



Childhood maltreatment and risk of metabolic dysfunction-associated steatotic liver disease – Evidence of sex-specific associations in the general population

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ABSTRACT

Background and aims: Childhood maltreatment (CM) is linked to self-reported liver disease in adulthood. However, specific diagnostic entities, e.g., metabolic dysfunction-associated steatotic liver disease (MASLD) as the most frequent chronic liver disease, and sex-differences have previously not been considered.

Methods: Cross-sectional analyses were conducted in 4188 adults from a population-based cohort in Northeastern Germany after excluding individuals with excessive alcohol consumption, cirrhosis, or chronic viral hepatitis. CM-exposure was assessed using the Childhood Trauma Questionnaire (CTQ). Liver-related outcomes included serologic liver enzymes, fibrosis-4 score (FIB-4) and, in 1863 subjects who underwent magnetic resonance imaging examination, liver fat content. Sex-stratified linear regression and logistic regression models predicting liver-related outcomes and risk for MASLD, respectively, from overall CTQ scores were adjusted for age, school education, alcohol consumption, and waist circumference. Exploratory analyses investigated effects of CTQ-subscores on liver-related outcomes and risk for MASLD.

Results: In both sexes, overall CM-exposure was associated with higher levels of serum aspartate aminotransferase and FIB-4 score. In men, effects were mainly driven by physical abuse, and in women by emotional neglect. Only in men, overall CM-exposure ($\beta = 0.70$, 95%-CI 0.26–1.13, $p = 0.002$) and four CTQ-subscores were associated with greater liver fat content, and physical abuse (aOR = 1.22, 95%-CI 1.02–1.46, $p = 0.034$) and physical neglect (aOR = 1.25, 95%-CI 1.04–1.49, $p = 0.015$) were associated with higher risk for MASLD.

Conclusions: These results suggest sex differences in the association between CM and objective serum and imaging markers of MASLD in adulthood. For men especially, a history of CM-exposure may increase risk of developing MASLD in adulthood.

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1. Introduction

Childhood maltreatment (CM) refers to different forms of abuse (i.e., sexual, physical, emotional) and neglect (i.e. emotional and physical) during early developmental periods and represents a significant global public health burden [1]. CM is a well-established risk factor for a variety of adverse health outcomes across the lifespan [2–4], including mood disorders [5], type 2 diabetes (T2D), cardiovascular disease (CVD) [6,7], obesity [4,8], and liver disease [4,9]. Little attention has been paid to the specific association between CM-exposure and liver disease in adulthood, although some epidemiological data suggest an almost 3-fold increased risk in individuals with CM-exposure compared to unexposed individuals [4]. Further, CM-associated mood disorders are considered to play a key role in modulating both liver disease and the development of systemic metabolic disorders [10]. Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease (NAFLD), is characterized by an abnormal accumulation of hepatic fat ($\geq 5\%$ liver fat content) in the absence of excessive alcohol consumption [11,12]. MASLD is the most common chronic liver disease worldwide and its prevalence is projected to substantially increase in high-income countries, thus contributing to a considerable future disease burden [13]. MASLD may progress to more severe forms of hepatic disease (i.e., metabolic dysfunction-associated steatohepatitis [MASH], cirrhosis and hepatocellular carcinoma) [11], is comorbid with extra-hepatic disease (e.g., T2D, CVD, chronic kidney disease) [11], and is associated with increased all-cause mortality [14]. Given the increased risk of hepatic disease in CM-survivors [4,9] and the respective contributions of both CM-exposure and MASLD to poorer cardiometabolic health, a better understanding of their association may provide novel insights into CM-associated long-term risk. In this regard, it is noteworthy that only limited empirical evidence is available on this topic and several outstanding questions have not yet been addressed.

For instance, MASLD-related research has been criticized for an insufficient consideration of sex-related differences [15], despite the fact that prevalence, MASLD-related risk factors, metabolic disease mechanisms, and clinical outcomes show significant sex-differences [15,16]. Epidemiological data reveal an up to 3-fold increased prevalence of MASLD in men compared to women of reproductive age and a comparable prevalence in men and postmenopausal women, thereby suggesting a protective role of estrogens in liver fat metabolism [17]. In contrast, women show higher rates of overall CM-exposure [3,18] and single CM-subtypes, such as childhood sexual abuse, than men [19]. Further, conditions that are closely linked to MASLD, such as T2D [20], CVD [21], and obesity [8,22] show sex-dependent relationships with CM-exposure. For example, after CM-exposure, women have an increased risk of obesity [22] and CVD [21], while men are at higher risk of developing T2D [20]. As another limitation, the available literature on CM-associated liver disease has so far exclusively relied on subjective self-reports of unspecified liver disease [9,23]. There is no evidence for associations between CM-exposure and specific diagnostic entities of hepatic disease (e.g., MASLD) validated by diagnostic tools that are routinely used in clinical and/or research settings [4,9,23]. As a consequence, the pertinent literature lacks outcome specificity, the use of validated diagnostic procedures, and, through omission of sex-stratified analyses, may obscure potentially meaningful etiological pathways where both the exposure (i.e., CM) and outcome measures (i.e., MASLD) show important sex differences.

