National Institute of Environmental Health Sciences

2023 Environmental Epidemiology of Autism Research Network (EEARN) Meeting

Thursday, May 4, 2023

6:00-9:30 p.m.

Room: Salons 5 and 6
Scandic Grand Central Hotel
Stockholm, Sweden

Hosted by the National Institute of Environmental Health Sciences and Autism Speaks

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Agenda

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All times are Central European Time (CET)

Agenda

6:00-6:25 p.m. **Networking, Ice-Breaking Event, and Welcome**
Cindy Lawler, National Institute of Environmental Health Sciences (NIEHS)

6:25-7:10 p.m. **Lightning Talks on Resources**
Moderator: Jennifer Ames, Kaiser Permanente

The Avon Longitudinal Study of Parents and Children (ALSPAC) (3 minutes)
Dheeraj Rai, University of Bristol

Swedish Register Data Linkages: A Flash Introduction (3 minutes)
Renee Gardner, Karolinska Institutet

Autism Research with the Danish iPSYCH Resource (3 minutes)
Amy Kalkbrenner, University of Wisconsin-Milwaukee

Environmental Influences on Child Health Outcomes (ECHO) (3 minutes)
Kristen Lyall, Drexel University

BERTHA — the Danish Big Data Centre for Environment and Health (3 minutes)
Astrid Haugen, NIEHS

Round Robin and Discussion (30 minutes)

7:10-8:10 p.m. **Advancing Diversity and Inclusion in Environmental Epidemiology of Autism Research**

Moderator: Alycia Halladay, Autism Science Foundation

We will listen to three examples of research highlighting the impact of disparities in exposure, diagnosis, and autism risk in populations historically underrepresented in research. These will be followed by a discussion on challenges, opportunities, and engagement with communities to address critical research questions.

Speakers

Aisha Dickerson, Johns Hopkins Bloomberg School of Public Health (10 minutes*)*

Laura McGuinn, University of Chicago (10 minutes*)*

Cecilia Magnusson, Karolinska Institutet (10 minutes*)*

Discussion (30 minutes)

Potential Topics

- How do we study this? What data do we need? Different methods vs. current approaches?
- How do we include DEIA individuals in the research process?
- How do we make the jump as a researcher to CBPR and intervention work when certain academic disciplines may not always place a high priority on this (i.e., criteria for tenure or promotion)?
- How do we ensure equitable access to digital health technologies in the autism community and general public (with a particular focus on digital divide for marginalized and lower socioeconomic status populations)?

8:10-8:40 p.m. **Poster Session**

Travel Awardees and Invited Presenters

8:40-8:50 p.m. **Break**

8:50-9:15 p.m. **Autism Research Career Pathways**

Travel Awardees and Junior Investigators

9:15-9:30 p.m. **Next Steps and Adjourn**

Travel Reimbursement Awardee Abstracts

Donovan Calvert, *University of Texas Health Science Center at Houston*

Interaction Between Maternal and Progeny Glutathione S-Transferase Genes in Relation with Autism Spectrum Disorder in Jamaican Children

Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder. Although the etiology of ASD is not completely known, it is believed to involve complex interactions between/among genes or gene-environment interaction.

Objectives: In this research, we investigated the association of genotypes for three metabolic glutathione S-transferase (GST) genes (GSTM1, GSTT1, and GSTP1) in both mothers and their progeny with ASD case status in the children, and with ASD severity only in the children with ASD.

Methods: We used data from 68 pairs (n=136) of Jamaican children (2-8 years old) with ASD and their 1:1 sex- and age-matched typically developing (TD) controls who were enrolled in the Epidemiological Research on Autism in Jamaica (ERAJ) study. The genotypes for GST genes were also evaluated in mothers of the enrolled children. We applied univariable and multivariable conditional logistic regression (CLR) models to explore additive and interactive effects of GST genotypes in mothers and their progeny in relation to ASD status, as well as ASD severity as measured by the Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) total comparison score in children with ASD.

