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## Biological embedding of stress through inflammation processes in childhood

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Children exposed to adverse psychosocial experiences show elevated disease risk in adulthood.<sup>1</sup> It is therefore important to characterize the biological mechanisms through which children may acquire such lasting vulnerability to disease, namely, the mechanisms of biological embedding.<sup>2</sup>

Recent studies suggest that inflammation could be an important developmental mediator translating childhood psychosocial into biological risk. We previously showed that adult individuals exposed

to childhood maltreatment had elevated levels of inflammation biomarkers.<sup>3</sup> The elevation in inflammation levels was most evident in adults exposed to childhood maltreatment who also experienced depression at the time of inflammation assessment.<sup>4</sup> These epidemiological findings from a population-representative birth cohort are supported by experimental evidence in animal models.<sup>5</sup> In turn, elevated inflammation levels in adulthood have been linked to elevated risk of mental and physical illness.<sup>6</sup>

A key unanswered question is when the effect of childhood stress on inflammation emerges. The significance of this question lies in its potential to uncover the origins of enduring disease vulnerability in children exposed to adverse psychosocial experiences, and to suggest the best timing for effective interventions.

To test the possible emergence of the effect of stress on inflammation in childhood, we studied a sample of 12-year-old children participating in the Environmental Risk Longitudinal Twin Study.<sup>7</sup> We studied children from 41 homes where we found evidence of physical maltreatment. We compared them with children from homes where we found no evidence of maltreatment. These two groups of children were matched with regard to family socio-economic status, gender and zygosity. Children's exposure to physical maltreatment was prospectively assessed during their first decade of life using a standardized interview with mothers having documented validity and reliability. Childhood depressive symptoms at age 12 were assessed using the Children's Depression Inventory, and children scoring higher than its validated clinical cut-off point (CDI  $\geq$  20) were classified as depressed. Inflammation at age 12 was assessed based on levels of high-sensitivity C-reactive protein (hsCRP) collected through blood spots.<sup>8</sup> Measures of body temperature and waist-hip ratio, two important potential intervening variables, were also collected at the time of blood spot collection (see Supplementary Methods).

Based on our previous findings that elevated inflammation levels were concentrated among adults exposed to childhood maltreatment who also experienced depression at the time of inflammation assessment,<sup>4</sup> we hypothesized that maltreated children who also experienced depression at the time of inflammation assessment would show elevated hsCRP levels. We therefore divided our sample into four groups: children from maltreatment-free homes without depression (controls), children from maltreatment-free homes with current depression (depressed-only), children from homes with maltreatment but no depression (maltreated-only), and children from homes with maltreatment with current depression (depressed + maltreated). We found significant mean differences in hsCRP across these four groups (Table 1, panel 1). Depressed + maltreated children showed a significant mean elevation in hsCRP levels compared with control children. In contrast,

**Table 1** Descriptive statistics and association analysis for inflammation biomarker and potential intervening variables stratified by the four study groups

	Controls (n = 84)	Depressed- only (n = 8)	Maltreated- only (n = 69)	Depressed + maltreated (n = 13)	P-value
<i>Panel 1: Inflammation biomarker</i>					
CRP, geometric mean (95% CI)	0.28 (0.24–0.33) <sup>a</sup>	0.25 (0.16–0.38) <sup>a</sup>	0.28 (0.23–0.35) <sup>a</sup>	0.49 (0.28–0.84) <sup>a</sup>	0.016
P-value <sup>b</sup>	—	0.587	0.937	0.045	
<i>Panel 2: Matching variables</i>					
SES, mean (s.d.)	1.76 (0.82)	1.50 (0.93)	1.61 (0.83)	1.77 (0.60)	0.592
Male sex, n (%)	39 (46.4)	5 (62.5)	38 (55.1)	4 (30.8)	0.316
Dizygotic twin, n (%)	47 (56.0)	7 (87.5)	40 (58.0)	8 (61.5)	0.383
<i>Panel 3: Potential intervening variables</i>					
Body temperature, mean (s.d.)	36.37 (0.40)	36.04 (0.51)	36.36 (0.46)	36.47 (0.26)	0.147
Waist–hip ratio, mean (s.d.)	0.84 (0.07)	0.84 (0.09)	0.85 (0.06)	0.83 (0.06)	0.616

Abbreviations: CI, confidence interval; CRP, C-reactive protein; SES, socioeconomic status.

<sup>a</sup>Confidence intervals are adjusted for the effect of familial clustering.

<sup>b</sup>P-values from *a-priori* defined contrasts testing differences between single study groups and control group, adjusted for the effect of familial clustering.

depressed-only and maltreated-only children showed mean hsCRP levels similar to control children. The four groups did not differ on matching variables (childhood socioeconomic status, sex, zygosity; Table 1, panel 2) or on potential confounders (body temperature, waist–hip ratio; Table 1, panel 3). Therefore, matching variables and potential confounders could not explain group differences in inflammation levels (see Supplementary Results).

We found that children experiencing maltreatment and depression showed significantly elevated inflammation levels, regardless of their socioeconomic status, gender, zygosity, body temperature and waist–hip ratio. These findings are consistent with studies reviewed elsewhere,<sup>4</sup> suggesting that depressed + maltreated adults have enduring intertwined abnormalities in brain, endocrine and immune functioning. Results from the present study add to this literature, providing the first evidence that the origins of these abnormalities in stress-sensitive systems could be traced back to the childhood years.

Stress-related elevation in clinically relevant inflammation proteins could contribute to the biological embedding of childhood stress. Adverse childhood experiences may leave biological residues manifested by decreased glucocorticoid-related and increased proinflammatory gene expression,<sup>9</sup> presumably owing to epigenetic changes. These processes may have triggered elevation in hsCRP levels in depressed + maltreated children. In turn, childhood elevation in hsCRP levels has been linked to the presence of key preclinical indicators of adult disease risk in children, such as advanced atherosclerosis progression.<sup>10</sup> Interventions targeting children experiencing

maltreatment and depression could prevent long-term disease vulnerability by hampering the translation of psychosocial to biological risk through inflammation processes during a sensitive developmental window.

### Conflict of interest

The authors declare no conflict of interest.

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