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# Metabolic syndrome after childhood trauma: a 9-year longitudinal analysis

Camille Souama[1,2], Yuri Milaneschi[1,2,3,4], Femke Lamers[1,2], Christiaan H. Vinkers[1,2,3,5,6], Erik J. Giltay[7], Edith J. Liemburg[8] and Brenda W. J. H. Penninx[1,2,3]

[1]Department of Psychiatry, Amsterdam UMC, location Vrije Universiteit Amsterdam, Boelelaan 1117, Amsterdam, The Netherlands; [2]Amsterdam Public Health, Mental Health Program, Amsterdam, The Netherlands; [3]Amsterdam Neuroscience, Mood, Anxiety, Psychosis, Stress, and Sleep Program, Amsterdam, The Netherlands; [4]Amsterdam Neuroscience, Complex Trait Genetics, Amsterdam, The Netherlands; [5]Department of Anatomy & Neurosciences, Amsterdam University Medical Center location Vrije Universiteit Amsterdam, 1081 HV Amsterdam, The Netherlands; [6]GGZ inGeest Mental Health Care, 1081 HJ Amsterdam, The Netherlands; [7]Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands and [8]Rob Giel Research Center, Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

## Original Article

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**Corresponding author:**
Camille Souama;
Email: c.p.souama@amsterdamumc.nl

## Abstract

**Background.** Childhood trauma (CT) has been cross-sectionally associated with metabolic syndrome (MetS), a group of biological risk factors for cardiometabolic disease. Longitudinal studies, while rare, would clarify the development of cardiometabolic dysregulations over time. Therefore, we longitudinally investigated the association of CT with the 9-year course of MetS components.

**Methods.** Participants ($N = 2958$) from the Netherlands Study of Depression and Anxiety were assessed four times across 9 years. The CT interview retrospectively assessed childhood emotional neglect and physical, emotional, and sexual abuse. Metabolic outcomes encompassed continuous MetS components (waist circumference, triglycerides, high-density lipoprotein [HDL] cholesterol, blood pressure [BP], and glucose) and count of clinically elevated MetS components. Mixed-effects models estimated sociodemographic- and lifestyle-adjusted longitudinal associations of CT with metabolic outcomes over time. Time interactions evaluated change in these associations.

**Results.** CT was reported by 49% of participants. CT was consistently associated with increased waist ($b = 0.32$, S.E. = 0.10, $p = 0.001$), glucose ($b = 0.02$, S.E. = 0.01, $p < 0.001$), and count of MetS components ($b = 0.04$, S.E. = 0.01, $p < 0.001$); and decreased HDL cholesterol ($b = -0.01$, S.E.<0.01, $p = .020$) and systolic BP ($b = -0.33$, S.E. = 0.13, $p = 0.010$). These associations were mainly driven by severe CT and unaffected by lifestyle. Only systolic BP showed a CT-by-time interaction, where CT was associated with lower systolic BP initially and with higher systolic BP at the last follow-up.

**Conclusions.** Over time, adults with CT have overall persistent poorer metabolic outcomes than their non-maltreated peers. Individuals with CT have an increased risk for cardiometabolic disease and may benefit from monitoring and early interventions targeting metabolism.

More than a third of the population reports a history of childhood trauma (CT), including emotional abuse and neglect, physical abuse and neglect, as well as sexual abuse (Redican, Murphy, McBride, Bunting, & Shevlin, 2022; Witt, Brown, Plener, Brähler, & Fegert, 2017). CT is a well-known risk factor for a broad range of health issues (Hughes et al., 2017; Petruccelli, Davis, & Berman, 2019; Sonu, Post, & Feinglass, 2019). Adverse childhood experiences are associated with 36% increased odds of cardiometabolic disease (Appleton, Holdsworth, Ryan, & Tracy, 2017; Danese & Tan, 2014; Jakubowski, Cundiff, & Matthews, 2018). Several connected pathways may explain the association between CT and cardiometabolic disease in adulthood. Biological mechanisms such as reduced sensitivity to cortisol, microbiome alterations, and low-grade inflammation, as well as behavioral mechanisms such as disrupted sleep and substance abuse likely play a role (Baldwin & Danese, 2019).

Metabolic syndrome (MetS) is a condition that consists of interrelated biological risk factors for cardiometabolic disease (Lakka et al., 2002). MetS includes hyperglycemia, abdominal obesity, hypertension, and dyslipidemia. Investigating the association between CT and MetS in adulthood is crucial as it may indicate specific metabolic dysregulations that can be targeted to preserve the metabolic health of individuals with a history of CT. The association between CT and metabolic dysfunction has been supported by cross-sectional findings (Carroll et al., 2013; Kisely, Siskind, Scott, & Najman, 2023; Lee, Tsenkova, & Carr, 2014; Nasca et al., 2019; Tosato et al., 2021), but its longitudinal relationship has been only sporadically investigated in

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adulthood (Midei, Matthews, Chang, & Bromberger, 2013; Power, Pereira, & Li, 2015), despite the potential to uncover clinically relevant patterns over time.

