# A History of Childhood Maltreatment Has Substance- and Sex-Specific Effects on Craving During Treatment for Substance Use Disorders

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**Rationale:** Childhood maltreatment (CM) leads to detrimental mental health outcomes, such as substance use disorders (SUD). This study examined prevalence and severity of all five types of CM with respect to specific substances and sex in treatment-seeking individuals with SUD. The influences of type of CM and symptoms of depressiveness, anxiety, and perceived stress on substance craving at admission as well as craving reduction during SUD treatment were examined.

**Methods:** $N = 546$ patients in treatment for SUD and $N = 109$ individuals in opioid maintenance treatment filled out questionnaires regarding CM (Childhood Trauma Questionnaire) and psychopathologies. Substance craving was assessed throughout treatment using the Mannheim Craving Scale. Group differences in CM, type of substance and sex were examined. General linear models were applied to examine influences on substance craving.

**Results:** Higher prevalence and severity of all five subtypes of CM were observed in individuals with SUD compared to the general population. Women were more severely affected by emotional and sexual abuse than men. Patients with cannabis use disorder reported more severe experiences of emotional abuse compared to all other substances. Craving at admission to treatment was influenced by emotional abuse, however, symptoms of depressiveness, anxiety, and perceived stress contributed to craving at admission or craving reduction during treatment.

**Conclusion:** CM relates to SUD and should be incorporated in prevention and treatment of SUD. Underlying mechanisms of the association might relate to impairments in processing and regulation of stress, emotions, and interpersonal relations following a history of CM.

Keywords: childhood trauma, addiction, sex differences, substance craving, substance use disorder, perceived stress, addiction treatment

## INTRODUCTION

A variety of studies examined the consequences of adverse childhood experiences (ACE) that are related to the development of somatic and mental disorders (1). ACE are defined as household dysfunction but also childhood maltreatment (CM) (2, 3). Specifically, CM is operationalized as emotional, physical, and sexual abuse as well as emotional and physical neglect (4). A history of CM is related to the age of onset and severity of subsequent mental disorders, and reduces treatment response (4–9).

In Europe, high prevalence rates of CM have been reported for the general population: 29.1% for emotional abuse, 22.9% for physical abuse, 13.4% (female) and 5.7% (male) for sexual abuse, 16.3% for physical neglect and 18.4% for emotional neglect (10). Figures for Germany are comparable, between 6.5% for at least moderate emotional abuse and 22.4% for at least moderate physical neglect (11).

A history of CM is frequently observed in individuals with substance use disorders (SUD) (12–16). It increases the risk of developing a SUD (13, 17–19), and this extends also to non-substance use disorders such as problematic and pathological gambling (20, 21). Compared to the general population in Germany (22), individuals with SUD have experienced more severe forms of CM (23). For example, the prevalence in individuals with opioid use disorder (OUD) ranges between 16% for sexual abuse in men and 43% for emotional abuse (15).

Since prevalence number of SUD and relapse rates after SUD treatment are high [e.g., (24–26)], examining factors contributing to the development and maintenance of SUD are still of importance. A stable, mostly correlational, relation has been observed between CM and different kinds of SUD even after correction for comorbid psychiatric disorders and sociodemographic variables (27). The age of drinking onset was 1 year earlier in individuals with CM (28). Furthermore, exposure to several CM predicted SUD in young adults, irrespectively of sociodemographic variables (e.g., sex or ethnicity) and after controlling for prior mental disorders (29). Similarly, a cumulative effect of the number of types of CM events was observed regarding the severity of alcohol use disorder (AUD) (30). Regarding all five sub-types of CM, emotional abuse is the strongest predictor for the severity of AUD, followed by physical abuse (31). Further, women with CM, compared to women without CM or men, were observed to have a shorter timespan between onset of drinking and AUD and lower rates of abstinence after AUD treatment were associated with CM (28, 32). Contributing to this relation, it has been observed, that the association between cumulative CM and SUD was partly mediated by mood- and anxiety disorders that preceded SUD (33).

Besides CM being associated with SUD, substance craving contributes to relapse (34–37) and, thus, maintenance of the disorder. Further, an effect of stress on substance craving was observed for methadone (38), cocaine (39), or alcohol (40), possibly linking CM, if seen as early life stress, to craving and relapse (41).

Despite the above-mentioned impact of CM on characteristics of SUD, to our knowledge no study examined CM in individuals seeking treatment for SUD while directly comparing different SUDs, investigating sex effects, or addressing the influence of the type of CM on substance craving.

