



14: Nordic-Asia Pacific Collaboration in Real-World Evidence Studies: Lessons Learned and Opportunities for Future Research Networks

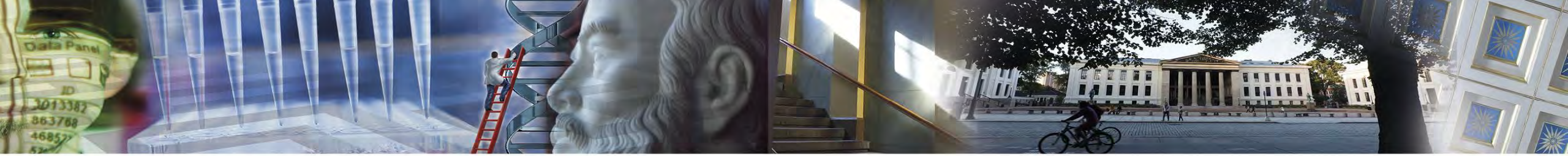
Moderator

Marleen van Gelder, PhD; Radboud university medical center, Nijmegen, Netherlands

Speakers

Hedvig Nordeng, PhD; University of Oslo, Oslo, Norway

Fei-Yuan Sharon Hsiao, PhD; College of Medicine, National Taiwan University, Taipei, Taiwan



UiO • **University of Oslo**

Radboudumc

Moderator Introduction

Marleen van Gelder, PhD

- Assistant professor in Pharmacoepidemiology, section Biostatistics, IQ Health science department, Radboud university medical center, Nijmegen, The Netherlands (since 2017)
- Senior researcher, Dept. of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo (since 2023)
- Member subcommittee on the Classification of Substances Toxic to Reproduction of the Health Council of the Netherlands (since 2022)
- Fellow, International Society for Pharmacoepidemiology (FISPE) (2025)





Medications are marketed globally...

Pandemics are global...



If you want to go fast, go alone.
If you want to go far,

GO TOGETHER.

African Proverb



Perinatal Pharmacoepidemiology

- Majority of pregnant women use medication in pregnancy
(Europe and North America: 80-90%)
- Only 5% of medications are adequately monitored, tested, and labeled with safety information for use during pregnancy and breastfeeding
- Methodologically challenging
 - Observational studies
 - Timing of events
 - Sample sizes





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ISPOR Real-World Evidence Summit 2025: Through the Lens of Asia Pacific
28-30 September 2025 | Tokyo, Japan

REAL-WORLD DATA SOURCES AND REAL-WORLD EVIDENCE IN NORDIC COUNTRIES



PROFESSOR HEDVIG NORDENG

HEAD, PHARMACOEPIDEMIOLOGY AND DRUG SAFETY RESEARCH GROUP,
DEPARTMENT OF PHARMACY, FACULTY OF MATHEMATICS AND NATURAL
SCIENCE, UNIVERSITY OF OSLO, NORWAY

PROFESSOR HEDVIG NORDENG



- Founder of the Pharmacoepidemiology and Drug Safety Research Group, Dept. of Pharmacy, the Faculty of Mathematics and Natural Sciences, University of Oslo (UiO) (2011)
- Full professor in Perinatal Pharmacoepidemiology at the Dept. of Pharmacy, Faculty of Mathematics and Natural Sciences, UiO (2011)
- Researcher II, The Norwegian Institute of Public Health (NIPH), Division of Child Health and Development, 2005 – present
- EU Commission–appointed expert to EMA’s PRAC (since 2018).
- Fellow, International Society for Pharmacoepidemiology (FISPE) (2020)
- Adjunct Professor in Clinical Pharmacology, University of Southern Denmark (since 2024).



OVERVIEW



Nordic countries
as a region



Our data and
experience
working in
federated way-

**Impact for
regulators**



Potential for
global
collaboration

NORDIC COUNTRIES (DENMARK, FINLAND, ICELAND, NORWAY, SWEDEN)

Population & density:

- ~28 million inhabitants
- density uneven (Denmark ~141/km² vs. Norway/Finland ~14–16/km²);
- births per year ~270,000.

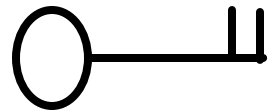
Welfare & care model: Tax-funded universal systems with low co-payment; parental leave ~11–16 months total, fathers' share ~2–6 months.

Health indicators:

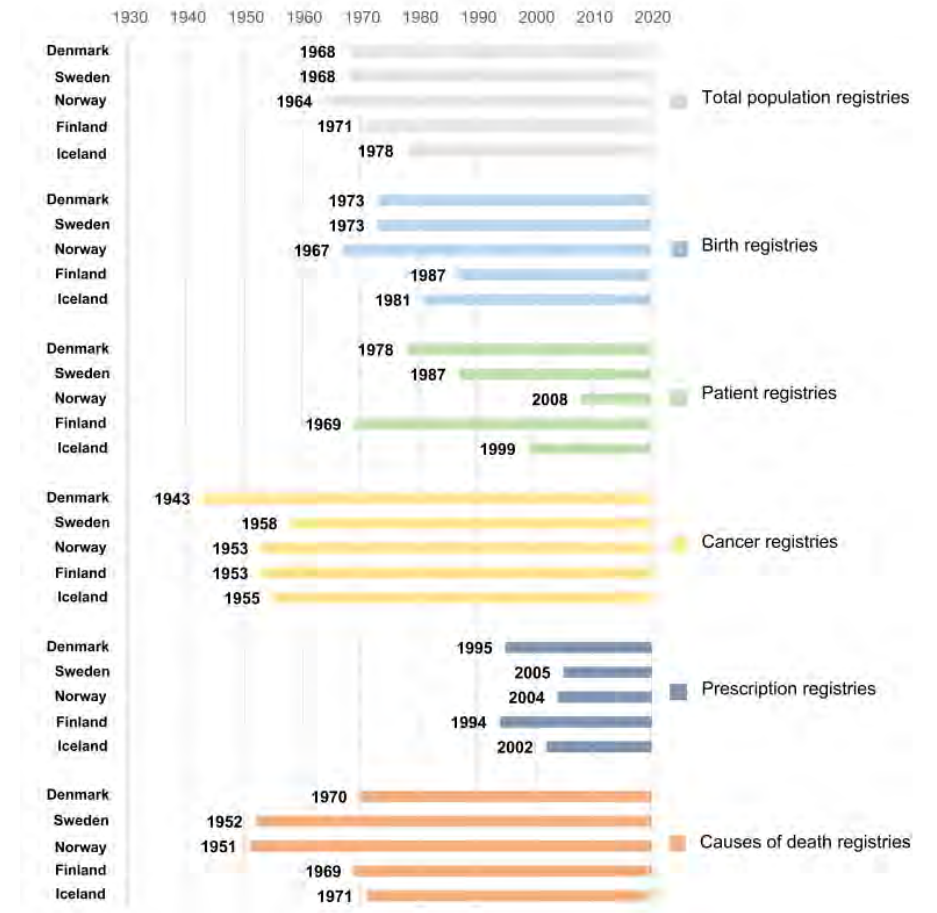
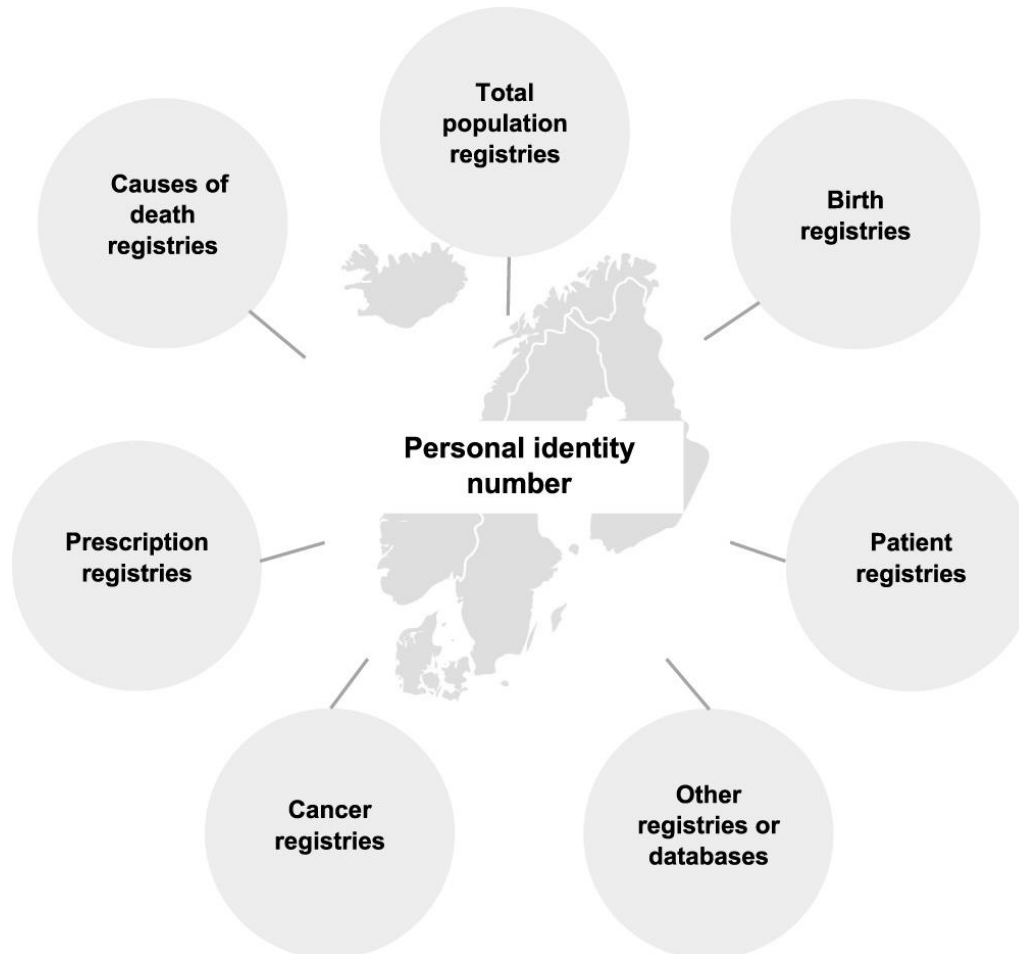
- Life expectancy ~81–83 years;
- Infant mortality <2–3 per 1,000;
- Child vaccine uptake high (~95–97%).



