Adverse Childhood Experiences Reported at Well-Child Visits and Transcriptional Response

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BACKGROUND

- A broad literature suggests that nutrition, physical activity, stress and the social environment affect gene expression
- Based upon research visit data, we previously demonstrated that children with higher parent-reported adverse childhood experiences (ACEs) are more likely to have increased expression of both inflammatory and interferon gene transcripts in children's circulating blood cells

- **Objective**: To determine whether ACE exposures reported during routine well-child care are associated with transcriptional response

METHODS

- Generally healthy pediatric patients age 3-11 years old were recruited from pediatric clinics to participate in the Building Resilient Families study
- Parent-reported ACE exposures were assessed during routine well-child care and the baseline research visit using the Whole Child Assessment (WCA)
- RNA sequencing was conducted on dried blood spot samples collected at the baseline research visit (N=149)
- Analyses were conducted on pro-inflammatory gene transcripts and Type I interferon response

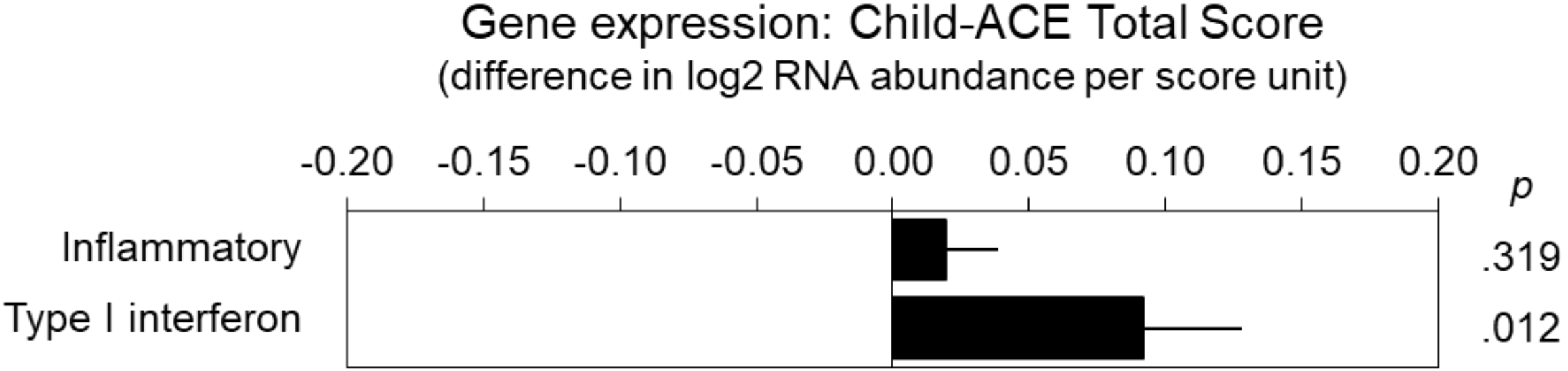
RESULTS

Child ACE Scores By Demographics

	WCA Clinic Total 0-1	WCA Clinic Total 2+
Age: median (SD)	6.25 (2.93)	7.5 (2.69)
Sex: N (%)		
Female	33 (41.8%)	36 (45.6%)
Male	37 (52.9%)	43 (54.4%)
Race/ethnicity: N (%)		
Hispanic	42 (60.0%)	54 (68.4%)
Black/African-American	4 (5.7%)	13 (16.5%)
White	9 (12.9%)	6 (7.6%)
Asian	10 (14.3%)	3 (3.8%)
Other	5 (7.1%)	3 (3.8%)

