DOCUMENT SUMMARY This research paper investigates the link between cumulative prenatal risk factors, neonatal epigenetics (specifically DNA methylation), and cognitive outcomes at age 3 in children born very preterm (<30 weeks gestational age). The study provides crucial biological evidence supporting the Enlitens view that life experiences, beginning in the womb, shape brain development through epigenetic mechanisms. The findings challenge simplistic diagnostic models by demonstrating that both environmental risk and biological markers independently predict cognitive scores, and that DNA methylation mediates the pathway from risk to outcome, literally showing how experience gets under the skin to influence a child's neurodevelopment.

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FORMATTED CONTENT

# Contributions of Prenatal Risk Factors and Neonatal Epigenetics to Cognitive Outcome in Children Born Very Preterm

## Why This Matters to Enlitens

This paper is core evidence for our mission. It provides a concrete, biological mechanism—epigenetics—that validates our foundational belief that "every brain makes perfect sense for the life it's lived." It shows that the process of adaptation begins in the womb, where prenatal risk factors (environmental stressors) leave a literal mark on a baby's DNA methylation, which in turn influences cognitive development.

This directly counters the pathology paradigm by framing neurodevelopmental differences as a logical outcome of environmental inputs, not as an inherent defect. The study's focus on cumulative risk and the heterogeneity of outcomes in a "high-risk" group dismantles the idea of a uniform "disorder" and supports our dimensional, individualized approach. The data on how small, additive effects can push a child over an arbitrary diagnostic cutoff on a standardized test (the Bayley Scales) is powerful ammunition for our critique of the testing industry and our advocacy for more humane, supportive assessment models.

## Critical Statistics for Our Work

### Participant Demographics & Attrition Bias

- **Initial Sample:** 1459 screened, 704 enrolled in the NOVI Study.
- **Final Analysis Sample:** 379 children (born to 335 mothers) with complete data.
- **Sex:** 54% male.
- **Gestational Age:** Born < 30 weeks GA; mean GA at birth was 27.04 weeks (SD=1.88).
- **Racial/Ethnic Diversity:** The sample was demographically diverse.
    - 55% identified as a minoritized race or ethnicity.
    - White: 47% (156/335).
    - Black or African American: 20% (68/335).
    - More than one race: 19% (64/335).
    - Hispanic/Latino/a ethnicity: 22% (74/335).
    - Asian: 3.9% (13/335).
    - Native Hawaiian or Other Pacific Islander: 1.5% (5/335).
    - American Indian/Alaska native: 0.3% (1/335).
    - Unknown/not reported race: 8.4% (28/335).
- **Attrition Bias:** Children included in the final analysis were more likely to be White (47% vs. 37%, p=.02) and to have shorter NICU stays (89.7 vs. 99.4 days, p=.005) compared to those excluded. There were no differences in cumulative prenatal risk scores for participants included versus excluded.

## Prenatal Risk Factors

- A cumulative risk index was created from 24 pre- and perinatal risk factors.
- The mean cumulative prenatal risk score was 0.15 (SD=0.10), corresponding to an average of 3.5 individual risk factors (SD=2.3).
- **Most Common Risk Factors:**
    - Minoritized race or ethnicity: 55%.
    - Obesity: 38%.
    - Hypertension: 27%.
    - Maternal education less than High School/GED: 14%.
    - Maternal tobacco use: 14%.
    - Maternal depression: 13%.
    - Maternal anxiety: 13%.

## Standardized Test Outcomes (Bayley Scales, BSID-III)

- The primary outcome was the cognitive composite score from the Bayley Scales of Infant and Toddler Development, third edition (BSID-III).
- **Average Score:** The mean BSID-III cognitive score was 93.6 (SD=13.5). (Note: Population mean is 100, SD is 15).
- **"Delay" Classification based on Arbitrary Cutoffs:**
    - 17% met the cutoff for mild delay (composite score <85).
    - 5.8% met the cutoff for severe delay (composite score <70).