The few existing longitudinal studies showed that individuals with CT have a higher MetS incidence over 7 years in mid-adulthood (Midei et al., 2013) and faster body mass index gains in early- to mid-adulthood, but not in childhood (Power et al., 2015) compared to peers without CT. These findings suggest that individuals with a history of CT, compared to those without, undergo a faster metabolic worsening in adulthood. These studies also found differential associations per CT type with some evidence supporting the role of physical abuse only (Midei et al., 2013), whereas other additionally support the role of neglect and sexual abuse (Power et al., 2015). Moreover, it is still unclear whether CT is differentially associated with metabolic outcomes in males and females (Danese & Tan, 2014; Jakubowski et al., 2018; Midei et al., 2013). Since sex differences exist in MetS prevalence and etiology (Pradhan, 2014), these differences may also influence the association between CT and metabolic health. Additionally, CT is known to be highly prevalent in psychiatric patients (Chen et al., 2010; Hovens et al., 2010) and such patients are also at an increased risk of metabolic dysregulations (Penninx & Lange, 2018), possibly meaning that metabolic dysregulations in individuals with CT may be driven by psychopathology. Further longitudinal research is therefore needed to clarify whether and how (i.e. across sex, psychopathology status, and CT types) CT is associated with the course of cardiometabolic risk factors.

This study investigates whether CT is associated with metabolic outcomes over time and whether these outcomes deteriorate faster in individuals with a history of CT than in peers without CT. This research is conducted in the Netherlands Study of Depression and Anxiety (NESDA), a large observational case–control cohort study with an overrepresentation of persons with depression and anxiety. First, we hypothesize that individuals with CT have a higher count of clinically elevated MetS components and worse continuous levels of MetS components over time. Second, we expect that CT is associated with a faster deterioration of the metabolic outcomes over follow-up. These two hypotheses are tested in primary analyses. In secondary analyses, we explore (1) the extent to which CT severity is linked to the metabolic dysregulations over time, (2) the moderating role of sex and current psychopathology, and (3) the potential differential effect of CT type. In sensitivity analyses, we evaluate the consistency of results across two different CT measures and the potential confounding effect of antidepressants use in the longitudinal association of CT with metabolic outcomes.

## Methods

### Design and sample

This research project uses data from NESDA, a multicenter longitudinal observational case–control study investigating the long-term course of depressive and anxiety disorders in the Netherlands (Penninx et al., 2021). This study was approved centrally by the Ethical Review Board of the Vrije Universiteit (Free University) University Medical Centre (reference number 2003/183) in Amsterdam, The Netherlands, and locally by the participating research centers' review boards. Participants provided written informed consent. Between 2004 and 2007, 2981 individuals were recruited from community samples, primary care practices, and mental health organizations and participated in the baseline assessment. A total of 1701 individuals had a current diagnosis (within the last 6 months) of depression and/or anxiety disorder, 628 had a remitted depression and/or anxiety disorder, and 652 were healthy controls. The inclusion criterion was age between 18 and 65. Exclusion criteria were being diagnosed with other clinically overt psychiatric disorders (e.g. psychotic, bipolar, addiction disorders) and not being fluent in Dutch. Participants were re-invited for 2-, 4-, 6-, and 9-year follow-up assessments. For the current analyses, participants were included if they had available data on CT at baseline, and on at least one MetS component at baseline and at one or more follow-up moments, yielding 2958 participants.

### Measures

#### Childhood trauma

CT was assessed at baseline with the CT interview, a retrospective semi-structured interview that was used in the Netherlands Mental Health Survey and Incidence Study (De Graaf, Bijl, Smit, Vollebergh, & Spijker, 2002). It evaluates the presence and frequency of four dimensions of trauma before the age of 16: physical, emotional, and sexual abuse, and emotional neglect. Each trauma type receives a score ranging from 0 to 2. A cumulative score, the Childhood Trauma Index (CTI), is then computed (score range 0–8) to measure CT severity (Hovens, Giltay, Van Hemert, & Penninx, 2016; Wiersma et al., 2009). As used elsewhere (Kuzminskaite et al., 2020), participants were assigned to one of three CT severity groups for extreme group comparisons: no (CTI = 0), mild ($1 \leqslant$ CTI $\leqslant 3$), or severe CT ($4 \leqslant$ CTI $\leqslant 8$) (see online Supplementary section S1 for additional details on questionnaire items and scoring).

