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The Metabolomic Signature of Childhood Trauma

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ABSTRACT

BACKGROUND: Although childhood trauma is an important risk factor for various diseases, the underlying biological mechanisms remain insufficiently understood. To deepen this understanding, we investigated the wide-spectrum metabolomic signature of childhood trauma exposure in a large adult cohort.

METHODS: Baseline and 6-year follow-up data from NESDA (Netherlands Study of Depression and Anxiety) were used ($N_{participants}$ = 2902, $N_{observations}$ = 4800). Childhood trauma exposure was retrospectively assessed with the Childhood Trauma Interview. Plasma metabolite levels were measured with the Metabolon mass spectrometry–based untargeted metabolomics platform at both time points. Mixed-effect models were used to evaluate the metabolomic associations of childhood trauma while controlling for sociodemographic, lifestyle, health-related, and technical covariates. We examined the overlap between the metabolomic profiles of childhood trauma and depression. External replication was tested in 308 additional participants.

RESULTS: Childhood trauma was associated in a dose-response manner with 18 metabolites. Upregulated metabolites were nominally enriched with compounds involved in fatty acid and branched-chain amino acid metabolism ($p = 3.91 \times 10^{-2}$, false discovery rate–corrected q [q_{FDR}] $> .05$) while downregulated metabolites were nominally enriched with corticosteroids ($p = 2.24 \times 10^{-3}$, $q_{FDR} > .05$). Six of the 18 metabolites were linked to childhood trauma but not depression. Findings were partially replicated using an alternative measure for childhood trauma (effect size correlation r = 0.94) and an external sample (r = 0.54).

CONCLUSIONS: Childhood trauma was linked in a dose-response manner to a biological signature encompassing a wide array of metabolites. Dysregulations were observed in amino acid and fatty acid metabolism as well as hypothalamic-pituitary-adrenal axis function. Future studies should corroborate these findings and develop early-intervention strategies that target trauma-related biological mechanisms to prevent cardiometabolic and psychiatric diseases.

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Childhood trauma is often defined as the experience of physical, emotional, or sexual abuse or physical or emotional neglect before the age of 18 years. Evidence shows that adults with adverse experiences during childhood, including childhood trauma, experience somatic disorders twice as often as adults without such a history (1–4). This elevated disease risk is likely explained by trauma-related behavioral and psychological mechanisms and biological dysregulations. As summarized in Kuzminskaite *et al.* (5), behavioral pathways likely include physical inactivity, poor diet, smoking, and excessive alcohol consumption. Psychological mechanisms may entail maladaptive coping strategies, negative cognitive biases about the self and the environment, and heightened stress reactivity. Biological disruptions likely encompass epigenetic modifications; stress and immune system dysregulations; and alterations in brain structure, functional activity, and neuronal connectivity. Together, these interconnected mechanisms are likely linked to metabolomic dysregulations, jointly contributing to disease risk. Specifically, metabolic dysregulations appear to mediate the development of cardiometabolic disorders after early-life stress (6). Therefore, investigating the metabolome, i.e., the extensive collection of all end products of metabolism in an organism, by mapping the metabolomic signature of childhood trauma may facilitate the understanding and prevention of the development of such diseases.

Individuals with a history of childhood trauma have impaired glucose metabolism (7), elevated dyslipidemia (8,9), and dysregulated cortisol activity (10). Targeted analyses of childhood trauma–related metabolomics indicate that physical and sexual abuse are linked to dysregulated metabolites within lipid, amino acid, carbohydrate, and fatty acid pathways (11,12) and are possibly involved in one-carbon metabolism, mitochondrial dysfunction, oxidative stress, and inflammation (13). However, most of these findings are based on small samples ($N < 100$) (11,13), assessing only 2 types of childhood trauma (11–13) and testing limited, targeted sets of metabolites (<100) (11,13).

The metabolome remains largely unexplored in the context of childhood trauma. An untargeted analysis of the entire

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metabolome would enable systematic and unbiased exploration, potentially leading to the discovery of previously unidentified childhood trauma–related pathways to disease. Only one study has tested childhood trauma–related metabolites and lipids using an untargeted metabolomics platform (14) and found that in 105 women at 3 months postpartum, childhood trauma was associated with 8 of 398 metabolites belonging to antioxidant-, lipid-, and endocannabinoid-associated pathways involved in oxidative stress and inflammation. However, the postpartum status and small size of the sample limited the findings' generalizability. Identifying childhood trauma–related metabolites using an untargeted platform in a large sample of both males and females would improve the understanding of the biological mechanisms that put individuals with a history of childhood trauma at a high risk of disease.

