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e-Congress in Pharmacoepidemiology 24th November 2023

Nordic initiative to improve knowledge about Medication Safety in Pregnancy and Lactation

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Disclaimer: This presentation presents my personal opinions and experience.
I have no conflict of Interest.

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Disposition

1. The Nordic registries
2. Secondary data - examples
   - Methodological challenges
   - Paternal exposure to valproate - NDDs
   - Maternal exposure to topiramate - NDDs
3. Primary data collection
   - The MoBa birth cohort

12/6/2023

Colourbox

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

France:
>700,000 births per year

Nordic perinatal statistics 2020 (julkari.fi)
www.europeristat.com

Cecarian section:	16% - 20%
Preterm birth:	4.8% - 6%
Smoking:	1.2% - 5.5%
Malformations:	2.7% - 2.9%
Infant mortality:	0.19% - 0.22%

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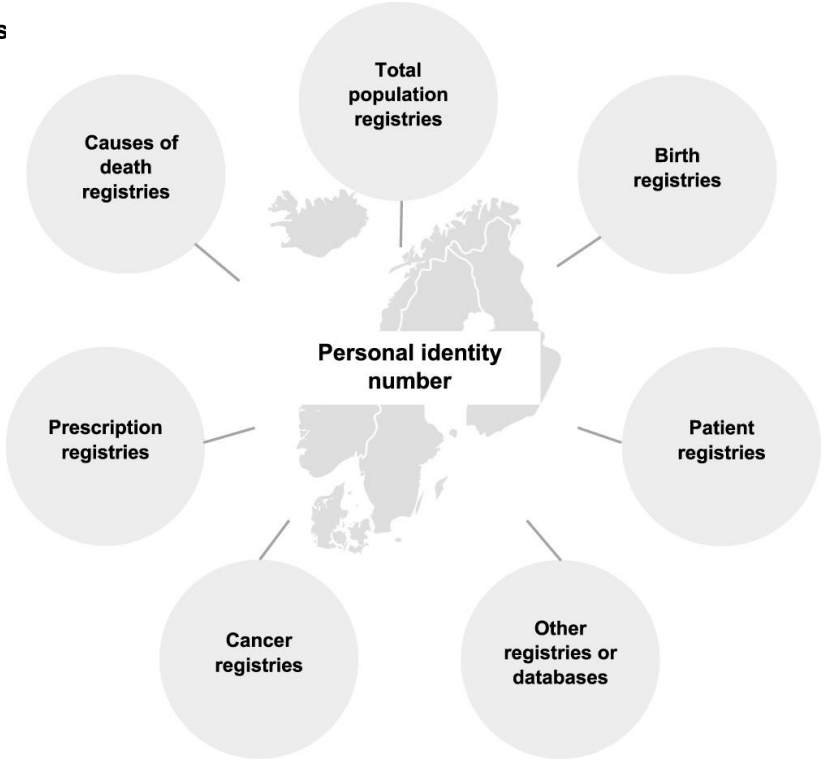

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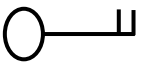
Long tradition of perinatal Nordic collaboration

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



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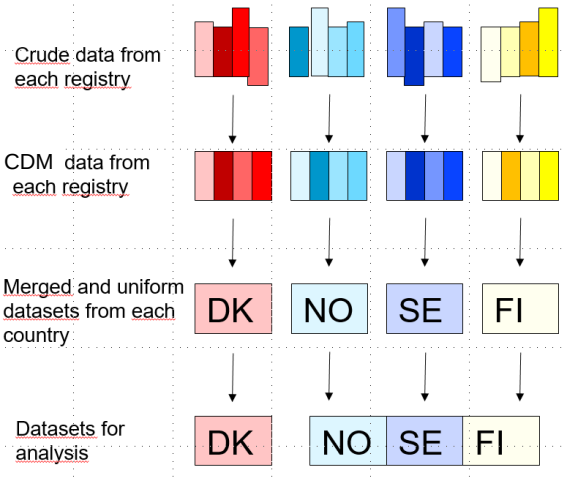

Hjorth S, Pottegård A, Broe A, Hemmingsen CH, Leinonen MK, Hargreave M, Nörby U, Nordeng H. **Prenatal exposure to nitrofurantoin and risk of childhood leukaemia: a registry-based cohort study in four Nordic countries.** Int J Epidemiol. 2022 Jun 13;51(3):778-788.

