Department of Mental Health
at
Johns Hopkins Bloomberg School of Public Health
• 1 in 48 boys (5 to 1)

• Autism in children costs $61 billion per year in US & $175 billion for adults on the spectrum*

• $50,000-$100,000 per family, depending on age and severity*

• Unmeasured family costs in time, lost wages/career opportunities, relationships

There is no medical detection or cure for autism

www.cdc.gov/ncbddd/autism/data.html

Wendy Klag Center for Autism and Developmental Disabilities

Wendy Klag Center for Autism and Developmental Disabilities

Lifecourse perspective

Descriptive (what, who, where)

Cause (Why, how; mechanisms)

Promotion, Prevention, Treatment, Recovery

Services, Policy

Biopsychosocial framework

Epidemiological methods
Our People

Director: Dani Fallin

Janet DiPietro
Research Initiatives

Liz Stuart
Statistical Methods

Li-Ching Lee
Global Epidemiology

Heather Volk
Environmental Epidemiology

Scientific Advisory Board
Maureen Black; John Constantino; Lisa Croen; Gary Goldstein; David Mandell

Associate Directors:

Janet DiPietro
Research Initiatives

Liz Stuart
Statistical Methods

Li-Ching Lee
Global Epidemiology

Heather Volk
Environmental Epidemiology

Administrator & Communications: Michelle Landrum

Project Coordinators: Jamie Dahm Kaczaniuk

Faculty affiliate members

Students

Study-specific staff
ASD Epidemiology Studies/Data Sets

• WKC Investigators work on multiple national studies

  – Surveillance
    • Autism Prevalence – Autism and Developmental Disabilities Monitoring (ADDM) Network

  – Case-control studies
    • SEED
    • CHARGE

  – Enriched risk cohorts
    • EARLI
    • IBIS
    • MARBLES
    • Boston Birth Cohort

  – Health Systems
    • Kaiser

  – National Registries
    • Denmark
Current ADDM Network Sites, Surveillance Years 2010 and 2012

Monitoring 8 year olds
- Autism
- Autism, Cerebral Palsy
- Autism, Intellectual Disability
- Autism, Cerebral Palsy, Intellectual Disability, Vision Impairment, and Hearing Loss

Monitoring 4 and 8 year olds
- Autism
- Autism, Cerebral Palsy
- Autism, Intellectual Disability
- Autism, Cerebral Palsy, Intellectual Disability, Vision Impairment, and Hearing Loss
Special Issue on: Global Autism Research

- Published online June 13, 2017
  DOI: 10.1177/1362361317704603

- Volume 21, Issue 5, July 2017
Autism Etiology: Why & How?

Genetics
- Inherited
  - Common SNP
  - Common CNV
  - Rare SNV
  - Rare CNV
- De novo
  - Rare SNV
  - Rare CNV

Environment
- Parental Characteristics
  - Age
  - Medical Conditions
  - Perinatal/Obstetric
  - Nutrition
- Toxicants
  - Chemical
  - Behavioral
  - Environmental
  - Occupational
  - Pharmaceutical
  - Biological

Gene x Environment
- Statistical and Epidemiologic Interactions
- Exposure modified by genetics
- Genetics modified by exposure
- Genetic and environmental synergism

Biological Interactions and Molecular Targets
- Exposure mediated by genetic alterations
- Gene product contact with exposure
- Epigenetics

Risk of Autism Spectrum Disorders

Bakulski KM, Singer AB, Fallin MD. 2014. *Frontiers in Autism Research*
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SEED is largest population-based US Case-Control Study of ASD (children 2-5 yrs)

- Genes and Environmental Risks
  - Maternal Interviews
  - Self-administered questionnaires
  - Medical record abstraction
  - Child clinical evaluation and physical exam
    - Developmental evaluation
    - Dysmorphism examination
  - Biosampling:
    - Cheek cells or saliva (parents, child)
    - Blood (parents, child)
    - Hair (child)
    - DNA and DNAmethylation

>2000 ASD cases
>2000 POP controls
Student SEED projects

- Occupational exposures
- Alcohol exposure
- Estrogen exposures
- Screening tool utility by race/ethnicity/SES
- Genetic and dysmorphology insights
- meQTL-based genomic integration
- eQTL-based genomic integration
- DNA methylation signatures of prenatal exposures
- Gene-environment interactions
Table 2. Exposure ORs (95% CIs) for autism, by category of distance from residence to the nearest freeway at time of birth (n = 563).