Results: In univariable analyses, we did not find any significant associations of the maternal GST genes with ASD in children (all $P > 0.3$). However, we found that the odds of ASD in children who were homozygous for the GSTT1 deletion allele (DD) was 5.5 times greater than in those with at least one active GSTT1 allele (I/*) [Matched odds ratio (MOR) (95% confidence interval (CI)) = 5.5 (1.9, 16.0); $P = 0.0017$]. In the interactive multivariable models, although we did not identify a significant interaction between progeny and maternal GST genes in relation to ASD (all $P \geq 0.06$), we found significant associations between children's genotype for GSTT1 and ASD only among children whose mothers had certain genotypes for GSTT1 and GSTP1. Specifically, among children whose mothers had GSTT1 DD genotype, the odds of ASD in those with GSTT1 DD genotype was 19.8 times that in children with GSTT1 I/* [MOR (95% CI) = 19.8 (2.5, 157.6); $P = 0.0048$]. Additionally, we found that among children whose mothers were homozygous Val/Val for the GSTP1 Ile105Val polymorphism, the odds of ASD in children with GSTT1 DD genotype was 14.3 times greater than in children with GSTT1 I/* [MOR (95% CI) = 14.26 (1.294, 157.1); $P = 0.030$]. Furthermore, we identified a significant interaction between maternal and children's GSTM1 genotypes in relation to ASD severity (Interaction $P = 0.02$). Specifically, among children whose mother had I* genotype for GSTM1, those with GSTM1 DD genotype had less severe ASD than those with GSTM1 I/* genotype [OR (95% CI) = 4.17 (1.39, 12.5); ($P = 0.01$)].

Conclusion: Multiple significant associations were found with ASD case status or ASD severity when gene-gene interactions for the GST genes were investigated. Such findings indicate that no single gene affects the association with ASD outcome status or severity, but rather the presence of multiple factors may have significant associations with increased odds of ASD outcomes and/or increased severity of ASD.

Paul Madley-Dowd, *University of Bristol*

Antiseizure Medication Prescribing During Pregnancy and Offspring Neurodevelopmental Outcome: A Study of Two Cohorts From the U.K. and Sweden

Background: The teratogenic potential of valproate, especially in relation to adverse neurodevelopmental outcomes, is well documented. However, the safety of other anti-seizure medications (ASMs) during pregnancy is not well understood. Recent work has suggested that use of topiramate during pregnancy may be a risk factor for neurodevelopmental outcomes including autism, intellectual disability (ID), and global developmental delay.
Objectives: To examine whether ASMs prescribing in pregnancy are associated with neurodevelopmental outcomes in exposed children.

Methods: This is an intergenerational study with prospectively collected data from the U.K. Clinical Practice Research Datalink (CPRD) GOLD (birth years 1995-2018) and the Swedish Developmental Origins of Health and Disease (DOHaD) dataset built from the national registers (birth years 1995-2020). CPRD GOLD holds primary care data from around 9% of the U.K. population and is approximately representative in terms of age and sex, while DOHaD contain information for nearly all births in the country. We identified maternal prescriptions for ASMs (carbamazepine, gabapentin, lamotrigine, levetiracetam, valproate, pregabalin, topiramate, or other) recorded during the preconceptional and pregnancy periods and their likely indications (including epilepsy, psychiatric conditions, and somatic conditions). Child neurodevelopmental outcomes included autism, attention deficit hyperactivity disorder (ADHD), and ID identified using Read codes and ICD-10 codes in the U.K. and ICD-10 codes in Sweden. We examined associations for indications and for prescribing any time in pregnancy using logistic regression adjusted for confounders and year of birth (to account for differing lengths of follow up). Results in each cohort were pooled using fixed effects meta-analysis. We further examined exposure in each trimester, initiation during the first trimester, and discontinuation early and late into pregnancy (results not shown) and implemented methods to aid with causal interpretation of findings including exposure discordant sibling analyses.

Results: Primary analyses: Associations with autism were found for carbamazepine (adjusted OR = 1.29; 95% CI = 1.09-1.54), topiramate (adjusted OR = 1.61; 95% CI = 1.09-2.39), and valproate (adjusted OR = 1.97; 95% CI = 1.64-2.37), but not lamotrigine (adjusted OR = 0.93; 95% CI = 0.79-1.09) in pooled analyses across the two cohorts. Sibling analyses: Strong evidence of a within-family effect of increased risk of autism was found for topiramate (within-family OR = 3.61; 95% CI = 1.29-10.07) in DOHaD only, supporting evidence for a causal effect (we were unable to estimate this in CPRD due to low counts of autism in exposure discordant families). Weaker evidence of within-family effects of increased risk of autism were found for carbamazepine in DOHaD only (within-family OR = 1.25; 95% CI = 0.73-2.14) and valproate (within-family OR = 1.40; 95% CI = 0.74-2.65) in pooled estimates.

