Toxics, Stress, and Genetics: Combined Impacts in Autism Research

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Today’s Talk

• Environmental risk factors for autism and neurodevelopmental traits

• Examples gene-environment interactions

• Potential for gene-environment interaction

• Challenges and opportunities ahead for gene-environment interaction in neurodevelopmental disorders
Autism

Impairments in social communication and social interaction

Restricted and repetitive behaviors and interests

- Inclusion of sensory interests and aversions
- Severity levels

Picture from: http://www.cdc.gov/ncbddd/autism/facts.html
US Prevalence Estimates Continue to Increase

Percentage of 8-year-old children identified with ASD by ADDM Network Site

4.0%
3.5%
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%

OVERALL: 2.3%

1 in 44
8-year-old children were identified with ASD in 2018 by the ADDM Network

More children are being identified with ASD by 48 months

ADDN Community Report on Autism, 2021
Genetic Variation in Neurodevelopmental Disorders and Traits

• Heritability moderate to high for many neurodevelopmental outcomes
  • Autism (50-80%)
  • ADHD (77-88%)
  • Cognition (20-70%)
  • IQ (60-80%)

• Genetic variation includes:
  • Functional Polymorphisms
  • Common Variation (GWAS)
  • Genomic Instability (Copy Number)
  • Rare Variation (WES or WGS)
Genetic Influences on Autism

- Factors responsible for severity may diverge from those responsible for disease occurrence
- Suggests role of the early, non-shared environment

Castelbaum et al., 2020

Fig. 1 Distributions of MZ twin-co-twin differences for autistic trait severity in superimposed density plots for the three respective samples in the study

Fig. 2 Scatter plots of MZ twin-co-twin data: a General population, Social Responsiveness Scale (SRS) scores; b Clinically-ascertained MZ twins, SRS; c Clinically-ascertained MZ twins, Autism Diagnostic Observation Scale (ADOS)
Autism is Increased in Siblings

- Autism is more common in full siblings
  - ~7-8 fold increase
  - Male sex and number of affected siblings are predictors

Ozonoff et al., 2011
Trait Distributions Are Also Shifted in Siblings

- Mean MSEL scores suggest decreased performance in autism and non-autism siblings
  - Messinger et al., 2015

- Greater proportion of “delayed” VABS scores in autism and non-autism siblings
  - Charman et al., 2018
Social Responsiveness Scale (SRS) in Siblings

- SRS Scores Elevated in familial instances
- Distribution of trait shifted across autism and non-autism

Frazier et al., 2015
Figure 1. Effect of neurotoxicants during early brain development
Exposures in early life to neurotoxic chemicals can cause a wide range of adverse effects on brain development and maturation that can manifest as functional impairments or disease at any point in the human lifespan, from early infancy to very old age.

Grandjean and Landrigan, 2015
What Can Environmental Epidemiology Tells Us About Neurodevelopment?

- Environment = chemical/physical, social, lifestyle, ecosystems
  - Possible target for intervention

- Population based studies can inform on:
  - Frequency of environmental factor
  - Magnitude of risk in the population

- Environmental studies can inform on:
  - Mechanism and pathways
  - Biomarkers of effect
Environments of Interest in NDDs

**Toxicants**
- Air Pollution
- Metals
- Pesticides
- Flame Retardants
- Phthalates

**Maternal Medical Factors**
- Pregnancy Complications
- Mode of Delivery
- Prenatal Vitamins / Folate / Vitamin D / PUFAS
- Infections / Fever
- Pre-pregnancy BMI / Diabetes

**Social Factors**
- SES
- Discrimination

**Demographics**
- Maternal Age
- Paternal Age
- Inter-pregnancy Interval

**Ecosystems**
- Greenspace
- Neighborhood Deprivation
What We Know:

• NDDs / ASD are heterogeneous
• Early detection is important
• Genetics matter
• Environmental risk factors are shared across NDDs