171073-32838



Personal
Identity
Number

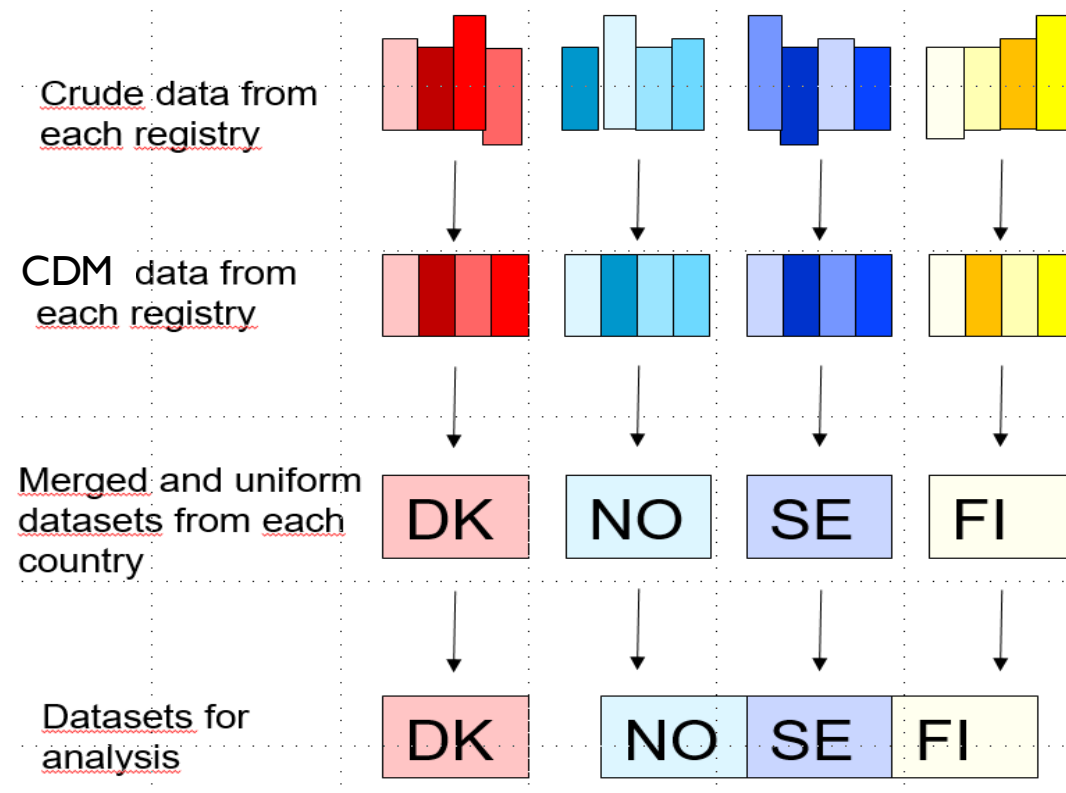


LONG TRADITION OF NORDIC COLLABORATION

Nordic countries:
28 million inhabitants
280,000 births per year

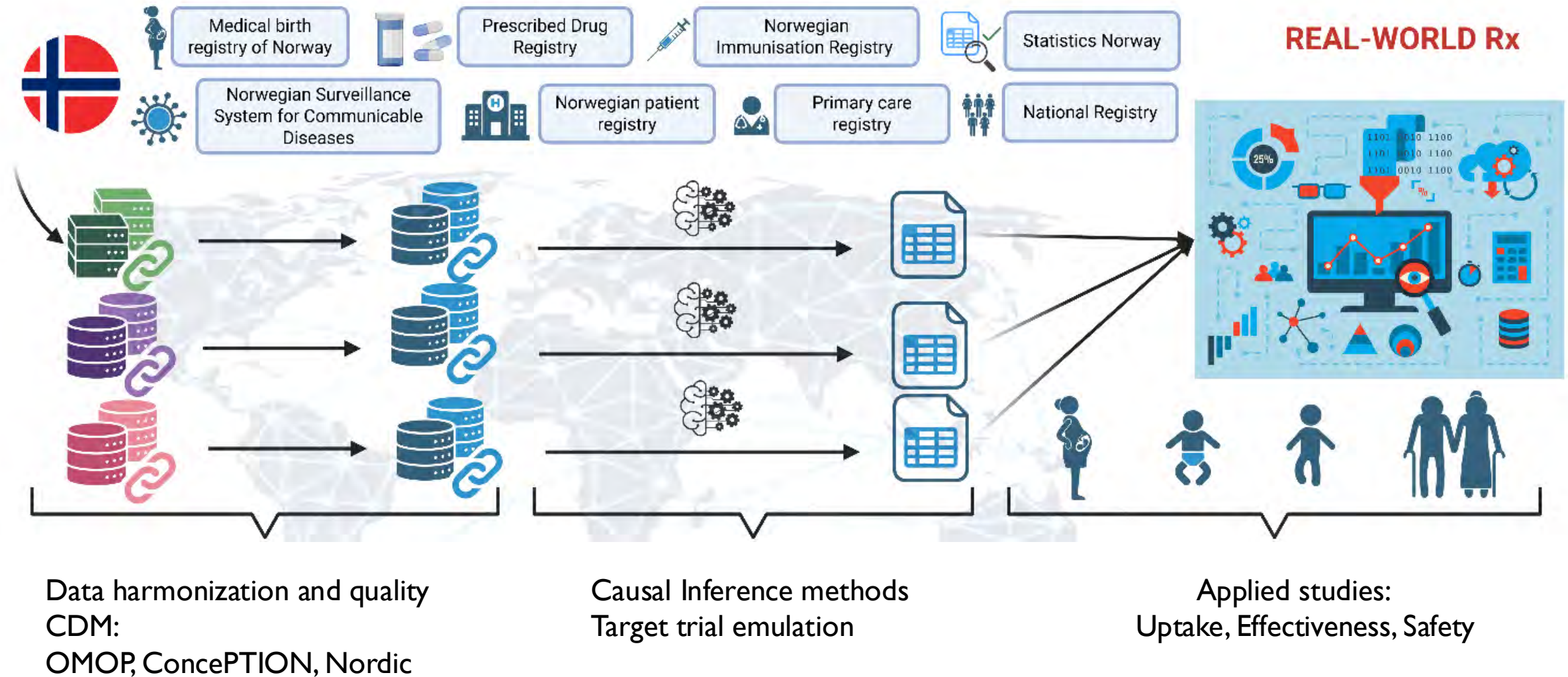
- Medical birth registries
- Prescription registries
- Patient registries
- Cancer registries

CDM: Common Data Model



Hjorth S, Pottegård A, Broe A, Hemmingsen CH, Leinonen MK, Hargreave M, Nörby U, Nordeng H.
Prenatal exposure to nitrofurantoin and risk of childhood leukaemia: a registry-based cohort study in four Nordic countries. Int J Epidemiol. 2022 Jun 13;51(3):778-788.