At the 4-year follow-up, the short version of the Childhood Trauma Questionnaire (CTQ-SF; Bernstein *et al.* 1994, 2003) was administered. We tested the consistency of the findings across instruments by repeating analyses with the CTQ-SF as a predictor. The CTQ, which is more commonly used than the CT interview to assess CT, has shown strong validity and reliability in clinical (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997) and community samples (Scher, Stein, Asmundson, McCreary, & Forde, 2001). However, the CTI was obtained at baseline, which enabled us to test associations in a larger sample than at the 4-year follow-up when the CTQ was administered. Therefore, the main analyses were conducted with the CTI while associations were compared across both instruments to assess their convergent validity. This also enabled to test the findings' reliability across waves, where the prevalence of current affective disorders decreased, checking for potential negative recall bias. The CTQ-SF contains 28 items among which 25 retrospectively measure five types of CT in childhood and adolescence: physical abuse and neglect, emotional abuse and neglect, and sexual abuse (see online Supplementary section S2). Each type of CT receives a score ranging from 5 to 25 and a total CT continuous score is computed (score range 25–125). The CTI and CTQ-SF have shown convergent validity in this sample and correlate moderately to strongly (Spearman's rank order correlation coefficients range between $\rho = 0.57$ and $\rho = 0.61$ depending on CT type) over a period of 4 years (Kuzminskaite et al., 2020; Spinhoven et al., 2014) and are therefore expected to give similar results.

#### Metabolic outcomes

Five MetS components were assessed at baseline, 2, 6, and 9 years of follow-up: waist circumference, triglycerides, high-density

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lipoprotein (HDL) cholesterol, blood pressure (BP), and fasting plasma glucose. Triglycerides, HDL cholesterol, and glucose levels were assessed from fasting blood samples analyzed using routine standardized laboratorial methods. As done previously (Révész, Milaneschi, Verhoeven, & Penninx, 2014; Van Reedt Dortland, Giltay, van Veen, Zitman, & Penninx, 2012), MetS components continuous measures were adjusted for the use of medication based on estimated effects. When participants used antidiabetics (Anatomical Therapeutic Chemical, ATC codes A10A*, A10B*, and A10X*) and had glucose levels <7.0 mmol/l, they were assigned a value of 7.0 mmol/l. When individuals used fibrates (ATC code C10AB), 0.10 mmol/l was subtracted from their HDL cholesterol levels and 0.67 mmol/l was added to their triglyceride levels. When individuals used antihypertensives (ATC codes C02A*, C02B*, C02C*, C02D*, C02K*, C02L*, and C02N*), 10 mmHg was added to their systolic BP and 5 mmHg to their diastolic BP. Waist circumference and BP were measured with anthropomorphic assessments. Waist circumference was measured with a measuring tape at the central point between the lowest rib and the highest front point of the pelvis, upon light clothing. Since pregnant women were originally included (pregnancy was not an exclusion criterion when NESDA participants were recruited), we removed the continuous measures of pregnant women's waist circumference from the sample (0.2% at baseline, 1.0% at the 2-year follow-up, 1.6% at the 6-year follow-up, and 0.5% at the 9-year follow-up). Waist circumference was specifically excluded because of the notable expansion of the uterus in pregnancy. Pregnancy may also affect other metabolic outcomes, but these were not removed from the dataset as such changes are expected to be more indirect (e.g. triggered by hormonal changes) and minor. Considering the percentage of pregnant women at each wave was small, removing them from the sample is unlikely to have had a substantial impact on the results. BP was measured twice during supine rest on the right arm with the Omron M4 IntelliSense (HEM-752A; Omron Healthcare, Inc. Bannockbrun, IL, USA) and was averaged over the two measurements.

In addition to continuous levels of individual MetS components, we calculated the count of MetS components scoring above a clinical threshold. We used the MetS diagnosis-adjusted criteria from the US National Cholesterol Education Program, Third Adult Treatment Panel (NCEP-ATP III; Grundy et al., 2005) to determine the clinical thresholds:

- Waist circumference is greater than 102 cm in men and 88 cm in women (pregnant women with a waist circumference higher than 88 cm were excluded from dataset).
- Triglyceride levels are higher than or equal to 1.7 mmol/l, or medication for hypertriglyceridemia is used.
- HDL cholesterol levels are lower than 1.03 mmol/l in men and 1.30 mmol/l in women, or medication for reduced HDL cholesterol is used.
- BP is greater than or equal to 130/85 mmHg, or antihypertensive medication is used.
- Fasting plasma glucose levels are superior or equal to 5.6 mmol/l, or anti-diabetic medication is used.

The resulting count variable ranges from 0 (no criterion is met) to 5 (all criteria are met).

### Covariates

All covariates were measured at baseline and included self-reported age, sex, years of education, and lifestyle. The latter included smoking status (dummy-coded variable: never [ref.], former, and current smoker), alcohol consumption (average number of alcoholic drinks per week) assessed with the Alcohol Use Disorders Identification Test questionnaire (De Meneses-Gaya, Zuardi, Loureiro, & Crippa, 2009; Saunders, Aasland, Babor, De La Fuente, & Grant, 1993), and physical activity over the previous week (metabolic equivalent total [MET]-minutes of vigorous, moderate, walking, and sitting activities) assessed with the short version of the International Physical Activity Questionnaire (IPAQ; Booth, 2000). The MET-minutes per week was calculated with the following formula (Craig et al., 2003):

$$\sum \text{MET minutes} = \sum (\text{MET level} \times \text{minutes of activity} \times \text{number of events per week})$$