In the current study, we investigated the metabolomic signature of childhood trauma by testing 820 metabolites from the untargeted Metabolon platform (15) measured twice in a large adult sample from NESDA (Netherlands Study of Depression and Anxiety) (16). Because the sample was enriched for depression, which has a specific metabolomic signature of its own (17) and is strongly associated with childhood trauma (18), we evaluated the degree of overlap of the metabolomic profiles of childhood trauma and depression by comparing our findings with the previously discovered depression-related metabolites (17). Additionally, we tested the robustness of our findings by replicating them using a different measure of childhood trauma assessed in the same sample 4 years later (internal replication) and in a new sample (external replication). Finally, we explored the effect of also adjusting for health-related variables on the associations found.

METHODS AND MATERIALS

Design and Sample

This investigation used data from NESDA, a multicenter longitudinal observational case-control cohort study that is aimed at exploring the course of affective disorders (16). Between 2004 and 2007, 2981 adults (ages 18–65 years) with or without a diagnosis of depression and/or anxiety disorder were recruited from community samples, primary care practices, and mental health organizations. Exclusion criteria were being diagnosed with a current clinically overt psychiatric disorder other than depression or anxiety (e.g., psychotic, bipolar, or addiction disorders) as well as lacking proficiency in Dutch. Participants were assessed and followed-up over 9 years, and 367 siblings were invited to partake in the study at the 9-year follow-up (details in Supplemental Section 1). Ethical approval was obtained centrally from the Ethical Review Board of the Vrije Universiteit Medical Centre (Reference No. 2003/183) in Amsterdam, the Netherlands, as well as from the ethics review boards of the participating research centers. Participants provided written informed consent.

Measures

Childhood Trauma. To assess childhood trauma exposure at baseline, trained research assistants administered the Childhood Trauma Interview (details in Supplemental Section 2), a retrospective semistructured interview originally developed for the Netherlands Mental Health Survey and Incidence Study (19). The interview assesses the occurrence and frequency of 4 dimensions of trauma before the age of 16: physical, emotional, and sexual abuse and emotional neglect. To assess childhood trauma severity, a cumulative score was computed, the Childhood Trauma Index (CTI) (range 0–8) (20,21). As used elsewhere (10), we explored the functional form of the CTI-metabolite associations by assigning participants to one of 3 severity groups: no (CTI = 0), mild ($1 \leq \text{CTI} \leq 3$), or severe ($4 \leq \text{CTI} \leq 8$) childhood trauma.

We also tested the robustness of the findings by repeating the analyses with another measure of childhood trauma, the short version (28 items) of the Childhood Trauma Questionnaire (CTQ) (details in Supplemental Section 3) (22). The CTQ was administered at the 4-year follow-up in the main sample and at the 9-year follow-up in siblings. It assesses 5 types of traumatic experiences in childhood: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. The total childhood trauma severity score ranges from 25 to 125.

Metabolites. Metabolite measurement and data preprocessing have been extensively described elsewhere (17). Briefly, fasting plasma samples were collected in the morning at baseline and at the 6-year follow-up and were stored at −80 °C. Samples were sent for analyses in 2 batches where metabolomic profiles were assessed using the mass spectrometry–based untargeted platform from Metabolon Inc. (see Supplemental Section 4 for details).

Covariates. Sex, age at baseline, education, physical activity, smoking, alcohol use, number of chronic diseases, shipment batch, and wave were included as covariates in the primary models used to assess the association of childhood trauma with metabolites. In a second step, we also adjusted for body mass index (BMI) (weight [kg]/height^2 [m^2]) and statin use (Anatomical Therapeutic Chemical code C10AA) because these may be linked to metabolite levels and childhood trauma (23) (covariate specification and imputation in Supplemental Section 5).

Statistical Analysis

Analyses were conducted in R version 4.2.3 (24), and the packages lme4 (v1.1-33) (25) and lmerTest (v3.1-3) (26) were used to run linear mixed-effect models. Descriptive statistics were used to characterize differences between individuals with no, mild, and severe childhood trauma.

