In utero experience, child development, and health outcomes in a national birth cohort: The Finnish Prenatal Studies

May 22, 2009

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Outline

- Rationale
- Description of the FiPS
- Applications

FiPS goals and objectives

- To examine the determinants of child and adult health outcomes in the offspring, using in utero serologic biomarkers and well-documented registry data in a national birth cohort
- To assess interactive and mediating relationships between in utero exposures, obstetric and neonatal complications, early childhood development, and early adult neurocognition on child/adult health disturbances
- To lay the groundwork for future genetic studies, including interactions between genetic polymorphisms and early developmental precursors, and epigenetic effects of in utero exposures, on health outcomes

Schizophrenia: A developmental perspective

Susceptibility Genes & Other Environmental Exposures

Stress

Cannabis

In Utero
- Infection
- Malnutrition
- Hypoxia
- Stress
- Toxins
- Paternal Age

Physiologic →

Epigenetic? →

De novo mutation? →

Birth
- Low birth weight
- Prematurity
- Low head circumference
- Labor/delivery complications
- Congenital anomalies

Childhood
- Delayed milestones
- Neuromotor dysfunction
- Social/cognitive disturbances
- Slower growth velocity

Adolescence
- Prodromal symptoms
- Decline in neurocognitive function

Adulthood
- Overt schizophrenia psychosis

Neural Processes

Limitations of previous work

- Limited statistical power due to small sample sizes
  - Assessment of interactive and mediating effects of exposures and infant/childhood developmental measures
  - Rare exposures
  - Exposures of small effect
  - Gene-environment interaction

- Exposure data
  - Restricted number of exposures
  - Few attempts to replicate existing findings
  - Lack of validation: maternal recall vs. biomarkers, interviews

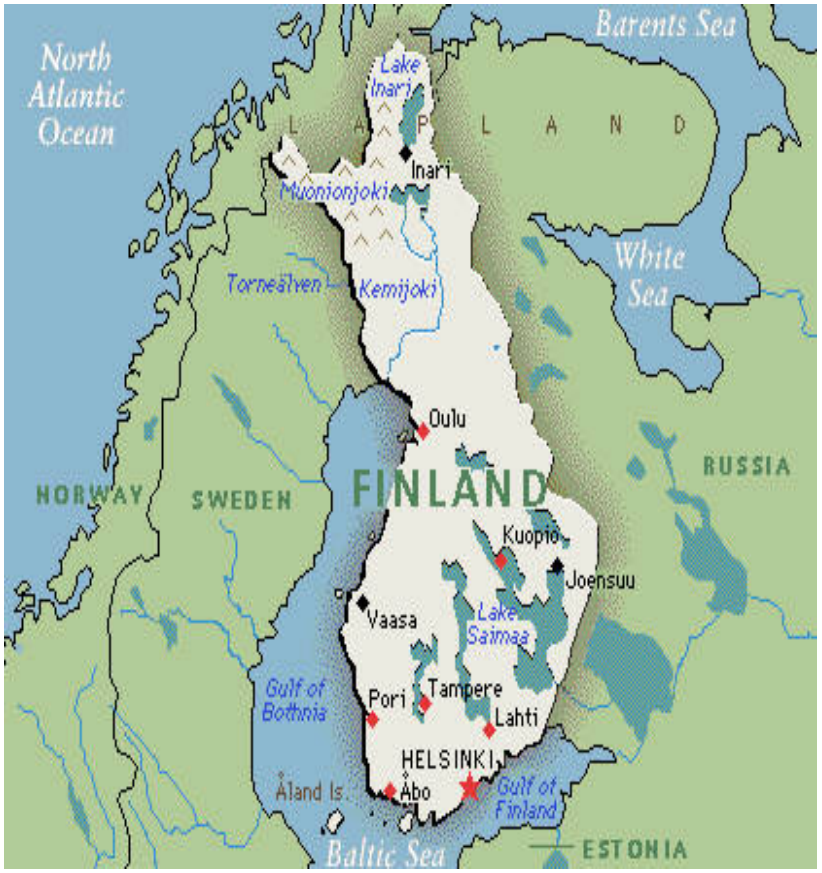
- Bias
  - Ascertainment
  - Loss to follow-up
  - Non-representative controls

Limitations of previous work (cont.)