What We Need to Know:

• Specificity of exposure effect
  • Disorder or trait or brain in general
• Exposure x Exposure Interaction
• Gene x Environment Interaction
• Pathways / mechanism / biomarkers
  • Experimental models
  • Population studies

Targets for intervention and prevention
What We Know:

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Targets for intervention and prevention
Air Pollution Has Broad Effects on Neurodevelopment

Environmental Research 196 (2021) 110320

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review article

Prenatal air pollution exposure and neurodevelopment: A review and blueprint for a harmonized approach within ECHO

Heather E. Volk a,*, Frederica Perera b, Joseph M. Braun c, Samantha L. Kingsley c, Kimberly Gray d, Jessie Buckley e, Jane E. Clougherty f, Lisa A. Croen g, Brenda Eskenazi h, Megan Herting i, Allan C. Just j, Itai Kloog k, Amy Margolis l, Leslie A. McClure m, Rachel Miller n, Sarah Levine b, Rosalind Wright o, on behalf of program collaborators for Environmental influences on Child Health Outcomes l
Autism and Air Pollution

23 studies included

A Systematic Review and Meta-Analysis of Multiple Airborne Pollutants and Autism Spectrum Disorder

Juleen Lam1*, Patrice Sutton2, Amy Kalkbrenner3, Gayle Windham4, Alycia Halladay5,6, Erica Koustas7, Cindy Lawler8, Lisette Davidson9, Natalyn Daniels10, Craig Newschaffer11, Tracey Woodruff12

Conclusion

After considering strengths and limitations of the body of research, we concluded that there is “limited evidence of toxicity” for the association between early life exposure to air pollution as a whole and diagnosis of ASD. The strongest evidence was between prenatal exposure to particulate matter and ASD. However, the small number of studies in the meta-analysis and unexplained statistical heterogeneity across the individual study estimates means that the effect could be larger or smaller (including not significant) than these studies estimate. Our research supports the need for health protective public policy to reduce exposures to harmful airborne contaminants among pregnant women and children and suggests opportunities for optimizing future research.
Is it Autism? Is it Something Else?

Increased Adaptive Deficits Among ASD Cases (N=327) With Increasing NO₂*

<table>
<thead>
<tr>
<th></th>
<th>NO₂</th>
<th>Ozone</th>
<th>PM₁₀</th>
<th>PM₂.₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>VABS Composite</td>
<td>-11.08%,</td>
<td>-3.54%,</td>
<td>5.52%, p=0.37</td>
<td>-5.58%, p=0.32</td>
</tr>
<tr>
<td></td>
<td>p=0.02</td>
<td>p=0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>-14.05%,</td>
<td>0.56%,</td>
<td>4.19%, p=0.55</td>
<td>-5.43%, p=0.39</td>
</tr>
<tr>
<td></td>
<td>p=0.01</td>
<td>p=0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socialization</td>
<td>-8.79%, p=0.06</td>
<td>-3.43%,</td>
<td>6.63%, p=0.27</td>
<td>-2.73%, p=0.62</td>
</tr>
<tr>
<td></td>
<td>p=0.56</td>
<td>p=0.56</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Regional pollution effects reflect risk of autism based on 2 standard deviations from the mean value, specifically per increase of 8.8 mg/m³ PM₂.₅, 12.4 mg/m³ PM₁₀, 9.0 ppb NO₂, and 13.6 ppb ozone.

Kerin et al., 2017
Pre- and Postnatal Fine Particulate Matter Exposure and Childhood Cognitive and Adaptive Function

Laura A. McGuinn ¹,*, Lisa D. Wiggins ², Heather E. Volk ³, Qian Di ⁴, Eric J. Moody ⁵, Eric Kasten ⁶‡, Joel Schwartz ⁷, Robert O. Wright ¹, Laura A. Schieve ², Gayle C. Windham ⁸‡ and Julie L. Daniels ⁹

**Figure 1.** Adjusted mean difference (95% CI) in the scores of the Vineland Adaptive Behavior Scales associated with a 1 µg/m³ increase in PM<sub>2.5</sub>, among ASD cases.
Is it Autism? Is it Something Else?