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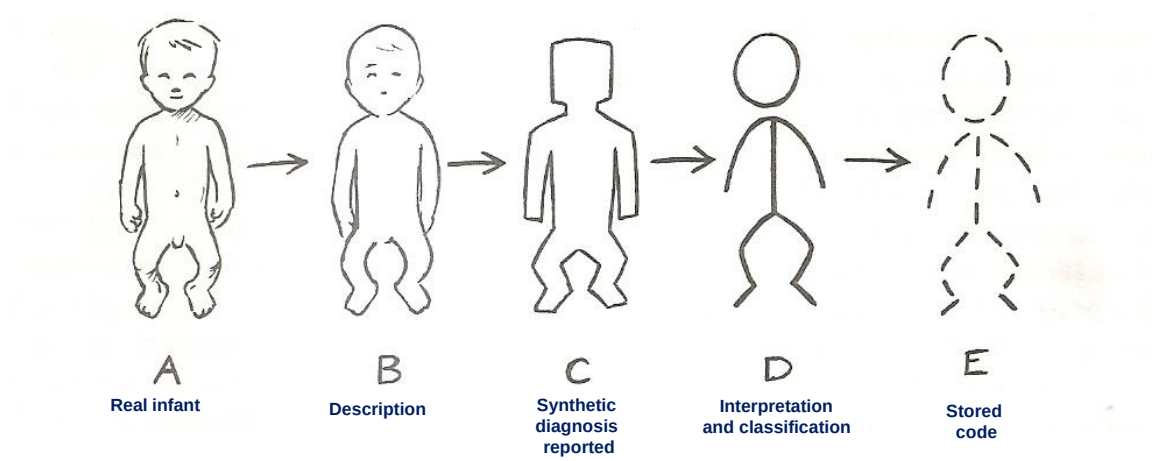
The risk of distortion of the information from infant to coded data is great …



Bengt Kallen, Epidemiology of Human Reproduction, CRC 1988

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Critical assessment – perinatal pharmacoepidemiology: The same as any pharmacoepi study

Material and Methods

- Data source
- Exposure measurement
- Selection of comparison groups
- Measurement of outcome
- Confounders
- Handling of missing data
- Statistical method
- Sensitivity analysis

Results & interpretation

- Magnitude and precision of effect estimates
- Robustness of results – sensitivity analyses
- Absolute risk

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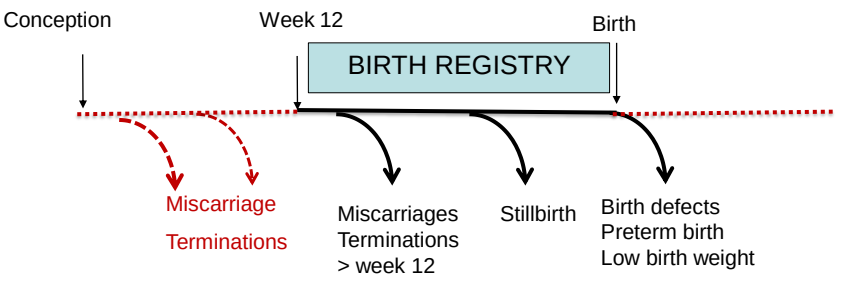
In practice, some especially challenging:

- Sample size requirements
- Capturing early miscarriages and terminations (see fig. below)
- Definition and classification of malformations
- Measuring long-term neurodevelopmental outcomes



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European surveillance of congenital anomalies (EUROCAT) classification system.

