Epigenetic Intergenerational Transmission: Mothers' Adverse Childhood Experiences and DNA Methylation

STUDY SYNOPSIS

Introduction Summary

Individual differences in risk for mental disorders over the lifespan are shaped by forces acting before the individual is born—*in utero,* but likely even earlier, during the mother's own childhood. The environmental epigenetics hypothesis proposes that sustained effects of environmental conditions on gene expression are mediated by epigenetic mechanisms. Recent human studies have shown that adversities in the early environment are correlated with DNA methylation in childhood.[1-5] However, these studies are limited by either (1) candidate-gene approaches, which look only at specific genes and CpG sites, precluding a broader understanding of methylation across the genome, or (2) methylome-wide approaches with small sample sizes, (eg, <200), increasing both type I and type II errors. One recent exception is a methylome-wide analysis in 691 children who were followed longitudinally since birth. In this study, Dunn *et al.* found that 38 CpG sites were differentially methylated in children at 7 years of age following exposure to adversities.[6] However, clear evidence of childhood adversity−induced DNA methylation conserved across decades, into adulthood, and whether it is passed on to offspring, is lacking.

In the current study, we will test whether adverse experiences in mothers' childhoods are correlated with DNA methylation in peripheral blood during pregnancy and in cord blood samples from their newborn infants. We expect to find differentially methylated CpG sites in pregnant women and in their newborn infants associated with mothers' adverse childhood experiences (ACEs), and we expect the differentially methylated regions to at least partially overlap between mothers and infants, indicating enduring and transmitted impacts of mothers' ACEs on DNA methylation. As a secondary analysis, we will test women's depression and anxiety symptoms during pregnancy as a possible mediator of the association between mothers' ACE exposure and prenatal/neonatal DNA methylation, given that (1) ACEs have consistently been shown to be associated with perinatal mood and anxiety disorders,[7] and (2) depression and anxiety have been correlated with DNA methylation in adults,[8] and prenatal anxiety and depression have been associated with DNA methylation in infant offspring.[9,10] We expect the associations between mothers' childhood adversities and DNA methylation in pregnancy and newborns to be partially but not fully mediated by mothers' prenatal depression and anxiety symptoms, demonstrating a pathway from ACEs to DNA methylation above and beyond ACEs' impact on prenatal mood symptoms.

Method Summary

Data are from the Avon Longitudinal Study of Parents and Children (ALSPAC) Accessible Resource for Integrated Epigenomic Studies (ARIES) substudy.[11] The ALSPAC design included all women in the Avon Health District in the United Kingdom who gave birth between April 1, 1991, and December 31, 1992. The ARIES subsample provided blood samples during pregnancy and umbilical cord blood samples upon delivery. Women provided retrospective self-reports during pregnancy of whether they had experienced during childhood the 10 ACEs studied in the flagship CDC-Kaiser ACE study. A cumulative score (0−10) will be used to measure ACEs. Genome-wide methylation status of more than 485,000 CpG sites was measured using the Illumina Infinium HumanMethylation450K BeadChip assay. To test whether mothers' ACE exposure is associated with methylation in DNA from maternal peripheral blood during pregnancy and cord blood at birth, we will use generalized linear regression models. β Values for the $\approx$450,000 probes on the Illumina bead chip that pass quality control checks will be the outcome variables. The 0−10 ACE summary score will be the main predictor variable. The following variables will be covariates: maternal age at pregnancy, parity, maternal smoking during pregnancy, maternal education, pre-pregnancy body mass index, gestational age at birth, cell type composition, and technical covariates identified in the epigenetics data quality check. The analysis with newborn DNA will also be conducted separately in male and female newborns, based on the hypothesis that male placentas, which typically have lower levels of X-linked O-linked *N*-acetylglucosamine transferase gene, are more likely to have epigenetic alterations with robust transcriptional responses to maternal prenatal stress.[12] In all analyses, the false discovery rate will be set at 0.05. To test for mediation, linear structural equation models will be used. β Values at CPG sites found to be significant in the primary analyses will be the outcome variables. The independent

variable and covariates will be the same as in the primary analyses. The Edinburgh Postnatal Depression Scale (EPDS) total score will be tested as a mediator.

Significance

This analysis tests an extended timeframe for the impact of childhood adversity, namely, mothers' childhood affecting DNA methylation in her newborn offspring, and could provide evidence for a novel biological pathway for the enduring impact of childhood adversity across generations. Understanding the biological mechanisms by which ACEs program future generations for mental health risk would expand the possibilities for designing and evaluating interventions to prevent and ameliorate the negative impacts of adversities on future generations' mental health.

Pamela Scorza, ScD
Cristiane S. Duarte, PhD
Seonjoo Lee, PhD
Haotian Wu, PhD
Jonathan E. Posner, PhD
Andrea Baccarelli, PhD
Catherine Monk, PhD

Accepted May 12, 2020.