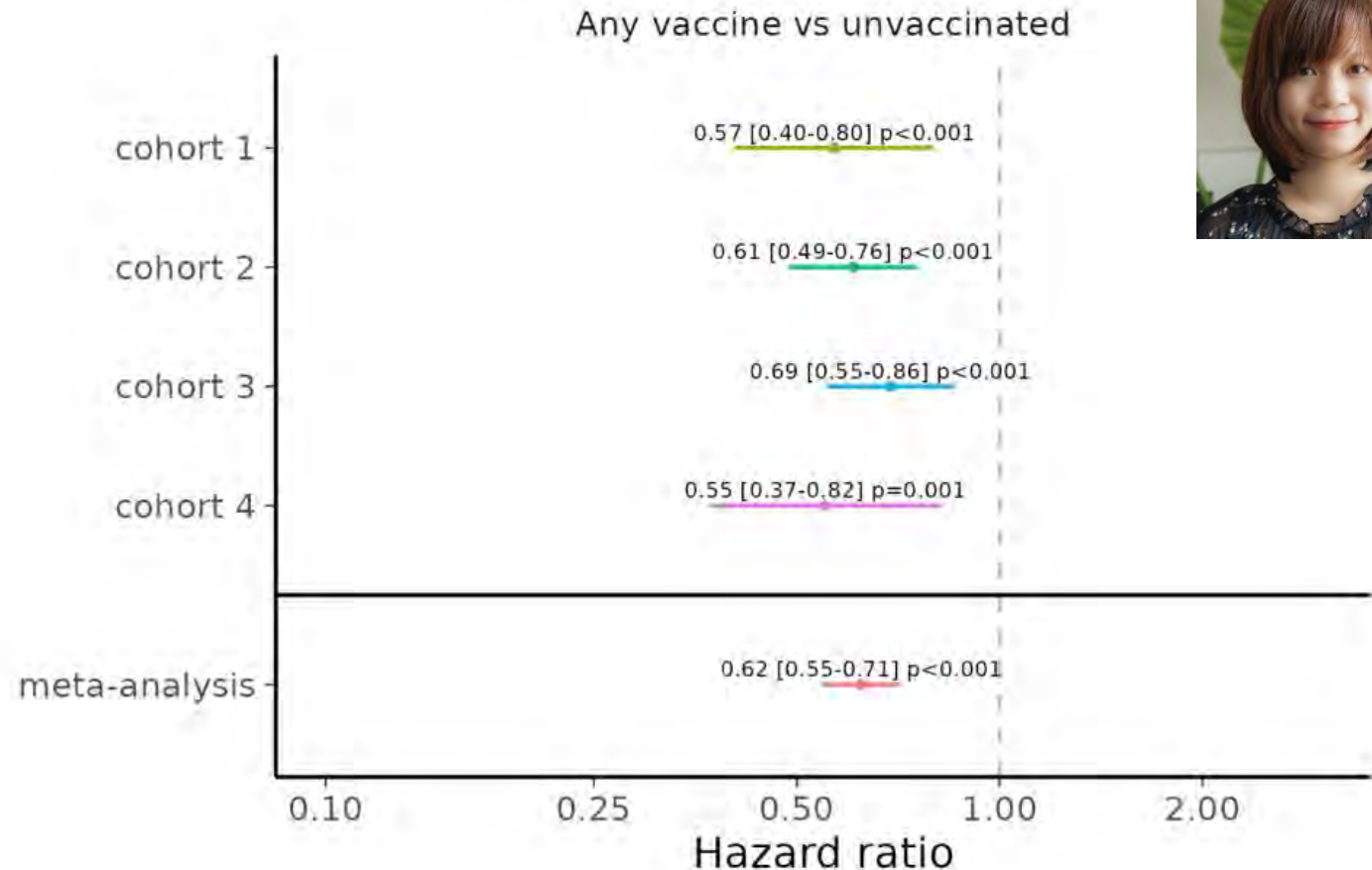
5.5 million inhabitants (2018-2021): 253 million drug exposure records, 142 million diagnosis, 15 million procedures, 7,7 measurements, 166K deaths, and 51K providers.
0.9 M pregnancy episodes (2008-2021)



EFFECTIVENESS OF COVID-19 VACCINES TO PREVENT LONG COVID: DATA FROM NORWAY

LANCET RESPIR MED. 2024 MAY;12:E33-E34.

Risk of post COVID-conditions reduced by 62% after vaccination



A total of 2,349,115 vaccinated and 1,422,670 unvaccinated individuals in Norway were included. Of these, 2,183 and 2,434 people respectively developed at least one persisting WHO-listed symptom recorded at least 90 days after a SARS-CoV-2 infection and were therefore identified as long COVID cases

IMPORTANCE FOR REGULATORY DECISION-MAKING

- **Fills evidence gaps** where randomized controlled trials (RCTs) are not feasible (e.g., in pregnant women, rare diseases, long-term effects).
- **Reflects real-life use** of medicines and vaccines across broader, more diverse populations.
- Evidence of effectiveness and safety is established in the post marketing phase



PHARMACOVIGILANCE RISK ASSESSMENT COMMITTEE (PRAC)

- The PRAC is the European Medicines Agency (EMA) committee **responsible for assessing and monitoring safety issues for human medicines.**
- This includes the detection, assessment, minimisation and communication relating to the risk of adverse reactions, while taking the therapeutic effect of the medicine into account.
- It also has responsibility for the design and evaluation of post-authorisation safety studies and pharmacovigilance audits.



GENERATING REAL-WORLD EVIDENCE (RWE) FROM REAL-WORLD DATA (RWD)

Regulatory informative RWE needs to be:

- Fast and transparent
- Representative
- Reproducible, replicable, and robust



DATA ANALYSIS AND REAL-WORLD INTERROGATION NETWORK (DARWIN EU ®)

Network that connects health data and expertise to provide the **European Medicines Agency** (EMA) with a better basis for decisions on the effectiveness and safety of medicines in the EU