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>n (cases/controls)</th>
<th>Crude</th>
<th>Adjusted$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 309 m from freeway (closest 10%)</td>
<td>38/19</td>
<td>1.86 (1.04–3.45)</td>
<td>1.86 (1.03–3.45)</td>
</tr>
<tr>
<td>309–647 m from freeway (10th to 25th percentile)</td>
<td>43/41</td>
<td>0.98 (0.60–1.59)</td>
<td>0.96 (0.58–1.56)</td>
</tr>
<tr>
<td>647–1,419 m from freeway (25th to 50th percentile)</td>
<td>77/63</td>
<td>1.14 (0.76–1.71)</td>
<td>1.11 (0.73–1.67)</td>
</tr>
<tr>
<td>&gt; 1,419 m from freeway (further 50%)</td>
<td>146/136</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

$^a$Model was adjusted for child sex (male vs. female), child race/ethnicity (Hispanic vs. white, black/Asian/other vs. white), maximum education of parents (parent with highest of four levels: college degree or higher vs. some high school, high school degree, or some college education), maternal age (> 35 years vs. ≤ 35 years), and maternal smoking during pregnancy (mother reported any smoking during pregnancy vs. mother reported no smoking during pregnancy)
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Infant siblings and the investigation of autism risk factors

Figure 6. EARLI Network core protocol data collection schedule
A researcher measures a family’s living room before gathering a dust sample, paying close attention to areas where pregnant mother sits.

At right, a researcher processes a placental sample, which may provide clues to the fetal environment.
Epigenetics: The study of heritable and reversible cellular information other than the DNA sequence itself

DNA methylation (DNAm)

- CH₃
- CH₃
- CH₃
- CH₃

Epigenetic machinery

- MBD2

ncRNAs

ACGCAGUGU
UGCGCUACA
AGACGCU

Histone tail modifications
- acetylation
- methylation
- phosphorylation

Chromatin structure
- loops
- compaction

mC

N

O
Epigenetics: Chemical Modifications of DNA that Control Expression of Genes

**B**

Gene “switched on”
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones

Gene “switched off”
- Silent (condensed) chromatin
- Methylated cytosines (red circles)
- Deacetylated histones

Transcription possible

↓ Methylation & ↑ H acetylation = ↑ Expression

Transcription impeded

↑ Methylation & ↓ H acetylation = ↓ Expression

Epigenetics control the flow of DNA-> RNA-> Protein

↓ Methylation & ↑ H acetylation = ↑ Expression

↑ Methylation & ↓ H acetylation = ↓ Expression
Role of DNA methylation in ASDs

Common DNA methylation alterations in multiple brain regions in autism

Prenatal  Birth  Lifespan  Post-mortem
Role of DNA methylation in ASDs

Prenatal | Birth | Lifespan | Post-mortem
Role of DNA methylation in ASDs
Paternal sperm DNA methylation associated with early signs of autism risk in an autism-enriched cohort

Jason I Feinberg,1,2 Kelly M Bakulski,1,2,3 Andrew E Jaffe,4,11 Rakel Tryggvadottir,2 Shannon C Brown,1,2 Lynn R Goldman,5,6 Lisa A Croen,7 Irva Hertz-Picciotto,8 Craig J Newschaffer,9,10 M Daniele Fallin5,11,1* and Andrew P Feinberg2,12,*

Candidate differentially methylated regions (DMRs) (n=4) in paternal semen that are associated with offspring 12-month AOSI scores, an indicator of autism risk.
Brain Development in Autism: Infant Siblings

UNC researchers unlock new clues in fight against autism

Low-Risk Infant with Normal MRI; ASD-negative at 24M

6M  12M  24M

High-Risk Infant with Increased Extra-Axial CSF; Diagnosed with ASD at 24M
Boston Birth Cohort

**Enrollment Summary**
8,500 mother-infant pairs (~2,500 preterm)

**Demographics**
Inner city, minority (65% blacks, 25% Hisp) in Boston

**Timepoints**
Enrolled at Birth, 24-72 hours after delivery
F/U at pediatric primary care visits

**Data Collected**
Prenatal and Perinatal EMR Data
Clinical Measurements including Growth and Development at F/U
Epidemiological questionnaires

