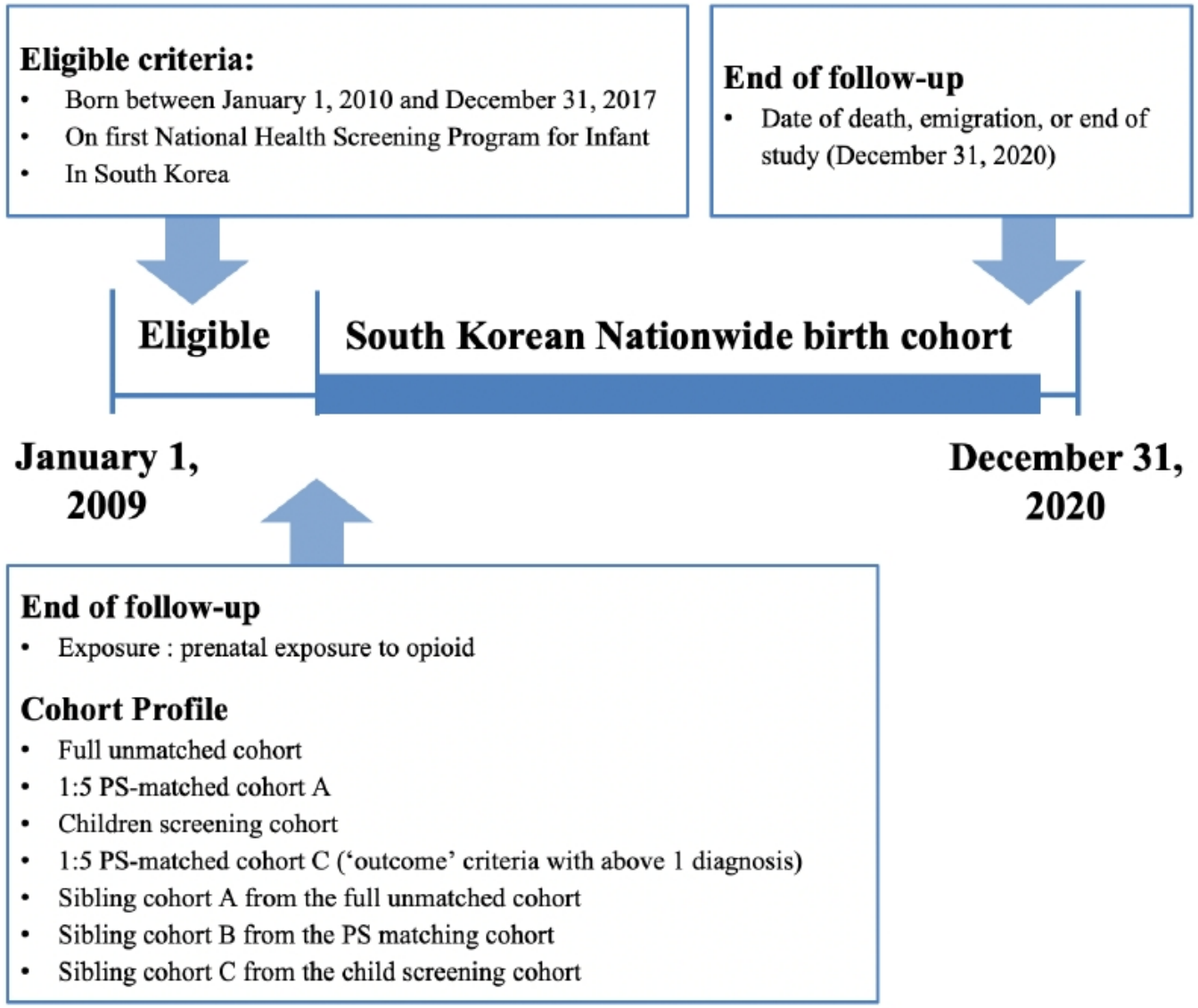
- A cohort of children who received the National Health Screening Program for infants and children at six months after birth to obtain information on their breastfeeding history

Sibling comparison cohort

- Approach to counter potential biases arising from unmeasured confounding factors, such as genetics, lifestyle, and environmental influences

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Study population and propensity score-matched cohort



Methods

Covariates

- Covariates related to mothers: maternal age, region of residence, household income level, parity, maternal mental illness, severe maternal morbidity score, delivery type, opioid prescription history, hospital admission, and outpatient, use of NSAIDs or acetaminophen during pregnancy, and history of maternal neuropsychiatric conditions.
- Covariates for infants: sex, birth season, year of delivery, preterm birth, low birth weight (≤2499 g), and breastfeeding history.