Discussion: Our results support recent findings that topiramate exposure during pregnancy may confer an increased risk of autism and ID. The results will help provide pregnant women and their clinicians with useful information to make informed choices about ASM use in pregnancy.

Marisa Patti, *Drexel University*

Examining and Communicating the Role of Neighborhood and Diet in the Study of Endocrine Disrupting Chemicals and Child Neurodevelopment: A Pilot Project

Background: Previous work has suggested associations between prenatal exposure to endocrine disrupting chemicals (EDCs), including phthalates and phenols, and autism or autism-related traits in children. Additionally, socioeconomic factors have been associated with exposure to EDCs, as well as the diagnosis of and access to autism-related services. However, existing work has not addressed how neighborhood-level factors and individual-level sources of EDCs may play into these relationships, which has implications for reducing observed disparities.

Objectives: Here, we examined the individual and joint effects of neighborhood socioeconomic position, dietary sources of a targeted set of EDCs, and biomarker-based levels, in association with child autism-related traits.

Methods: Participants (n=131 mother child dyads) were drawn from the Early Autism Risk Longitudinal Investigation (EARLI), a familial autism enriched longitudinal pregnancy and birth cohort study of pregnant participants who previously had a child diagnosed with autism. Concentrations of target EDCs, Bisphenol A (BPA) and summary di(2-ethylhexyl) phthalate (ΣDEHP), were quantified in maternal urine samples. Maternal dietary source of EDCs was ascertained via report on food frequency and food source questionnaires and quantified to develop a novel summary "burden score." Neighborhood deprivation was quantified using community socioeconomic deprivation (CSD) scores and Index of Concentration at the Extremes (ICE) scores based on factors collected during the first trimester. Child ASD-related traits were collected when children were approximately 3 years of age via caregiver reports on the preschool version of the Social Responsiveness Scale (SRS-2). We then evaluated the individual effects of the relationship between neighborhood socioeconomic position with both individual biomarkers (BPA and ΣDEHP) and summary burden scores of dietary sources of EDCs with autism-related traits in children.

Results: We did not observe a consistent association between terciles of ICE scores that jointly measured extreme conditions of income and race/ethnicity or CSD scores with average urinary concentrations of BPA or ΣDEHP. EDC summary burden scores were inversely associated with ICE scores. For example, compared to the lowest tercile of ICE scores that jointly measured extreme conditions of income and race/ethnicity, values of EDC burden scores increased from the lowest tercile, indicating the most deprivation to the highest tercile indicating the most privilege. In covariate adjusted models, compared to those in the tercile of highest privilege (ICE scores that jointly measured extreme conditions of income and race/ethnicity), those with moderate to higher deprivation had more autism-related traits (β: 3.66 (-1.02, 8.35); β: 3.56 (-1.64, 8.76), respectfully).

Conclusions: Diet is a source of exposure to some EDCs, and dietary sources of EDC exposure may be higher among those with more neighborhood deprivation, jointly measured by economic and racial/ethnic segregation. Higher levels of economic and racial/ethnic segregation during the first trimester were also associated with children having more autism-related traits in early childhood. Future work will explore how dietary sources and biomarkers of EDCs mediate the neighborhood deprivation and autism-related traits association.

Aws Sadik, *University of Bristol*

Approaches to Investigate Associations Between Parental Inflammatory Bowel Disease (IBD) and Autism in Children From Swedish Registers

We used four complementary approaches to investigate associations between parental inflammatory bowel disease (IBD) and autism in children: (i) In a nationwide population-based cohort study using Swedish registers, we found evidence of associations between parental diagnoses of IBD and autism in children. (ii) Polygenic risk score analyses of the Avon Longitudinal Study of Parents and Children, demonstrated associations between maternal genetic liability to IBD and autistic traits in children. (iii) Two-sample Mendelian randomisation analyses provided evidence of a potential causal effect of genetic liability to IBD, especially ulcerative colitis, on autism. (iv) And linkage disequilibrium score regression did not indicate a genetic correlation between IBD and autism. Triangulating evidence these four approaches, we found evidence of a potentially causal link between parental, particularly maternal, IBD and autism in children. Perinatal immune dysregulation, micronutrient malabsorption and anaemia may be implicated.