Biospecimens:
Maternal and Cord Blood, Placenta Tissue;
Venous Blood at F/U
The Association of Maternal Obesity and Diabetes With Autism and Other Developmental Disabilities

Mengying Li, MSPH, PhD candidate
PFRH
Figure 2. Forest plot comparing the Boston Birth Cohort results to previously reported results. The plot shows effect estimates and 95% confidence intervals for the association between infection or fever (at any point during pregnancy and by trimester) and autism.
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- Health Systems
  - Kaiser

- National Registries
  - Denmark
Kaiser Permanente Northern California

- Group practice prepaid integrated health program
- 3.5 million patients
- 8,000 physicians
- 21 hospitals
- Fully electronic health record
- Serves ~30% of population in geographic region
Nordic registries - Denmark

Science 31 March 2000:
Vol. 287 no. 5462 pp. 2398-2399

When an Entire Country Is a Cohort

‘Denmark has gathered more data on its citizens than any other country. Now scientists are pushing to make this vast array of statistics even more useful.’
Parental exposures to occupational asthmagens and risk of autism spectrum disorder in a Danish population-based case-control study

Alison B. Singer, Igor Burstyn, Malene Thygesen, Preben Bo Mortensen, M. Daniele Fallin, and Diana E. Schendel

<table>
<thead>
<tr>
<th>Asthmagen Type</th>
<th>% Exposed</th>
<th>Controls</th>
<th>Cases</th>
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<tbody>
<tr>
<td>Any Asthmagen</td>
<td>20.0</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>Any HMW</td>
<td>14.4</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Animals</td>
<td>0.9</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>0.4</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Flour</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Plants</td>
<td>&lt;0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Mites</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
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<tr>
<td>Enzymes</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Latex</td>
<td>11.3</td>
<td>10.1</td>
<td></td>
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<tr>
<td>Bioaerosols</td>
<td>0.7</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>1.3</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Any LMW</td>
<td>10.1</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Reactive</td>
<td>7.7</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Isocyanate</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Cleaning</td>
<td>6.2</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Wood</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Metals</td>
<td>1.1</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Any Mixed</td>
<td>1.7</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Metalworking</td>
<td>0.3</td>
<td>0.4</td>
<td></td>
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<tr>
<td>Textile</td>
<td>0.6</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Agricultural</td>
<td>0.8</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Irritant Peaks</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

Maternal Adjusted Odds Ratios and 95% CI
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  • Boston Birth Cohort

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  • Kaiser

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  • Denmark
Examples of WKC-affiliated Projects

- SEED – Prenatal anti-depressant use and interplay with (maternal and child) genetic and epigenetic factors

- EARLI-MARBLES – Prenatal folic acid supplementation, and interplay with genetic and epigenetic factors

- EARLI-MARBLES – Prenatal air pollution risk, and genetic predisposition

- EARLI-IBIS – Prenatal air pollution risk and early life brain imaging / behavior

- EARLI-MARBLES – Prenatal metals exposure and interplay with genetic and epigenetic factors

- ASD-ER – ECHO cohort participant, with focus on prenatal exposures measurable in shed baby teeth

- SEED 3 – new field recruitment
Researchers take on the role of tooth fairy to better understand autism

Scientists study an unexpected source of information about in utero exposure to harmful materials: baby teeth.
Join Us!

• **Internship** placements decided twice a year, with deadlines of Sept. 30 and Feb. 1. Paper applications here today, or see ‘For Students’ tab on [www.jhsph.edu/WKC](http://www.jhsph.edu/WKC).
  
  New this year:
  – Sheppard Pratt–Lieber Research Institute Adult Autism Registry
  – Diversity Fellowship with MCDD

• **Journal clubs** on the 1st Monday of the month
  – 12:15 - 1p.m., Room W4007
  – Topics and dates on [www.jhsph.edu/WKC](http://www.jhsph.edu/WKC) calendar

• **Other events** such as retreats and symposia

• **Pilot funding** for faculty and students. Applications typically due in March.