Primary Analyses. In primary analyses, we used mixed-effect models to test the associations of the CTI assessed at baseline with levels of each metabolite measured at baseline and at the 6-year follow-up, thereby utilizing full statistical power by including data available at both waves. In a first step, we adjusted models for sex, age at baseline, education, physical activity, smoking, alcohol use, number of chronic diseases, shipment batch, and wave. The models were specified with a Gaussian distribution, a random intercept at the participant level to take into account within-subject

correlations of repeated metabolite measurements and a maximum likelihood estimation method. To correct for multiple testing across the 820 metabolites, false discovery rate (FDR) correction was applied to the 820 model p values, and the significance level after correction was set at $\alpha = .05$. We conducted pathway enrichment analyses to investigate which of the 10 superpathways and 95 subpathways (17) might be under- or overrepresented among the significant metabolite set by using Fisher's exact tests. In a second step, BMI and statin use were included in the mixed-effect models as additional covariates. In a third step, we checked for collider bias by running the models of the significant metabolite set's associations with the CTI without adjusting for health-related factors.

Moreover, we explored the functional form of the CTI-metabolite associations by categorizing the independent variable into childhood trauma severity groups (3-level factor: no, mild, or severe). First, we examined the associations of the severity groups only with the metabolites that were initially associated with the CTI. Then, we explored the associations between all 820 models and the trauma severity levels, correcting for multiple testing with FDR correction to the 820 models' p values.

Comparison With Depression-Associated Metabolites. Because depression and a history of childhood trauma tend to co-occur in the same individuals, and depression may partially mediate the association of childhood trauma with metabolomic alterations, we explored the specificity of the metabolomic signature of childhood trauma versus depression. We compared the associations (standardized beta coefficients) of metabolites with CTI from the primary findings with the ones of depressive symptoms and current depression diagnosis from previously published NESDA findings (17). Specifically, we compared the association signs to know the consistency of their direction, and the association strengths by calculating the percentage of the CTI effect sizes relative to the effect sizes of the depressive symptoms and current depression diagnosis. Although antidepressant use was mostly unrelated to metabolite levels beyond depression's effects (17), it was linked to alterations in one metabolite (5-methylthioadenosine [MTA]) beyond depression in our sample. To detect a possible spurious association caused by the high rate of antidepressant use in this sample (16), the association of the CTI with MTA was specifically evaluated.

Secondary Analyses. To test the robustness of the findings, we first conducted internal replication analyses by modeling the associations of the CTI-associated metabolites with CTQ measured in the same sample at the 4-year follow-up with mixed-effect models and similar adjustments as in the primary model. Second, we conducted external replication analyses by comparing the associations of the significant metabolite set with the CTQ in the main sample versus CTQ in siblings with linear regression models and similar adjustments.

RESULTS

One half of the sample ($n = 2793$) had no history of childhood trauma while the other half reported either mild (27%) or severe (21%) childhood trauma (Table 1). Two-thirds of the participants were female, and the median age of the sample was 43 years. A history of childhood trauma, particularly severe trauma, was linked to being female, older age, current smoking, less alcohol use, more chronic diseases, a higher BMI, and more statin use. Consistent with previous findings (17), current major depressive disorder was diagnosed in 40% of the sample. At the 6-year follow-up ($n = 2007$), the sample distribution remained similar for all variables (Table S1) except that only 16% of the sample was then diagnosed with current major depressive disorder. The sibling sample ($n = 308$, 56% female) had a median age of 53 years (and less current major depressive disorder [11%]) and less extreme childhood trauma scores compared with the main sample (Table S2).

Primary analyses showed that after FDR correction, the CTI was significantly associated with 18 metabolites, 9 of which were upregulated and 9 of which were downregulated (Figure 1, Table 2, and Table S3). Beyond uncharacterized metabolites, the largest significant effect sizes were found for stachydrine ($\beta = 0.07$, SE = 0.02, $p = 3.09 \times 10^{-5}$), cortisol ($\beta = -0.06$, SE = 0.02, $p = 9.66 \times 10^{-5}$), and 2-methylbutyrylcarnitine ($\beta = 0.06$, SE = 0.01, $p = 2.32 \times 10^{-5}$), which belong to the xenobiotic, lipid, and amino acid superpathways, respectively. Metabolite enrichment was not found for any superpathway. However, upregulated metabolites from the fatty acid metabolism (overlapping with branched-chain amino acid [BCAA] metabolism) subpathway were nominally enriched ($p = .039$, $q_{FDR} = 1.000$) (Table S4). Among the 3 metabolites belonging to this subpathway, one was positively associated with CTI (propionylcarnitine, $\beta = 0.06$, SE = 0.02, $p = 1.37 \times 10^{-4}$). Downregulated metabolites from the corticosteroid subpathway were also nominally enriched ($p = .002$, $q_{FDR} = .213$) (Table S4). Among the 6 metabolites belonging to this subpathway, 2 were negatively associated with CTI (cortisol $\beta = -0.06$, SE = 0.02, $p = 9.66 \times 10^{-5}$; cortisone $\beta = -0.06$, SE = 0.02, $p = 4.60 \times 10^{-4}$). Second, after BMI and statin use were added to the models, all 18 metabolites remained significantly associated with CTI (Figure S1 and Table S5), although certain effect sizes were altered with an average absolute change of 12%. Third, we ran the models of the significant metabolite set without adjusting for health-related factors to evaluate whether significant associations might have been the product of potential collider bias. Associations remained largely identical (effect size correlation $r = 0.91$) (Table S5), with all the effect sizes keeping the same direction and their statistical significance, which increased our confidence that the associations were not a product of collider bias.