How do we measure malformations?

- **Definitions differ between birth registries:**

Example: Swedish MBR use "weeded malformation". Exclude some common, mild conditions: preauricular tag, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicles at preterm birth, unstable hip, and nevus.

- **What is the validity of malformations in the birth registries?**

- **What is a major malformation**?
  - Cryptorchidism with/without surgery?
  - Ventricular septal defects (VSD) that often close spontaneously?
  - Patent ductus arteriosus (IQ25) if gestational age < 37 weeks

- **Minor malformations are often excluded:**

→ Are minor malformations not important?

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Table S1. ICD-10 Codes of Birth Defect Categories

Specific birth defect categories	ICD-10 codes	ICD-10 codes for minor defects excluded from evaluation
Craniosynostosis	Q750	
Cleft palate alone	Q35	
Cleft lip with or without cleft palate	Q36-Q37,	
Other craniofacial defects	Q183, Q188, Q755, Q758, Q759	
Middle ear defects	Q162, Q163, Q164	
Limb defects	Q66-Q74	Q662-Q669, Q670-Q678, Q680, Q682A, Q683-Q685, Q740G
Limb reduction defects	Q71-Q73	
Polydactyly	Q69	
Syndactyly	Q70	
Diaphragmatic hernia	Q790	
Heart defects overall	Q20-Q26	Q211C, Q250 (if gestational age <37)
Tetralogy of Fallot	Q213	
Pulmonary artery hypoplasia	Q257F	
Ventricular septal defects	Q210	
Hypoplastic left heart	Q234	
Birth defects overall	Q00-Q07, Q10-Q18, Q20-Q28, Q30-Q34, Q35-Q37, Q38-Q43, Q440-Q446, Q447A, Q447C-447G, Q45, Q50-Q56, Q60, Q610-Q619 (but not Q619A), Q62-Q64, Q66-Q74, Q750, Q755, Q758, Q759, Q76, Q770, Q773-Q779, Q78, Q790-Q795, Q798, Q799,Q80-Q84, Q88-Q89	Q101-Q103, Q105, Q135, Q170-Q175, Q179, Q180-Q182, Q184-Q187, Q189, Q211C, Q250 (if gestational age <37), Q270, Q314, Q315, Q320, Q331, Q381, Q382, Q385, Q400, Q401 , Q430, Q523 Q525 Q53, Q552F, Q610, Q627, Q633, Q662-Q669, Q670-Q678, Q680, Q682A, Q683-Q685, Q740G, Q752, Q753, Q760, Q764L, Q765, Q766C, Q766D, Q767C, Q825, Q833, Q845, Q899

Example

- Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med 2013;369:830-9.

- Danish registries
- European surveillance of congenital anomalies (EUROCAT) classification system.
- Validation study: → Correct for 89-90% of cardiac malformations

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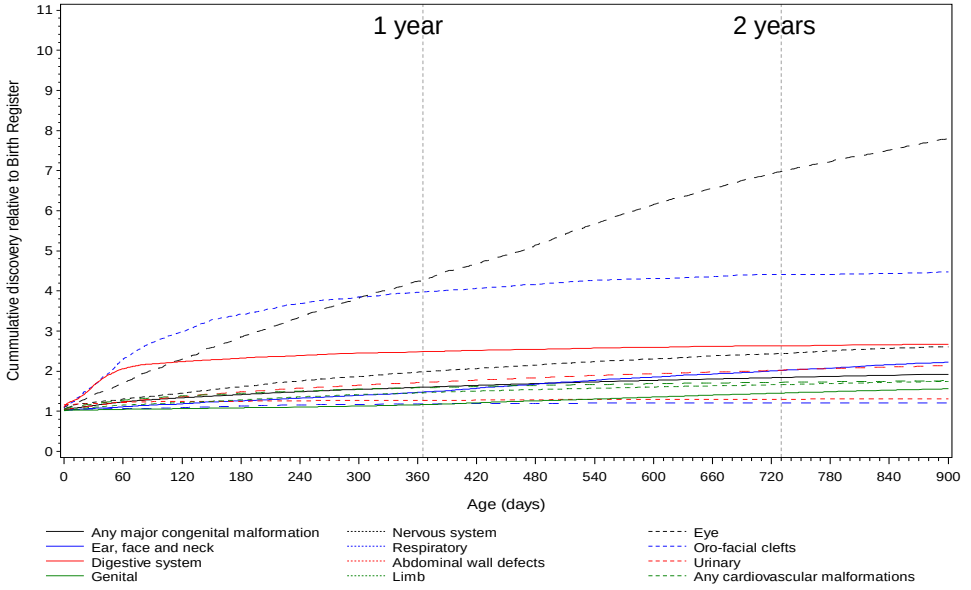
Time of detecting malformation - information recorded in the Swedish Medical Birth Registry