Drs. Scorza, Duarte, Lee, Wu, Posner, Baccarelli, and Monk are with Columbia University, New York. Drs. Wu and Baccarelli are also with the Mailman School of Public Health, Columbia University, New York. Drs. Duarte, Lee, Posner, and Monk are with the New York State Psychiatric Institute.

This work is supported by the National Institute of Mental Health grant K01MH117443.

Author Contributions:
Conceptualization: Scorza, Duarte, Lee, Wu, Posner, Baccarelli, Monk
Funding acquisition: Scorza
Methodology: Scorza, Duarte, Lee, Wu, Posner, Baccarelli, Monk
Software: Lee
Supervision: Duarte, Posner, Baccarelli, Monk
Writing—original draft: Scorza
Writing—review and editing: Duarte, Lee, Wu, Posner, Baccarelli, Monk

Dr. Lee served as the statistical expert for this research.

Disclosure: Dr. Duarte has received research funding from the National Institutes of Health Office of the Director (NIH OD), the National Institute on Drug Abuse (NIDA), the National Heart, Lung, and Blood Institute (NHLBI), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute on Alcohol Abuse and Alcoholism. Dr. Lee has received research funding from the National Institute on Aging (NIA), the National Institute of Mental Health (NIMH), and NICHD. Dr. Wu has received research funding from the National Institute of Environmental Health Sciences (NIEHS) and the National Institute on Minority Health and Health Disparities. Dr. Posner has received research funding from NIMH, NIA, NIEHS, Aevi Genomic Medicine, and Shire (a Takeda company) and consultancy fees from Innovative Science. Dr. Baccarelli has received research funding from NIEHS and NIMH. Dr. Monk has received research funding from NIH OD, NICHD, NIMH, and Johnson and Johnson. Dr. Scorza has reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Pamela Scorza, ScD, Department of Obstetrics and Gynecology, Columbia University, 622 West 168th Street, PH 1540, New York, NY 10032; e-mail: pls2122@cumc.columbia.edu

https://doi.org/10.1016/j.jaac.2020.03.008

REFERENCES

1. Bouvette-Turcot A-A, Meaney MJ, O'Donnell KJ. In: Noll JG, Shale I, eds. Epigenetics and Early Life Adversity: Current Evidence and Considerations for Epigenetic Studies in the Context of Child Maltreatment. The Biology of Early Life Stress. New York: Springer; 2018:89-119.
2. Bustamante AC, Aiello AE, Galea S, *et al*. Glucocorticoid receptor DNA methylation, childhood maltreatment and major depression. J Affect Disord. 2016;206: 181-188.
3. Shields AE, Wise LA, Ruiz-Narvaez EA, et al. Childhood abuse, promoter methylation of leukocyte NR3C1 and the potential modifying effect of emotional support. 2016;8: 1507–1517.
4. Non AL, Hollister BM, Humphreys KL, *et al*. DNA methylation at stress-related genes is associated with exposure to early life institutionalization. Am J Phys Anthropol. 2016; 161:84-93.
5. Esposito EA, Jones MJ, Doom JR, MacIsaac JL, Gunnar MR, Kobor MS. Differential DNA methylation in peripheral blood mononuclear cells in adolescents exposed to significant early but not later childhood adversity. Dev Psychopathol. 2016;28: 1385-1399.
6. Dunn EC, Soare TW, Zhu Y, *et al*. Sensitive periods for the effect of childhood adversity on dna methylation: results from a prospective, longitudinal study. Biol Psychiatry. 2019; 85:838-849.
7. Choi KW, Sikkema KJ. Childhood maltreatment and perinatal mood and anxiety disorders: a systematic review. Trauma Violence Abuse. 2016;17:427-453.
8. Jovanova OS, Nedeljkovic I, Spieler D, *et al*. DNA methylation signatures of depressive symptoms in middle-aged and elderly persons: meta-analysis of multiethnic epigenome-wide studies. JAMA Psychiatry. 2018;75:949-959.
9. Sosnowski DW, Booth C, York TP, Amstadter AB, Kliewer W. Maternal prenatal stress and infant DNA methylation: a systematic review. Dev Psychobiol. 2018;60:127-139.
10. Czamara D, Eraslan G, Page CM, *et al*. Integrated analysis of environmental and genetic influences on cord blood DNA methylation in new-borns. Nat Commun. 2019; 10:2548.
11. Relton CL, Gaunt T, McArdle W, *et al*. Data resource profile: Accessible Resource for Integrated Epigenomic Studies (ARIES). Int J Epidemiol. 2015;44:1181-1190.
12. Rosenfeld CS. Sex-specific placental responses in fetal development. Endocrinology. 2015;156:3422-3434.