When we grouped participants into those with no, mild, and severe childhood trauma, we found that absolute effect sizes of the 18 CTI-associated metabolites were 131% larger on average for severe childhood trauma (vs. no trauma) than for mild childhood trauma (vs. no trauma) (Figure 2). Across the whole metabolomics panel, severe childhood trauma was associated with 19 metabolites (overlap of 72% with the 18 metabolites associated with the CTI), while mild childhood trauma was associated with none after FDR correction (Table S3).

When we compared the metabolomic signature of childhood trauma with the one of depression (17), we found that 12

Table 1. Descriptive Statistics for the Main Study Variables

	No Childhood Trauma, *n* = 1430 (51%)	Mild Childhood Trauma, *n* = 766 (27%)	Severe Childhood Trauma, *n* = 597 (21%)	Overall, *N* = 2793
Sociodemographic Factors				
Sex, Female	61%	72%	72%	66%
Age, Years	41.0 [28.0–52.8]	43.0 [31.0–53.0]	46.0 [37.0–55.0]	43.0 [31.0–53.0]
Years of Education	12.0 [10.0–15.0]	12.0 [10.0–15.0]	11.0 [9.0–15.0]	12.0 [10.0–15.0]
Childhood Trauma				
CTI	0 [0–0]	2 [1–2]	5 [4–6]	0 [0–3]
CTQ-Short Version	32 [28–36]	40 [34–47]	56 [47–67]	36 [31–46]
Lifestyle and Health Factors				
Smoking Status				
Never	32%	25%	24%	28%
Former	32%	39%	32%	34%
Current	36%	36%	45%	38%
Alcohol Use, Drinks/Week	3.8 [0.4–8.8]	3.8 [0.2–8.3]	2.4 [0.2–8.3]	3.8 [0.2–8.8]
Physical Activity, 1000 MET-Min/Week	2.9 [1.5–5.2]	2.8 [1.4–4.8]	2.8 [1.4–5.1]	2.8 [1.4–5.0]
Number of Chronic Diseases	0 [0–1]	0 [0–1]	1 [0–1]	0 [0–1]
Body Mass Index	24.4 [21.9–27.7]	24.4 [22.0–27.9]	25.7 [22.9–29.4]	24.6 [22.1–28.1]
Statins Use	6%	6%	10%	7%

Values are presented as % or median [interquartile range]. All measures were assessed at baseline except CTQ, which was assessed at the 4-year follow-up. CTI = 0 for no childhood trauma, 1 ≤ CTI ≤ 3 for mild childhood trauma, and 4 ≤ CTI ≤ 8 for severe childhood trauma.

CTI, Childhood Trauma Index; CTQ, Childhood Trauma Questionnaire; MET, metabolic equivalent total.

metabolites of the 18 associated with CTI were also associated with depressive symptoms or current major depressive disorder, while 6 were not associated or were oppositely associated with depression (Table S6). Among the characterized metabolites associated with CTI, cortisol, 1,5-anhydroglucitol, indoleacetylglutamine, perfluorooctanesulfonate (PFOS), and *N*-acetylglycine were not associated or were oppositely associated with depression. Moreover, the 18 CTI-associated metabolites had consistently stronger associations with childhood trauma than with depression, because effect sizes of CTI were 70% to 103% larger on average than the ones for depressive symptoms and diagnosis (Figures S2 and S3). MTA, the metabolite that likely captures antidepressant use beyond depression's effects (17), was not associated with CTI ($\beta = 0.02$, SE = 0.02, $p = 1.26 \times 10^{-1}$).

Internal replication analyses showed that replacing CTI with CTQ completed by the same participants 4 years later affected the results only marginally (Table S7) because the 2 trauma measures had highly correlated effect sizes for the 18 CTI-related metabolites ($r = 0.94$) (Figure S4) with 100% consistency in the direction of effects (Table S7). External replication analyses showed that the associations were partially replicated in the sibling sample ($n = 308$) (Table S7); the effect sizes of CTQ were moderately correlated across the 2 samples ($r = 0.54$) (Figure S5) and had highly consistent directions (83%) (Table S7).