### Autism, Quantitative Traits, and Air Toxics in Families

<table>
<thead>
<tr>
<th></th>
<th>ASD Diagnosis OR (95% CI)</th>
<th>Change in SRS (95% CI)</th>
<th>Change in CSS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl tert butyl ether (MTBE)</td>
<td>2.33 (1.31, 4.15) *</td>
<td>5.88 (-0.60, 12.36)</td>
<td>0.07 (-0.54, 0.68)</td>
</tr>
<tr>
<td>Propionaldehyde</td>
<td>1.92 (1.33, 2.77) *</td>
<td>2.65 (-1.46, 6.77)</td>
<td>0.19 (-0.18, 0.56)</td>
</tr>
<tr>
<td>Diesel Particulate Matter</td>
<td>1.44 (1.06, 1.97) **</td>
<td>3.23 (-0.33, 6.79)</td>
<td>0.00 (-0.33, 0.32)</td>
</tr>
<tr>
<td>1,4-Dichlorobenzene (p-Dichlorobenzene)</td>
<td>0.25 (0.09, 0.66)*</td>
<td>-15.24 (-25.12, -5.36)</td>
<td>-1.41 (-2.28, -0.54)*</td>
</tr>
</tbody>
</table>

*Statistically significant after FDR =0.1; **Statistically significant at p=0.05

- All models include the single log-transformed air toxic, contrasting the levels of air toxics listed in table X (usually 75% vs. 25%), with a random effect for family, and adjust for the mean air toxic level in the family, birth year, and the census block group population density, education level, and median rent.
What We Know:
• NDDs / ASD are heterogeneous
• Early detection is important
• Genetics matter
• Environmental risk factors are shared across NDDs

What We Need to Know:
• Specificity of exposure effect
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  • Population studies

Targets for intervention and prevention
**Exposure x Exposure Interaction**

Fig. 1 Key pathways that may link environmental exposures, nutrients, and neurodevelopmental outcomes

Bragg et al., 2022
Environment x Social Factors

Distribution of Absolute burden of PM(2.5) emissions from NEI facilities by race/ethnicity & poverty

Air pollution, neighborhood deprivation, and autism spectrum disorder in the Study to Explore Early Development

Laura A. McGuinn, Gayle C. Windham, Lynne C. Messer, Qian Di, Joel Schwartz, Lisa A. Croen, Eric J. Moody, Ana G. Rappold, David B. Richardson, Lucas M. Neas, Marilie D. Gammon, Laura A. Schieve, Julie L. Daniels

Results: Neighborhood deprivation modified (P<0.05 for interaction) the association between PM_{2.5} exposure during the first year of life and ASD, with a stronger association for those living in high (OR=2.42, 95% CI = 1.20, 4.86) rather than moderate (OR=1.21, 95% CI = 0.67, 2.17) or low (OR=1.46, 95% CI = 0.80, 2.65) deprivation neighborhoods. Departure from additivity or multiplicativity was not observed for roadway proximity or exposures during pregnancy.

Conclusion: These results provide suggestive evidence of interaction between neighborhood deprivation and PM_{2.5} exposure during the first year of life in association with ASD.
Environment x Social Factors

(1) Investigate race and sociodemographic differences in exposure sources and biological measures as a function of environmental justice issues and *health disparities*.

(2) Examine how these hazardous environmental exposures interact with both area-based and individual-level psychosocial stressors to alter associations with multiple neurodevelopmental outcomes (ASD, ADHD, and ID).