We therefore analyzed the association of self-reported CM-exposure with established serologic liver enzymes (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyltransferase [GGT]), non-invasive biomarkers of liver fibrosis (i.e., fibrosis-4 score [FIB-4]), as well as liver fat content through magnetic resonance imaging (MRI) [24] in a large, population-based cohort study in Northern Germany, the Study of Health in Pomerania (SHIP) [25]. In accordance with recent recommendations [26], we have disaggregated the analyses based on the self-reported sex of participants.

2. Materials and methods

2.1. Study population - the Study of Health in Pomerania (SHIP)

The present cross-sectional study is based on data from the population-based Study of Health in Pomerania (SHIP) which was conducted in Northeast Germany [27] in an ethnically homogeneous (i.e., Caucasian White) population. The study design and recruitment strategy have been described elsewhere [25,28]. Our analyses are based on data obtained from the second independent cohort, SHIP-TREND-0, established between 2008 and 2012 [25]. In brief, a stratified random sample of 8826 adults, aged 20 to 79 years, was selected from the population of West Pomerania, the north-eastern region of Germany. Participation in the first SHIP-cohort was an exclusion criterion. In total 4420 subjects participated in SHIP-TREND-0 (response 50.1%).

Of the 4420 individuals examined in SHIP-TREND-0, we excluded 173 subjects with missing data in the Childhood Trauma Questionnaire (CTQ), school education, or serum liver enzymes. We further excluded 59 individuals who we considered at high risk for liver-related abnormalities (i.e., >60 g/day of alcohol, cirrhosis, chronic viral hepatitis) resulting in a study population of 4188 subjects (2176 women; 52.0%) aged 20 to 84 years. Among them, 1863 subjects (968 women; 52.0%) underwent liver magnetic resonance imaging (MRI) examination (Fig. S1). All participants gave their written informed consent. The study was approved by the Local Ethics Committee of the University of Greifswald and followed the Declaration of Helsinki.

2.2. Childhood maltreatment

Participants provided self-reports about CM-exposure using the validated German version of the CTQ [29,30], an instrument to retrospectively assess early experiences of abuse and neglect. The CTQ captures five different types of CM: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. For each CTQ-subscale, five items are rated on a 5-point Likert scales (i.e., 1 = “never true” – 5 = “very often true”). Thus, each CTQ-subscale ranges from 5 to 25, with higher scores indicating higher CM-severity. Additionally, CTQ-sum score (range: 25–125) is indicating an overall CM-severity. For the main analyses, we used the CTQ-sum score as the primary exposure variable. Additionally, we performed secondary analyses using the CTQ-subscores to explore type-specific effects.

2.3. Laboratory assessment of serum liver enzymes

For laboratory examinations, fasting blood samples were drawn from the cubital vein in the supine position. Serum levels of liver enzymes, i.e., ALT, AST, and GGT were measured photometrically (Hitachi 704 and 171, Roche Diagnostics, Mannheim, Germany) [31]. The inter-assay coefficients of variations for serum ALT, AST and GGT levels were 4.2%, 3.9% and 3.9%, respectively. Serum liver enzyme concentrations were expressed as IU/L. The FIB-4 score was calculated using the following formula: age (years) $\times$ AST [U/L]/(platelets [10^9 /L] $\times$ (ALT [U/L])^{1/2}) [32].

2.4. Magnetic resonance imaging

Liver MRI examinations were performed by using a 1.5-Tesla MR imaging system (Magnetom Avanto, software version VB15; Siemens Healthineers Erlangen, Germany) with a 12-channel phased-array surface coil [33]. Three-dimensional chemical shift encoded gradient-echo data with three echoes and flyback readout gradient were acquired from an axial slab during a single 19-s breath hold. Imaging parameters included repetition time, 11 ms; echo times, 2.4, 4.8, and 9.6 ms; flip angle, 10°; number of signals acquired, one; bandwidth, ± 1065 Hz per pixel; matrix, $224 \times 168 \times 64$; field of view, 410×308 mm; parallel imaging effective acceleration factor, 1.8; and section thickness, 3.0

mm. Offline reconstructions of a proton-density fat fraction (PDFF) map (including correction for T1 bias and T2* decay) and a transverse relaxation rate (R2*) map (based on T2* decay measurement of PDFF) were performed [34]. Fat and water ambiguities were resolved by using the phase of the acquired data [34]. Parametric maps of PDFF and R2* were used for further analyses.