• **To join WKC contact list**, email mlandru5@jhu.edu
Public Health Approaches in
Autism and Developmental Disabilities
330.700.01
Term 3, AY 2017 –2018
Instructors: Dani Fallin & Li-Ching Lee
with guest expert lecturers

Autism spectrum disorder (ASD) is a major public health issue. In this course, students will learn about ASD and measurement issues from an epidemiologic perspective, as well as updates on the prevalence of ASD and how prevalence is estimated. The course also covers etiological research methods and findings to date, and discusses the emerging questions for Public Health including etiology, comorbidity, policy and services.

Course content includes:

- History of ASD and DD diagnoses
- Screening and diagnostic assessments
- Prevalence
- Co-occurring conditions
- Life-course presentation
- Demographic risk factors
- Genetic risk factors
- Environmental risk factors
- Current intervention strategies
- Early detection
- Findings and challenges of global public health efforts
- Medical and education-based services
- Emerging biomarkers
<table>
<thead>
<tr>
<th>Awardee and Type</th>
<th>Proposal Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calliope Holingue (Student) Department of Mental Health</td>
<td><strong>Microbiome Composition and Structure of Children with Autism Spectrum Disorder</strong></td>
</tr>
<tr>
<td>Chris Ladd-Acosta (Faculty) Department of Epidemiology</td>
<td><strong>Prostaglandin E2 (PGE2) and risk for autism spectrum disorder (ASD)</strong></td>
</tr>
<tr>
<td>Heather Volk (Faculty) Department of Mental Health</td>
<td><strong>Measurement of Environmental Exposure Biomarkers in Shed Deciduous Teeth</strong></td>
</tr>
<tr>
<td>Vanya Jones (Faculty) Department of Health Behavior &amp; Society</td>
<td><strong>Childhood Unintentional Injury Safety Practices: What are the experiences of parents of children with Autism Spectrum Disorder</strong></td>
</tr>
<tr>
<td>Dr Robert Gilman (Faculty) Department of International Health</td>
<td><strong>Smell as diagnostic aid for autism in Peru</strong></td>
</tr>
<tr>
<td>Martha Brucato (Student) Dept of Epidemiology</td>
<td><strong>Developing methods utilizing Machine Learning and Latent Class Analysis to Identify children with ASD in administrative health data</strong></td>
</tr>
<tr>
<td>Bo Y. Park (Postdoctoral Fellow) Department of Mental Health</td>
<td><strong>Maternal metabolic syndrome and Autism Spectrum Disorder (ASD) risk</strong></td>
</tr>
<tr>
<td>Li-Ching Lee (Faculty) Department of Epidemiology</td>
<td><strong>Parent-Mediated In-Home Intervention for Children with Autism Spectrum Disorder in Bangladesh</strong></td>
</tr>
<tr>
<td>Kripa Raghavan (Doctoral Student) Department of Population, Family, and Reproductive Health</td>
<td><strong>Micronutrient Determinants of ASD and Developmental Disabilities in a US Urban Low Income Minority Birth Cohort</strong></td>
</tr>
<tr>
<td>Elise Pas (Faculty) Department of Mental Health</td>
<td><strong>Reducing Behavior Problems among Students with an ASD through Coaching Teachers in a Mixed-Reality Setting</strong></td>
</tr>
<tr>
<td>Alden Gross (Faculty) Department of Biostatistics</td>
<td><strong>Development and validation of a continuous scale of autism severity across ADOS modules</strong></td>
</tr>
<tr>
<td>Allan Andersen (Doctoral student) Department of Mental Health</td>
<td><strong>A survey of cost and effectiveness of parental responses to elopement among children with ASD in the Interactive Autism Network</strong></td>
</tr>
<tr>
<td>Kelly Bakulski (Postdoctoral Fellow) Department of Epidemiology</td>
<td><strong>Heavy metals exposure and autism spectrum disorders in the Early Autism Risk Longitudinal Investigation (EARLI)</strong></td>
</tr>
<tr>
<td>Luke Kalb (Doctoral Student) Department of Mental Health</td>
<td><strong>Effects of Federal Mental Health Parity on Psychiatric Department Use among Privately Insured Children with Autism Spectrum Disorder</strong></td>
</tr>
</tbody>
</table>
Further information on Autism

WKC Website: www.jhsph.edu/wkc


Sesame Street Continues to Teach Us All

- https://www.youtube.com/watch?v=uR0nuBr8xZg