Sepideh Saroukhani, *University of Texas Health Science Center at Houston*

Frequency of Fruits and Vegetables Consumption and Their Possible Interactions With Genotypes of Gluthathione S-Transferase Genes in Relation to ASD and ASD Severity in Jamaican Children

Background: Atypical selective eating, with reduced preference for fruits and vegetables (FVs), is common in children with autism spectrum disorder (ASD). These children are prone to deficiency of phytonutrients with antioxidant effects. Polymorphisms in glutathione S-transferase (GST) genes can also influence susceptibility to increased oxidative stress, a possible underlying mechanism for ASD.

Objective: To investigate associations of the frequency of FV consumption, and its interactions with GST genes, in relation to ASD and ASD severity in Jamaican children.

Methods: Using exploratory factor analysis, we identified seven groups of FVs. Factor scores were calculated by summing reported weekly basis intakes of the factor food items and analyzed as scores: ≥ 3rd quartile vs. < 3rd quartile representing high vs. low consumption. Using data from 242 pairs of age-(± 6 months) and sex-matched ASD cases and typically developing (TD) controls (n=484), we assessed additive and interactive associations of the frequency of FV consumption with polymorphisms in three GST genes (GSTM1, GSTP1, and GSTT1) in relation to ASD, using conditional logistic regression models. With data from (n=242) ASD cases, we used general linear models to assess the association of the frequency of FV consumption, and its possible interaction with the GST genes in relation to ASD severity as measured by the Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) standardized total, as well as the Social Affect (SA) and Restricted and Repetitive Behaviors (RRB) domains specific comparison scores (CSs).

Results: After adjusting for the child's age and socioeconomic status, ASD cases consumed significantly fewer servings of all groups of FV than TD controls (all matched odds ratios ranging from 0.14 to 0.64, and all $P \leq 0.02$). Among ASD cases, high consumption of fruits high in unsaturated fatty acids, legumes, and unpeeled fruits was associated with less severe social and/or behavioral signs of ASD (all $P \leq 0.03$). Additionally, the presence of at least one Val allele for GSTP1 was associated with consuming fewer servings of fruits high in unsaturated fatty acids, vitamin A, C and beta-carotene, antioxidants, and fruits and/or vegetable juice by ASD cases than TD controls (all $P \leq 0.01$, and P for interaction ≤ 0.02). GSTT1 and GSTM1 I/I or I/D genotypes were also associated with consuming fewer servings of legumes and any types of unpeeled fruits by ASD cases than TD controls (P for interaction = 0.02 and 0.03, respectively). Furthermore, high versus low consumption of legumes and juices was associated with significantly lower ADOS-2 SA CS only among ASD cases homozygous for GSTP1 Ile105 ($P = 0.01$ and 0.03, respectively; P for interaction ≤ 0.04). Similarly, high consumption of fruits high in antioxidants had an inverse association with ADOS-2 RRB CS only among ASD cases with GSTP1 Ile/Ile genotype ($P < 0.01$; P for interaction ≤ 0.03).

Conclusions: Our findings suggest the frequency of fruits and vegetables consumption is associated with ASD and ASD severity, and the genotype for GST genes may have a modifying role on these associations in Jamaican children, though they require replication in other populations.

Rose Schrott, *Johns Hopkins Bloomberg School of Public Health*

Germline Aging in Sperm Is Associated With Quantitative Autistic Traits in an Autism-Enriched Cohort

Background: Advanced paternal age is among the prevailing hypotheses for paternal contributions to autism in children. This is due in part to increased rates of DNA mutations and fragmentation in sperm, and decreased efficacy of DNA proofreading and repair enzymes. However, how other biological indicators of aging that are detectable in sperm – such as epigenetic germline age – are associated with autism or autistic traits has not been assessed. This is important, given that the faithful transfer of gametic genetic and epigenetic information to the developing fetus is essential for neurodevelopment. Recently, a model was developed that uses the sperm DNA methylome to predict an individual's germline age. This can serve as a biomarker for germline aging and allow for the investigation of how deviations from one's chronological age might be associated with autistic traits in children.

Objectives: Given that advanced paternal age is associated with autism likelihood in children, we hypothesized that accelerated germline age, relative to chronologic age, is associated with quantitative autistic traits in 3-year-old children from an autism-enriched cohort.