A single experienced radiologist who was blinded to participants' clinical details reviewed PDFF and R2* maps. Mean PDFF and R2* values were determined at operator-defined regions of interest placed at the center of the liver, by using Osirix (v3.8.1; Pixmec Sarl, Bernex, Switzerland). Care was taken when the regions of interest were placed to avoid blood vessels and regions that were obviously contaminated by partial volume effects and motion artifacts [33].

MASLD was defined as follows: MRI-PDFF >5% [34].

2.5. Covariates

Sociodemographic information and alcohol consumption was obtained through computer-assisted personal interviews [25]. Participants provided information about their age, sex, and years of school education. A categorical variable was then created for education indicating low (<10 years), medium (10 years), and high (>10 years) level of school education, according to the German school system. A school education of 10 years equivalent to Junior High School/ Middle School in the US, and an education of >10 is equivalent to graduating from High School. The average alcohol consumption over the past 30 days (in grams per day, g/d) was calculated by multiplying frequency and amount of alcohol from beer, wine, and spirits, respectively, using a standard ethanol content of 4.8 vol% in beer, 11 vol% in wine, and 33 vol% in spirits for conversion [31]. In accordance with WHO-recommendations [35], waist circumference was measured by trained study nurses with a flexible, non-stretchable graduated tape. Subjects were instructed to stand upright with the study nurse standing in lateral position behind the participants. To measure waist circumference the examiner palpated the iliac crest and the lowest rib at the lateral part of the body. Measurements were made in the middle of these two reference points. Finally, lifetime history of major depressive disorder (MDD) was assessed using a computerized version of the Munich-Composite International Diagnostic Interview (M-CIDI) [36], a standardized fully structured instrument to assess psychiatric disorders according to DSM-IV criteria [37]. The diagnostic interview was conducted by experienced clinical psychologists during face-to-face sessions between 2008 and 2012. A participant was classified as positive for lifetime MDD if he or she fulfilled the DSM-IV-based criteria [37] for MDD *at least once* during their lifetime.

2.6. Statistical analyses

Characteristics of the study population are presented stratified by sex as mean values ($\pm$ standard deviation) for continuous variables and as numbers and percentages for categorical variables. Tests for significant sex-differences are based on the Kruskal-Wallis tests for continuous variables and chi-squared tests for categorical variables, respectively. CTQ-sum scores and CTQ-subscores were associated with serum liver enzymes, FIB-4 score, and MRI-PDFF assessed liver fat content by linear regression models adjusted for age, school education, alcohol consumption, and waist circumference. As MASLD exhibits qualitative sex-dependent phenotypic differences and should thus be qualified as sexually dimorphic condition [16,38,39], all analyses were conducted disaggregated by sex in accordance with recent recommendations [40]. Adjusting for the abovementioned covariates, odds ratios and 95%-confidence intervals (95% CI) of the associations of total CTQ-sum scores and CTQ-subscale scores with risk for MASLD were derived from logistic regression models. A $p < 0.05$ was considered statistically significant. Multiple supplemental analyses were conducted, which included the following: a) intercorrelations of individual CTQ-scales as

well as liver-related outcomes, b) non-sex-stratified CTQ-sum scores x sex interactions for main outcomes, c) adjustment for multiple testing using the Bonferroni-method (Bonferroni-adjusted p -value = 0.004), and d) main regression models were additionally adjusted for lifetime MDD diagnosis.

All statistical analyses were conducted with Stata 17.0 (Stata Corporation, TX, USA).

3. Results

The final sample consisted of 4188 German adults who were included in the analyses. Sex-stratified descriptive data on study variables are shown in Table 1. Compared to men, women were slightly overrepresented (52.0%) and had a lower median age (51 years vs. 53 years). Significant sex-differences were observed for all liver-related outcomes (i.e., serum ALT, AST, GGT, AST/ALT ratio, FIB-4 score, and liver fat content on MRI-PDFF). With the exception of AST/ALT ratio, all liver markers were significantly higher in men than in women (all $p < 0.001$). The prevalence of MRI-based MASLD ($n = 1863$) was 46.9% for men and 32.4% for women ($p < 0.001$). We observed a small but significant sex-difference in the CTQ-sum score, with women reporting more severe overall CM-exposure compared to men ($p < 0.001$). Considering the CTQ-subscores, women reported a significantly higher severity of emotional and sexual abuse, while men reported a significantly higher severity of physical abuse as well as emotional and physical neglect (Table 1). Individual CTQ-scales as well as most liver-related outcomes show moderate to strong intercorrelations (Supplemental Tables S1 and S2).