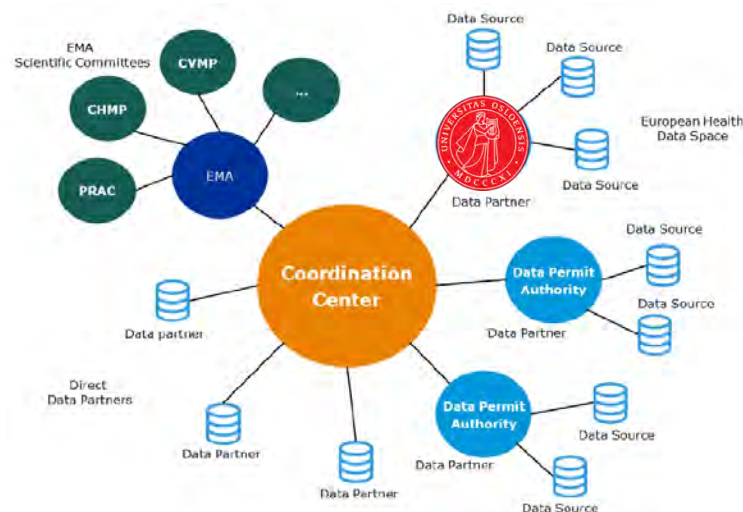
- Health data from 160 million patients in Europe
- 100 pharmacoepidemiological studies annually
- 40 data partners incl. the Nordic countries
- Data remain local. Uses OMOP Common Data Model to conduct studies.

* The Observational Medical Outcomes Partnership (OMOP)



DARWIN EU®: a transformation in the use of real-world health data for regulatory purpose in the EU

DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**



FEDERATED NETWORK PRINCIPLES

- Data stays **local**
- **Use of Common Data Model** to perform studies in a timely manner and increase consistency of results

P2-C3-004	HPV vaccine effectiveness
P3-C1-001	JAKi Drug Utilization
P3-C3-001	Baseline rates of AESIs
P3-C3-008	NSAIDs, contraceptives and VT
P3-C1-018	Cardiomyopathy Disease characteristics
P3-C2-002	Opioids Drug Utilization
P3-C1-020	HIV Pediatrics
P3-C3-009	Miscarriage Benzodiazepines
P3-C3-011	Paed. Pulmonary Hypertension
P4-C2-003	Antipsychotics in children
P4-C2-002	Paracetamol Overdose
P4-C2-006	Drug Utilization ADHD
P4-C2-012	Drug Utilization Sartans in children
P4-C1-016	Influenza vaccine effectiveness
P4-C1-008	Drug Utilization on Cystic Fibrosis
P4-C2-007	Characterisation CF patients

Coordination center:

Erasmus **University Medical Center Rotterdam**



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> Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures

Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures

 Share

12 January 2024

EMA's safety committee (PRAC) is recommending precautionary measures for the treatment of male patients with valproate medicines.

News

Human

Pharmacovigilance

Referrals

ONGOING STUDIES - EXAMPLES

- Valproate Use by Fathers During Spermatogenesis and Risk of Neurodevelopmental Disorders in Children: A Cross-National Study from Norway and Taiwan
- Paternal use of metformin and risk of major congenital malformations: a meta-analysis of data from 5 different countries (Norway, Denmark, Taiwan, Israel, US)



WHY A NORDIC–ASIA PACIFIC COLLABORATION?



Societal challenges are global: Need for effective and safe medications.



Stronger generalizability and causal inference: Heterogeneity is an asset: true effects should be invariant across contexts.



Stronger impact: Complementary strengths enable earlier signal detection, robust replication, and decision-grade RWE.



Creates new opportunities: broadens perspectives, researcher mobility, funding opportunities



INTERESTED IN
JOINING A NORDIC-
ASIA PACIFIC RWE
NETWORK FOR
PERINATAL AND
PEDIATRIC
RESEARCH?

CONTACT:
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Speakers

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Speaker Introduction

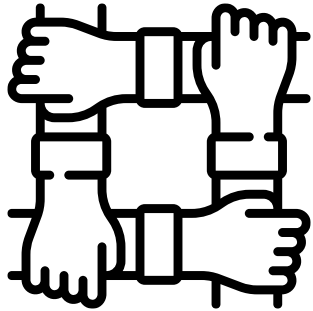


- Fei-Yuan Sharon Hsiao
- National Taiwan University, Graduate Institute of Clinical Pharmacy
 - Assistant professor, 2010-2015; Associate professor, 2015-2020
 - Director, 2018-2024; Professor, *2020-current*; Endowed Professor, *2025-current*
- Public services
 - Board member of Drug Safety Committee, TFDA, Taiwan (*2014-current*)
 - Board member of expert committee in Medical Review and Pharmaceutical Benefits Division, National Health Insurance Administration (NHIA), Taiwan (*2015-current*)
 - Board member of Pharmaceutical Benefit and Reimbursement Scheme Joint Committee (PBRs), NHIA, Taiwan (*2017-current*)
 - President, Taiwan Society of Pharmacoeconomics and Outcome Research (TaSPOR), (*2024-current*)

Multi-national database for RWE Studies

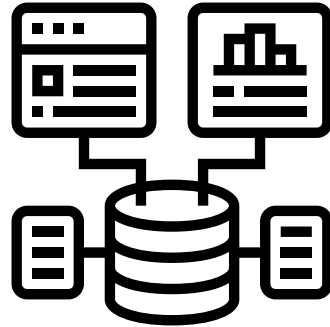
Practical consideration

1



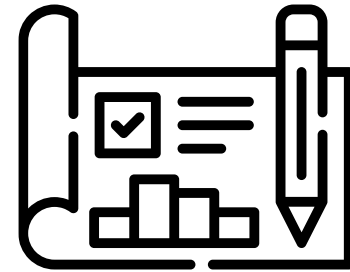
Team

2



Data

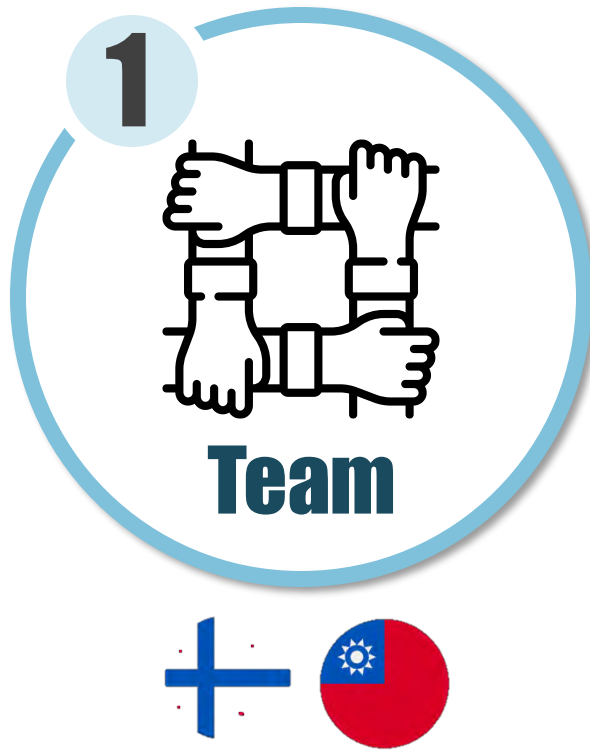
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Protocol