Opportunities and Infrastructure Fund

Aisha Dickerson
What We Know:

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• Environmental risk factors are shared across NDDs

What We Need to Know:

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  • Disorder or trait or brain in general
• Exposure x Exposure Interaction
• Gene x Environment Interaction
• Pathways / mechanism / biomarkers
  • Experimental models
  • Population studies

Targets for intervention and prevention
Epidemiology of NDDs

Genetics

Environment

Gene X Environment

Disorder / Trait / Brain Measure
Gene-Environment Interaction in Neurodevelopmental Disorders

• What’s the goal?
  • Identification of new genes / environments associated with an outcome?
  • Account for inherited risk?
  • Study joint effects of gene and environment?

Sample size needs increase as E and G become more rare!
GWAS Exist For Many Neurodevelopmental Outcomes

General Cognitive Function
Trampush et al., 2017

ASD
Grove et al., 2019

Digit Symbol (Executive Function)
Ibrahim-Verbaas et al., 2016

ADHD
Demontis et al., 2019
ASD GWAS...Now With Hits!

N=2503 / 7271

N=7387 / 8567
PGC

N=18,381 / 27,969
iPSYCH + PGC
From GWAS to Polygenic Risk Score (PRS)

PGC+iPSYCH GWAS findings:
- 18,381 ASD cases
- 27,969 controls
- >9 million SNPs

p-value threshold & pruning

ASD-risk SNPs >20k

Compute ASD-PRS in familial samples

From Discovery . . .

To Target Sample

<table>
<thead>
<tr>
<th>Individual 1</th>
<th>SNP 1</th>
<th>Weighted ASD-PRS</th>
<th>Weighted Cross-Disorder PRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>5.34</td>
<td>7.34</td>
</tr>
<tr>
<td>1.2</td>
<td>2.06</td>
<td>10.69</td>
<td>25.6</td>
</tr>
<tr>
<td>0</td>
<td>1.03</td>
<td>7.4</td>
<td>2.03</td>
</tr>
<tr>
<td>2.4</td>
<td>2.06</td>
<td>22.94</td>
<td>15.31</td>
</tr>
</tbody>
</table>

Kelly Benke
Genetic Susceptibility for ASD and Related Traits

• Build polygenic risk scores (PRS) from genome-wide data in several ASD studies:
  – Longitudinal Sibling Cohort Designs
    • EARLI Autism Risk Longitudinal Investigation (EARLI)
    • Markers of Autism Risk in Babies Learning Early Signs (MARBLES)
    • Infant Brain Imaging Study (IBIS)
    • Baby Sibling Research Consortium (BSRC)
**ASD-PRS and ASD Diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All (n=648)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>1.21</td>
<td>0.96, 1.51</td>
<td>0.099</td>
</tr>
<tr>
<td>EARLI</td>
<td>1.17</td>
<td>0.70, 1.96</td>
<td>0.55</td>
</tr>
<tr>
<td>IBIS</td>
<td>1.31</td>
<td>0.91, 1.89</td>
<td>0.15</td>
</tr>
<tr>
<td>MARBLES</td>
<td>1.08</td>
<td>0.74, 1.58</td>
<td>0.70</td>
</tr>
</tbody>
</table>

- **Use PRS as a tool for:**
  - **Prediction** (e.g. early screening)
  - **Etiology** (e.g. GxE, traits, co-occurring conditions)
ASD-PRS Association with ASD

p-value threshold = 0.05

 Associations with ASD-PRS Quintiles

All European Quintiles

PRS Quintile

logOR (SE)

quintile1  quintile2  quintile3  quintile4  quintile5

-2.0 -1.5 -1.0 -0.5 0.0 0.5 1.0 1.5 2.0

European

PRS Quintile
ASD-PRS Association with Cognition (Mullen Scales of Early Learning)

PER COHORT

Mullen Score

Frequency

TD
Non-TD
ASD

PRS P-value Threshold

Beta (SE)