3.1. Sex-specific associations of CTQ-sum scores and CTQ-subscores with serum liver enzymes, FIB-4 score, and liver fat content

In sex-stratified analyses, overall CM-exposure was significantly

Table 1
Characteristics of the study population stratified by sex ($n = 4188$).

	Men	Women	P-value ^a
N	2012 (48.0%)	2176 (52.0%)	
Age; years	52.18 (15.59)	50.87 (15.11)	0.006
School education			<0.001
Low (<10 years)	478 (23.8%)	451 (20.7%)	
Medium (10 years)	955 (47.5%)	1226 (56.3%)	
High (>10 years)	579 (28.8%)	499 (22.9%)	
Alcohol consumption; g/day	12.03 (12.96)	3.80 (5.68)	<0.001
Waist circumference; cm	97.29 (12.78)	85.02 (13.43)	<0.001
ALT; IU/L	32.00 (19.02)	21.68 (13.33)	<0.001
AST; IU/L	21.74 (11.79)	17.21 (8.61)	<0.001
GGT; IU/L	52.36 (58.08)	31.91 (29.43)	<0.001
AST/ALT ratio	0.76 (0.33)	0.88 (0.36)	<0.001
FIB-4	1.07 (0.79)	0.86 (0.54)	<0.001
MRI-PDFF Liver fat; %	7.21 (6.61)	5.86 (6.25)	<0.001
MASLD	420 (46.9%)	314 (32.4%)	<0.001
Lifetime MDD diagnosis	284 (14.1%)	497 (22.8%)	<0.001
CTQ-sum score	33.11 (8.37)	33.19 (10.47)	<0.001
Emotional abuse	6.00 (1.95)	6.45 (2.81)	0.003
Physical abuse	5.68 (1.69)	5.68 (2.10)	<0.001
Sexual abuse	5.08 (0.67)	5.35 (1.68)	0.005
Emotional neglect	9.21 (4.35)	8.85 (4.42)	<0.001
Physical neglect	7.19 (2.59)	7.02 (2.61)	0.008

Note: Data are expressed as means and standard deviation (continuous data) or in absolute numbers and percentages (categorical data) of sex-stratified subgroups. Hepatic steatosis was defined as MRI-PDFF >5%.

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTQ = Childhood Trauma Questionnaire; FIB-4 = fibrosis-4 score; GGT = Gamma glutamyl transferase; MASLD = Metabolic dysfunction-associated steatotic liver disease; MDD = Major Depressive Disorder; MRI = Magnetic resonance imaging; PDFF = proton-density fat-fraction.

^a p -values are based on the chi-squared test for categorical variables and the Kruskal-Wallis tests for continuous variables, respectively.

Table 2

Adjusted^a β -coefficients (95% confidence interval [CI]) of the sex-specific associations of CTQ-sum scores and CTQ-subscale scores with serum liver enzymes, fibrosis-4 score (FIB-4) and percentage of liver fat content (assessed by MRI-derived PDFF), and adjusted^b odds ratios (OR; 95% CI) of the sex-specific associations of CTQ-sum scores and CTQ-subscale scores with risk for MASLD.