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EU RMP category 1 (imposed as condition of marketing authorisation)
EMEA/H/A-31/1454

A post-authorization safety study (PASS) to evaluate the **paternal exposure to valproate and the risk of neurodevelopmental disorders** including autism spectrum disorders as well as congenital abnormalities in offspring - a population-based retrospective study

Nordic registries – NO-SE-FI

sanofi

20 March 2023

Epilim® (Valproate) - Risk of neurodevelopmental disorders including autism spectrum disorders in children after paternal exposure

Dear Healthcare Professional,

Sanofi-Aventis Singapore Pte Ltd would like to inform you of new safety updates regarding a higher risk of neurodevelopmental disorders (NDDs), including autism spectrum disorders, in children after paternal exposure to valproate as compared to lamotrigine/levetiracetam.

Key information

- **A retrospective observational study on electronic medical records in 3 European Nordic countries indicated an increased risk of NDDs in children (from 0 to 11 years old) born to men treated with valproate at the time of conception compared to those treated with lamotrigine or levetiracetam.**
- **The adjusted cumulative risk of NDDs ranged between 5.6% to 6.3% in the valproate group versus between 2.5% to 3.6% in the composite lamotrigine/levetiracetam monotherapy exposure. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.47 (95% CI: 1.10, 1.96).**

Sanofi press release March 2023:

- HR for NDDs: 1.47 (95% CI: 1.10, 1.96)
- Paternal valproate group: 5.6 – 6.3%
- Paternal lamotrigine/levetiracetam monotherapy: 3.6%

28/03/2019

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ansm

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< Retour ACTUALITÉS > SURVEILLANCE > PHARMACOVIGILANCE > EVALUATION EUROPÉENNE DU RISQUE POTENTIEL DE TROUB...

PUBLIÉ LE 16/05/2023 - MIS À JOUR LE 16/08/2023

Evaluation européenne du risque potentiel de troubles neurodéveloppementaux chez les enfants dont le père a été traité par valproate dans les mois précédant la conception

A+ A-

Actualisation du 3/8/2023

Information des professionnels de santé et des patients dans l'attente des conclusions sur l'évaluation du risque de troubles neurodéveloppementaux

L'Agence européenne du médicament (EMA) poursuit l'évaluation du risque potentiel de troubles neurodéveloppementaux chez les enfants dont le père a pris du valproate ou un de ses dérivés dans les trois mois précédant la conception.

› Communiqué de presse publié par l'Agence européenne du médicament

Dans l'attente des conclusions de cette évaluation, nous adressons une lettre d'information à l'ensemble des professionnels de santé concernés pour les alerter sur ce risque potentiel. Une fiche d'information pour les patients a aussi été conçue, elle est mise à disposition de chacun sur notre site afin d'être remise aux patients lors de la prescription ou de la délivrance d'une spécialité à base de valproate ou un de ses dérivés.