10^-8 10^-6 10^-4 10^-3 0.01 0.05 0.1 0.2 0.5 1

-5 -3 -1 1

ALL
MARBLES
IBIS
EARLI

Mullen Score

Frequency

0 5 10 15 20 25 30

40 60 80 100 120 140 160

0 5 10 15 20 25 30

10^-5 10^-4 10^-3 10^-2 10^-1 10^0 10^1

ASD-PRS

Non-TD

TD

Frequency

0 5 10 15 20 25 30

40 60 80 100 120 140 160

0 5 10 15 20 25 30

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ASD-PRS

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MARBLES
IBIS
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0 5 10 15 20 25 30

10^-5 10^-4 10^-3 10^-2 10^-1 10^0 10^1

ASD-PRS

Non-TD

TD
ASD-PRS Association with Cognition (Mullen Scales of Early Learning)

p-value threshold = 0.05
Planned GxE Analyses

• What is the joint effect of organic chemicals during pregnancy and ASD-PRS?

• Explore additional genetic risk scores (GRS)
  • Other disorders
  • Pathway-based GRS

Power for Detecting Environmental Effect when there is a GxE (2DF test)
Convergence of placenta biology and genetic risk for schizophrenia

Gianluca Ursini1,2, Giovanna Punzi1,2, Qiang Chen, Stefano Marenco4, Joshua F. Robinson1, Annamario Porcelli1, Emily G. Hamilton5, Marina Mitjans6, Giancarlo Maddalena1, Martin Bergemann2, Jan Seidel7, Hidenaga Yanamoto7, Andrew E. Jaffe1,8, Karen F. Berman7, Michael F. Egan7, Richard E. Straub1, Carlo Calantuono1, Giuseppe Biasi9, Ryota Hashimoto10, Dan Bujescu10, Hannelore Ehrenreich1, Alessandro Bertolino1 and Daniel R. Weinberger2,3

• PRS + ELCs helped both be characterized
• Prediction implications are important!
Sidenote: PRS Might Predict Progression Over Time

Chaudhury et al., 2019

PRS for Alzheimer’s Disease
- Controls vs. Late Onset AD
- Non-Converters vs. Late Onset AD
- Higher Deciles Have More Late Onset AD
Moving Toward GxE in ASD

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*
Limited Work on GxE in ASD:
~12 Published Studies

Genetic Factors Studied:
- Functional Polymorphisms (6 studies)
- Copy Number Variants (3 studies)
- De Novo Mutations (1 study)
- ASD associated Variants (1 study)
- Oxidative Stress Risk Score (1 study)

Environmental Factors Studied:
- Air Pollution (2 studies)
- Folate / Prenatal Vitamins (2 studies)
- 1st Trimester Ultrasound (1 study)
- Infection / Fever During Pregnancy (1 study)
- Phthalates (1 study)
- Familial Psychiatric Disorders (1 study)
- Metals (3 studies)
- Mix of Environmental Chemicals (1 study)
Folic Acid and MTHFR

**FIGURE 2.** ORs (95% CIs) for associations between mean maternal daily folic acid intake (≥600 µg compared with <600 µg) during the first month of pregnancy and autism spectrum disorder by maternal and child MTHFR genotype. ORs were adjusted for maternal educational level and child’s birth year. Categories of folic acid intake were created on the basis of the recommended intake during pregnancy (600 µg/d). Analyses were based on 272 children with autism spectrum disorder and 275 of their mothers, and 154 children with typical development and 163 of their mothers with MTHFR 677 genotype and folic acid intake data. The frequencies of participants in each category of folic acid intake and MTHFR 677 genotype are presented in Supplemental Table 1 under “Supplemental data” in the online issue.
Air Pollution and MET in ASD