	CTQ-Sum Score	Emotional abuse	Physical abuse	Sexual abuse	Emotional neglect	Physical neglect
β (95% CI), p-value						
Serum ALT (IU/L)						
Men	0.73 (−0.24; 1.69), 0.143	1.32 (0.29; 2.36), 0.013	0.63 (−0.30; 1.56), 0.185	−0.17 (−1.78; 1.42), 0.831	0.43 (−0.43; 1.28), 0.326	0.23 (−0.64; 1.10), 0.609
Women	0.51 (−0.01; 1.04), 0.055	0.40 (−0.09; 0.90), 0.111	0.14 (−0.37; 0.65), 0.597	0.22 (−0.21; 0.66), 0.319	0.92 (0.35; 1.48), 0.001	0.08 (−0.50; 0.66), 0.778
Serum AST (IU/L)						
Men	0.86 (0.24; 1.48), 0.007	0.93 (0.27; 1.59), 0.006	1.17 (0.58; 1.76), 0.000	−0.14 (−1.16; 0.88), 0.793	0.49 (−0.05; 1.03), 0.077	0.39 (−0.17; 0.94), 0.173
Women	0.57 (0.23; 0.91), 0.001	0.39 (0.06; 0.71), 0.019	0.26 (−0.07; 0.59), 0.129	0.06 (−0.23; 0.34), 0.692	0.87 (0.51; 1.24), 0.000	0.22 (−0.15; 0.60), 0.242
Serum GGT (IU/L)						
Men	2.72 (−0.33; 5.77), 0.080	2.25 (−1.01; 5.51), 0.177	4.18 (1.27; 7.09), 0.005	−0.12 (−5.15; 4.91), 0.962	1.69 (−0.99; 4.36), 0.216	0.64 (−2.09; 3.37), 0.647
Women	0.84 (−0.34; 2.01), 0.163	0.15 (−0.95; 1.26), 0.785	0.23 (−0.91; 1.36), 0.695	−0.04 (−1.00; 0.93), 0.938	0.98 (−0.28; 2.24), 0.129	1.31 (0.01; 2.60), 0.048
AST/ALT ratio						
Men	0.01 (−0.01; 0.02), 0.508	0.00 (−0.02; 0.01), 0.710	0.01 (0.00; 0.03), 0.127	−0.01 (−0.04; 0.02), 0.556	0.00 (−0.01; 0.02), 0.711	0.01 (−0.01; 0.02), 0.358
Women	0.01 (0.00; 0.03), 0.079	0.01 (0.00; 0.03), 0.081	0.01 (0.00; 0.02), 0.152	0.00 (−0.02; 0.01), 0.537	0.02 (0.00; 0.31), 0.058	0.00 (−0.01; 0.02), 0.852
FIB-4 score						
Men	0.04 (0.01; 0.08), 0.019	0.03 (−0.01; 0.07), 0.119	0.08 (0.05; 0.11), 0.000	0.00 (−0.06; 0.05), 0.883	0.02 (−0.01; 0.05), 0.262	0.02 (−0.01; 0.06), 0.139
Women	0.03 (0.01; 0.04), 0.002	0.02 (0.00; 0.03), 0.037	0.02 (0.01; 0.04), 0.005	0.01 (−0.01; 0.02), 0.361	0.03 (0.01; 0.05), 0.001	0.01 (0.00; 0.03), 0.128
Liver fat (%)						
Men	0.70 (0.26; 1.13), 0.002	0.81 (0.32; 1.30), 0.001	0.76 (0.34; 1.18), 0.000	1.17 (0.42; 1.92), 0.002	0.35 (−0.05; 0.75), 0.090	0.52 (0.10; 0.94), 0.016
Women	−0.21 (−0.52; 0.11), 0.193	−0.15 (−0.45; 0.14), 0.308	−0.15 (−0.47; 0.17), 0.362	0.06 (−0.22; 0.33), 0.681	−0.29 (−0.64; 0.07), 0.114	−0.18 (−0.55; 0.19), 0.336
OR (95% CI), p-value						
MASLD						
Men	1.19 (0.98; 1.43), 0.079	1.20 (0.98; 1.49), 0.084	1.22 (1.02; 1.46), 0.034	1.35 (0.94; 1.94), 0.104	1.00 (0.85; 1.19), 0.974	1.25 (1.04; 1.49), 0.015
Women	0.93 (0.79; 1.09), 0.369	0.99 (0.93; 1.05), 0.704	0.96 (0.82; 1.12), 0.618	0.93 (0.78; 1.10), 0.392	0.94 (0.78; 1.12), 0.485	0.88 (0.73; 1.06), 0.189

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CI = confidence interval; CTQ = Childhood Trauma Questionnaire; GGT = Gamma glutamyl aminotransferase; MRI = Magnetic resonance imaging; PDFF = proton-density fat-fraction; MASLD = Metabolic dysfunction-associated steatotic liver disease (MRI-PDFF >5% [34]).

^a β coefficients are derived from sex-stratified linear regression models adjusted for age, education, alcohol consumption, and waist circumference.

^b OR are derived from sex-stratified logistic regression models adjusted for age, education, alcohol consumption, and waist circumference.