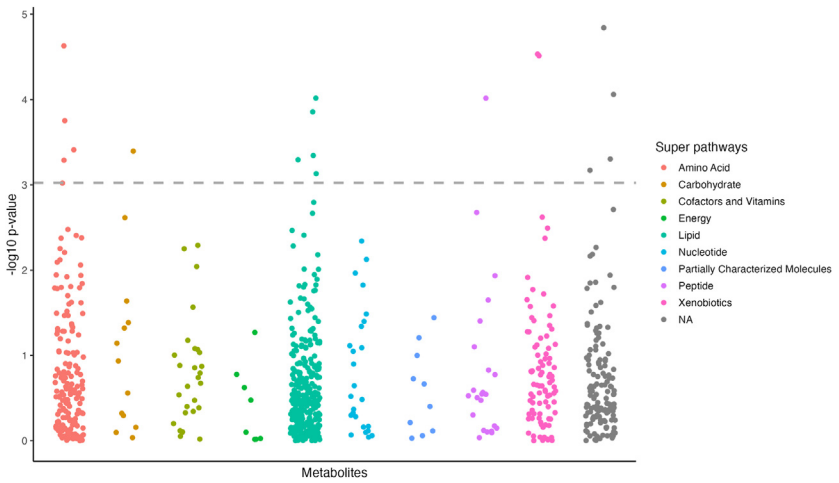

Figure 1. Manhattan plot of the metabolomics associations of childhood trauma per superpathway at baseline and at the 6-year follow-up ($N_{participants}$ = 2902, $N_{observations}$ = 4800). Models were adjusted for age, sex, education, physical activity, smoking status, alcohol consumption, number of chronic diseases, shipment batch, and wave. The plot shows that 18 of the 820 metabolites were associated with the Childhood Trauma Index at a false discovery rate–corrected $p = .05$ (dotted horizontal line). NA, no pathway assigned.

Table 2. Significant Metabolomics Associations of CTI at Baseline and at 6-Year Follow-Up After FDR Correction (N = 2902, $N_{observations}$ = 4800)

	CTI				
Metabolite	β	SE	p	Superpathway	Subpathway
X-17654	−0.075	0.017	1.44×10^{-5}	NA	NA
Stachydrine	0.071	0.017	3.09×10^{-5}	Xenobiotics	Food component/plant
Cortisol	−0.064	0.016	9.66×10^{-5}	Lipid	Corticosteroids
2-Methylbutyrylcarnitine (C5)	0.063	0.015	2.32×10^{-5}	Amino acid	Leucine, isoleucine, and valine metabolism
X-11847	0.063	0.016	8.72×10^{-5}	NA	NA
Propionylcarnitine (C3)	0.063	0.016	1.37×10^{-4}	Lipid	Fatty acid metabolism (also BCAA metabolism)
1,5-Anhydroglucitol	−0.061	0.017	4.03×10^{-4}	Carbohydrate	Glycolysis, gluconeogenesis, and pyruvate metabolism
X-24494	−0.061	0.018	4.99×10^{-4}	NA	NA
Gamma-Glutamylglutamate	0.061	0.016	9.67×10^{-5}	Peptide	Gamma-glutamyl amino acid
Indoleacetylglutamine	0.06	0.016	1.77×10^{-4}	Amino acid	Tryptophan metabolism
Methionine	−0.058	0.016	3.87×10^{-4}	Amino acid	Methionine, cysteine, SAM, and taurine metabolism
Cortisone	−0.057	0.016	4.60×10^{-4}	Lipid	Corticosteroids
X-11849	0.055	0.016	6.74×10^{-4}	NA	NA
Perfluorooctanesulfonate	−0.055	0.013	2.92×10^{-5}	Xenobiotics	Chemical
Branched Chain 14:0 Dicarboxylic Acid	−0.054	0.016	7.33×10^{-4}	Lipid	Fatty acid, dicarboxylate
3-(4-Hydroxyphenyl)lactate	−0.054	0.016	5.27×10^{-4}	Amino acid	Tyrosine metabolism
N-Acetylglycine	0.054	0.016	9.47×10^{-4}	Amino acid	Glycine, serine, and threonine metabolism
1-Stearoyl-GPC (18:0)	0.054	0.015	5.02×10^{-4}	Lipid	Lysophospholipid

Models were adjusted for age, sex, education, physical activity, smoking status, alcohol consumption, number of chronic diseases, shipment batch, and wave. The table shows all statistically significant associations of metabolites with CTI after FDR correction to all 820 models' p values. Metabolites are ranked in descending order based on their associations' absolute effect sizes with CTI. The associations of CTI with all 820 metabolites regardless of statistical significance can be found in Table S3. Metabolites whose names start with X- are uncharacterized molecules.