Within the current project we hypothesized that (1) in individuals with SUD, prevalence of all forms of CM is higher in individuals with OUD compared to all other substances; that (2) the severity of CM is strongest in individuals with OUD compared to all other substances. For both (1, 2) women are more severely affected than men. We further hypothesize that (3) in SUD, the severity of CM is positively associated to the severity of depressive and anxious symptoms, and perceived stress; that (4) emotional abuse followed by physical abuse are predictors for the severity of craving at admission to SUD treatment; and that (5) experiences of emotional abuse and physical abuse hamper the decrease of substance craving during SUD treatment while sex and type of SUD but not age exert an effect on the latter two relationships (hypotheses 4 and 5).

## MATERIALS AND METHODS

### Procedure and Participants

The aggregated dataset ($N$ = 655 individuals) derives from two sources. Firstly, between 2016 and 2020, individuals with different kinds of SUD ($N$ = 546, sample 1) participated in a questionnaire-based examination during their treatment in the Clinic of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Mannheim, Germany. In either an inpatient or a day care setting they received a detoxification and a psychological SUD-related treatment including motivational and cognitive behavioral elements with the goal of continuous abstinence (42). SUD patients filled out several questionnaires at admission and once weekly during the treatment period of 24 ± 9.7 days. In case of repeated admissions during the data collection period of 2016 and 2020, the most recent admission time point was chosen. Diagnoses of substance addiction and additional comorbid mental disorders were made by trained medical staff following the International Classification of Diseases (ICD-10). Regarding SUD as described in the Diagnostic and statistical manual of mental disorders, 5th version (DSM-5) (43), substance addiction corresponds to moderate to severe SUD (44).

Secondly, data ($N$ = 109, sample 2) from a research project including outpatients of the opioid maintenance treatment (OMT) of the Central Institute of Mental Health, Mannheim, were included to enrich the first dataset with individuals suffering from OUD. Data collection and diagnostic procedures also were performed by trained medical staff and a senior psychiatrist. A study description of sample 2 has previously been published (45).

For all individuals (samples 1 and 2), general inclusion criteria were: age over 18 years, sufficient knowledge of the German language (oral and in writing), main diagnosis of SUD and availability of data regarding the CM. Please see **Supplementary Figure 1** for details of the data collection, preparation and allocation process.

The local Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Germany, approved the here presented study procedures (approval number 2018-531N-MA and 2018-807R-MA). Information for the first dataset (sample 1) was collected during the patients' inpatient treatment for clinical purpose and later used for retrospective analyses. Following the recommendation of the ethics committee to protect data privacy the data set was anonymized. Regarding the second dataset (sample 2), in accordance with the Declaration of Helsinki, all participants provided written informed consent prior to study participation.

## Measures

As the focus of this study, all five sub-types of CM, namely emotional, physical, and sexual abuse as well as emotional and physical neglect, were assessed retrospectively using the reliable ($0.87 <$ alpha $< 0.95$) childhood trauma questionnaire (CTQ), a previously validated self-report questionnaire that addresses the childhood up to the age of 18 years (46). All items of the German version were answered on a 5-point Likert scale ("not at all" to "very often") leading to sum scores between 5 (no CM) and 25 (severe form of CM) for each subscale, respectively (23). As reported by others (11, 47, 48), the severity of each subscale of CM was additionally described by aggregating the CTQ score for each subscale separately into none-minimal, minimal-moderate, moderate-severe and severe-extreme. Further, prevalence was calculated following Witt et al. (11). To do so, all subscales of the CTQ were dichotomized into "having experienced this form of CM" including moderate to extreme CM and "not having experienced this form of CM" including none to moderate CM. The number of overall CM was calculated by summing up affirmed, dichotomized CTQ subscales.

To characterize sample 1 ($N = 546$), besides assessing the main diagnosis of SUD and sociodemographic variables (e.g., age, gender, employment, marital status, and education), additional questionnaires were administered. The CTQ, Perceived Stress Scale (PSS) (49), and Fagerstrom Test for Nicotine Dependence (FTND) (50) were administered only once, at least 1 week after admission. The Beck Depression Inventory (BDI) (51, 52), Beck Anxiety Inventory (BAI) (53), and Mannheimer Craving Scale (MACS) (54) were administered at admission and every 7 days during treatment. The MACS retrospectively measures overall craving during the last 7 days independent of the substance and has shown to be highly reliable ($0.87 <$ alpha $< 0.93$). MACS was applied at admission, after 1 and 2 weeks (at T01, T07, and T14), respectively. The reduction of craving after 2 weeks as the difference T01 minus T14 was used to address the course of the treatment. Regarding sample 2 of $N = 109$ OMT individuals, the same sociodemographic variables were assessed and the CTQ was administered.