Statistical Analysis

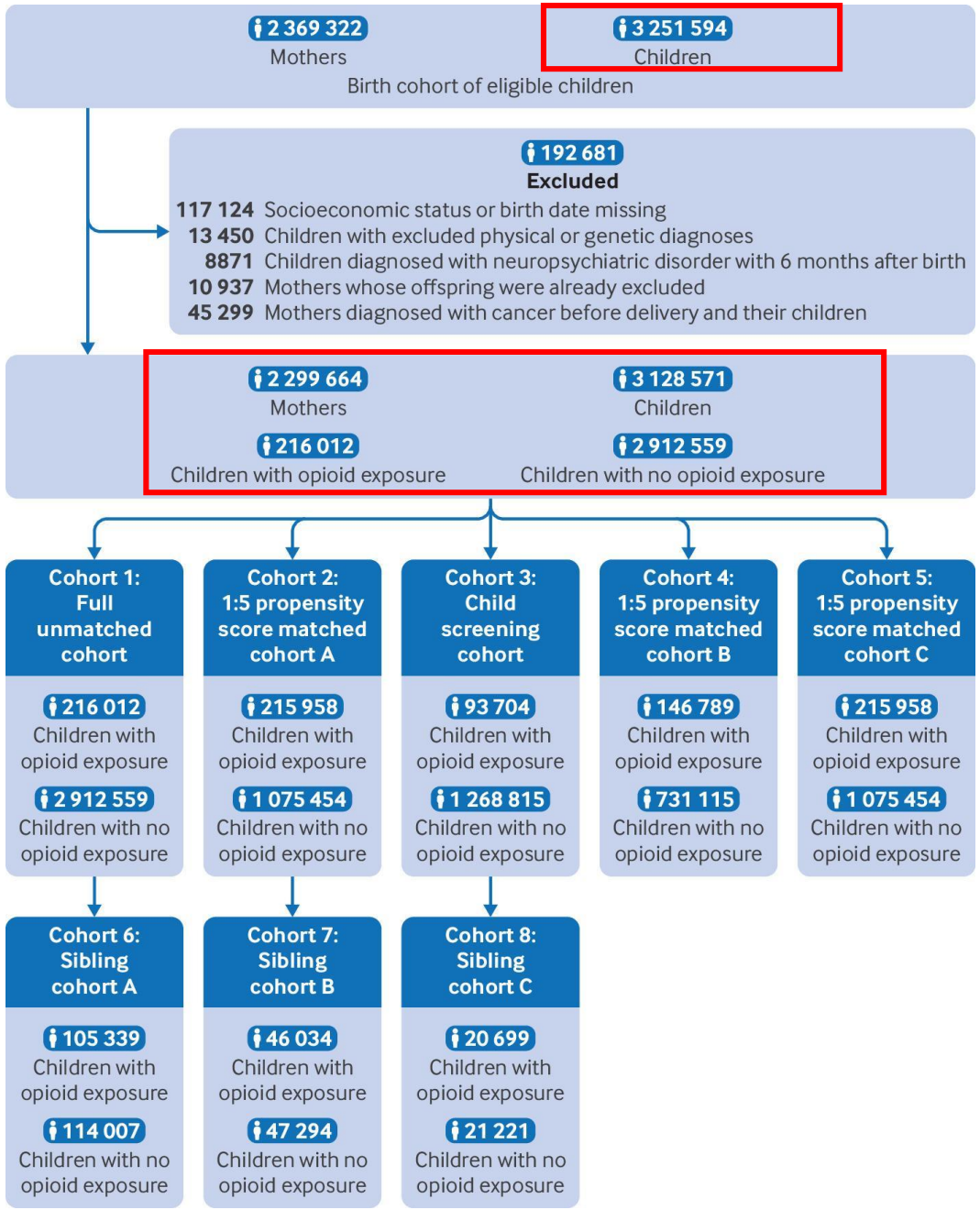
1) Cox proportional hazards model for estimation Hazard ratios
2) Stratification analysis
3) Sensitivity Analysis

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Results~ 1/5

In the full matched cohort, 2,299,664 mothers included in the study, 3,128,571 infants were linked and identified

- 93.1% (n=2,912,559) infants with no prenatal opioid exposure
- 6.9% (n=216 012) infants with prenatal opioid



All 3,251,594 infants (paired mothers, n=2,369,322; age 32.1 years), with follow-up from the date of birth until the date of death or 31 December 2020, were included.