Methods: This work was conducted in the Early Autism Risk Longitudinal Investigation (EARLI) – a prospective pregnancy cohort that enrolled pregnant people with a child diagnosed with autism. Autistic traits were measured by 1) the Social Responsiveness Scale (SRS), a 65-item questionnaire measuring social communication deficits; 2) the Vineland Adaptive Behavior Scale (VABS), a semi-structured interview that assesses adaptive functioning across multiple domains; and 3) the Mullens Scale for Early Learning (MSEL) that measures cognitive functioning. Sperm was collected from fathers around the time of conception and DNA methylation was analyzed on the Infinium HumanMethylation450 BeadChip platform. We computed estimated germline age (years) using the Jenkins clock, and accelerated epigenetic age was defined as the positive residual obtained from regressing chronologic age on germline age. Generalized linear models adjusting for child sex, paternal education, and genetic ancestry principal components were run to determine how germline age associated with composite and subscale scores for SRS (n=29), VABS (n=33), and MSEL (n=32).

Results: After adjusting for confounders, we demonstrated that accelerated germline age was associated with deficits in social communication for SRS composite scores (β=3.88, p = 0.04, for a one-unit increase), as well as deficits in the cognition (β=0.93, p = 0.01) and communication (β=1.42, p = 0.04) subscales. Decelerated germline age was associated with increased adaptive functioning for VABS composite (β=-2.42, p = 0.007, for a one-unit decrease) and subscale scores across the communication (β=-1.43 p = 0.03), daily living (β=-1.11, p = 0.02, and socialization (β=-1.23, p = 0.01) domains. We did not observe any significant associations between germline age and MSEL composite or subscale scores, though the direction of the relationship between germline aging and trait-outcomes was consistent with observations for SRS and VABS.

Conclusions: We demonstrate that accelerated paternal germline aging is associated with deficits in social communication and adaptive functioning in children from an autism-enriched cohort. These findings provide further support for the role of nongenetic paternal contributions to autism liability.

Ashley Song, *Johns Hopkins Bloomberg School of Public Health*

Air Pollution Exposure, Autism Diagnosis, and Autism-Related Quantitative Traits by Neighborhood Deprivation

Background: A growing body of literature suggests that exposure to early life air pollution is associated with increased risk for autism spectrum disorder (ASD). Recent studies have shown that community-level socioeconomic status (SES) may modify the association between air pollution and child health outcomes. Few studies have examined the potential synergistic effects of neighborhood characteristics and air pollution exposure on ASD or associated traits.

Objectives: To examine the modifying role of neighborhood deprivation for the association between prenatal and postnatal ambient air pollution and ASD risk and ASD-related quantitative traits in children.

Methods: Data came from two prospective pregnancy cohorts enriched for a family history of ASD (n=409), Early Autism Risk Longitudinal Investigation (EARLI), Markers of Autism Risk in Babies – Learning Early Signs (MARBLES). Weekly air pollution exposures were estimated based on maternal residential address during pregnancy and the first year of life using inverse-distance squared spatial interpolation. Community socioeconomic deprivation was derived from indicators in the American Community Survey data and categorized into tertiles: low, moderate, and high deprivation. Multivariable logistic and linear regression models were completed to evaluate the association between pregnancy and first year of life air pollution exposures and ASD diagnosis and ASD-related traits (Social Responsiveness Scale [SRS]) stratified by neighborhood deprivation. Distributed lag models examined sensitive windows of exposure between air pollutants and SRS by neighborhood deprivation.

Results: We observed an increased risk of having a child with ASD for each 1-unit increase in NO2 exposure during pregnancy (aOR=1.25 95% CI: 0.99-1.64, P=0.07) and the first year of life (aOR=1.51, 95% CI: 1.15, 2.10, P<0.01) in the low deprivation group. Inverse associations between air pollution during the first year of life and risk of ASD were observed for O3 (aOR=0.81, 95% CI: 0.64, 0.99, P=0.05), PM2.5 (aOR=0.62, 95% CI: 0.35, 1.03, P=0.08), and PM10 (aOR=0.79, 95% CI: 0.61, 0.97, P=0.04) in the low deprivation group. Increasing PM2.5 during the preconception period was associated with lower SRS raw scores (less autistic traits) in the low deprivation group (weeks 1-5) and with higher SRS raw scores (more autistic traits) in the moderate deprivation group (weeks 1-12).