### Moderators

Because depression and anxiety appear to be related to metabolic dysregulations (Penninx & Lange, 2018) and our sample has an overrepresentation of individuals with these disorders, we tested whether current psychopathology (absent *v.* present) moderated the relationship between CT and MetS components. Current psychopathology was defined as the presence of depressive (major depression and dysthymia) and/or anxiety (social phobia, panic, agoraphobia, and generalized anxiety) disorders within the last 6 months using the Composite International Diagnosis Interview version 2.1 (CIDI, Robins et al., 1988) according to the Diagnostic and Statistical Manual of Mental Disorders criteria (4th ed.; DSM–IV; American Psychiatric Association, 1994). Moreover, as the relationship between CT and metabolic health has earlier been found to differ for males and females (Danese & Tan, 2014), we assessed whether sex (males *v.* females) moderated the associations of CT with the various MetS components.

## Statistical analyses

All analyses were conducted in the program R version 4.0.5 (R Core Team, 2021). To carry out the linear mixed-effects models, we used the package 'lme4' (v1.1-33). An example of the R-script used for the primary analyses can be found in the online Supplementary section S3. We winsorized univariate outliers with values above the 99th percentile. Baseline descriptive statistics tested non-adjusted differences in the measures of interest between individuals with and without a history of CT.

For the primary analyses, we used longitudinal models to investigate whether the independent variable, CT, was associated with the trajectory of the dependent variables, the metabolic outcomes, over the follow-up period. To model the relationship between CTI and the count of MetS components with a score above a clinical threshold (fixed-effect slope) over the follow-up, we used a generalized linear mixed-effects model with a Poisson distribution, a random intercept at the subject level, and a maximum likelihood estimation method. To evaluate the relationship between CTI and the continuous levels of MetS components (fixed-effect slope) over the follow-up period, we used linear mixed-effects models with a Gaussian distribution, a random intercept at the subject level, and a maximum likelihood estimation method. To correct for multiple testing across MetS components, a false discovery rate (FDR) correction was applied to *p* values (six models). Specifically, the FDR correction was applied to the primary longitudinal models testing the continuous levels

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of the MetS components, and not to the secondary models nor the model testing the count of MetS components since the latter combines and overlaps with the continuous MetS outcomes. In all analytical models, we initially controlled for sociodemographic covariates (age, sex, and education) and in a second step we controlled for sociodemographic covariates as well as lifestyle factors (smoking status, alcohol use, and physical activity) to explore whether lifestyle adjustments may have explained the potential associations. We evaluated whether the associations between CT and MetS components remained consistent over time by testing the interaction term CTI-by-time in the fully adjusted (generalized) linear mixed-effects models. The variable time was coded as a factor reflecting the assessment wave when data were collected (levels: baseline, 2-year follow-up, 6-year follow-up, and 9-year follow-up). Time was dummy coded with baseline assessment as the reference level.

We also conducted secondary analyses. Because previous research suggests that only moderate/severe CT is associated with MetS symptoms (Lee et al., 2014), we carried out extreme-group comparisons with CT cases categorized as no *v.* mild *v.* severe CT. Additionally, we explored the moderating role of sex and current psychopathology by testing the CTI-by-sex and CTI-by-current psychopathology interaction terms in generalized linear mixed-effects models. The associations of different CT types with the metabolic outcomes were also tested conducting generalized linear mixed-effects models separately for each type of CT (physical abuse, emotional abuse, sexual abuse, and emotional neglect) as a predictor.

Finally, we carried out sensitivity analyses. To test the consistency of results across CT assessments, analyses were repeated in a sample with data available on both the CTI and the CTQ-SF ($n$ = 2299): once using the CTI and once using the CTQ-SF total score as a predictor. The CTI and the CTQ-SF total score were standardized to be able to compare effect sizes. Also, tricyclic antidepressants (TCAs), but not selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitor antidepressants, were found to be associated with MetS in NESDA (Van Reedt Dortland, Giltay, Van Veen, Zitman, & Penninx, 2010). Therefore, the potential confounding effect of frequent TCA use (ATC code N06AA) was evaluated by repeating the analyses on samples excluding TCA users.

## Results

Table 1 describes the baseline sample (67% female, average age = 41.8 years). Half of the sample reported no CT ($n$ = 1521) while the other half was split between mild CT ($n$ = 797) and severe CT ($n$ = 640). Females and older participants reported more CT than males and younger participants. Participants with CT differed from those without CT on several characteristics. For instance, those with more severe CT were more often smokers, had less years of education, more psychopathology, and an overall worse metabolic profile (larger waist circumference, slightly increased glucose, higher diastolic BP). MetS components at baseline were weakly to strongly correlated with each other (range [−0.09 to 0.79]; online Supplemental Table S1).