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Results~ 2/5

Table 2 | Hazard ratio models of the association between prenatal opioid exposure during pregnancy and neuropsychiatric disorders in children with the 1:5 propensity score matched cohort A from 2010 to 2017

Outcome	No (%)	Neuropsychiatric disorder events (%)	Person years	Neuropsychiatric incidence rate, per 1000 years	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted‡
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)	7398 (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)*
Timing of opioid exposure:							
No opioid exposure	1 075 454 (83.3)	36 648 (3.4)	6 650 015	5.5	1 (reference)	1 (reference)	1 (reference)
First trimester only	87 567 (6.8)	3327 (3.8)	532 956	6.2	1.15 (1.11 to 1.19)*	1.12 (1.08 to 1.16)*	1.11 (1.07 to 1.15)*
Second trimester only	50 765 (3.9)	1599 (3.2)	290 988	5.5	1.02 (0.97 to 1.07)	1.03 (0.98 to 1.09)	1.04 (0.98 to 1.09)
Third trimester only	61 122 (4.7)	1863 (3.1)	354 590	5.3	0.96 (0.92 to 1.01)	1.01 (0.96 to 1.05)	1.01 (0.97 to 1.06)
More than one trimester	16 504 (1.3)	609 (3.7)	93 419	6.5	1.21 (1.12 to 1.31)*	1.25 (1.15 to 1.35)*	1.21 (1.11 to 1.31)*
Dose-dependent association, MME:							
None	1 075 454 (83.3)	36 648 (3.4)	6 650 015	5.5	1 (reference)	1 (reference)	1 (reference)
Low dose user	161 695 (12.5)	5732 (3.5)	1 000 524	5.7	1.04 (1.01 to 1.07)*	1.05 (1.02 to 1.08)*	1.06 (1.03 to 1.09)*
High dose user	54 263 (4.2)	1666 (3.1)	271 429	6.1	1.18 (1.12 to 1.24)*	1.18 (1.12 to 1.24)*	1.15 (1.09 to 1.21)*
Opioid prescriptions, days:							
0	1 075 454 (83.3)	36 648 (3.4)	6 650 015	5.5	1 (reference)	1 (reference)	1 (reference)
1-29	212 839 (16.5)	7267 (3.4)	1 255 284	5.8	1.07 (1.04 to 1.09)*	1.07 (1.05 to 1.10)*	1.07 (1.04 to 1.10)*
30-59	2824 (0.2)	112 (4.0)	15 196	7.4	1.39 (1.15 to 1.67)*	1.44 (1.20 to 1.73)*	1.34 (1.12 to 1.62)*
≥60	295 (0.0)	19 (6.4)	1,473	12.9	2.54 (1.62 to 3.97)*	2.53 (1.62 to 3.96)*	1.95 (1.24 to 3.06)*
No of opioid prescriptions:							
0-1	1 075 454 (83.3)	36 648 (3.4)	6 650 015	5.5	1 (reference)	1 (reference)	1 (reference)
2	104 991 (8.1)	3508 (3.3)	626 586	5.6	1.03 (0.99 to 1.06)	1.03 (0.99 to 1.06)	1.03 (1.00 to 1.07)
≥3	110 967 (8.6)	3890 (3.5)	645 367	6.0	1.11 (1.08 to 1.15)*	1.13 (1.09 to 1.17)*	1.12 (1.08 to 1.16)*

Prenatal exposure to opioids was associated with an increased risk of neuropsychiatric disorders

the first trimester showed an increased risk of neuropsychiatric disorders

Risk of neuropsychiatric disorders in the offspring increased in a dose-dependent manner with opioid dose

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Results~ 3/5

Table 3 | Stratification analysis for hazard ratio models of the association between opioid exposure during pregnancy and neuropsychiatric disorders in children with the 1:5 propensity score matched cohort A from 2010 to 2017