En parallèle, nous avons demandé aux laboratoires commercialisant ces médicaments qu'ils nous soumettent dès à présent une demande de modification de leurs autorisations de mise sur le marché afin que ce risque potentiel figure dans le résumé des caractéristiques du produit et dans les notices de ces médicaments. Nous leur avons également demandé de nous soumettre des documents complémentaires afin d'informer au mieux les patients et les professionnels de santé sur ce risque et la conduite à tenir afin de le réduire.

Les résultats d'une étude, demandée aux laboratoires pharmaceutiques dans le cadre de la surveillance au niveau européen des médicaments contenant du valproate et ses dérivés, suggèrent une augmentation du risque de troubles neurodéveloppementaux chez les enfants dont le père a été traité par valproate dans les trois mois avant la conception. Cette étude présente des limites qui ne permettent pas de tirer de conclusions définitives à ce stade.
L'Agence européenne du médicament (EMA) a demandé aux laboratoires des analyses complémentaires pour évaluer la robustesse de ces données.

Nous souhaitons partager dès à présent ces résultats. S'ils étaient confirmés, ils pourraient conduire à de nouvelles mesures de sécurité.

En 2018, l'EMA a demandé que les laboratoires pharmaceutiques commercialisant les médicaments contenant du valproate ou un de ses dérivés mènent des études visant à mieux caractériser les risques liés à leur prise. Une de ces études avait pour objectif d'évaluer les risques malformatifs et neurodéveloppementaux chez les enfants dont le père avait été traité par valproate ou un de ses dérivés, avant la conception.

Cette étude, conduite sur la base de plusieurs registres scandinaves (Norvège, Suède et Danemark) sur une longue période, a comparé les enfants dont le père était traité au valproate dans les trois mois qui précèdent la conception, par rapport aux enfants dont le père était traité par lamotrigine ou lévétiracétam.

Ces résultats suggèrent une augmentation du risque de troubles neuro-développementaux, comme des troubles du spectre autistique, chez les enfants dont le père a été exposé au valproate. Ce risque varie entre 5,6 % et 6,3 % chez les enfants nés de père exposé au valproate contre 2,5 % et 3,6 % pour les enfants nés de père traité par lamotrigine ou lévétiracétam. Pour rappel, ce risque de troubles neurodéveloppementaux est de l'ordre de 30 à 40 % après une exposition maternelle au valproate.

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EMA review of data on paternal exposure to valproate

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Press release 16/08/2023

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is reviewing data on the potential risk of neurodevelopmental disorders (NDDs) in children conceived by fathers taking valproate medicines.

The review is focussing on data from a retrospective observational study conducted by companies as an obligation following a previous review of valproate use during pregnancy.

This retrospective observational study compared the risk of NDDs (including autism spectrum disorder) in children born to men taking valproate with the risk in children born to men taking lamotrigine or levetiracetam (other treatments for epilepsy). It was carried out using multiple registry databases in Denmark, Norway and Sweden.

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PRAC starts review of topiramate use in pregnancy and women of childbearing potential

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News 02/09/2022

EMA's safety committee (PRAC) has started a review of topiramate and the risk of neurodevelopmental disorders in children whose mothers were taking topiramate during pregnancy. Topiramate is a medicine used in the EU for the treatment of epilepsy, prevention of migraine and, in some countries, in combination with phentermine for body weight reduction.

Use of topiramate in pregnant women is known to increase the risk of birth defects. Women with epilepsy who are being treated with topiramate for their seizures are advised to avoid becoming pregnant, and to consult their doctor for advice if they wish to become pregnant. Topiramate must not be used to prevent migraine or control body weight in pregnant women and in women of childbearing potential (women able to have children) who are not using highly effective birth control methods (contraception).

doi:10.1001/jamaneurol.2022.1269

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SmPC of topiramate reflects risks of birth defects

Section 4.3 (Contraindication) Migraine prophylaxis in pregnancy. In WOCBP, if highly effective method of contraception is not used.