Multi-national database for RWE Studies

Practical consideration



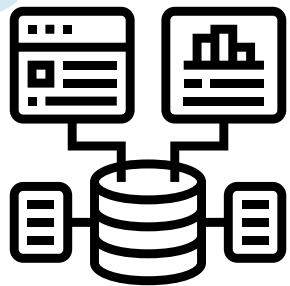
Key questions

- **Shared Research Interests?**
 - Pharmacoepidemiology research and applications
 - Maternal health outcomes and interventions
- **Aligned Core Capabilities/Feasibility?**
 - Real-world evidence (RWE) study design
 - Real-world data (RWD) analytical techniques
- **Complementary Strengths?**
 - Expertise areas, or resources that each party brings
- **Trust and Professional Relationship?**
 - Demonstrated mutual respect through constructive dialogue
 - Productive academic discussion and knowledge exchange

Multi-national database for RWE Studies

Practical consideration

2



Data



Evidence of feasibility from previous studies

Concomitant use of antidepressants and benzodiazepines during pregnancy and associated risk of congenital malformations: a population-based cohort study in Taiwan

Hui-Min Chuang, Lin-Chieh Meng, Chih-Wan Lin, Wen-Wen Chen, Yi-Yung Chen, Chi-Yung Shang, Liang-Kung Chen, Fei-Yuan Hsiao

Summary

Background Despite the frequent co-administration of antidepressants and benzodiazepines, the association between such concomitant use during pregnancy and the risk of congenital malformations remains inadequately explored. This study aims to examine the association between concomitant use of antidepressants and benzodiazepines during the first trimester and organ-specific congenital malformations.

Methods We conducted a population-based cohort study using Taiwan's National Birth Certificate Application database, the Maternal and Child Health database, and Taiwan's National Health Insurance database. Pregnant people aged 15–50 years with singleton births between Jan 1, 2004, and Dec 31, 2018, were included. Use of antidepressants and benzodiazepines was defined as at least one prescription during the first trimester, and concomitant use was defined as the overlapping prescription of both drugs with an overlapping prescription period. The primary outcomes were overall congenital malformations and eight organ-specific malformations, consisting of the nervous system, heart, respiratory system, oral cleft, digestive system, urinary system, genital system, and limb malformations. Logistic regression models with propensity score fine stratification weighting approach were used to control for measured confounders. Analyses controlling for confounding by indication and sibling comparison analyses were done to address unmeasured confounders. No individuals with lived experience participated in the research or writing process.

Lancet Psychiatry 2024;
31: 600–610
Published Online:
July 2, 2024
[https://doi.org/10.1016/S1473-9842\(24\)00079-7](https://doi.org/10.1016/S1473-9842(24)00079-7)
See Comment page 577
Graduate Institute of Clinical
Pharmacy, College of Medicine,
National Taiwan University,
Taipei, Taiwan
(H-M Chuang PharmD),
L-C Meng MS,
Pill-F-I Hsiao PhD, Taiwan
Drug Relief Foundation, Taipei,
Taiwan (C-W Lin PhD),
W-W Chen PharmD,
Department of Obstetrics and
Gynecology, MacKay Memorial
Hospital, Taipei, Taiwan

Lancet Psychiatry. 2024;11(8):601–610

RESEARCH ARTICLE

Uses of antiseizure medication among pregnant women with epilepsy and risk of adverse obstetric outcomes: A group-based trajectory analysis

Yi-Chin Lin^{1,2} | Chih-Wan Lin³ | Lin-Chieh Meng¹ | Shih-Tsung Huang⁴ | Yi-Yung Chen⁵ | Shuu-Jiun Wang^{6,7} | K. Arnold Chan^{8,9,10} | Fei-Yuan Hsiao^{1,11,12}

¹Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

²Department of Pharmacy, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan

³Taiwan Drug Relief Foundation, Taipei, Taiwan

⁴Center for Healthy Longevity and Aging Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan

⁵Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan

⁶Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan

Epilepsia

Epilepsia. 2024;65(9):2599–2611

JAMA Psychiatry | Original Investigation

Benzodiazepine Use During Pregnancy and Risk of Miscarriage

Lin-Chieh Meng, MS; Chih-Wan Lin, PhD; Hui-Min Chuang, PharmD, MS; Liang-Kung Chen, MD, PhD; Fei-Yuan Hsiao, PhD

Supplemental content

IMPORTANCE Benzodiazepine use during pregnancy has raised significant concerns due to the potential harmful effects of this drug class on neonates. Studies on the association between benzodiazepine use and the risk of miscarriage are limited.

OBJECTIVE To quantify the risk of miscarriage associated with benzodiazepine use during pregnancy after controlling for unmeasured confounders and exposure time trends.

DESIGN, SETTING, AND PARTICIPANTS This was a nationwide, population-based case-time-control study using Taiwan's National Birth Certificate Application database and the National Health Insurance database. Pregnancies resulting in miscarriage between 2004 and 2018 were included in the case group and were 1:1 matched with exposure time-trend control individuals using disease risk score, considering demographic characteristics and pre-pregnancy comorbidities. Data were analyzed from August 2022 to March 2023.