Prenatal Benzo(a)Pyrene Exposure Reduces MET Protein Expression in Mouse Cortex

Sheng et al., 2010

Joint Effect of MET and Air Pollution in CHARGE

<table>
<thead>
<tr>
<th>MET rs1858830 Genotype</th>
<th>C/C</th>
<th>C/G or G/G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>2.9 (1.0-10.4)</td>
<td>1.3 (0.73-2.2)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>0.80 (0.47-1.4)</td>
<td>reference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Nitrogen Dioxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET rs1858830 Genotype</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Exposed</td>
</tr>
<tr>
<td>Unexposed</td>
</tr>
</tbody>
</table>

Volk et al., 2014
Copy Number Burden x Air Pollution in CHARGE

Kim et al., 2017
Maternal Infection X CNV Burden

Figure 1. Autism symptomatology and cognitive and adaptive functioning of children with autism spectrum disorder–associated copy number variants (CNVs) and history of maternal infection or fever during pregnancy (N = 1971). Error bars = 95% confidence interval. As shown in graph C ($p = .010$), a main effect for presence of infections is demonstrated. As shown in graphs G ($p = .019$) and H ($p = .049$), main effects for presence of CNV are demonstrated. As shown in graphs A–E: (A) $p = .006$; (B) $p = .006$; (C) $p = .017$; (D) $p = .012$; (E) $p = .014$, significant interactions are observed. No significant interactions are observed in graphs F and H.

Mazina et al., 2015
First Trimester Ultrasound x CNV

Table 2

Proband Age, mean Standard Test scores (SD), and regression results for all children with ASD, with an identified CNV, and absence (‘No U1’) or presence (‘U1’) of first trimester ultrasound.

<table>
<thead>
<tr>
<th></th>
<th>ASD with CNV N = 133</th>
<th>ASD+CNV No U1</th>
<th>ASD+CNV U1</th>
<th>Beta</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>49</td>
<td>84</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mos)</td>
<td>118.5 (42.5)</td>
<td>111.4 (41.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                |                       |                |            |      |                |         |
| Adaptive and Cognitive |     |               |            |      |                |         |
| VABS-II        | 73.5 (10.1)           | 71.0 (13.4)    | -4.11      | -8.56 to 0.35 | 0.07   |
| Verbal IQ      | 81.8 (32.6)           | 73.6 (30.5)    | -9.39      | -21.37 to 2.59| 0.12   |
| Nonverbal IQ   | 87.7 (27.6)           | 76.8 (25.8)    | -11.16     | -21.08 to -1.24| 0.03   |

Webb SJ, et al., 2017 Autism Research
Antidepressant Use x Large Gene Disrupting Mutations

Fig. 1 Interaction between antidepressant (AD) exposure and LGD mutation on ASD symptoms (ADOS CSS): significant interactive effect: F (1, 2542) = 4.882, p = 0.027. *Error bars* 95% CI

Fig. 2 Interaction between antidepressant (AD) exposure and LGD mutation versus ASD severity (ADI-R): significant interactive effect in ADI-R verbal communication domain: F (1, 2397) = 4.554, p = 0.033. *Error bars* 95% CI

Ackerman et al., 2018 JADD
Table 2

Proband Age, mean Standard Test scores (SD), and regression results for all children with ASD, with an identified CNV, and absence (‘No U1’) or presence (‘U1’) of first trimester ultrasound.

<table>
<thead>
<tr>
<th></th>
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<th>ASD+CNV No U1</th>
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<th>Beta</th>
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<tbody>
<tr>
<td>N</td>
<td>N = 133</td>
<td>49</td>
<td>84</td>
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<td>Age (mos)</td>
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Adaptive and Cognitive

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Webb SJ, et al., 2017 Autism Research
**First Trimester Ultrasound x CNV**

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Webb SJ, et al., 2017 Autism Research
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Adaptive and Cognitive

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Webb SJ, et al., 2017 Autism Research
Further Considerations in GxE

Genotyping
• Other Types of Burden Scores
  • Copy number, rare variant, etc.
• Mom or Child Genotype?
• Comparability of discovery and target samples

Analytic Challenges
• Categorial outcomes or continuous traits? Subgroups?
• Which test to use?
  • Discovery? Joint effects? Prediction?
  • 1, 2, or 3 degree of freedom tests

Environment
• Exposure Assessment Harmonization
• Exposure Misclassification
Infrastructure for GxE:
- 18 Network Sites (plans to add more)
  - ~175,000 individuals
- Translation to Laboratory Models
  - Mini-brain Models
- Community Advisory Board and Outreach

Our **goal** is to establish a network for the evaluation of gene-environment interaction in Autism Spectrum Disorder (ASD).