- Lack of assessment of developmental trajectories
- Population stratification
- Specificity of outcome rarely addressed
- High costs
- Lack of available cases given long latency period between initial insult and onset of the disorder

Finnish maternity cohort

- Mandatory prenatal screening for HIV, syphilis, rubella (first-second trimester)
- Compliant population
- Archived prenatal serum specimens on virtually all pregnant women in Finland from 1983 to present (and ongoing)
- Stored frozen in a single biorepository at NPHI in Oulu, Finland (Helja-Marja Surcel, Director)
- 1.5 million pregnancies (about 60,000 births/year)
- Maternal specimens have been analyzed for multiple biomarkers in nearly 100 previous publications (none on mental disorders)



The FMC serum repository

Finnish national registries

Domain	Registry	Description of Data
Population data	Population	Vital status, place of birth, lifetime residence, emigration status, marital status
Diagnosis	Hospital discharge and Outpatient	All recorded diagnoses from hospitals and all recorded diagnoses from outpatient health contacts
Prenatal/perinatal Complications	Medical birth	Comprehensive, standardized data on pregnancy, perinatal, neonatal periods
Infancy/childhood data	Well baby/childhood health	Nationally standardized developmental assessments at 1-15 months, 2-6 years
Premorbid neurocognitive data	Finnish defense forces	Age 18, detailed assessment of intellectual ability

Challenges and solutions of birth cohort studies

CHALLENGES	SOLUTIONS
• Statistical power ◦ Interactive and mediating effects of early exposures and childhood development ◦ Rare exposures ◦ Exposures of small effect ◦ Gene-environment interactions	• Large sample size
• In utero exposure data ◦ Validity ◦ New exposures ◦ Replication of previous findings	• Archived prenatal sera assayed for maternal biomarkers
• Bias ◦ Ascertainment ◦ Loss to follow-up ◦ Non-representative controls	◦ A national cohort: virtually all pregnancies and all cases ◦ Low migration and mortality rate ◦ Complete population registries
• Developmental trajectories ◦ Early ◦ Late	◦ Well baby/child health clinics ◦ Neurocognitive measures in early adulthood
• Population stratification	• Ethnically homogeneous population
• Specificity of outcome	• Inpatient/outpatient registers on wide range of health outcomes
• High costs	• Use of existing resources
• Lack of available cases	• Most data are already available

Specific aims of FiPS-S

- Examine relation between schizophrenia and several serologically documented prenatal biomarkers, including infections (influenza, toxoplasmosis, herpesviruses, chlamydia), C-reactive protein, thyroid hormone, cotinine
- Assess interactive and mediating relationships between prenatal and perinatal risk factors for schizophrenia
  - Do perinatal events mediate the effects of prenatal exposures?
- Assess relationships between postnatal factors (childhood, adulthood) and prenatal exposures
  - Does childhood growth (height, head circumference) mediate assns. between prenatal factors and schizophrenia
  - Does premorbid intellectual function at age 19 interact with effects of prenatal exposures on schizophrenia risk
- Ascertain interactions between prenatal exposures and family history of schizophrenia
- Future aims: Gene-environment interaction, epigenetic effects of in utero exposures

In utero exposure to SSRI: FiPS-SRI

- Rodent models of fetal exposure to SSRIs indicate anxiety and depressive-type behaviors in offspring
- Goal: To examine whether SSRI use during pregnancy is associated with perinatal and neuropsychiatric outcomes during childhood and adolescence
- Identified 15,000 pregnancies with prescribed SSRIs from the Finnish Drug Prescription register
- Record linkages with:
  - Medical birth register: prenatal/perinatal complications, neonatal outcomes
  - Inpatient/outpatient registers: learning, motoric, speech deficits, mental retardation, attention deficit disorder, anxiety and affective disorders, oppositional/conduct disorders
- Collaborations with investigators in basic neuroscience, high risk/clinical genetics, perinatal depression/fetal physiology (Sackler Center)

Sample sizes in FiPS studies

Study	Topic	N	Funding agency
FiPS-S	Schizophrenia	5,000	NIMH
FiPS-B	Bipolar	2,000	NARSAD
FiPS-A	Autism	1,500	Autism Speaks
FiPS-SSRI	SSRI exposure	15,000	Sackler Center

Birth cohort studies: A research agenda for the 21st century

- Adoption of translational approaches
  - Epidemiology
  - Genetics
  - Clinical neuroscience: phenotyping
  - Basic neuroscience: mechanisms
- Identification of environmental exposures can lead to discovery of susceptibility genes
- Complementary approach: Integrate strengths of different birth cohort study designs

The FiPS research team

Acknowledgements

NYSPI—Division of Epidemiology

Unit in Birth Cohort Studies

P. Nina Banerjee

Lauren Ellman

Aundrea Cook

David Kern

Elena Derkits

Nicole Stephenson

Misty May

Justin Penner

Lilli Arader

NYSPI—Director, Division of Epidemiology

Myrna Weissman

Finland

Andre Sourander (Turku Univ., CU/NYSPI)

Helja Marja Surcel (NIHW)

Thedi Ziegler (NIHW)

Solja Niemela (Turku Univ.)

Funding sources

NIMH: 1R01MH082052,

2K02MH065422 (A. Brown, PI)

NARSAD (A. Sourander, PI)

Sackler Center

“Finnish”ed!

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