Variables	No (%)	Neuropsychiatric disorder events (%)	Person years	Neuropsychiatric incidence rate, per 1000 years	Hazard ratio (95% CI)		
					Crude	Adjusted†	Fully adjusted‡
Infant's sex:							
Male	110 487 (51.2)	5139 (4.7)	647 771	7.9	1.06 (1.03 to 1.09)*	1.06 (1.03 to 1.09)*	1.06 (1.03 to 1.09)*
Female	105 471 (48.8)	2259 (2.1)	624 182	3.6	1.11 (1.06 to 1.16)*	1.11 (1.06 to 1.17)*	1.11 (1.06 to 1.16)*
Season of birth:							
Spring	53 214 (24.6)	1731 (3.3)	308 294	5.6	1.10 (1.04 to 1.15)*	1.11 (1.05 to 1.17)*	1.10 (1.05 to 1.16)*
Summer	58 434 (27.1)	2061 (3.5)	345 916	6.0	1.09 (1.04 to 1.14)*	1.10 (1.04 to 1.15)*	1.09 (1.04 to 1.15)*
Autumn	51 687 (23.9)	1838 (3.6)	307 232	6.0	1.03 (0.98 to 1.08)	1.03 (0.98 to 1.09)	1.03 (0.98 to 1.08)
Winter	52 623 (24.4)	1768 (3.4)	310 511	5.7	1.07 (1.02 to 1.13)*	1.08 (1.02 to 1.13)*	1.08 (1.02 to 1.13)*
Year of delivery:							
2010-12	69 874 (32.4)	4315 (6.2)	604 966	7.1	1.11 (1.07 to 1.15)*	1.11 (1.07 to 1.14)*	1.10 (1.07 to 1.14)*
2013-15	76 952 (35.6)	2300 (3.0)	455 484	5.0	1.05 (1.00 to 1.09)	1.04 (1.00 to 1.09)	1.04 (1.00 to 1.09)
2016-17	69 132 (32.0)	783 (1.1)	211 503	3.7	1.02 (0.94 to 1.10)	1.03 (0.95 to 1.11)	1.03 (0.95 to 1.11)
Maternal medical conditions:							
No mental illness	168 481 (78.0)	4437 (2.6)	989 756	4.5	1.06 (1.03 to 1.10)*	1.07 (1.03 to 1.10)*	1.07 (1.03 to 1.10)*
Mental illness	47 477 (22.0)	2961 (6.2)	282 197	10.5	1.06 (1.02 to 1.11)*	1.07 (1.03 to 1.11)*	1.07 (1.03 to 1.11)*
Delivery type:							
Vaginal delivery	115 174 (53.3)	3722 (3.2)	695 745	5.3	1.03 (1.00 to 1.07)	1.04 (1.00 to 1.08)	1.04 (1.00 to 1.08)
Caesarean section	100 784 (46.7)	3676 (3.7)	576 208	6.4	1.09 (1.05 to 1.13)*	1.13 (1.09 to 1.17)*	1.12 (1.08 to 1.17)*

The subsequent risk of neuropsychiatric disorders with maternal opioid use was associated with caesarean sections in comparison to vaginal of hazard ratio 1.08 (95% CI 1.03 to 1.14)

Table 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 propensity score matched cohort A from 2010 to 2017

	Overall			Low dose users (<25.5 MME)			High dose users (≥25.5 MME)		
Outcome	Events, no (%)	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)‡
Mood disorders, excluding those with psychotic symptoms:									
No opioid exposure	2594/1 075 454 (0.2)	1 (reference)	1 (reference)	2594/1 075 454 (0.2)	1 (reference)	1 (reference)	2594/1 075 454 (0.2)	1 (reference)	1 (reference)
Opioid exposure	535/215 958 (0.3)	1.15 (1.05 to 1.27)*	1.15 (1.04 to 1.26)*	418/161 695 (0.3)	1.12 (1.01 to 1.24)*	1.12 (1.01 to 1.24)*	117/54 263 (0.2)	1.29 (1.07 to 1.55)*	1.24 (1.03 to 1.50)*
Attention deficit hyperactivity disorder:									
No opioid exposure	12 170/1 075 454 (1.1)	1 (reference)	1 (reference)	12 170/1 075 454 (1.1)	1 (reference)	1 (reference)	12 170/1 075 454 (1.1)	1 (reference)	1 (reference)
Opioid exposure	2452/215 958 (1.1)	1.12 (1.07 to 1.17)*	1.12 (1.07 to 1.16)*	1953/161 695 (1.2)	1.11 (1.06 to 1.16)*	1.11 (1.06 to 1.16)*	499/54 263 (0.9)	1.18 (1.08 to 1.29)*	1.14 (1.04 to 1.25)*
Intellectual disability:									
No opioid exposure	3554/1 075 454 (0.3)	1 (reference)	1 (reference)	3554/1 075 454 (0.3)	1 (reference)	1 (reference)	3554/1 075 454 (0.3)	1 (reference)	1 (reference)
Opioid exposure	864/215 958 (0.4)	1.31 (1.21 to 1.41)*	1.30 (1.21 to 1.40)*	651/161 695 (0.4)	1.23 (1.13 to 1.34)*	1.23 (1.13 to 1.34)*	213/54 263 (0.4)	1.63 (1.42 to 1.87)*	1.59 (1.39 to 1.83)*
Severe neuropsychiatric disorder:									
No opioid exposure	1354/1 040 160 (0.1)	1 (reference)	1 (reference)	1354/1 040 160 (0.1)	1 (reference)	1 (reference)	1354/1 040 160 (0.1)	1 (reference)	1 (reference)
Opioid exposure	318/208 878 (0.2)	1.30 (1.15 to 1.47)*	1.30 (1.15 to 1.46)*	253/156 216 (0.2)	1.29 (1.13 to 1.47)*	1.29 (1.13 to 1.48)*	65/52 662 (0.1)	1.36 (1.06 to 1.74)*	1.31 (1.02 to 1.68)*