## Key Findings Linking Risk, Epigenetics, and Cognitive Scores

- **Independent Effects:** Cumulative prenatal risk and DNA methylation were each independently associated with child cognitive ability.
    - A 1-SD increase in cumulative prenatal risk was associated with a 2.9 point (0.21 SD) decrease in BSID-III cognitive scores (p<.001).

    - A 1-SD increase in DNA methylation of cg20276927 (TNS3 gene) was associated with a 3.2 point (0.23 SD) decrease in BSID-III scores (p<.001).
    - A 1-SD increase in DNA methylation of cg22358121 (TRAPPC4 gene) was associated with a 2.7 point (0.20 SD) decrease in BSID-III scores (p<.001).
- **Clinical Relevance & "Mild Delay" Risk:**
    - A 1-SD increase in cumulative prenatal risk was associated with a 1.47 increase in odds of scoring in the mild delay range (<85).
    - A 1-SD increase in DNA methylation of cg20276927 was associated with a 1.50 increase in odds of mild delay.
    - A 1-SD increase in DNA methylation of cg22358121 was associated with a 1.53 increase in odds of mild delay.
- **Mediated Effects (Epigenetics as the Mechanism):**
    - High-dimensional mediation analysis (DACT) identified 309 CpG sites where DNA methylation significantly mediated the association between prenatal risk and cognitive ability.
    - For the top mediating CpG sites, the proportion of the total effect of prenatal risk on cognitive scores that was explained by DNA methylation ranged from 10% to 18%.

# Methodology We Can Learn From

This study uses a sophisticated approach that aligns with our philosophy of embracing complexity over simplistic labels.

- **Cumulative Risk Index:** Instead of isolating single risk factors, the researchers summed 24 different factors (demographic, health, substance use, etc.) to create a holistic measure of prenatal adversity. This approach acknowledges that risks often co-occur and have compounding impacts, moving beyond a single-cause model.
- **Epigenome-Wide Association Study (EWAS):** They analyzed DNA methylation across the entire genome (~450,000 sites) to find associations with cognitive outcomes, rather than pre-selecting a few "candidate genes." This is an unbiased, discovery-oriented approach.
- **High-Dimensional Mediation Analysis (HDMA):** This is a cutting-edge statistical method used to test if a large number of potential mediators (in this case, hundreds of thousands of DNA methylation sites) explain the relationship between an exposure (prenatal risk) and an outcome (cognitive ability). It's specifically designed to handle the complexity of genomic data and is more powerful than testing one potential mediator at a time.
- **Non-Invasive Data Collection:** They measured DNA methylation from buccal (cheek) swabs collected near NICU discharge. This demonstrates the feasibility of collecting important biological data in a non-invasive, accessible way.

# Findings That Challenge the System

This study provides powerful evidence against the simplistic, pathology-focused model of neurodevelopment.

- **Heterogeneity Defies Categorization:** Even in this high-risk group of children born very prematurely, there was "considerable heterogeneity in outcomes." Longitudinal studies

show that "upwards of two-thirds of children score within normal limits on standardized assessments." This undermines the idea that a risk factor (like preterm birth) leads to a predictable "disorder," supporting our view of individualized, dimensional outcomes.
- **Critique of Single-Variable Thinking:** The study explicitly argues against investigating single risk factors in isolation. An "individual variable approach may not capture the full extent of prenatal programming effects" because risks co-occur and compound. This supports our holistic, interview-based approach that considers the entire context of a person's life.
- **Biological Mechanisms for Environmental Influence:** The study identified DNA methylation as a plausible "molecular mediator linking prenatal risk factors to children's cognitive development." This provides a hard-science basis for the impact of environment and lived experience on the brain, moving the conversation away from purely genetic or "unknown" causes of "disorders."
- **Standardized Test Cutoffs are Arbitrary and Harmful:** The authors note that while the individual effects of risk factors on Bayley scores may seem small (~3 points), these "small to moderate effect sizes could have enhanced clinical importance." These small shifts can be what "push children's scores into the range of 'mild' or 'moderate' delay," which has significant consequences for classification and access to services. This is a direct indictment of the arbitrary nature of standardized test cutoffs and their disproportionate impact on high-risk populations.