## Analyses and Statistics

The main SUD diagnosis was grouped into six categories: alcohol use disorder (AUD), cannabis use disorder (CUD), cocaine and stimulant use disorder (CSUD), sedative, hypnotics, or anxiolytic use disorders (SHA), opioid use disorder (OUD, sample 1 only), and opioid use disorder during opioid maintenance (OMT; sample 2 only). OMT and OUD samples were compared using independent samples $t$-tests and chi-square tests including available data for both samples to justify merging both data sets (samples 1 and 2, OUD + OMT) analyses including the CTQ (see **Supplementary Material**).

A sample description was created, and group differences were examined using analyses of variance (ANOVA) or Welch-Test for continuous data, and chi-square tests for dichotomous data. *Post hoc* tests included Tukey's or Games–Howell tests for ANOVAs and Welch-Tests. Adjusted $z$-scores and a transformation into $p$-values were performed using chi-square tests according to García-pérez and Núñez-antón (55). Further, the total number of additional SUD diagnoses and a dichotomous item on comorbid mental disorders (yes/no) were calculated. Relevant clinical variables (i.e., CM, substance craving, and symptoms of depressiveness or anxiety, perceived stress) were correlated pairwise (Pearson correlation) to assess bi-directional relations within the overall sample and separated by sex. General linear models (GLM, univariate) were used to assess the influences of CM and clinical variables (i.e., symptoms of depressiveness or anxiety, perceived stress) as well as sociodemographic variables (i.e., age and sex) on the SUD outcome (i.e., substance craving at admission, reduction of craving over the first 2 weeks of treatment). Descriptive and statistical analyses were performed in SPSS (Statistics for Windows, Version 27.0, IBM Corp., Armonk, NY, United States). To counteract multiple testing problems and following Storey (56) false discovery rate (FDR) using the Benjamini and Hochberg method was applied when adequate and results were reported when surviving the correction ($p < 0.05$).

## RESULTS

## Sample Composition

Out of $N = 1,599$ data sets, $N = 804$ data sets with information regarding the CTQ questionnaire (50%) were available. After excluding duplicate data sets due to readmission ($N = 78$) and individuals without a main diagnosis of SUD ($N = 72$), $N = 655$ data sets were available for subsequent analyses (41%), see flow-chart in the **Supplementary Material**. Between January 2016 and December 2020, $N = 655$ individuals provided information regarding the CTQ and additional questionnaires. Data were collected from the day care clinic ($N = 391$), the inpatient treatment ($N = 136$) and the outpatient opioid maintenance program ($N = 109$).

Participants were between 18 and 86 years of age (mean $= 42.0 \pm 13.0$). They were mostly male (73.3%), single (51.0%) and had no children (40.9%). They received primary and secondary education of 12.8 years, but more than half were currently not steadily employed (57.4%). The majority of participants were tobacco smokers (74.8%). In sample 1, 66.7% ($N = 364$) were diagnosed with AUD as the main diagnosis, 21.6% ($N = 118$) with CUD, 7.8% ($N = 43$) with CSUD, 2.2% ($N = 12$) with SHA, and 1.6% ($N = 9$) with OUD, respectively. Sociodemographic and clinical variables differed between substance groups. See **Tables 1**, **2** for more details regarding sociodemographic and clinical information.