Maternal opioid use increased the risk of several neuropsychiatric diseases, including mood disorder (adjusted hazard ratio 1.15, 95% CI 1.04 to 1.26), attention deficit hyperactivity disorder (1.12, 95% CI 1.07 to 1.17), and intellectual disability (1.30, 95% CI 1.21 to 1.40)

國立成功大學公共衛生學系
National Cheng Kung University
Department of Public Health

Results~ 5/5

Table 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, propensity score matched cohort A, and child screening cohort from 2010 to 2017

Opioid exposure during pregnancy	No (%)	Neuropsychiatric disorder events (%)	Person years	Neuropsychiatric incidence rate, per 1000 person years	Hazard ratio (95% CI)		
					Crude*	Adjusted†	Fully adjusted‡
Sibling cohort A from the full unmatched cohort:							
No exposure	114 007 (52.0)	5008 (4.4)	760 040	6.6	1 (reference)	1 (reference)	1 (reference)
Exposure	105 339 (48.0)	2754 (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 propensity score matched cohort A:							
No exposure	47 294 (50.7)	2049 (4.3)	303 650	6.9	1 (reference)	1 (reference)	1 (reference)
Exposure	46 034 (49.3)	1391 (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:							
No exposure	21 221 (50.6)	1066 (5.0)	152 981	7.0	1 (reference)	1 (reference)	1 (reference)
Exposure	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)

Associations were observed when performing the same analysis in the full unmatched and child screening cohorts stratified by breastfeeding history.

No significant associations were noted between breastfeeding and subsequent risk for neuropsychiatric disorders.

Discussion

- An increased risk of neuropsychiatric disorders was observed and limited to high opioid doses, more than one opioid, longer duration of exposure, opioid exposure during early pregnancy, and only to certain specific neuropsychiatric disorders
- Comparison with other studies, study is large scale nationwide cohort study (3.12 million pregnancies), offers a more sophisticated understanding supported by statistical analyses, control potential confounders
- The elucidated mechanisms presented in this study are speculative and require further validation.
- These results support cautious opioid prescribing during pregnancy, clinicians and patients should pay attention to opioid use in the first trimester or caesarean section, high dose, or long-term intake.

Limitations

- While prescriptions are recorded, they may not always reflect the actual consumption of the medication, leading to potential exposure misclassification.
- Study could not account for other potential risk factors for neuropsychiatric disorders, such as infection, epilepsy, fever, and vaccination. And, NSAIDs are not categorized as prescription drugs, an underestimation regarding their consumption is possible.
- The cohort was restricted to pregnancies that resulted in live births and excluded terminated pregnancies due to the absence of gestational age data for non-live births.

Comparison of the two papers

	Paper 1	Paper 2
Study Question	Is prenatal analgesic opioid exposure associated with ADHD in children?	Is there association between maternal opioid exposure and the subsequent risk of neuropsychiatric disorders in children?
Study Design	A cohort study	
Data Source	Data from the MoBa, the MBRN, the NorPD, and the NPR, a nationwide birth cohort study linked to national health registries	Data from the National Health Insurance Service (NHIS) of South Korea
Participants	A total of 73,784 live-born singleton children born to 62,013 mothers	3,251,594 infants ,paired mothers n=2,369,322

Criticism on method of participants selection

	Paper 1	Paper 2
Participants selection	• Pregnant women from all over Norway were recruited through a postal invitation in connection with their routine ultrasonography examination in GW 17 or 18. • Mothers were followed up by paper-based questionnaires during pregnancy.	• Children were subsequently paired with their mothers using the unique family insurance identification numbers allocated to every individual in the NHIS data. • Study used eight cohorts to comprehensively understand the association between maternal opioid prescriptions and risk of neuropsychiatric disorders in their child.