Conclusions: Our results suggest that air pollution impacts on ASD risk and ASD-related traits are present among children with higher SES (low or moderate neighborhood deprivation). Such results should be studied in the context of access to care indicators to better identify vulnerable populations or assess the role of diagnostic bias in ASD.

Logan Williams, *University of California, Davis*

Concentration of Placenta Folate Metabolites in a High-Risk Autism Cohort Is Associated With DNA Methylation in Genomic Regions Involved in Neurodevelopment

Background: While the etiology of autism spectrum disorder (ASD) is partially genetic, numerous environmental exposures have been associated with ASD risk. Prior studies have highlighted prenatal folic acid levels as one such potential ASD-associated environmental exposure, with disruptions to folate metabolism potentially inducing downstream epigenetic dysregulation as detected by DNA methylation. Nonetheless, few studies have attempted to directly identify associations between folate metabolite levels and placental DNA methylation genome-wide. Identifying signatures of DNA methylation associated with ASD-implicated environmental exposures may help illuminate the mechanisms by which folate metabolism converges with ASD development.

Objectives: By identifying differential methylation patterns associated with both placental folate metabolite levels and placental DNA methylation in a high-risk ASD cohort, this study aimed to highlight the gene networks associated with folate metabolites to gain insights into folate's protective role in the molecular etiology of ASD.

Methods: Whole genome bisulfite sequencing (WGBS) was performed on DNA from 95 placentas from the MARBLES high-risk prospective ASD cohort. Concentrations of folate metabolites tetrahydrofolic acid (THF), 5-formyl-tetrahydrofolate (5-Fo-THF), 5-methyl-tetrahydrofolate (5-Me-THF), and folic acid (FA) from those same placentas were measured using a LC-MS/MS. WGBS data from the placenta samples were then used to generate comethylation networks via the Comethyl R package. The associations between comethylation modules and various sample traits, including placenta folate metabolite levels and child ASD diagnoses, were then tested, with comethylation modules showing significant associations with either trait annotated to investigate genomic membership.

Results: None of the comethylation modules found to be significantly associated with maternal use of folate-containing vitamin supplements were also associated with measured placenta folate-related metabolite levels. No significant associations were identified between placenta 5-Me-THF and placenta THF levels. Placenta 5-Fo-THF and placenta FA levels each were associated with one comethylation module (salmon and yellow modules, respectively). Hypermethylation of the salmon comethylation module was associated with increased placenta 5-Fo-THF levels, and hypomethylation was associated with increased ADOS score and increased likelihood of ASD diagnosis. Upon annotation, the salmon module was observed to contain the genes PLCB1 and PLCB4, both of which are implicated in reproduction and immune pathways. Hypomethylation of the yellow comethylation module was associated with increased placenta FA levels and with higher child Mullens Scores. The yellow module contained AUTS2, a protein-coding gene involved in neurodevelopment and implicated in multiple neurological disorders, including ASD.

Conclusions: This study identified two comethylated gene networks associated with placental folate metabolite concentrations and neurodevelopmental outcomes. Further investigation will be required to determine whether placenta folate metabolites are directly altering placental DNA methylation in gene pathways relevant to neurodevelopmental outcomes.

Caichen Zhong, *Drexel University*

Prevalence of Self-Reported Medication Use During Early Pregnancy in the Early Autism Risk Longitudinal Investigation (EARLI)

Background: Medication use during pregnancy presents considerations for both the mother and child. Previous work has described commonly used medications among pregnant women in the general population, and their relationships to child outcomes like autism, but medication use during early pregnancy among women who have a prior child with a developmental disorder, which may alter medication use patterns and prevalence, is less well characterized.

Objectives: To characterize common maternal medication use during early pregnancy in families with at least one child with autism.

Methods: Participants were drawn from the Early Autism Risk Longitudinal Investigation (EARLI) study, a cohort enrolling pregnant mothers who already had a child with autism and followed the subsequent child to 36 months of age. Data on self-reported maternal medication use during first- or second-trimester pregnancy was used to estimate the prevalence of medication use during early pregnancy and to ascertain the most commonly reported medications. Descriptive statistics were used to assess potential differences in medication use by maternal characteristics. Medications were classified into 10 drug class coalitions according to the Slone Drug Dictionary. In addition, the prevalence of medication use by coalitions was compared to external reference samples.