R01 ES034554 (MPI Volk, Ladd-Acosta)
Flexible Structure for Study of GxE in Epidemiologic Data

Repository for Study of GxE in Laboratory Model
## Planned Analyses

<table>
<thead>
<tr>
<th>ASD outcome domain (measure)</th>
<th>Participants</th>
<th>Environment</th>
<th>Genetic measure</th>
<th>Detectable effect size*</th>
<th>Power increase**</th>
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<tr>
<td>(i) Cognitive ability (MSEL)</td>
<td>All</td>
<td>Air pollutants</td>
<td>16p11.2 deletion</td>
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<td>15x</td>
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<td>(ii) Diagnosis (ASD)</td>
<td>All</td>
<td>Maternal infection</td>
<td>SNP genotypes</td>
<td>1.13</td>
<td>16x</td>
</tr>
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<td>(iii) Severity (SRS)</td>
<td>ASD cases</td>
<td>Folic acid/vitamins</td>
<td>Rare variant burden</td>
<td>1.14</td>
<td>10x</td>
</tr>
<tr>
<td>(iv) Health conditions (anxiety)</td>
<td>ASD cases</td>
<td>Air pollutants</td>
<td>ASD polygenic burden</td>
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*Using anticipated total number of ~170,000 participants in total and ~85,000 ASD cases (see details in Table 2)

**Increase from largest sample size for published GxE result to date (n=2,514)

ASD = autism spectrum disorder; SRS = social responsiveness scale; MSEL = Mullen Scales of Early Learning;
Develop and implement a pipeline for outreach and dissemination of GxE findings that informs action. Using a multi-pronged communication strategy, we will:

- Develop and transmit material to community partners, stakeholders, clinicians, and educators to translate our findings into actionable public health messaging.
- Actively seek input from stakeholders, including autistic people and their families, to foster collaborative partnership and design effective and valued communication.
What We Know:

- NDDs / ASD are heterogeneous
- Early detection is important
- Genetics matter
- Environmental risk factors are shared across NDDs

What We Need to Know:

- Specificity of exposure effect
  - Disorder or trait or brain in general
- Exposure x Exposure Interaction
- Gene x Environment Interaction
- Pathways / mechanism / biomarkers
  - Experimental models
  - Population studies

Targets for intervention and prevention
Moving Toward Intervention and Prevention

• Disorder severity and trait measures
• Co-occurrence of physical health conditions
• Many types of exposures (together!)
• Diverse populations

With Collaboration We Can Effectively Address Challenges and Improve Children’s Health!
Thank you!

Thank you to our funders: NIH (OD023342, ES032469, HD103538, ES029511, ES030893, ES026961, HD055741, ES025531, ES023780 ), CDC (DD00129), Autism Speaks (#7785, 8463), Autism Science Foundation
Contact Us: AIRP@mednet.ucla.edu

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Thursday 1/19/23
From 4-5pm EST

**AIR-P Presents:** Claims Data as a Big Data Tool for Autism Research Focused on Physical Health

**Presented by** Dr. Lindsay Shea and Lauren Bishop

Claims data are a useful big data tool that emerge from health systems and provide translational research opportunities to improve health outcomes across large groups and communities. Claims data are generated at local, state, and federal levels, and from multiple insurance sources. In this webinar, we will describe existing approaches to the use of claims data for autism research focused on physical health and present and discuss opportunities for future research.