- The self-selection of the healthiest women into the cohort, it might have selection bias impact on the results. It was probably non-differential misclassification on outcome.
- To mitigate potential confounding and to balance demographic covariates between the groups exposed to opioids and groups not exposed, study use of various study designs, including the full unmatched population based, propensity score matched, child screening, sibling comparison cohorts from the full unmatched, propensity score matched, and child screening cohorts, and multiple subgroup analyses, enhanced the results of our findings, exposure misclassification due to over-the-counter was unlikely.

Criticism on Confounding

	Paper 1	Paper 2
Covariates	• Maternal age, marital status, maternal education, maternal income, parity, pre-pregnancy BMI, folic acid supplement, smoking habits, alcohol use, illicit drug use, maternal chronic conditions in early pregnancy, symptoms of anxiety and depression, number of pain episodes and co-medications during pregnancy, and familial risk of ADHD. • Additional factors eg, child and paternal characteristics, maternal ADHD Self-report Scale.	• Covariates related to mothers: maternal age at delivery, region of residence, household income level, parity, maternal mental illness, severe maternal morbidity score, delivery type, opioid prescription history, hospital admission, and outpatient in the year before pregnancy, use of NSAIDs or acetaminophen during pregnancy, and history of maternal neuropsychiatric. • Covariates for infants: sex, birth season, year of delivery, preterm birth, low birth weight, and breastfeeding history.
Mitigate potential confounding	• Propensity score (PS)–based methods with inverse probability of treatment weights (IPTW) • The hazard ratio (HR) for ADHD, we performed crude and weighted Cox regression analysis with robust standard errors. • Sensitivity analyses	• Hazard ratios with 95% confidence intervals (CIs) using Cox proportional hazards model for estimation • A dose dependent analysis, a multiplicative interaction analysis

Association of Timing and Duration of Prenatal Analgesic Opioid Exposure With Attention-Deficit/Hyperactivity Disorder in Children

Commentor:
2st Year PhD student
曾元聰(Yuan-Tsung Tseng)

Comment 1

- In this study, the authors acknowledge they cannot exclude the influence of "**pain severity**" and the effects of individual components in pharmaceutical combinations, which may lead to the possibility of confounding by indication.

- Do you think this limitation potentially biases the observed associations in this study?

Comment 2

- Why would the risk of **ADHD diagnosis** be slightly elevated in the long-term exposure group, while **ADHD symptoms** reported by parents when children were 5 years old showed no significant change?

Table 3. Association Between Duration of Prenatal Analgesic Opioid Exposure and ADHD Diagnosis and ADHD Symptoms in Children Aged 5 Years

Length of exposure	No.	Events, No.	IR per 1000 person-years	Crude HR (95% CI)	Weighted HR (95% CI)
ADHD diagnosis sample					
Exposed in ≤4 weeks	1084	48	4.0	1 [Reference]	1 [Reference]
Exposed ≥5 weeks	642	43	6.2	1.60 (1.06 to 2.41)	1.60 (1.04 to 2.47)
ADHD symptoms sample					
Length of exposure	**No.**	**Mean**	**SD**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Exposed in ≤4 weeks	423	1.41	0.40	[Reference]	[Reference]
Exposed ≥5 weeks	244	1.40	0.40	−0.01 (−0.18 to 0.15)	−0.05 (−0.25 to 0.15)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio; IR, incidence rate.

Response to Comment 1

- All women included in the study reported having an underlying indication for treatment with analgesic opioids, ie, pain conditions. There is a heterogeneity of pain-related disorders
- Study included a second comparator group, pre-pregnancy opioid use only may be a fairer comparison group, with a more similar confounder structure as women using opioid analgesics in pregnancy.
- Residual confounding by indication for use is reduced.
- Future studies on the long-term safety of analgesic opioids should include measures of dose and pain severity and include more domains of neurodevelopment, including cognition.