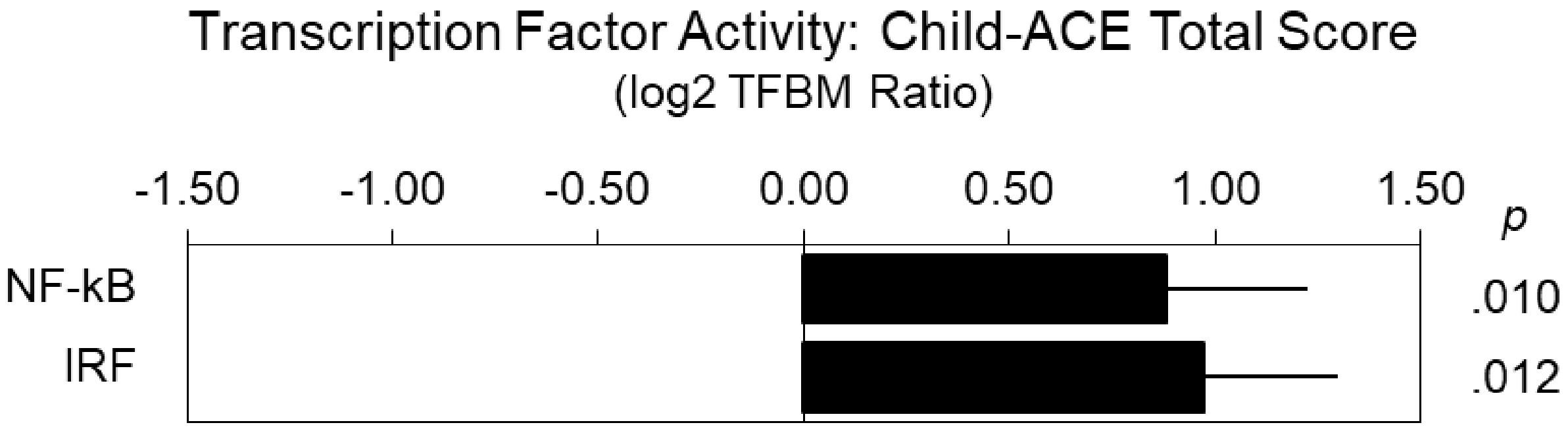
Inflammatory Gene Expression

- WCA-Clinic Total scores were associated with up-regulated activity of both inflammatory and antiviral gene pathways. In analyses of pre-specified gene sets, this was most pronounced for the antiviral/Type I interferon genes (not significant for the inflammatory genes)
- These results were robust to control for covariates (time point, age, sex, race/ethnicity) and for major leukocyte subset markers



