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

May 22, 2009

Alan S. Brown, M.D., M.P.H.
asb11@columbia.edu
College of Physicians and Surgeons of Columbia University
New York State Psychiatric Institute
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.
Neural Processes

- Proliferation
- Differentiation
- Migration
- Synaptogenesis
- Pruning
- Myelination

Susceptibility Genes & Other Environmental Exposures

- Stress
- Cannabis

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

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

Stress

- Hypoxia
- Infection
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Neuromotor dysfunction

Social/cognitive disturbances

Slower growth velocity

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Schizophrenia: A developmental perspective
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

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

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

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<thead>
<tr>
<th>Study</th>
<th>Topic</th>
<th>N</th>
<th>Funding agency</th>
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<tbody>
<tr>
<td>FiPS-S</td>
<td>Schizophrenia</td>
<td>5,000</td>
<td>NIMH</td>
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<tr>
<td>FiPS-B</td>
<td>Bipolar</td>
<td>2,000</td>
<td>NARSAD</td>
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<tr>
<td>FiPS-A</td>
<td>Autism</td>
<td>1,500</td>
<td>Autism Speaks</td>
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<tr>
<td>FiPS-SSRI</td>
<td>SSRI exposure</td>
<td>15,000</td>
<td>Sackler Center</td>
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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!
Alan S. Brown, M.D., M.P.H.
E-mail: asb11@columbia.edu
Director, Unit in Birth Cohort Studies
Division of Epidemiology
College of Physicians and Surgeons of Columbia University
New York State Psychiatric Institute
1051 Riverside Dr., Unit 23
New York, NY 10032

Phone: 212-543-5629
FAX: 212-543-6225