Response to Comment 2

Table 3. Association Between Duration of Prenatal Analgesic Opioid Exposure and ADHD Diagnosis and ADHD Symptoms in Children Aged 5 Years

Length of exposure	No.	Events, No.	IR per 1000 person-years	Crude HR (95% CI)	Weighted HR (95% CI)
ADHD diagnosis sample					
Exposed in ≤4 weeks	1084	48	4.0	1 [Reference]	1 [Reference]
Exposed ≥5 weeks	642	43	6.2	1.60 (1.06 to 2.41)	1.60 (1.04 to 2.47)
ADHD symptoms sample					
Length of exposure	**No.**	**Mean**	**SD**	**Crude β (95% CI)**	**Weighted β (95% CI)**
Exposed in ≤4 weeks	423	1.41	0.40	[Reference]	[Reference]
Exposed ≥5 weeks	244	1.40	0.40	−0.01 (−0.18 to 0.15)	−0.05 (−0.25 to 0.15)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio; IR, incidence rate.

- If the association between prenatal analgesic opioid exposure and ADHD were causal, we would have expected a higher proportion of children displaying ADHD symptoms at age 5 years and a positive association in our positive control analysis of opioid-containing cough medications.
- It could not rule out that loss of follow-up in the MoBa study have affected our findings on ADHD symptoms.

Comment for Chiu-wen's paper

PhD 2nd Year Student
T88121502 Hung-Jui Chen
2025/03/19

Comment 1

In table 1, the number and percentage of the 'At-risk newborn' covariate seems different between the 'Full unmatched cohort' and the 'Propensity score matched cohort A'. Could you explain why?

Characteristics	Full unmatched cohort (n=3 128 571)*		Propensity score matched cohort A (n=1 291 412)†		Standardised mean difference‡
	Children with prenatal opioid exposure	Children without prenatal exposure	Children with prenatal opioid exposure	Children without prenatal exposure	
Total, no	216 012	2 912 559	215 958	1 075 454	—
Unmatching variables					
Delivery type, no (%):					0.16
Vaginal delivery	115 193 (53.3)	1 693 716 (58.2)	115 174 (53.3)	659 523 (61.3)	
Caesarean section	100 819 (46.7)	1 218 843 (41.9)	100 784 (46.7)	415 931 (38.7)	
Use of NSAIDs during pregnancy, no (%)	103 912 (48.1)	482 329 (16.6)	103 877 (48.1)	204 829 (19.1)	0.65
Use of acetaminophen during pregnancy, no (%)	148 024 (68.5)	789 528 (27.1)	147 981 (68.5)	328 716 (30.6)	0.82
Infant characteristics:					
Infant sex, no (%)					<0.01
Male	110 511 (51.2)	1 495 374 (51.3)	110 487 (51.2)	551 281 (51.3)	
Female	105 501 (48.8)	1 417 185 (48.7)	105 471 (48.8)	524 173 (48.7)	
Birth season, no (%)					0.07
Spring	53 228 (24.6)	756 304 (26.0)	53 214 (24.6)	279 000 (25.9)	
Summer	58 458 (27.1)	708 808 (24.3)	58 434 (27.1)	261 523 (24.3)	
Autumn	51 697 (23.9)	718 496 (24.7)	51 687 (23.9)	268 571 (25.0)	
Winter	52 629 (24.4)	728 951 (25.0)	52 623 (24.4)	266 360 (24.8)	
Year of delivery, no (%)					0.11
2010 to 2012	69 885 (32.4)	1 119 845 (38.5)	69 874 (32.4)	400 367 (37.2)	
2013 to 2015	76 973 (35.6)	997 353 (34.2)	76 952 (35.6)	378 610 (35.2)	
2016 to 2017	69 154 (32.0)	795 361 (27.3)	69 132 (32.0)	296 477 (27.6)	
At-risk newborn, no (%)					0.07
Preterm birth	10 817 (5.0)	103 949 (3.6)	203 182 (94.1)	1 028 054 (95.6)	
Low birth weight	7860 (3.6)	83 354 (2.9)	12 776 (5.9)	47 400 (4.4)	

Comment 2

In the method, mothers were categorized into non-user, user of low dose, and user of high dose by using the **75th percentile** as the cutoff.

What is the reason for selecting the 75th percentile rather than the 50th percentile or dividing the data into quartiles?"