Results: A total of 234 pregnant mothers were included in the analyses. Use of any medications during first- or second-trimester pregnancy was reported by 84% (n=197) of mothers, with most reporting central nervous system (CNS) agents (n=161, 69%). In addition, 41% of those reporting any medication use reported use of gastrointestinal drugs, 28% reported the use of anti-infective agents, 23% reported autonomic medications, 20% reported hormones and synthetic substitutes, 18% reported antihistamines, 15% reported respiratory drugs, 10% reported skin and mucous membrane agents, and 10% reported herbal/natural products/vitamins/electrolytes. The five most commonly reported medications were acetaminophen (n=142, 61%), followed by calcium carbonate (n=49, 21%, antacid), ibuprofen (n=46, 21%), dextromethorphan (n=27, 12%, cough suppressants), and pseudoephedrine (n=25, 11%, nasal decongestants). Despite the overall high prevalence of any medication use, use of prescription drugs was similar in this population to reference comparison groups, including NHANES. Comparing mothers who reported any medication use to those with no reported use, the majority of the former group reported white race, while mothers who reported no medication use were more likely to report non-white race. Mothers in the medication-use group also had a higher average BMI (mean=28.0, SD=7.06) relative to mothers in the non-use group (mean=25.7, SD=5.17). Those in the non-use group were more likely to have a lower income (50k-100k) than the medication-use group (40.5% vs. 29.4%).

Conclusions: In this autism family cohort, medication use during pregnancy across coalitions of medications was common, with CNS agents being the most commonly reported drug coalition. Approximately three in five mothers reported the use of acetaminophen during the first half of the pregnancy. Differences in medication use by maternal BMI and race support the need to account for these factors in analyses of associations with child outcomes. Further analyses will examine drug coalitions in association with child autism-related outcomes in this population.

Additional Abstracts

Amanda Garton, *National Institute of Environmental Health Sciences, Research Triangle Park, N.C.*

Engaging Communities During Development of a Web-Based Tool for Communication About Environmental Health Research in Autism

Background: Both heritable (genetic) and nonheritable (environmental) factors contribute to the alterations in biological processes that lead to autism and its co-occurring conditions. One subset of nonheritable factors that have been increasingly studied are environmental chemicals, such as air pollution or pesticides. Communication about this rapidly growing body of research is important for a broad range of stakeholders. Scoping reviews and evidence maps are tools for researchers to summarize the current state of the peer-reviewed literature. However, these tools have limitations, including that they are static one-time assessments and are primarily written and developed for use by other researchers and may not be accessible to a wider audience. To address these challenges and provide a resource to communicate about the state of environmental health research in autism for both researchers and the broader autism community, the National Institute of Environmental Health Sciences (NIEHS) is developing a web-based tool for Autism Research and the Environment (aWARE). For such a tool to be successful, it must incorporate features and functionality that make it useful for the multiple and complex intended audiences. To understand exactly what those features are, input from those audiences is needed.

Objectives: To engage with and collect feedback from an inclusive set of stakeholders that would inform the development of aWARE.

Methods: Four listening sessions and a meeting of the Environmental Epidemiology of Autism Research Network (EEARN) were held in the summer and autumn of 2022 to gather feedback and input regarding aWARE. Participants representing autistic individuals and families, advocacy and funding organizations, physicians and clinicians, and researchers were included in the listening sessions. During both the EEARN meeting and listening sessions, the aWARE project was briefly described before a longer guided discussion where participants were asked open-ended questions about how communities could use this tool and what features would make it more useful. Following these meetings, comments from participants were analyzed and themes identified.

Results: Participants in the series of listening sessions spoke to various themes that reflected their lived experiences and how they and their communities interact with scientific literature. Different stakeholder groups emphasized distinct features (e.g., accessibility, lay language) and metrics (details extracted from publications) that would make this tool most useful for their community. Participants provided information about various resources for web-tool and science communication development that can be incorporated in aWARE. A common theme across discussions was the scope of environmental health research, which indicates the need for clear definitions when describing the tool. Multiple sessions highlighted the opportunity that this tool presents to help educate a large range of stakeholders about environmental health research and reading scientific literature as a body rather than as individual papers. Integrating this feedback from the community as the development of the tool continues will be a major consideration.

Conclusions: Engagement with a broad range of stakeholders and communities has already provided valuable information and identified key opportunities for aWARE. Continuing this engagement throughout development and deployment of this web-based evidence map will be critical for its success.

