

Unique registers and advanced family designs to address causes and consequences of common childhood disorders

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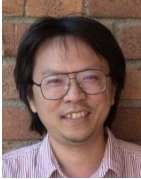

Aims

- 1. Causes and ...
- 2. ... consequences of common childhood disorders ...
- 3. ... to be addressed using unique registers and advanced family designs

Introduction

- most childhood disorders influenced by genetic and early environmental factors
- the effect of childhood disorders on subsequent development may be confounded by genetic and early environmental factors
- innovation – to apply advanced family (twin, sibling, and cousin-comparisons i.e. within twin/sibling/cousin) designs to account for confounding
- unique new and established health registers

Co-investigators

- Anastasia Iladou Nyman, MEB 
- Arvid Sjölander, MEB 
- Brian D'Onofrio, University of Indiana USA 
- Henrik Larsson, MEB 
- Paul Lichtenstein, MEB 
- Sara Öberg, MEB and Harvard School of Public Health 
- Tove Fall, Uppsala University 
- Yudi Pawitan, MEB 
- Catarina Almqvist Malmros, MEB and Astrid Lindgren Children's Hospital 

Registers

National Board of Health and Welfare

- Medical Birth Register
- National Patient Register
- Prescribed Drug Register

Statistics Sweden

- Multi-Generation Register, Migration
- LISA, Education, School registers

Others

- Conscript and Crime registers
- Swedish Twin Registry

Quality health registers

- PASTILL, Hab, Bipolär
- RIKSÄT
- Q-IVF
- Dog ownership registers
- DSD, congenital hypothyreosis
- National diabetes register, SWEDIABKIDS
- SNQ

Family design

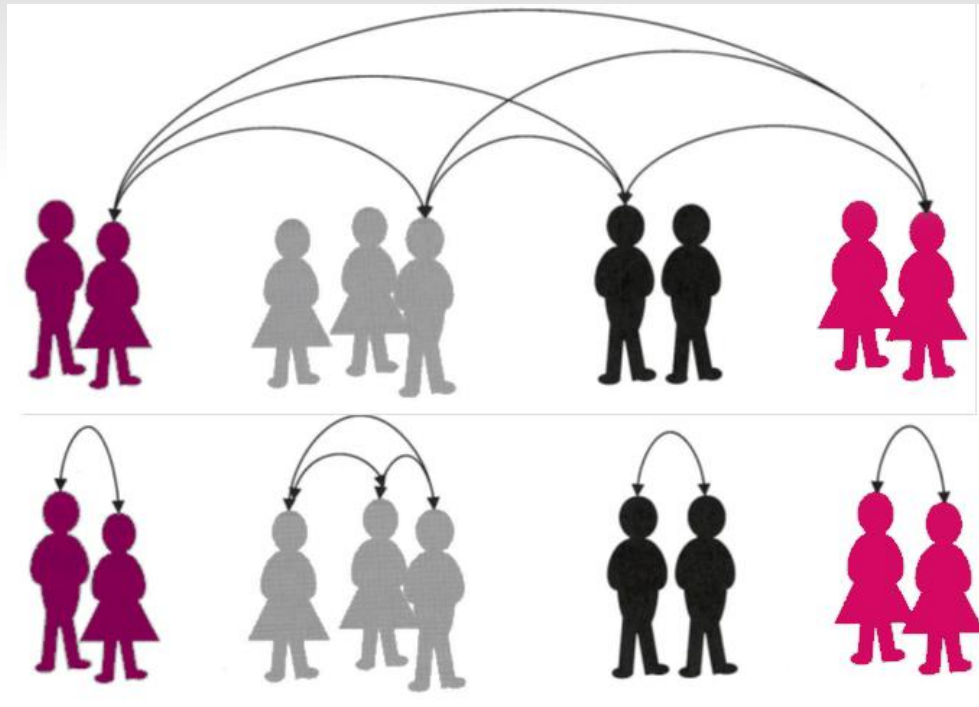


Figure 2. A traditional between-family analysis (upper panel) compares individuals from different families. A within-family analysis (lower panel) compares individuals within the same family (siblings or twins), thus adjusting for all potential confounders that are constant within the family

1. To determine early risk factors for childhood disorders

Aim 1a

- infertility and the use of assisted reproductive techniques (ART)