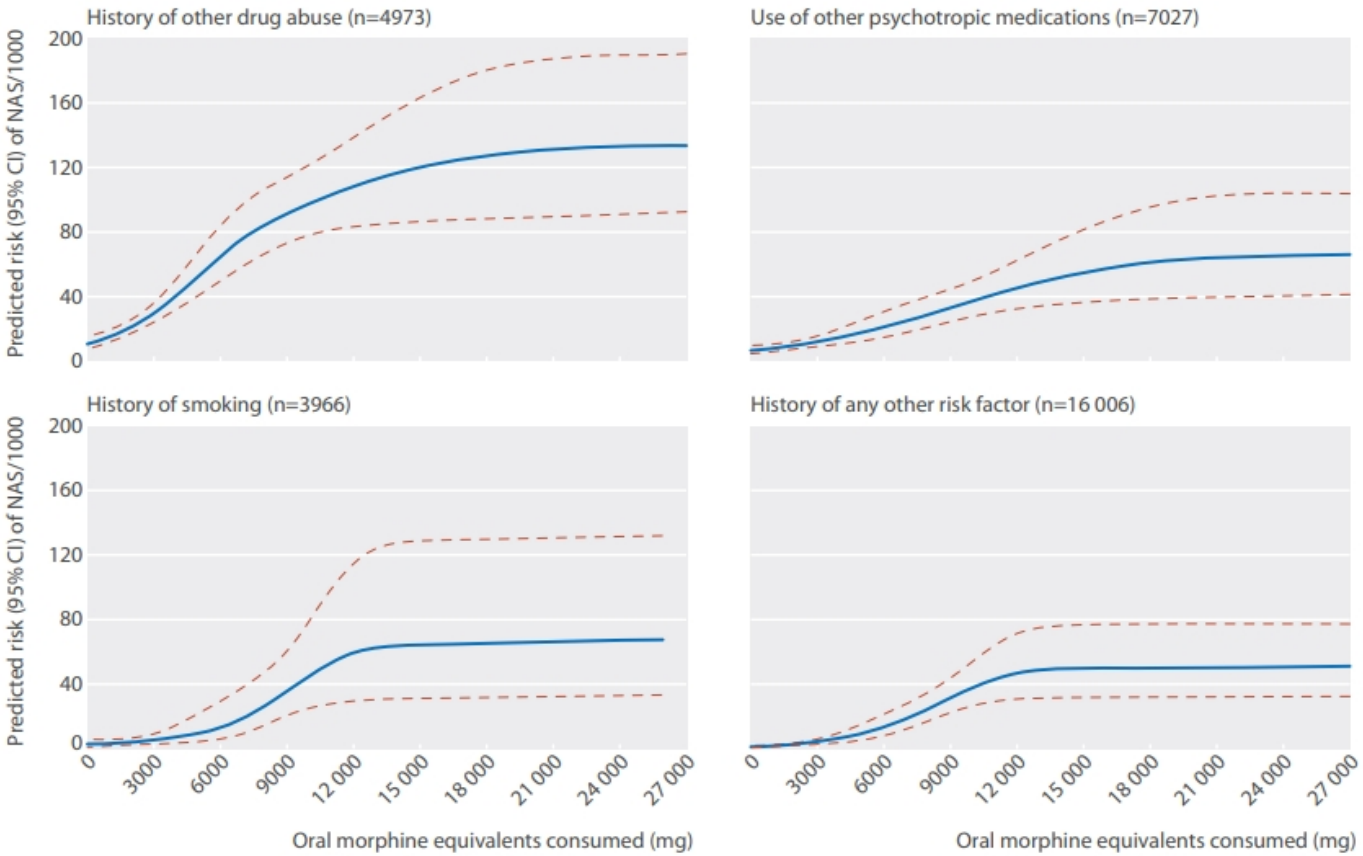
Reply to Comment 1

	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	
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)	
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

- After 1:5 propensity score matching, the standardized mean difference values were less than 0.1, indicating no major imbalances in the general characteristics.
- Study could not account for other potential risk factors for neuropsychiatric disorders, such as infection, epilepsy, fever, and vaccination. Because NSAIDs are not categorized as prescription drugs, an underestimation regarding their consumption is possible.

Reply to Comment 2

- Following the exposure criteria as per previous studies. Opioid exposure assessed characteristics including duration of therapy and cumulative dose (in morphine equivalent milligrams). For the dose-response analysis, it was estimated cumulative dose in morphine equivalent mg.
- The characteristics of prescription opioid exposure, including cumulative days of use and cumulative dose (in oral morphine equivalents), during pregnancy were reported as median (interquartile range)
- The total opioid intake was calculated based on morphine milligram equivalents, and mothers were categorized into non-user, user of low dose, and user of high dose by using the 75th percentile as the cutoff (25.5 morphine mg equivalents).



Source: BMJ 2015; 350 doi: https://doi.org/10.1136/bmj.h2102 (Published 14 May 2015)