Section 4.6 (Pregnancy)

- Teratogenic in mice, rats and rabbits
- North American Antiepileptic Drug pregnancy registry, infants exposed to monotherapy have:
  - 3-fold higher prevalence of major congenital malformations (4.3%) vs reference group not taking AEDs (1.4%).
  - After 1st trimester exposure: Cleft lip/palate, hypospadias, anomalies various body systems.

Indication epilepsy

- Consider alternative therapeutic options in WOCBP.
- If topiramate used in WOCBP, highly effective contraception recommended (see 4.5), woman fully informed of known risks of uncontrolled epilepsy & potential risks of topiramate to fetus.

Section 4.4 (special warnings) contains warning as well

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Research

JAMA Neurology | Original Investigation

Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability

Marte-Helene Bjørk, MD, PhD; Helga Zoega, PhD; Maarit K. Leinonen, MD, PhD; Jacqueline M. Cohen, PhD; Julie Werenberg Dreier, PhD; Kari Furu, PhD; Nils Erik Gilhus, MD, PhD; Mika Gissler, PhD; Óskar Hálfdánarson, PhD; Jannicke Igland, PhD; Yuelian Sun, PhD; Torbjörn Tomson, MD, PhD; Silje Alvestad, MD, PhD; Jakob Christensen, MD, PhD

IMPORTANCE Women with epilepsy frequently need antiseizure medication (ASM) to prevent seizures in pregnancy. Risk of neurodevelopmental disorders after prenatal exposure to AMSs is uncertain.

OBJECTIVE To determine whether children exposed prenatally to ASMs in monotherapy and duotherapy have increased risk of neurodevelopmental disorders.

Multimedia

Supplemental content

- **Data from Denmark, Finland, Iceland, Norway and Sweden**
- **More than 24,000 children exposed to at least one anti-epileptic medicine before birth.**
- **471 were exposed to topiramate alone, including 246 children born to mothers who had epilepsy.**

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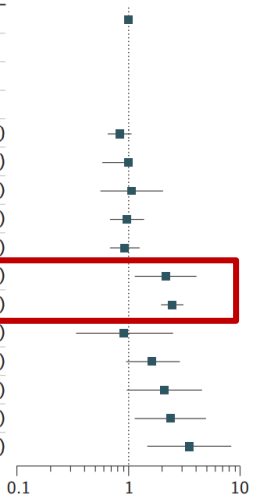
Figure 2. Association Between Prenatal Antiseizure Medication (ASM) Exposure and Child Neurodevelopmental Disorder (ND)

A Children of women with epilepsy

ASD, n= NA, aHR: 2.77 (95% CI 1.35 – 5.65)

Exposure	8-y Incidence, %	No. with ND	aHR (95% CI)
Unexposed, n = 21 634	2.4	443	1 [Reference]
Pregabalin, n = 91	NA	<5	NA
Gabapentin, n = 110	NA	<5	NA
Phenobarbital, n = 45	NA	<5	NA
Lamotrigine, n = 5073	1.8	81	0.83 (0.65-1.06)
Clonazepam, n = 318	4.5	15	1.00 (0.58-1.04)
Levetiracetam, n = 1004	2.1	10	1.06 (0.56-2.02)
Oxcarbazepine, n = 1429	2.0	[a]	0.97 (0.68-1.37)
Carbamazepine, n = 2609	1.9	65	0.92 (0.68-1.25)
Topiramate, n = 246	5.1	10	2.13 (1.13-4.01)
Valproate, n = 1884	6.5	152	2.44 (1.94-3.07)
Lamotrigine + levetiracetam, n = [a]	1.6	[a]	0.91 (0.34-2.48)
Valproate + lamotrigine, n = 312	5.5	[a]	1.65 (0.95-2.85)
Lamotrigine + oxcarbazepine, n = [a]	4.3	[a]	2.07 (0.96-4.49)
Lamotrigine + topiramate, n = 123	7.5	[a]	2.35 (1.13-4.87)
Levetiracetam + carbamazepine, n = [a]	5.7	[a]	3.46 (1.46-8.18)