Aim 1b

- pre- and perinatal factors, including medication use during pregnancy

Aim 1c

- early life exposure and subsequent risks

1b. Antibiotics in fetal or early life and childhood asthma

- Increasing asthma prevalence parallell with increased antibiotics; a causal association? (*Goksör PAI 2013; Mai Clin Exp Allergy 2010; Alm, Pediatrics 2008*)
- Antibiotics **during pregnancy** have been proposed
 - to trigger the disease prenatally in genetically predisposed individuals (*McKeever, Am J Resp Crit Care Med 2002; Rusconi Am J Resp Crit Care Med 2007, Stensballe, J Pediatr 2013*)
 - to affect microbial colonisation in newborns (*Stokholm, Lancet Respir Med 2014*)
- Antibiotics **efter birth** have been proposed
 - to affect microbial colonisation of the child and to disturb development of the immune systemet (*Noverr, Clin Exp Allergy 2005*)
 - to be confounded by respiratory tract infections; reverse causation or confounding by indication

1b. Antibiotics in fetal or early life and childhood asthma

Aim

- to study the association between antibiotics from start of pregnancy to school age and the risk of childhood asthma
- to assess whether the association can be explained by a) respiratory tract infections and b) genetic and environmental factors shared by families

Study population

- Whole cohort (N=493 785); children born to women pregnant from July 2005 to December 2010, identified from the Medical Birth Registry
- Sibling cohort (n=180 894); children with at least one full sibling identified from the Multi-generation register



Ortqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, Ye W, Almqvist C. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *BMJ*. 2014; 349: g6979

1b. Antibiotics in fetal or early life and childhood asthma

Methods

- **Antibiotics** from the Prescribed Drug Register categorised based on indication; (all indications; antibiotics to treat 1) airway 2) urinary tract- and skin infections)
- **Asthma** defined as a combination of asthma diagnosis from the National Patient Registry and prescribed asthma drugs from the Prescribed Drug Register
- **Confounders**; maternal smoking, parity, family situation, mother's country of birth, parental education, maternal asthma

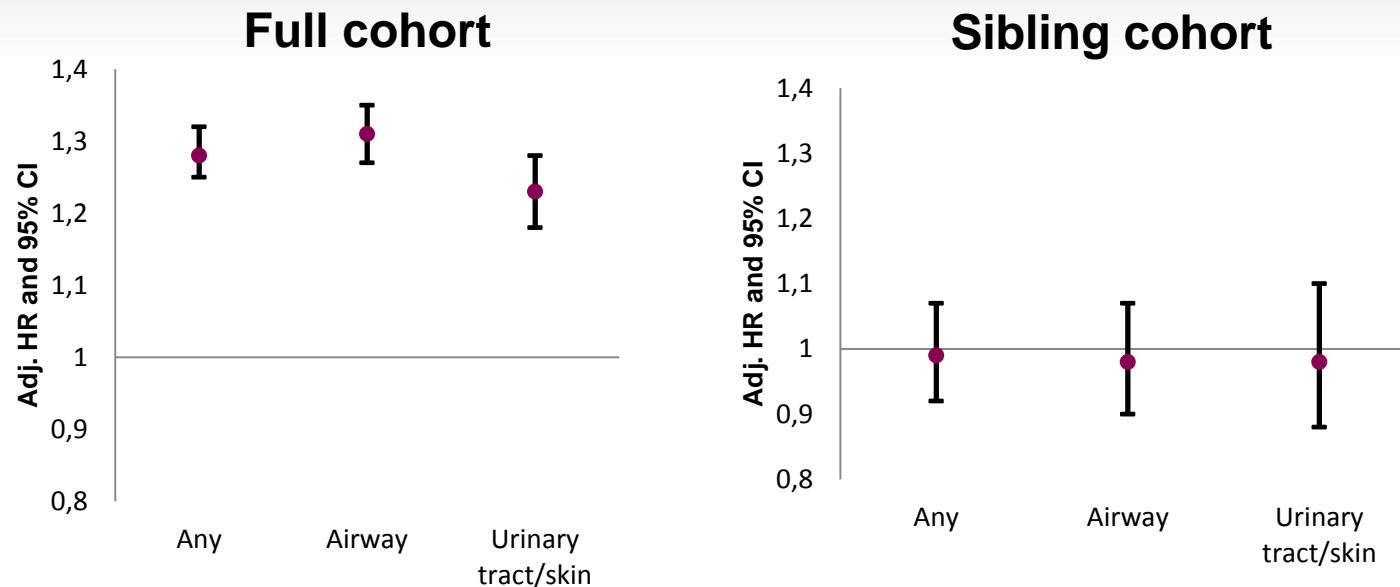
Statistical analyses

- **Whole cohort**; Cox proportional hazard regression
- **Sibling cohort** sibling control design; Cox conditioned on sibling group