BCAA, branched chain amino acid; CTI, Childhood Trauma Index; FDR, false discovery rate; NA, no pathway assigned; SAM, *S*-adenosylmethionine.

DISCUSSION

In this study, we investigated the metabolomic signature of childhood trauma. Based on the untargeted analysis of 820 plasma metabolites, exposure to childhood trauma was found to be associated in a dose-response manner with 18 compounds that belong to a wide array of superpathways because none of them were overrepresented. Metabolites from subpathways involved in fatty acid metabolism, amino acid metabolism, and corticosteroids were nominally overrepresented in individuals exposed to childhood trauma. Despite some overlap between the metabolomic signature of childhood trauma and the one of depression, our findings showed that the observed signature was partially unique to childhood trauma.

Childhood trauma was associated with several metabolites indicating dysfunctions of amino acid and lipid metabolism. Specifically, childhood trauma exposure was linked to higher plasma levels of the short-chain acylcarnitines propionylcarnitine and 2-methylbutyrylcarnitine, suggesting disruptions in BCAA and fatty acid metabolism (27). These disruptions are indicative of mitochondrial dysfunction (28); have been linked to Alzheimer's disease (29); and possibly contribute to insulin resistance (30), cardiometabolic disease (31–35), and depression (36,37). Additionally, plasma levels of 1-stearoyl-GPC (18:0), a phospholipid, were also elevated in individuals with a history of childhood trauma and have been linked to plaque development in atherosclerosis (38) and to depression (17). Although previous findings have supported this association inconsistently (14,39–41), discrepancies may be explained by the use of relatively small sample sizes or differences in study design. Furthermore, we found that childhood trauma was associated with lower plasma levels of branched-chain 14:0 dicarboxylic acid, a fatty acid involved in breaking down excessive amounts of other fatty acids, further supporting the alteration of fatty acid metabolism. Therefore, our findings suggest that childhood trauma may lead to disruptions of both amino acid and fatty acid metabolism, possibly contributing to cardiometabolic, psychiatric, and other diseases.

Childhood trauma was also associated with lower plasma levels of cortisol and cortisone, as highlighted by the nominal overrepresentation of the corticosteroid subpathway. Cortisol and cortisone are compounds released by the hypothalamic-pituitary-adrenal (HPA) axis in stressful situations. When such stressful situations remain chronic, long-term dysregulations of the HPA axis occur, possibly evoking various diseases (42). The lower levels of cortisol and cortisone linked to childhood trauma were mostly consistent with previous NESDA findings showing lower levels of the same markers in depression (17), although the previous cortisol association with depression was not statistically significant (Table S6). To evaluate whether the difference in statistical significance may indicate a vulnerability for depression after a history of childhood trauma, we ran post hoc analyses to test cortisol and cortisone differences between individuals with a history of childhood trauma (mild or severe) with depression versus no depression at baseline. Results showed no difference between individuals with depression and individuals without depression with a history of