The primary analyses were based on 8038–9188 observations and showed that over 9 years of time, a higher CTI score was associated with higher waist circumference ($b$ = 0.32, S.E. = 0.10, $p$ = 0.001) and glucose levels ($b$ = 0.02, S.E. = 0.01, $p$ < 0.001), and with lower HDL cholesterol ($b$ = −0.01, S.E. < 0.01, $p$ = 0.020) and systolic BP ($b$ = −0.33, S.E. = 0.13, $p$ = 0.010; Table 2). The CTI was also associated with a higher count of MetS components scoring above a clinical threshold ($b$ = 0.04, S.E. = 0.01, $p$ < 0.001) over the follow-up. These associations remained statistically significant after FDR correction, and similar after additional adjustment for lifestyle, although the association with HDL cholesterol was not significantly different from zero anymore. We then assessed whether the association between the CTI and MetS components varied over time by evaluating the CTI-by-time interaction terms. Almost all associations in the fully adjusted (generalized) linear mixed-effects models were consistent over 9 years of time, and not increasing or decreasing, as indicated by statistically non-significant interaction terms (online Supplementary Table S2).

To illustrate these findings, Fig. 1 shows that participants with more severe CT consistently maintained a higher count of MetS components, waist circumference, and glucose level across assessments, as compared to subjects without CT. It seems that severe CT, but not mild CT, was associated with the metabolic outcomes (online Supplementary Table S3), since for most outcomes mild CT could not be distinguished from controls. These associations had overall small effect sizes (absolute Cohen's $d$ range [0.00–0.26] for mild *v.* no CT, and [0.02–0.39] for severe *v.* no CT; online Supplementary Table S4). Figure 1 also illustrates the statistically significant time interactions for systolic and diastolic BP, although the one for diastolic BP did not survive multiple testing correction. At baseline, participants with more CT had a lower systolic BP, while at the 9-year follow-up they had a higher systolic BP.

In secondary analyses, fully adjusted models showed no significant interaction between CTI and sex for any MetS component, except glucose ($b$ = −0.03, S.E. = 0.01, $p$ = 0.029, online Supplementary Table S5). Also, no interaction was found between the CTI and current psychopathology at baseline for any metabolic outcome, implying that the relationship between CT and metabolic deterioration over time is independent of initial depression and anxiety (online Supplementary Table S6). Longitudinal associations of the metabolic outcomes with specific types of CT in fully adjusted models showed, in general, the same direction across CT types (online Supplementary Table S7 and Fig. S1).

Sensitivity analyses carried out with the CTQ-SF as a predictor mostly showed consistent associations with the ones found when using the CTI as a predictor (online Supplementary Table S8). Although there were some differences in statistical significance level for some outcomes (the CTQ-SF, but not the CTI, was significantly associated with triglycerides and HDL cholesterol; and the CTI, but not the CTQ-SF, was significantly associated with systolic BP), effect sizes were of comparable order pointing toward the consistency of the two CT measures. Moreover, analyses carried out on a sample excluding individuals with frequent use of TCAs ($n$ = 79, online Supplemental Table S9) showed consistent results, suggesting that the inclusion of frequent TCA users did not bias the estimated associations.

## Discussion

The present study, based on a large-scale cohort, examined the longitudinal associations between history of CT and adult metabolic outcomes over 9 years. Our first hypothesis was supported since adults with a history of CT showed an overall worse metabolic profile over time. Our second hypothesis, however, was not supported by our findings since individuals with CT showed a consistently higher cardiometabolic risk which did not deteriorate

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**Table 1.** Descriptive statistics (means and standard deviations unless otherwise specified) of the sample at baseline ($n = 2958$)