06.12.2023

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Strengths

Study design several notable strengths:

large, well-established, population-based health-care registers from countries with similar health-care & data structure

Limitations

Confounding by indication:

- topiramate 2nd/3rd line drug

Study power:

- Children exposed to topiramate: 471 total; 246 mothers in epilepsy
- 12 children autism spectrum disorders; 6 children intellectual disability
- ASD, Epilepsy: n not presented (data protection rules because of low numbers; <5)
- Absolute risk not be estimated/ presented due to low number of events

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What should we do with ….

- 1 code of autisme at 6 months
- 1 code of language impairment at 1 year
- 1 code of ADHD at 2 years

Outcome misclassification ?!

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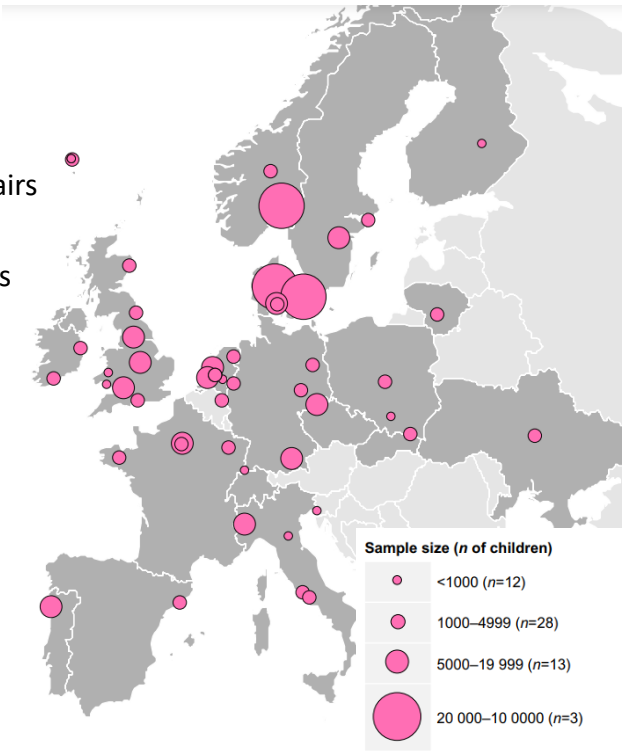
Primary data collection

Colourbox

- 35 prospective European pregnancy and birth cohorts with > 300 mother-child pairs
- > 500,000 live-born European children.
- 19 countries with the majority of cohorts located in Northern and Western Europe. www.birthcohorts.net

  - The Norwegian Mother, Father and Child Cohort, n=108,000
  - Danish MoBa, n= 106,370



JAMA Network | Open July 2022

Original Investigation | Pediatrics

Analysis of Prenatal Exposure to Opioid Analgesics and Scholastic Skills in Children in Fifth Grade in Norway

Johanne Naper Trønnes, MSc, Pharm; Angela Lupattelli, PhD; Eivind Ystrom, PhD; Hedvig Nord

Abstract

IMPORTANCE Few studies have examined the neurodevelopmental consequences exposure to opioid analgesics. Therefore, it is necessary to gain knowledge to inform decisions for pregnant women with moderate to severe pain.

Findings In this cohort study of 64 256 children, exposure to opioid analgesics in the first trimester or during two to three 4-week intervals during pregnancy was associated with lower scores in literacy and numeracy tests, compared with only prepregnancy exposure. However, the differences may not be clinically relevant.