Astrid Haugen, *National Institute of Environmental Health Sciences, Research Triangle Park, N.C.*

Environmental Contributors to Autism Spectrum Disorder in Federal-Funded Research

Background: The National Institutes of Health (NIH) of the U.S. Department of Health and Human Services (DHHS) is the primary government agency whose mission is to conduct and support biomedical research in the interest of impacting public health. The NIH includes 27 Institutes and Centers, each responsible for defined, mission-relevant biomedical and scientific disciplines. The National Institute of Environmental Health Sciences (NIEHS) is an NIH institute focused on environmental exposures and human health. Environmental factors pertaining to the NIEHS mission are human-made or natural chemical substances, whereas others (e.g., nutrition or infection) are within the primary mission responsibility of other NIH institutes. All NIH institutes depend on portfolio analyses to better understand gaps and trends in funding and science, including in autism spectrum disorder (ASD) and environment research. This project used a comprehensive definition of environment.

Objectives: NIEHS presents findings from a portfolio analysis of ASD and the environment, comprising FYs 2001-2019, and its relationship to similarly supported research across NIH institutes and other federal agencies.

Methods: Federal grant data were collected, coded, and analyzed for trends in funding, environmental health factors, study types, impacts, and growth. Global networks and thematic components were extracted and visualized with software tools like Gephi.

Results: Five federal agencies funded ASD-environment projects with the NIH funding the majority (87.8%). Most NIH projects were awarded by the National Institute of Mental Health (NIMH) (33.9%), NIEHS (32.1%), and the National Institute of Child Health and Disease (NICHD) (18.2%). The most researched environmental factors were maternal immune, psychosocial, pharmaceutical drugs, air pollutants, and nutrition. NIEHS supported nearly all research involving industrial chemicals and environmental pollutants. These frequently co-occurred with other in-mission and out-of-mission exposures (e.g., maternal infection), partly due to more cohort and observational studies. NIMH and NICHD primarily focused on single environmental factors with NIMH supporting more mechanistic projects with model systems. Temporal analysis of the NIEHS portfolio revealed a few metals (e.g., mercury), brominated (e.g., PBDEs), and chlorinated compounds (e.g., PCBs) before 2006. The portfolio evolved (through 2019) to include more variety of metal exposures, endocrine disrupters, and new categories like air pollutants. Immune-related genes appeared central in a co-occurrence network when we looked for biological and mechanistic themes. We visualized the genes in a bipartite network, finding associations with various environmental factors. Sixty-four percent were not in the SFARI database of autism susceptibility genes and probably considered for mechanistic or toxicological roles in exposure-related research. They may eventually merit future inclusion in the SFARI database of autism susceptibility genes.

Conclusions: Evaluating federal support of research in nongenetic factors and ASD provides a bird's-eye view of the influential role government has on the state of the science and its evolution. This work provides context to help interested parties see gaps and opportunities for future research, including underlying biological associations with symptoms and co-occurring conditions. Innovation and new knowledge may accelerate their translation to interventions and services that help minimize the negative aspects of ASD-related symptoms and conditions for autistic individuals and their families.

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The Genomics and Environmental Science to Accelerate Actionable Research and Practice in ASD (GEARs) Network

Much like the Psychiatric Genetics Consortium launched a unifying infrastructure for scaling genome-wide association studies in autism spectrum disorder (ASD), the Combining Advances in Genomics and Environmental Science to Accelerate Actionable Research and Practice in ASD (GEARs) Network effort allows a centralized mechanism for GxE activities in ASD across multiple studies. As such, it establishes a network for the investigation of gene-environment interaction in ASD and outcomes among people with ASD. Robust evaluation of GxE requires a large sample size, harmonized data on both genetics and the environment, and novel statistical methods for measuring and summarizing environments, genetics, and phenotypes. The GEARs Network seeks to complement work in population studies with experimental models leveraging 3D brain organoids, reflecting multiple ASD-associated genetics backgrounds on which the impact of environmental risk can be evaluated on ASD-relevant neurophysiology endpoints. Finally, the GEARs Network will develop and implement a pipeline for outreach and dissemination of GxE findings. The successes of ASD genomics, emerging environmental evidence, and models of effective network collaborations for large-scale efforts make this the ideal time to create a GxE infrastructure for ASD research. This translational approach, informed by public health, will lead to improved understanding of both causes and consequences of ASD.

2023 Environmental Epidemiology of Autism Research Network (EEARN) Meeting

Stockholm, Sweden

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