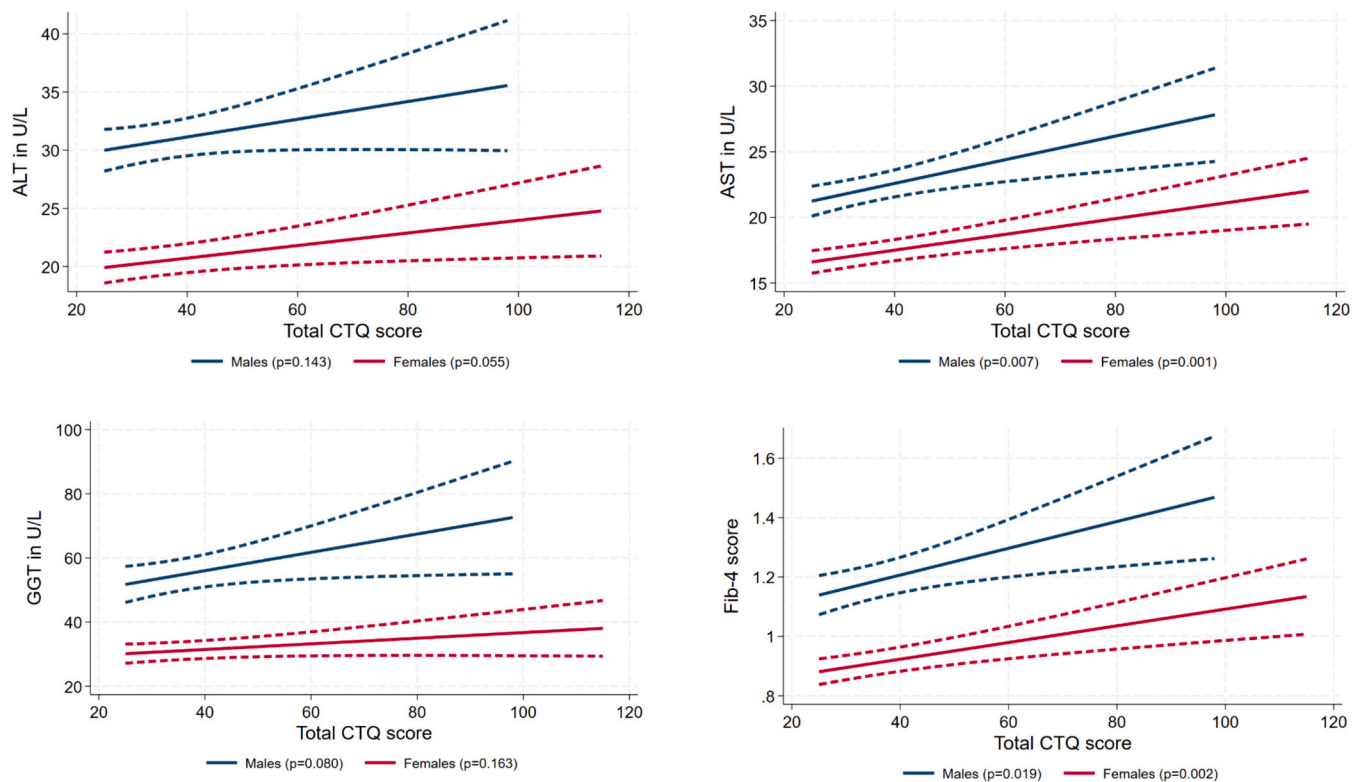


Fig. 1. Sex-stratified regression models for continuous CTQ sum scores and serum liver enzymes or FIB-4 score; all regression models are adjusted for age, education, alcohol consumption, and waist circumference.

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTQ = Childhood Trauma Questionnaire; FIB4- = fibrosis 4 score; GGT = Gamma glutamyl aminotransferase.

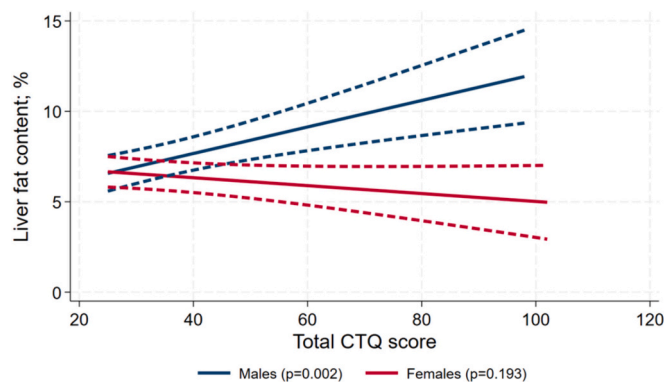


Fig. 2. Sex-stratified regression models for continuous CTQ sum scores and liver fat content on MRI-PDFF; all regression models are adjusted for age, education, alcohol consumption, and waist circumference.

Abbreviations: CTQ = Childhood Trauma Questionnaire.

associated with higher levels of serum AST and FIB-4 scores in both sexes (Table 2 and Fig. 1). In contrast, CTQ-sum scores were significantly associated with greater MRI-PDFF liver fat content only in men (Table 2 and Fig. 2). After Bonferroni-correction, associations between CTQ-sum scores and AST and FIB-4 scores remained significant only in women, while male-specific associations of CTQ-sum scores and liver fat content were also significant after adjustment for multiple testing (Table S5). In non-sex-stratified regression models, we found significant CTQ-sum scores x sex interactions only for liver fat content, but not for the other outcomes (Table S3). For the outcomes GGT and the Fib-4-score, however, the p -values were not far away from 0.1, which represents the cut-off for a significant interaction.

In men, all CTQ-subscores, except emotional neglect, were positively associated with liver fat content (see Table 2 and Fig. S3). These associations remained significant after Bonferroni-correction, except physical neglect (Table S5). Emotional abuse was further associated with serum ALT and AST levels (Fig. S2), but not after Bonferroni-correction (Table S5). Physical abuse was further associated with serum AST, GGT, and FIB-4 scores (Fig. S2 and S3). The association of physical abuse and serum GGT was not significant after Bonferroni-correction (Table S5).