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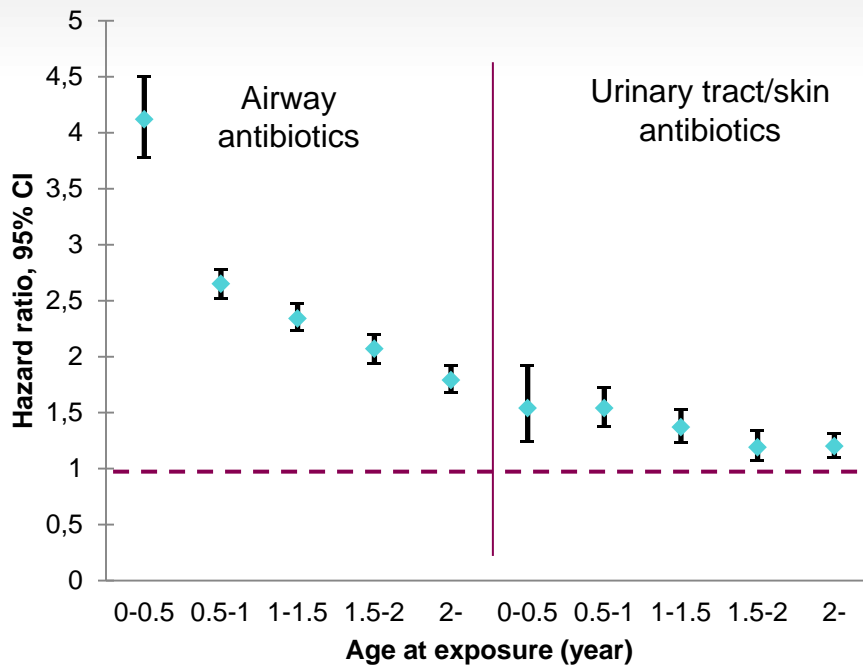
1b. Antibiotics in fetal life and childhood asthma



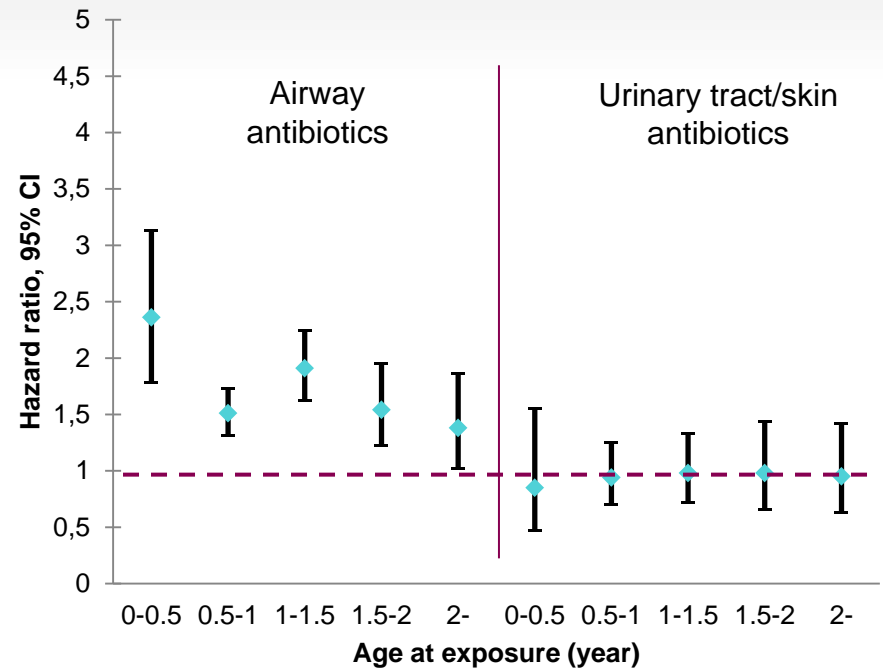
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1b. Antibiotics in early life and childhood asthma

Whole cohort



Sibling cohort



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1b. Conclusion

- Full cohort and sibling design - account for shared genetic and early environmental factors
 - Cohort
 - Sibling
- Groups of antibiotics allow to assess reverse causation and confounding by indication
 - Any
 - Airway antibiotics
 - Urinary tract/skin antibiotics

2. To assess consequences of childhood disorders

Aim 2a

- the effect of early childhood disorders on *subsequent* somatic and psychiatric disorders, and social factors (socioeconomic status and mobility)