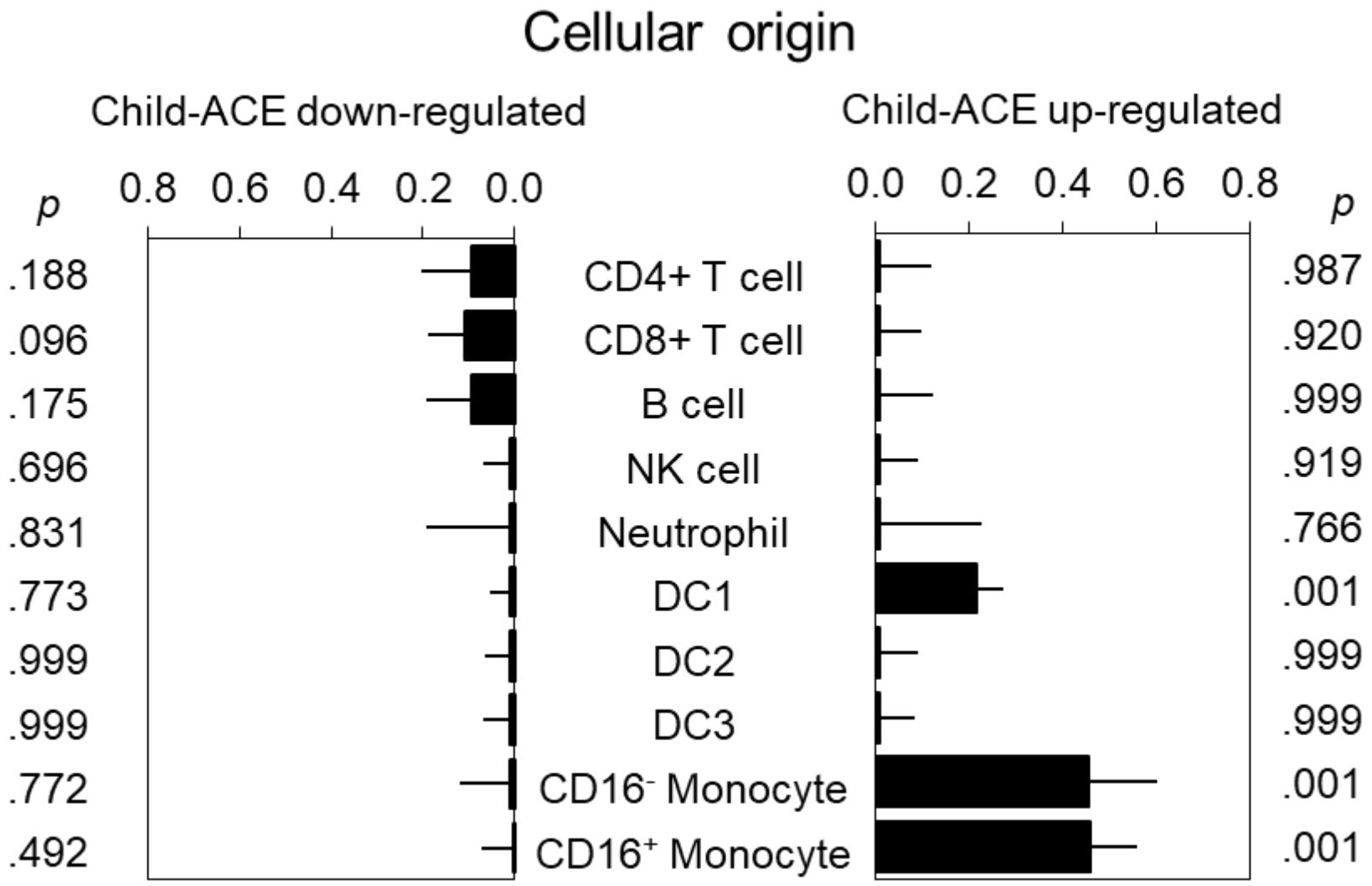
Transcription Factor Activity

- We also quantified transcription factor activity using bioinformatic analysis of genome-wide transcriptome differences and found evidence for upregulated activity of both Interferon Response Factors (IRFs, mediating Type I interferon responses) and pro-inflammatory signaling pathways (NF-kappaB, AP1).
- These results are robust to control for covariates and for variations in leukocyte subset abundance.