In women, emotional abuse was positively associated with serum AST and FIB-4 score. Physical abuse was positively associated with FIB-4 scores, while sexual abuse was not associated with any liver-related outcome. Emotional neglect was positively associated with serum ALT, AST, and FIB-4 scores. Physical neglect was positively associated with serum GGT (Table 2 and Fig. S2 and S3). After adjustment for multiple testing, the associations of emotional and physical neglect, but not emotional or physical abuse with liver-related outcomes remained significant (Table S5).

After additional adjustment for lifetime MDD diagnosis, all reported results remained statistically significant at $p < 0.05$ (Table S4).

3.2. Sex-specific associations of CTQ-sum scores and CTQ-subscores with risk of MASLD

In men, physical abuse and physical neglect showed a significant positive relationship with the risk of having MASLD (assessed by MRI-PDFF). On the other hand, overall CM-exposure and the subscores emotional abuse, sexual abuse, and emotional neglect were not associated with a higher risk for MASLD. In women, overall CM-exposure and all five CTQ-subscores were not associated with a higher risk of MASLD (Table 2). None of these associations remained significant after Bonferroni correction (Table S5). Additional adjustment for lifetime MDD did not significantly alter the observed associations the observed

associations (Table S4).

4. Discussion

This large cross-sectional study aimed to explore associations between CM-exposure and established liver tests/ enzymes and markers of risk for MASLD in a community-based cohort of German adults with a particular focus on sex-differences. Analyses revealed that in both men and women increased levels of CM-exposure were associated with increased serum concentrations of AST and higher FIB-4 scores (a validated biomarker of liver fibrosis), with higher absolute values in men for both parameters. Positive associations between CM and MRI-assessed liver fat content were observed in men, but not in women.

Regarding the subtypes of CM-exposure, in men, physical abuse was the CTQ-subscale with the highest number of significant associations (i. e., with four out of six outcomes); emotional neglect (i.e., associations with three outcomes) in women. Regarding the liver-related outcome parameters, liver fat content on MRI-PDFF was the liver marker most consistently associated with CM-exposure in men (i.e., with the CTQ-sum score and four subscales) and the FIB-4 score in women (i.e., with the CTQ-sum score and three subscales). Finally, in men, but not in women, both physical abuse and physical neglect were associated with a modestly increased risk for MASLD. Taken together, these results indicate a pattern of associations characterized by complex interactions of CM-exposure and sex in predicting objective serum and imaging markers of risk for MASLD in adulthood.

To our knowledge, this is the first population-based study showing associations of overall CM-exposure and CM-subtypes with a range of established biomarkers of MASLD and liver fat content derived from laboratory and MRI examinations in a large sample of adult subjects. In contrast to a recent meta-analysis [4] showing an increased risk of self-reported liver disease in adults with multiple categories of CM and other adverse childhood experiences (e.g., parental substance abuse or mental illness) compared to unexposed individuals (adjusted OR = 2.76), we did not find a generally increased risk for MASLD, but only a moderate risk in men for specific forms of CM.

While all studies meta-analyzed by Hughes et al. [4] were adjusted for the possible confounding effects of sociodemographic variables including sex and age, we performed sex-disaggregated analyses that were subsequently adjusted for age, education, alcohol consumption, and waist circumference, and therefore revealed effects of CM independent of and beyond the effects of obesity and smaller amounts of alcohol. Notably, we also excluded participants with viral and alcohol-induced liver diseases to examine the more distinct diagnostic category MASLD, while former studies did not exclude these disease entities and used the generic term “liver disease” to include hepatitis and jaundice [9]. Dong et al. [9] showed that the association of CM with higher risk of self-reported liver disease was likely mediated by substance abuse (e.g., injected street drugs) and high-risk sexual activity (e.g., multiple sexual partners).

MASLD is considered the hepatic manifestation of the metabolic syndrome and likely reflects the consequences of health risk behaviors (e.g., unhealthy diet, physical inactivity) associated with impaired cardiometabolic health. While plausible, CM-liver associations remained significant after controlling for waist circumference and can therefore not be explained by CM-associated obesity. It has been shown in population-based studies that women and men differ in their cardiometabolic health after exposure to CM. Women appear particularly prone to obesity and CVD after CM [8,21,22], while men are more likely to develop T2D [20]. Our findings are consistent with these findings and suggest that CM-exposure may pose men at greater risk of developing MASLD in the long-term. For instance, and bearing in mind that increased liver fat content is an indicator of insulin resistance [16], this may suggest dysregulation in glucose-metabolism as one plausible male-biased pathway linking CM-exposure to the long-term risk of developing MASLD. Mechanistically, CM is associated with long-term dysregulation