| | No CT, $n = 1521$ (51%) | Mild CT, $n = 797$ (27%) | Severe CT, $n = 640$ (22%) |
|---|---|---|---|
| *Demographics* | | | |
| Sex, % | | | |
| Male | 39% | 28% | 27% |
| Female | 61% | 72% | 73% |
| Age, median (IQR) | 41 (28–52) | 43 (31–53) | 46 (36–54) |
| Years of education, median (IQR) | 12 (10–15) | 12 (10–15) | 11 (9–15) |
| *Childhood trauma* | | | |
| CTI, median (IQR) | 0 (0–0) | 2 (1–2) | 5 (4–6) |
| Physical abuse, % | 0% | 8% | 53% |
| Emotional abuse, % | 0% | 17% | 93% |
| Sexual abuse, % | 0% | 36% | 40% |
| Emotional neglect, % | 0% | 66% | 98% |
| *Metabolic outcomes at baseline* | | | |
| Count of clinical MetS components, median (IQR) | 1 (0–2) | 1 (0–2) | 1 (1–3) |
| Waist circumference (cm), median (IQR) | 87 (78–97) | 86 (78–96) | 90 (81–101) |
| Triglycerides (mmol/l), median (IQR) | 1.1 (0.8–1.5) | 1.1 (0.8–1.5) | 1.1 (0.8–1.7) |
| HDL cholesterol (mmol/l), median (IQR) | 1.6 (1.3–1.9) | 1.6 (1.3–2.0) | 1.6 (1.3–1.9) |
| Glucose (mmol/l), median (IQR) | 5.0 (4.6–5.4) | 5.0 (4.7–5.5) | 5.1 (4.8–5.6) |
| Systolic BP (mmHg), median (IQR) | 132.5 (122.0–147.5) | 131.5 (121.5–145.5) | 132.5 (122.0–147.5) |
| Diastolic BP (mmHg), median (IQR) | 81.2 (10.8) | 81.5 (10.5) | 83.0 (10.7) |
| *Lifestyle at baseline* | | | |
| Alcohol use, median (IQR) | 3.7 (0.2–8.7) | 3.7 (0.2–8.3) | 2.4 (0.2–8.2) |
| Smoking status, % | | | |
| Never smoker | 32% | 24% | 23% |
| Former smoker | 31% | 39% | 32% |
| Current smoker | 37% | 36% | 45% |
| Physical activity, MET-mn/week, median (IQR) | 2874.0 (1425.0–5155.5) | 2720.8 (1356.0–4882.9) | 2772.0 (1287.8–5134.1) |
| *Psychopathology at baseline* | | | |
| Current psychopathology | 47% | 63% | 73% |
| Current depressive disorder, % | 30% | 43% | 56% |
| Current anxiety disorder, % | 36% | 49% | 57% |
| Frequent TCAs use, % | 2% | 3% | 4% |

CT, childhood trauma; IQR, interquartile range; CTI, Childhood Trauma Index; MetS, metabolic syndrome; HDL, high-density lipoprotein; BP, blood pressure; MET, metabolic equivalent of task; TCAs, tricyclic antidepressants.
*Note*. Means and standard deviations are presented for continuous variables with a normal distribution, medians and interquartile ranges are shown for continuous variables with a skewed distribution, and proportions are described for count variables.

more rapidly than in those without CT but remained overall stably present over the entire follow-up period. Specifically, they had a higher count of MetS components, higher waist circumference, lower HDL cholesterol, and higher glucose. In contrast, the association of CT with systolic BP changed over time: although adults with a history of CT initially had a lower systolic BP, at the end of the follow-up they showed a higher systolic BP than their peers without CT. The results also support a dose–response association between CT and poorer metabolic outcomes, with the strongest associations observed for those with severe CT. Lifestyle did not appear to strongly contribute to the poorer metabolic outcomes in persons with CT, with the exception of HDL cholesterol whose association with CT became statistically non-significant after lifestyle adjustment. Findings were mostly similar for males and females and for those with and without psychopathology.

The longitudinal findings broaden the scope of the existing cross-sectional evidence linking CT to cardiometabolic risk factors (Danese & Tan, 2014; Flores-Torres et al., 2020). Individuals with CT had overall poorer metabolic outcomes at baseline than those without CT, and such differences remained stable over 9 years. Isolated evidence (Midei et al., 2013) conflicts

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**Table 2.** Main effects of CTI on metabolic outcomes in minimally and fully adjusted models

| | Model 1, minimally adjusted | | | | | Model 2, fully adjusted | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | *b* | S.E. | *p* | *q* | *n* | *b* | S.E. | *p* | *q* |
| Count of clinical MetS components | 2942 | 0.04 | 0.01 | **<0.001** | | 2747 | 0.04 | 0.01 | **0.007** | |
| Waist | 2955 | 0.32 | 0.10 | **0.001** | **0.003** | 2757 | 0.31 | 0.10 | **0.003** | **0.016** |
| Triglycerides | 2949 | 0.01 | 0.01 | 0.166 | 0.199 | 2752 | <0.01 | 0.01 | 0.586 | 0.586 |
| HDL cholesterol | 2950 | −0.01 | <0.01 | **0.020** | **0.031** | 2753 | <0.01 | <0.01 | 0.152 | 0.228 |
| Glucose | 2948 | 0.02 | 0.01 | **<0.001** | **0.003** | 2751 | 0.02 | 0.01 | **0.005** | **0.016** |
| Systolic BP | 2958 | −0.33 | 0.13 | **0.010** | **0.020** | 2760 | −0.30 | 0.13 | **0.022** | **0.045** |
| Diastolic BP | 2958 | 0.07 | 0.08 | 0.322 | 0.322 | 2760 | 0.05 | 0.08 | 0.544 | 0.586 |

*n*, sample size; *b*, regression coefficient; *q*, FDR-corrected *p* value; S.E., standard error; MetS, metabolic syndrome; HDL, high-density lipoprotein; BP, blood pressure.
*Note*. The minimally adjusted model, model 1, is adjusted for age, sex, and education. The fully adjusted model, model 2, is adjusted for age, sex, education, alcohol consumption, smoking status, and physical activity. All models have a random intercept at the individual level.