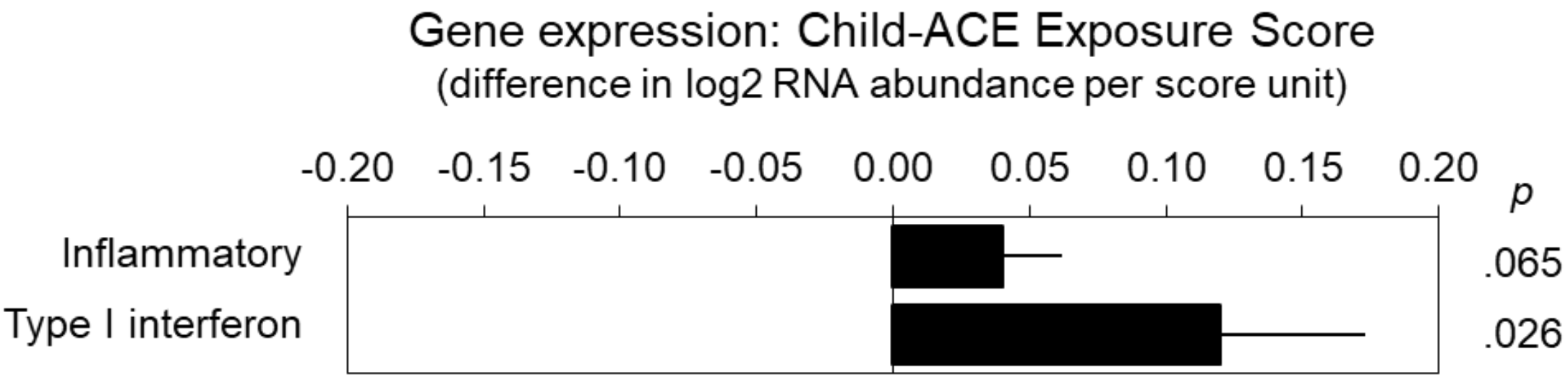
Cellular Origins

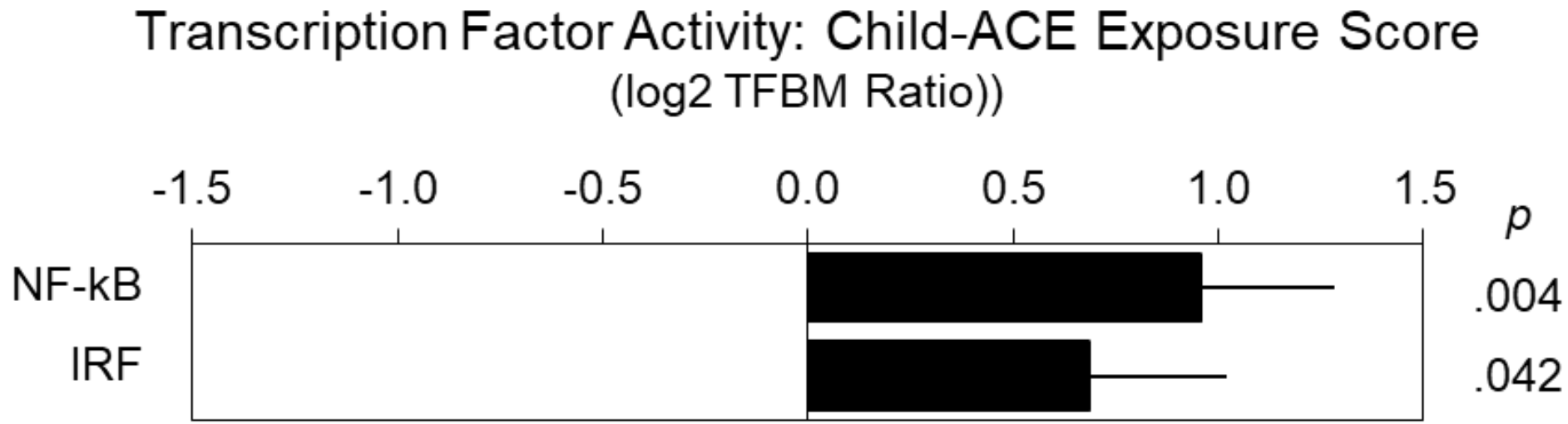
Analyses of cellular mechanisms indicate that these effects emerged primarily from up-regulated activity of monocytes and dendritic cells, and down-regulated activity of CD4+ and CD8+ T cells, and B cells



Child ACE Measures

- Similar findings emerged for WCA-Clinic Exposure scores, whereas WCA-Clinic Risk scores had weaker associations, suggesting that the bulk of the WCA-Clinic Total score was being driven by the effects of ACE exposures rather than ACE risk factors
- WCA Research scores suggest a similar set of findings


Gene expression: Child-ACE Exposure Score
(difference in log2 RNA abundance per score unit)
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
0.20
p
Inflammatory
.065
Type I interferon
.026


Transcription Factor Activity: Child-ACE Exposure Score
(log2 TFBM Ratio))
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
p
NF-kB
.004
IRF
.042

CONCLUSION

- Parent-reported ACE exposures at well-child care visits are associated with increased expression of both inflammatory and interferon gene transcripts in children's circulating blood cells;
- This supports the validity of our prior findings on a research sample, and suggests the potential utility of transcriptional response as a clinical metric of risk for chronic disease

FUTURE RESEARCH

- Evaluate whether the association with Child ACEs results in persistent group differences over time;
- Determine whether interventions to reduce stress at home alter transcriptional response;
- Explore associations with child lifestyle, caregiver mental health and parent-child relationships

REFERENCES

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- Marie-Mitchell A, Watkins HBR, Copado IA, Distelberg B. “Use of the Whole Child Assessment to Identify Children at Risk of Poor Outcomes.” Child Abuse and Neglect, 104: 104489, 2020.
- Marie-Mitchell A, Cole SW. “Adverse Childhood Experiences and Transcriptional Response in School-Age Children.” Development and Psychopathology, 1-7, 2021.
- Patel NS, Watkins H, Marie-Mitchell A. “Predictive Validity of the Whole Child Assessment in a Generally Healthy Pediatric Cohort.” Journal of Primary Care & Community Health, 14: 1-7, 2023.