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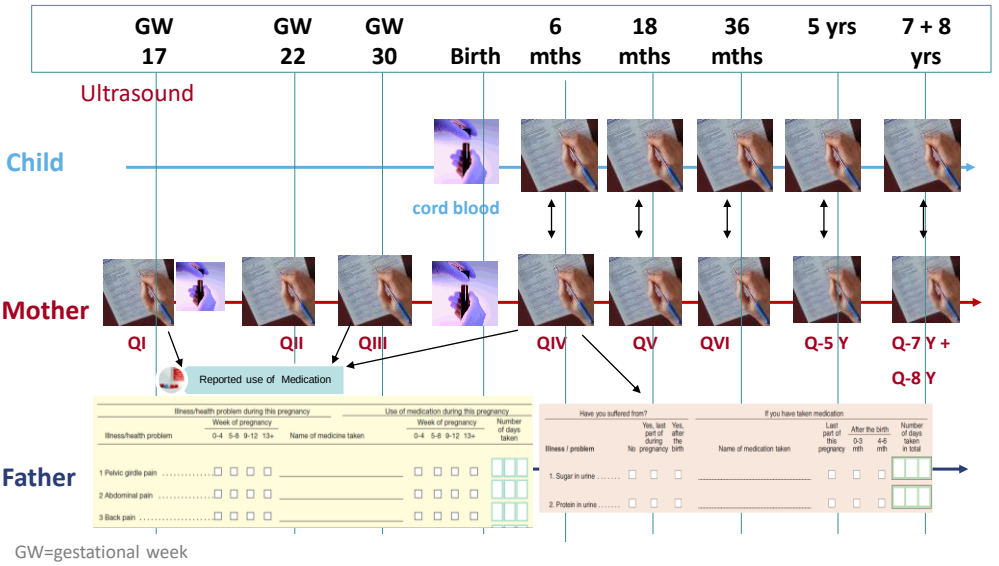
Methods

Data collection in MoBa



GW=gestational week

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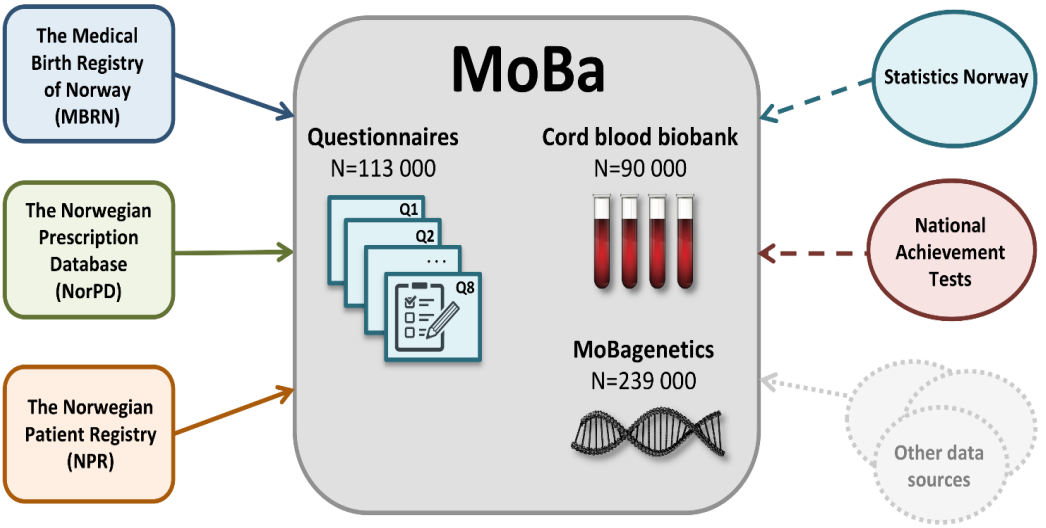

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Concluding remarks

- Long tradition of perinatal Nordic collaboration using linked registry data
- Regulatory decisions are often based on perinatal observational studies with linked registry data from the Nordic registry data

As with all observational studies, there are important methodological considerations

- If these limitations are not well understood and addressed, studies based on these data sources can misinform risk-benefit decisions for drugs

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