# Populations Discussed

- **Very Preterm Infants:** The study population consists of infants born at less than 30 weeks gestational age, a group at high risk for neurodevelopmental delays.
- **Racial and Ethnic Diversity:** 55% of the maternal sample identified as a minoritized race or ethnicity. The most common single prenatal risk factor in the sample was "minoritized race or ethnicity" (55%).
- **Attrition Bias by Race:** The study acknowledges a significant limitation: "Children included were more likely to be White" compared to those lost to follow-up or excluded from the final analysis. This highlights the systemic problem of research attrition disproportionately affecting families of color, potentially skewing results and limiting generalizability—a key critique Enlitens levels against the evidence base for standardized testing.

# Alternative Approaches Mentioned

While the study uses a standardized test (Bayley Scales) as its outcome measure, its core methodology represents a significant departure from simplistic research models.

- **Cumulative Risk Models:** The use of a cumulative risk index is an alternative to single-factor research. This approach "may have greater power to detect associations with child outcomes as opposed to individual variable approaches." It aligns with an "allostatic load perspective that emphasizes additive effects of environmental risk factors."
- **High-Dimensional Mediation Analysis (HDMA):** This statistical technique is a direct response to the limitations of traditional methods. Traditional approaches that test one mediator at a time are not sufficient for identifying statistical mediators in complex genomic data. HDMA was "specifically developed to address the large number of composite null hypotheses" involved in testing thousands of mediators simultaneously.

# Quotes We Might Use

- **On Heterogeneity:** "Despite this overall trend, there is considerable heterogeneity in outcomes for this high-risk group."
- **On Moving Beyond Single Risk Factors:** "...to the extent that prenatal risk factors cooccur and/or have compounding impacts on development, an individual variable approach may not capture the full extent of prenatal programming effects."
- **On Epigenetics as the Link:** "...preliminary findings are promising and suggest the plausibility of DNA methylation as a potential molecular mediator linking prenatal risk factors to children's cognitive development."
- **On the Power of Multiple Small Effects:** "Although each individual association might be of small magnitude, it is notable that experiencing higher levels of prenatal risk in tandem with increased DNA methylation of one or both CpGs could be associated with larger, compounded associations of 0.5 SD or more."
- **On the Arbitrary Nature of Diagnostic Cutoffs:** "Thus, what may be considered a small shift in the absolute value of scores could constitute a meaningful shift in the number of preterm children classified as having a developmental delay or disability (Carey et al., 2023) and who therefore would qualify for additional services or interventions."
- **On the Need for Holistic Understanding:** The study suggests the "utility of better understanding both domains [prenatal risk and DNA methylation] in tandem in order to enhance risk stratification."
- **On the Future of Intervention:** "Clinicians could use information about children's prenatal risk factors in combination with their DNA methylation profiles to identify children at highest risk for cognitive delay and provide additional supports to disrupt the negative developmental sequelae."

# Clinical Implications

The study's conclusions directly support Enlitens' clinical model:

1. **Look Beyond the Presenting Behavior:** Clinicians should consider prenatal risk factors as a key part of a child's history. These factors are an "indicator of which neonates may require more extensive follow-up or early intervention." This validates our intake process that gathers extensive developmental and environmental history.
2. **Biological Markers as Guides, Not Labels:** Neonatal DNA methylation can serve as an "early indicator of cognitive development." The goal is not to label a child as "biologically flawed" but to "use information about children's prenatal risk factors in combination with their DNA methylation profiles to identify children at highest risk... and provide additional supports." This aligns with our goal of using assessment to understand and support, not to pathologize.
3. **Focus on Buffering and Support:** The final sentence of the paper is a call to action that mirrors our strengths-based philosophy: "Future research might investigate whether there are factors in the postnatal environment that buffer preterm children from poor outcomes, especially those who have experienced a multitude of prenatal risk factors." This shifts the focus from fixing the child to changing the environment and providing the necessary support to thrive, which is the entire purpose of the Enlitens approach.