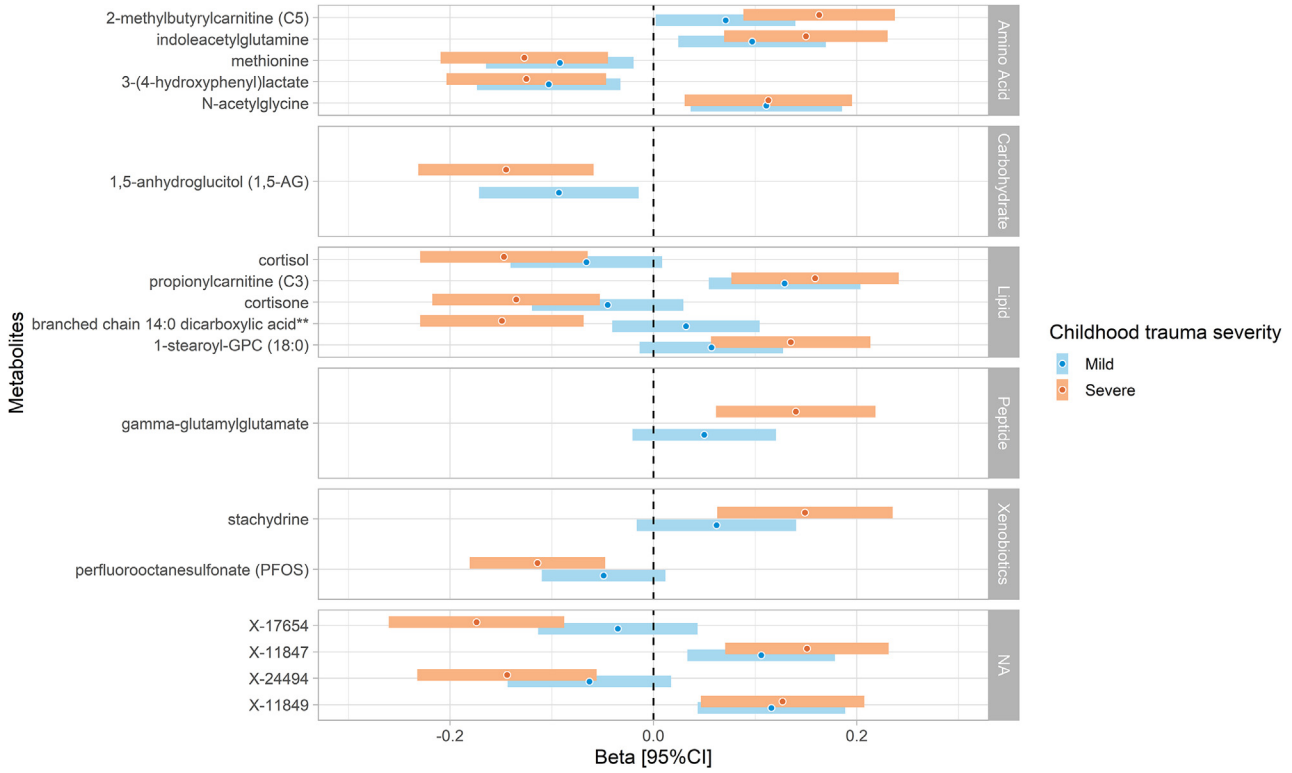

Figure 2. Forest plot of the associations of the childhood trauma severity groups (vs. no trauma) with the significant metabolite set at baseline and at the 6-year follow-up ($N_{participants}$ = 2902, $N_{observations}$ = 4800). Models were adjusted for age, sex, education, physical activity, smoking status, alcohol consumption, number of chronic diseases, shipment batch, and wave. Metabolites are ranked in descending order based on their associations' absolute effect sizes with the Childhood Trauma Index. The associations of the childhood trauma severity groups with all 820 metabolites can be found in Table S3. NA, no pathway assigned.

childhood trauma, challenging the hypothesis that discrepancies in cortisol and cortisone levels reflect a vulnerability to depression among people with a history of childhood trauma. Our findings are consistent with meta-analytic evidence that has highlighted blunted cortisol levels in blood samples of adults exposed to early-life stress (43,44). However, debate remains regarding the relationship of the HPA axis to childhood trauma and posttraumatic stress disorder (PTSD) (45) possibly due to the high variability of cortisol levels across time of the day, tissue (e.g., saliva, blood), and assay (46), warranting caution interpreting the findings.

Psychopathological, lifestyle, environmental, and somatic health factors may also play a role in the associations that we observed. Childhood trauma has been shown to be causally linked to depression, anxiety, and other psychiatric illnesses later in life (47), which may explain some of the metabolomic dysregulations that we observed. We found that the metabolomic signature of childhood trauma partially overlapped with the one observed for depression in the current sample (17). Elevated levels of short-chain acylcarnitines were linked to both depression and childhood trauma. Furthermore, overlap can be observed in the lysophospholipids: Childhood trauma was linked to elevated levels of 1-stearoyl-GPC, and the literature supports lysophospholipid dysregulations in depression (48,49), with a wide range of potential downstream health consequences from inflammation to nervous system development. Beyond this overlap, 6 metabolites were found to be uniquely associated with childhood trauma, which suggests that part of its metabolomic signature is independent of depression. For example, in our sample, childhood trauma was linked to downregulated metabolites nominally enriched with corticosteroids, whereas this was not true for depression (17). Instead, depression was associated with disruptions in long-chain saturated and monounsaturated fatty acids and hemoglobin and porphyrin metabolism, which were not found in childhood trauma, denoting their distinct metabolomic signatures. Additionally, PTSD may partially explain the metabolomic disruptions that have been observed in individuals with a history of childhood trauma. For example, previous studies have linked PTSD to reduced energy utilization and mitochondrial dysfunction (50), which are consistent with the observed disruptions associated with childhood trauma. However, a current clinically overt diagnosis of PTSD was an exclusion criterion in our sample selection procedure, which prevented us from evaluating its potentially mediating role in the tested associations. Other mechanisms that may explain the metabolomic associations of childhood trauma include lifestyle factors. Although the associations were controlled for smoking, alcohol consumption, and physical activity, diet was not accounted for and might have influenced the trauma-