with our findings by showing no support of a cross-sectional association between CT and MetS at baseline in a sample of midlife women. Additionally, this evidence suggests that physical abuse (but not emotional nor sexual abuse) was linked to an increased MetS incidence over 7 years. Notwithstanding, the study was carried out in an exclusively female sample, a tenth of the size of NESDA and the authors did not report how CT across all types was linked to MetS incidence over time. Essentially, a large body of the literature supports the link between CT and metabolic abnormalities and indicate that CT-related metabolic abnormalities may have their onset in early to mid-adulthood (Noll, Zeller, Trickett, & Putnam, 2007; Power et al., 2015; Su et al., 2015). Taken together, these findings suggest that individuals with a history of CT, compared to their peers without CT, may undergo a faster metabolic deterioration in early to mid-adulthood, leading to a worse metabolic profile which stabilizes over time. Alternatively, individuals with CT possibly undergo a faster metabolic deterioration prolonged throughout adulthood, but this progression may require decades to become evident and may here be masked by the relatively limited assessed timespan. Systolic BP was the only metabolic outcome that was not stably worse after CT: compared to those without CT, participants with CT developed a higher systolic BP at the end of the follow-up. Similar results have previously been found (Su et al.,

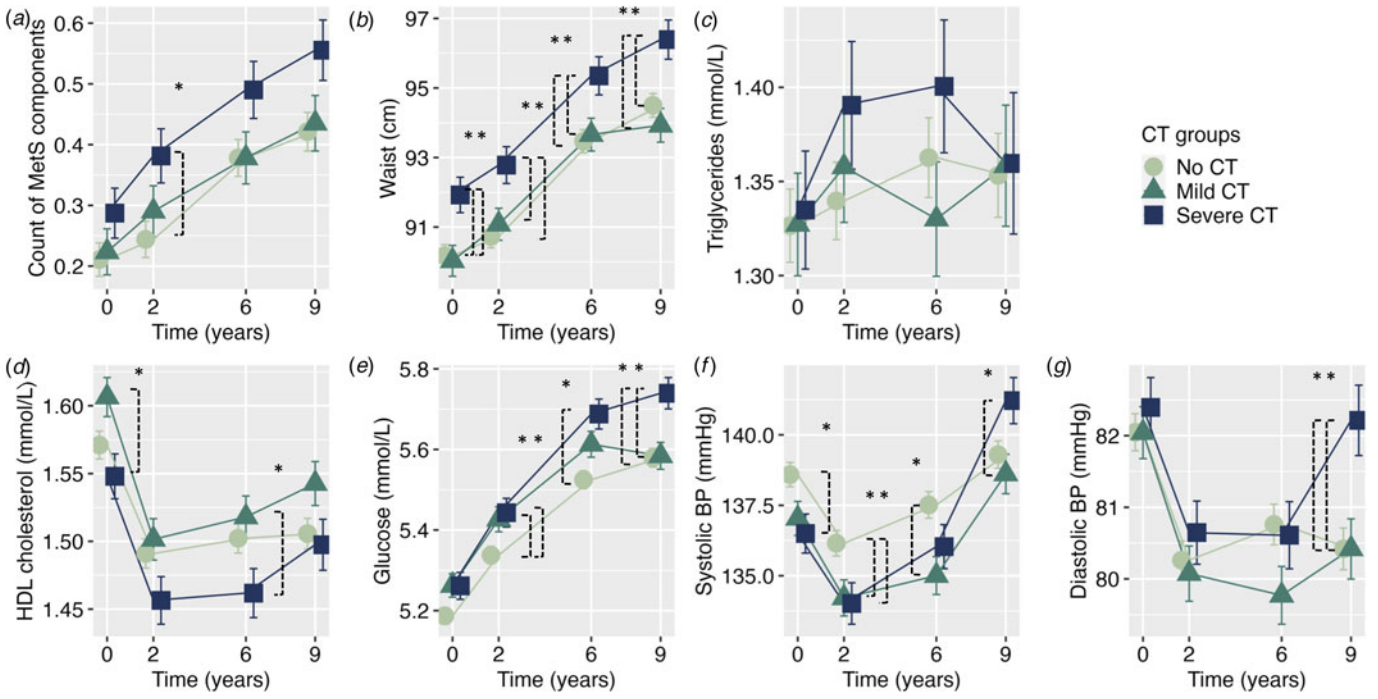


**Figure 1.** Estimated means and standard errors of (a) count of clinical MetS components, (b) waist circumference, (c) triglycerides, (d) HDL cholesterol, (e) glucose, (f) systolic BP, and (g) diastolic BP over time per CT severity group from fully adjusted models. CT, childhood trauma; MetS, metabolic syndrome; HDL, high-density lipoprotein; BP, blood pressure.
*Note*. Asterisks show statistically significant pairwise contrasts between CT groups at each timepoint. Standardized group mean differences can be found in online Supplementary Table S4.

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2015) where individuals who experienced multiple adverse childhood events (ACEs) had faster rises in BP compared to those without ACEs, but only in mid-adulthood.