of stress mediators [41,42], especially glucocorticoids. CM-associated alterations in stress-regulatory pathways may increase vulnerability to metabolic disorders [43] and could therefore contribute to increased lipid accumulation in the liver, possibly more so in men. Today it is accepted that men and women might be considered two different biological entities. Besides many different characteristics between men and women, one of the most important ones could be the different exposition to different sex hormones during the life course, which would lead to different cardiovascular and metabolic responses to the same exposition [16,17,38]. Sex hormones play an important role in hepatic and extra-hepatic lipid accumulation, and carbohydrate and protein metabolism [44]. Estrogens have a protective regulatory function in liver lipid metabolism, inhibiting lipogenesis and lipid uptake [45]. In addition to sex as a potential moderator in CM-associated cardiometabolic risk, age and menopausal status may be of particular interest in future research on CM-associated liver risk to improve prevention, diagnosis, prognosis, and treatment for MASLD in individuals exposed to CM.

We acknowledge several limitations of our study. First, our analytical approach was exploratory and results need to be further replicated in other independent studies, e.g. in ethnically diverse populations for greater robustness and generalizability. Second, individual CTQ-scales as well as most liver-related outcomes show moderate to strong intercorrelations. To achieve exposure-specific prediction by single subscales, we would have to adjust for all other subscales of the CTQ in the individual regression models. We have refrained from making this adjustment because of the risk of multicollinearity and subsequent variance inflation. Third, CM was measured by retrospective self-report which, even though it may introduce reporting bias, non-disclosure, and recollection errors [46,47], remains irreplaceable in research on long-term health consequences associated with CM [47] for practical reasons. Fourth, we chose to investigate CM-associations using the FIB-4 score as liver-related outcome. The FIB-4 has been validated to non-invasively measure liver fibrosis in patients with established MASLD [48]. However, others have also found that an increased FIB-4 score is associated with liver-related and all-cause mortality in the general adult population [49,50] thus justifying its use in population-based cohort studies. Fifth, participation in the MRI examination was voluntary and possibly healthier subjects were more willing to participate. Finally, after adjustment for multiple testing, some of our previously statistically significant results did not remain significant. However, the considered liver parameters are not independent of each other and overall we had the two general hypotheses that CM is associated with liver markers in men and in women. Due to the correlation of the liver markers, our analyses cannot be compared to hypotheses-free approaches such as genome-wide association analyses, in which indeed correction for multiple testing is mandatory. In hypothesis-driven analyses, it is more important to look at the pattern of the associations than just applying an arbitrary cut-off for significance.

A major strength of our study is the use of serological markers of liver function that are routinely used in clinical practice and the assessment of liver fat content through MRI-based PDFF, which is considered the gold standard for the non-invasive measurement of liver fat [51]. We further controlled for important confounders that have been related to MASLD-risk, including age, education, central obesity, and alcohol consumption, while excluding subjects with other liver conditions such as cirrhosis, chronic viral hepatitis, or excessive alcohol consumption. Given the sexually dimorphic nature in MASLD [15,16], we propose that our sex-sensitive analyses are likely more appropriate for the research question than merely adjusting for sex as a covariate. Sex is not a “covariate” but instead a major modifier of health, disease, and medicine [52]. The American Heart Association has recently published a scientific statement encouraging systematic identification of mechanisms linking CM-exposure and compromised cardiometabolic health in adulthood [53]. In particular, the authors stated the need to consider sex-specific pathways in this context in order to tailor effective prevention and intervention efforts within the framework of Personalized Medicine. We

believe that the results of our population-based study comply with this demand and may be helpful in the identification of CM-exposed individuals with increased risk of MASLD, which continues to represent an increasing global public health issue. Regarding treatment efforts of MASLD, so called “cofactors” of MASLD have come into focus with the aim to identify more homogenous patient subgroups [54,55]. CM might be considered a previous condition potentially predisposing people to being less likely to adopt healthy lifestyle habits. As a consequence, MASLD patients with a history of CM-exposure may profit from specific therapeutic approaches, such as psychotherapeutic treatment and/or psychopharmacological treatment of affective symptoms [56] in addition to pharmacological treatment of MASLD.

CRedit authorship contribution statement

Ulrike Siewert-Markus: Writing – review & editing, Writing – original draft, Conceptualization. **Till Ittermann:** Writing – review & editing, Supervision, Investigation, Formal analysis, Conceptualization. **Johanna Klinger-König:** Writing – review & editing, Methodology. **Hans J. Grabe:** Writing – review & editing, Supervision, Methodology, Data curation. **Sylvia Stracke:** Writing – review & editing, Supervision. **Henry Völzke:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation. **Giovanni Targher:** Writing – review & editing, Supervision. **Marcus Dörr:** Writing – review & editing, Supervision. **Marcello R.P. Markus:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization. **Philipp Töpfer:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychores.2024.111829>.

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