related metabolomic signature. Adverse childhood events have been linked to poor diet quality (51) and eating disorders in adulthood, such as binge eating disorder (52), as well as behaviors such as increased comfort eating, which may contribute to malnutrition and metabolic disruptions consistent with the observed changes. The effects of the environment on the metabolome are also supported by alterations in xenobiotic levels. Remarkably, participants exposed to childhood trauma tended to have increased stachydrine and reduced PFOS levels. Stachydrine is a naturally occurring compound found in plants such as citrus fruits, which has shown health protective effects in cellular and animal models (53), although little is known about its effects in humans. PFOS is a man-made xenobiotic widely found in the environment due to its industrial use. The main source of exposure to PFOS in humans is diet, particularly the consumption of fish and other seafood (54). Perhaps the reduced PFOS levels in participants exposed to childhood trauma denote a lower socioeconomic status (55) linked to reduced fish intake (56). Finally, somatic health factors also appear to explain some of the metabolomic signatures of childhood trauma because subsequently adjusting associations for BMI and statin use resulted in a 12% average absolute change in effect sizes, although the statistical significance was maintained. Therefore, the interplay between childhood trauma, disease risk, metabolomic disruptions, and other risk factors is complex and dynamic and likely involves bidirectional effects. It has been hypothesized that childhood trauma initiates psychological, lifestyle, environmental, and biological dysregulations, including metabolomic changes, which influence each other and are linked in ways that promote disease development over time (57).

The current study has several strengths. First, it applied an untargeted platform to explore the metabolome of a large sample of males and females in relation to childhood trauma. Second, it evaluated the functional form of the metabolomic associations by observing metabolite levels across participants with no, mild, and severe childhood trauma. This categorization highlighted that metabolomic changes were most prominent in individuals exposed to severe childhood trauma, supporting the idea that intensity of stress exposure matters in long-lasting modulation of health-related biological processes as supported by the increased disease risk previously observed after severe, but not mild, childhood trauma (7). Although differences in metabolite levels were most statistically detectable for severe trauma, individuals with a history of mild trauma showed small metabolomic changes in a similar, but not statistically significant, direction (Figure 2), suggesting more subtle disruptions that may not directly translate into clinical risk. Third, the sample included individuals with and without an affective disorder, which enabled the comparison of the metabolomic signature of childhood trauma with the one of depression to specify their overlap versus uniqueness. Lastly, we conducted internal and external replication analyses. While the internal replication highlighted the robustness of the findings when another measure of childhood trauma was assessed 4 years later, the external replication in the siblings sample showed only moderately correlated effect sizes (r = 0.54). This may indicate the limited generalizability of our findings to clinical populations because the siblings had a lower rate of psychopathology than the main sample. The current study also has limitations. The sample mostly included Dutch participants of North-European descent, which limits the generalizability of the findings to other ethnicities. Additionally, we pooled different types of childhood trauma to obtain an overall trauma index. Although different types of traumas tend to co-occur (58), and their effects are therefore difficult to disentangle, they may be linked to distinct metabolomic disruptions (59) that should be investigated in future studies. Moreover, because individuals with affective disorders were oversampled in NESDA, there is a risk of selection bias. Similarly, individuals with overt clinical diagnoses other than affective disorders were excluded, which might have led to the sampling of individuals who were more resilient and/or had a history of less severe childhood trauma. As a mitigating measure, replication analyses were conducted in siblings, who were invited to partake in the study regardless of their psychopathology. The final limitation regards the relatedness of the participants in the main sample to their siblings in the external replication sample. Because of the shared genetic vulnerabilities and early-life familial environment, this replication was not fully independent.

Conclusions

Our findings uncovered the metabolomic signature of childhood trauma. The metabolome of individuals with such a history showed disruptions in fatty acid and amino acid metabolism as well as in HPA axis functioning, even decades after the trauma. These dysregulations, in turn, are likely involved in developing illnesses such as psychiatric and cardiometabolic diseases later in life. Having identified this metabolomic signature may help elucidate mechanisms that lead to disease in adulthood and potentially inform the development of early interventions to prevent the deterioration of health.

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