Various pathways possibly explain the association found between CT and metabolic outcomes. Biological, behavioral, and psychological mechanisms likely link stress, including CT, to metabolic disorders (Kivimäki, Bartolomucci, & Kawachi, 2023). Suspected biological mechanisms involve increased glycemia and insulin resistance (Nasca et al., 2019; Tosato et al., 2021), immune dysfunction and increased inflammation (Crick et al., 2022), accelerated biological aging (Rentscher et al., 2019), and increased adiposity and changes in body composition (Danese & Tan, 2014; Hemmingsson, Johansson, & Reynisdottir, 2014). Additional recent evidence points toward the role of epigenetics through which the effects of CT would become biologically embedded to affect adult health (Womersley et al., 2021). Through DNA methylation, CT could upregulate the expression of stress-responsive molecules, contributing to cardiovascular risk (Zannas et al., 2019). Unhealthy behaviors such as alcohol consumption, reduced physical activity, smoking, and sleep disturbances may also play a role, although our results suggest that lifestyle does not fully explain the relationship between CT and metabolic outcomes. Psychological mechanisms such as depression, anxiety, or post-traumatic stress disorder have also been suggested to mediate the association between stress and metabolic abnormalities (Kivimäki et al., 2023).

Most associations found between CT and metabolic outcomes seem to be driven by severe CT. Previous findings also support this dose–response relationship between ACEs and cardiometabolic alterations in adulthood (Appleton et al., 2017; Hemmingsson et al., 2014). Although effect sizes remained relatively small (absolute Cohen's *d* range [0.02–0.39] when comparing no and severe CT), the associations of this early-life trauma with health outcomes decades later attest of its lifelong significance.

We explored the potential differentiating roles of sex and current psychopathology on the association of CT with metabolic outcomes. The results indicate that CT is associated with most metabolic outcomes similarly across sex and across persons with and without current depressive and/or anxiety disorders. Despite this overall pattern, one difference was found across sex: females with a history of CT appeared to suffer less from hyperglycemia than males with the same history. Although the reason for this difference is unknown, it could be a chance finding due to the high number of tests performed in exploratory analyses. Moreover, we found that the association between CT and metabolic outcomes did not significantly differ across individuals with *v.* without current depressive and/or anxiety disorders. Even assuming a stronger association in participants with psychopathology *v.* those without, the difference in these associations, unless very large, may be statistically difficult to detect with interaction terms with the present sample size.

Also, all CT types were found to be associated with at least one metabolic outcome. Since previous meta-analytical evidence shows no clear difference in the associations of physical, emotional, and sexual abuse with metabolic outcomes (Hemmingsson et al., 2014) and that CT types have different prevalence rates and tend to co-occur (Lee et al., 2014) making it hard to disentangle their single effects, differential effects of CT types should be interpreted cautiously.

Methodological strengths and limitations of the study should be considered. The study investigated the association between CT and various metabolic outcomes over 9 years. Moreover, the models carried out were each performed on more than 8000 observations. This great amount of data increases the precision and reliability of the association estimates. Additionally, recall bias has been suspected to influence retrospective self-reports of CT (Sheikh, Abelsen, & Olsen, 2016) and to be particularly present in depressed females (Bone, Lewis, Roiser, Blakemore, & Lewis, 2021). Nevertheless, we were able to confirm the consistency of findings with another CT measure that was assessed 4 years later, when fewer participants had a current disorder than at baseline, indirectly supporting a limited impact of psychopathology-related negative recall bias on the results. To overcome potential recall bias in future research, we suggest to compare findings across diverse populations and instruments (e.g. subjective *v.* objective measures, self-report *v.* informant-report) although these options' results should be interpreted collectively. Also, it is noteworthy that cardiometabolic disease is age-related (Sinclair & Abdelhafiz, 2020) and although the study investigates the intermediate phenotype of MetS, associations between CT and certain metabolic outcomes may remain undetected in this relatively young sample, with an average age of 41.8 years at baseline. We recommend that future research takes a lifelong approach to investigate metabolic alterations. Finally, the generalizability of our findings may be limited. Participants with severe psychiatric diagnoses other than affective disorders and non-Dutch speakers were excluded from our sample. Possibly, these criteria concurrently exclude some individuals with a history of severe trauma and/or a migration background. The validity of our findings should therefore be further investigated across different disorders and migration backgrounds.

In sum, the current study indicates that individuals with a history of CT have an overall poorer metabolic profile than their peers without CT. Despite worse metabolic outcomes, the pace of metabolic deterioration seems to be mostly similar across individuals with and without a history of CT. This implies that CT-related metabolic dysregulations may occur relatively early in life and remain chronic thereafter. These findings highlight the need for physicians to consider early-life stress, specifically CT, in assessing risk for cardiometabolic disease. Individuals with a history of CT may benefit from careful monitoring of metabolic deteriorations. This monitoring and potential early (preventive) interventions involving lifestyle and medication could help preserve the metabolic health of exposed individuals and may be more effective if provided early, before metabolic dysregulations emerge.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003264

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**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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