Aim 2b

- consequences of pharmacological treatment for common childhood disorders

3. To develop statistical methods to address causal effects using genetically informed population based data

Aim 3

- have developed and will use family designs (within twin/sibling/individual designs) to rigorously test causal hypotheses
- identified a need for further methodological development
- to develop new models for estimating within and between-within effects

Data

- CRIME (Paul Lichtenstein, Henrik Larsson, Catarina Almqvist Malmros)
- Dog and Child (Tove Fall, Catarina Almqvist Malmros)
- The Reproductive database (Anastasia Iliadou Nyman)

Cohorts cont'd

- **CATSS** – Child and Adolescent Twin Study in Sweden; all 9-12 year old twins, N~24,000
- **STOPPA** – Swedish Twin study On Perinatal characteristics to Prevent Asthma
PI Catarina Almqvist Malmros <http://ki.se/meb/stoppa>
 - MZ and DZ twins 9-14 years, discordant, concordant for asthma. Clinical examination for lung function, blood (DNA, serology), saliva (cortisol), fecal (μ biota) urine (metabolites)
- **UppStART** – Uppsala-Stockholm Assisted Reproductive Techniques study
PI Anastasia Iliadou Nyman <http://ki.se/meb/uppstart>
 - Couples followed; risk factors for unsuccessful treatment and short term health effects, growth and epigenetics in offspring
- **Born into Life**
 - Women recruited from LifeGene, followed through pregnancy, delivery and children 6, 12 and 24 months
- **MAESTRO** – Maternal Asthma Events, STress and Offspring <http://ki.se/meb/maestro>
 - Pregnant women recruited from antenatal clinics, followed through pregnancy and post-delivery

Collaborators SIMSAM-MEB family design

National

- **MEB** (many); **KEP** (Sven Cnattingius, Helle Kieler), **KBH Astrid Lindgren** (Sven Bölte, Olle Söder, Anna Nordenström), **CPF** (Eva Serlachius, David Mataix-Cols) **Göteborg university** (Mikael Landén), **Sophiahemmet** (KG Nygren), **Stockholm University** (Erik Bihagen, Carina Mood) and other **SIMSAM** nodes
- **Centre for Allergy Research, CfA** (funded by the Astra Zeneca-KI joint research program); Gunilla Hedlin, Sven-Erik Dahlén, Göran Pershagen, Erik Melén
- Strategic Research Program in Epidemiology at KI (**SFO-epi**); Lifespan approach to health and disease – three SIMSAM co-PIs received Young Scholar Awards
- **SIMSAM grants** ”Transmitted and acquired determinants of health across the Life-Span” (PI Weimin Ye), 2009-2013 – three SIMSAM co-PIs on both grants

Collaborators SIMSAM-MEB family design

International

- **England**; Senior lecturer Seena Fazel, Oxford University; Prof Avi Reichenberg, Institute of Psychiatry, London
- **USA**; A/Prof Sonia Hernandez Diaz head of the Pharmacoepidemiology program at the Harvard School of Public Health; Prof Kenneth Kendler, Medical College of Virginia; Profs Patrick Sullivan and Cindy Bulik, University of North Carolina
- **Canada**; Prof Anita Kozyrskyj, University of Manitoba in Canada
- **Australia** Prof Guy B Marks, University of Sydney, Prof Nick Martin Queensland Institute of Medical Research.
- **European Network** financed by the EU 7th framework integrating research on development and ageing (IDEAL www.ideal-ageing.eu) and ; Prof Eleni Petridou, University of Athens, Prof Anja Pinborg, Copenhagen University Hospital, Prof Jaakko Kaprio University of Helsinki Finland

Contribution to national SIMSAM

▪ Courses

- Family design, Causal inference (Arvid Sjölander), Modelling and simulation (Pär Sparén), Competing risks and multi-state models (Paul Dickman), R

▪ Competenses

- Biostatistics, DBA routines, clinical relevance and close collaborations (pediatricians, veterinarians, psychiatrists)
- Pediatric, reproductive and psychiatric epidemiology
- Family design, registers
- Methodology
- Medicinska riksstämman www.sls.se

More information

- SIMSAM home page <http://simsam.nu/network-nodes/simsam-meb-family-design/>
- KI new home page <http://ki.se/en/meb/simsam-meb-family-design>
- Webb profile <http://ki.se/en/people/catalm>
- Barnläkaren (Journal of Swedish Pediatric Association) www.barnlakaren.se
- SVEPET (Journal of Swedish Medical Society Section for Epidemiology) www.svepet.se
- CURIE <http://www.tidningencurie.se/>