JAMA Psychiatry. 2024;81(4):366–373



Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Unveiling the hidden triad of antidepressants, benzodiazepines, and Z-hypnotics during pregnancy: A 15-year population-based study in Taiwan

Hui-Min Chuang¹, Lin-Chieh Meng¹, Chih-Wan Lin¹, Wen-Wen Chen¹, Yi-Yung Chen¹, Chi-Yung Shang¹, Liang-Kung Chen^{1,2,3}, Fei-Yuan Hsiao^{1,4,5,6,7}

¹Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan

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³Department of Obstetrics and Gynecology, MacKay Memorial Hospital, Taipei, Taiwan

⁴Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan

⁵Center for Healthy Longevity and Aging Sciences, National Yang Ming Chiao Tung University, Taipei, Taiwan

⁶Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan

⁷Taipei Municipal Sun-Tsu Hospital (Managed by Taipei Veterans General Hospital), Taipei, Taiwan

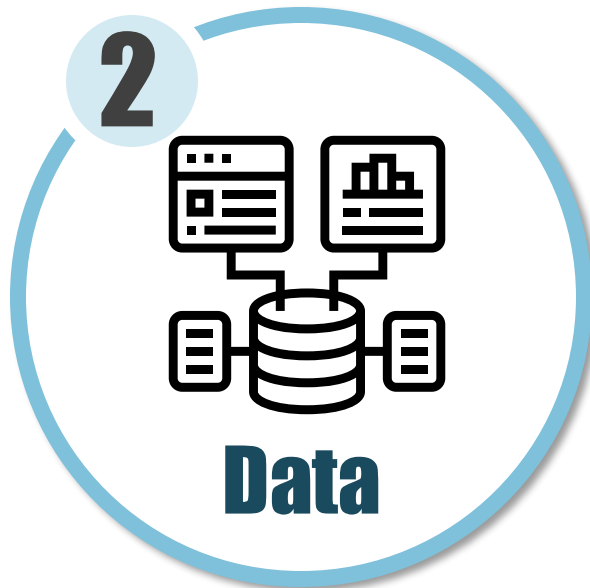
⁸School of Pharmacy, National Taiwan University, Taipei, Taiwan

⁹Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan

J Affect Disord. 2025;385:119372

Multi-national database for RWE Studies

Practical consideration



Meta data table (i.e. data description)



National Taiwan Birth Certificate Application

Data on the mothers

weeks of pregnancy at delivery, type of delivery,
demographic (age, nationality, high-risk lifestyle)...

Data on the newborns

birth date, singleton or multiples, birth weight, immediate
adverse neonatal outcomes (stillbirth, birth defects)...



Taiwan's National Health Insurance Research Database

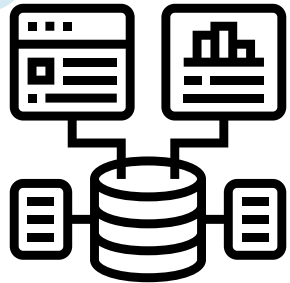
Patient demographic and healthcare information

age, sex, disease diagnoses, outpatient visits, hospital
admissions, procedures, prescribed medications, prenatal
care, diagnostic tests and examinations...

Multi-national database for RWE Studies

Practical consideration

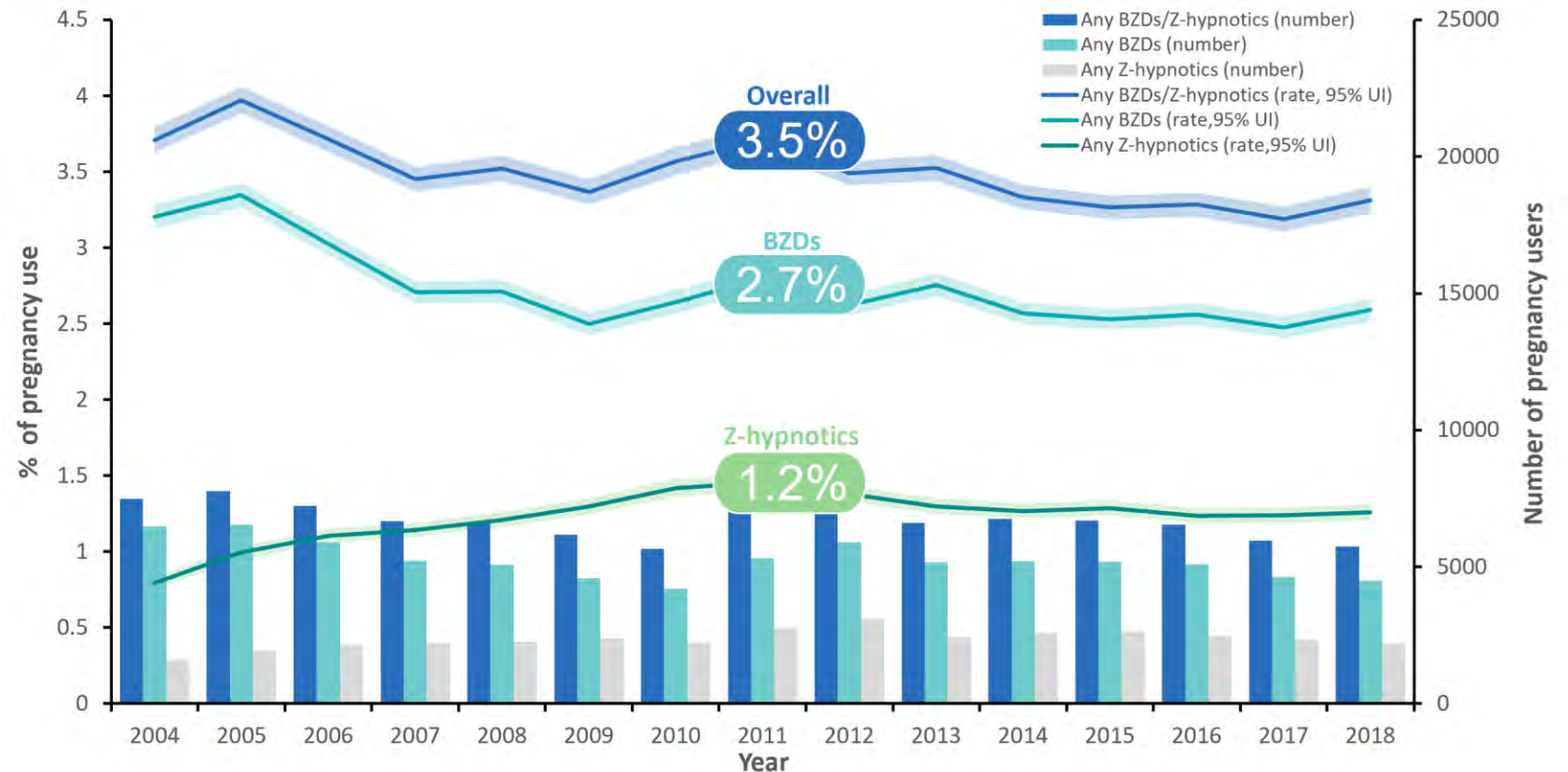
2



Data



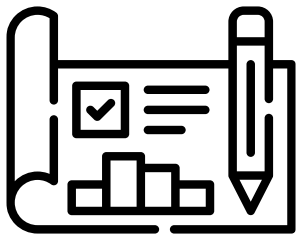
Data check (e.g. exposure pattern)



Multi-national database for RWE Studies

Practical consideration

3



Protocol



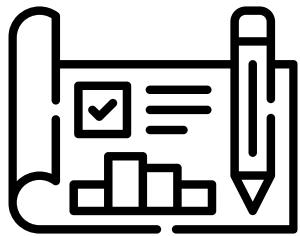
Fully agreed protocol

- **Comprehensive study design**
 - Study cohort
 - Exposure definition
 - Outcome definition
 - Timeline
- **Data harmonization plan**
- **Statistical analysis plan**
- **Consider register the protocol in a public domain**
 - e.g. HMA-EMA Catalogues of RWE registry

Multi-national database for RWE Studies

Practical consideration

3



Protocol



Fully agreed protocol

- **Comprehensive study design**

Characteristics

Healthcare utilization

No. of outpatient visits, Hospitalizations, ER visits

1-year before LMP

LMP

LMP-180 days

Demographic characteristics

Mother's age at birth, Infants' sex,
Nationality

Birth

Psychiatric medical conditions

Anxiety, Insomnia, Depression, Schizophrenia, Epilepsy, Bipolar disorder

Life style factors

Overweight/obesity, Tobacco abuse, Alcohol abuse, Drug abuse

Chronic comorbidities

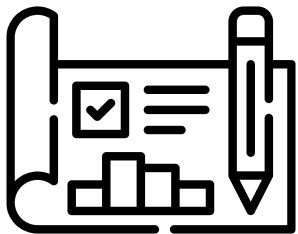
Asthma, Hyperthyroidism, Cardiac valvular disease

Obstetric comorbidity index (OCI)

Multi-national database for RWE Studies

Practical consideration

3



Protocol



Fully agreed protocol

- Comprehensive study design

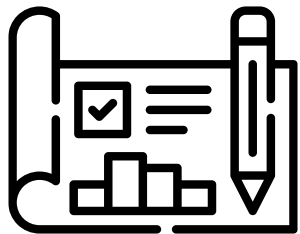
Five pregnancy-related periods



Multi-national database for RWE Studies

Practical consideration

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Protocol



Fully agreed protocol

- **Comprehensive study design**
 - Outcome definition

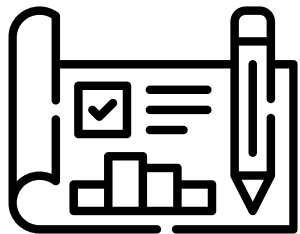
Outcomes were determined using data from the MBRN, which is a member of EUROCAT.

Outcome	Values
Any congenital malformation	
Congenital malformations	1 = Yes
Specific category malformation	
Neural tube defects	1 = Yes
Congenital heart defects	1 = Yes
Cleft lip with or without cleft palate	1 = Yes
Cleft palate without cleft lip	1 = Yes
Hypospadias	1 = Yes
Clubfoot	1 = Yes
Chromosomal abnormality	1 = Yes

Multi-national database for RWE Studies

Practical consideration

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Protocol



Fully agreed protocol

- **Comprehensive study design**
 - Outcome definition



Other specific category malformation		
Neural tube defects	740.xx, 741.xx, 742.0x	Q00.xx, Q01.xx, Q05.xx
Cleft lip with or without cleft palate	749.1x, 749.2x	Q36.xx, Q37.xx
	Except 749.02, or if occurring with 740.xx, 742.26	Except Q35.7, or if occurring with Q00, Q04.2x
Cleft palate without cleft lip	749.0x	Q35.xx
	Except 749.02, or if occurring with 740.xx, 742.26, 749.1x, 749.2x,	Except Q35.7, or if occurring with Q00.xx, Q04.2x, Q36.xx, Q37.xx
Hypospadias	752.61, 752.63	Q54.xx
Clubfoot	745.50, 745.51	Q66.0x

Acknowledgement

- Students

- Lin-Chieh Meng, Hui-Min Chuang, Yi-Chin Lin, Chih-Wan Lin, Shih-Tsung Huang, Hsi-Yu Lai,

- Clinicians

- Wen-Wen Chen, Liang-Kung Chen, Yi-Yung Chen, Chi-Yung Shang, Shuu-Jiun Wang, K Arnold Chan

- Grants

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- NSTC 113-2314-B-002-167-MY3

- The Norwegian Research Council

- Grant No 322176





Thank you very much



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Attendees will gain practical insights, establish new connections, and contribute to shaping future research directions in this rapidly evolving field.



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Moderator

Marleen van Gelder, PhD; Radboud university medical center, Nijmegen, Netherlands

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