**TABLE 1 |** Sociodemographic data of the overall sample.

| | AUD | CUD | CSUD | SHA | OUD + OMT | Descriptive statistics |
|---|---|---|---|---|---|---|
| N | 364 (55.6%) | 118 (18.0%) | 43 (6.6%) | 12 (1.8%) | 118 (18.0%) | 655 |
| Age | **47.23 (12.66)[1,2,3]** | **28.6 (7.5)[1,4,5,6]** | **33.3 (7.2)[2,4,7,8]** | **42.9 (9.7)[5,7]** | **42.1 (8.1)[3,6,8]** | $F_{(4,68.6)} = 103.59, P < 0.00$ |
| Gender (male, %) | 74.2 | 73.7 | 74.4 | 58.3 | 71.2 | $\chi^2(4) = 0.90, p = 0.824$ |
| Family status (single yes, %) | 37.6 | 78.0 | 69.8 | 50.0 | 65.7 | **$\chi^2(4) = 69.30, p < 0.001$[a]** |
| Children (yes, %) | 42.0 | 22.9 | 32.6 | 28.6 | 46.5 | $\chi^2(4) = 16.38, p < 0.001$[a] |
| Years of education | **13.5 (2.7)[1,2,3]** | **12.4 (2.6)[1,4]** | **12.2 (2.6)[2]** | 13.8 (2.9) | **11.3 (2.4)[3,4]** | $F_{(4,561)} = 14.90, p < 0.001$ |
| Employed (yes, %) | 36.8 | 31.4 | 23.3 | 22.2 | 19.7 | **$\chi^2(4) = 22.60, p < 0.001$[a]** |

*Mean values (standard deviation) or percentage values are displayed. Group differences are highlighted. N, total sample size; AUD, alcohol use disorder; CSUD, cocaine and stimulant use disorders; CUD, cannabis use disorder; SHA, sedative, hypnotics, or anxiolytic use disorders; OUD + OMT, opioid use disorders + opioid maintenance treatment.* [1,2,3,4,5,6,7,8]*Superscripted numbers describe significant group differences following post hoc tests.* [a]*Following post hoc testing including correction for multiple comparison, no statistically significant group-differences emerged. Significant results are highlighted in bold.*

**TABLE 2 |** Clinical data of sample 1.

| Sample 1 | AUD | CUD | CSUD | SHA | OUD | Descriptive statistics |
|---|---|---|---|---|---|---|
| N | 364 | 118 | 43 | 12 | 9 | 546 |
| Type of stay (inpatient:day care-clinic, %) | 26.9:73.1 | 21.2:78.8 | 20.9:79.1 | 58.3:41.7 | 44.4:55.6 | **$\chi^2(4) = 9.70, p = 0.021$[a]** |
| Mental comorbidities, current (yes, %) | 47.5 | 51.7 | 48.8 | 66.7 | 88.9 | $\chi^2(4) = 7.72, p = 0.103$ |
| Mental comorbidities, lifetime (yes, %) | 56.6 | 56.8 | 55.8 | 75.0 | 88.9 | $\chi^2(4) = 5.33, p = 0.255$ |
| Total number of SUD, current | **1.8 (0.9)[1,2]** | **2.5 (1.0)[1]** | **2.7 (1.2)[2]** | 2.8 (1.3) | 3.1 (1.4) | **$F_{(4,33.4)} = 14.94, p < 0.000$** |
| Total number of SUD, lifetime | **2.0 (1.0)[1,2]** | **2.7 (1.1)[1]** | **3.2 (1.4)[2]** | 2.8 (1.5) | 3.1 (1.4) | **$F_{(4,33.5)} = 14.87, p < 0.001$** |
| Smokers (yes, %) | 59.6 | 79.7 | 65.1 | 75.0 | 93.2 | **$\chi^2(4) = 54.62, p < 0.001$[a]** |
| FTND of smokers[b] | 5.3 (2.4) | 4.9 (2.2) | 5.3 (2.0) | 5.0 (1.8) | 5.6 (1.4) | $F_{(4,359)} = 0.494, p = 0.740$ |
| BDI at admission | **18.9 (11.8)[1]** | **25.2 (12.0)[1]** | 21.1 (11.5) | 29.2 (10.2) | 25.2 (12.0) | **$F_{(4,466)} = 6.94, p < 0.001$** |
| BAI at admission | **16.9 (13.0)[1]** | 19.4 (13.0) | **15.9 (10.2)[2]** | **31.5 (11.0)[1,2]** | 19.4 (13.0) | **$F_{(4,459)} = 3.49, p = 0.008$** |
| PSS[b] | **20.8 (6.3)[1]** | **23.5 (5.4)[1]** | 22.5 (5.8) | 24.4 (5.4) | 23.5 (5.4) | **$F_{(4,406)} = 4.08, p = 0.003$** |
| MACS at admission | **16.6 (9.8)[1,2]** | **20.4 (10.2)[1]** | **21.0 (9.4)[2]** | 25.0 (8.9) | 19.8 (7.7) | **$F_{(4,467)} = 5.27, p < 0.001$** |

*Mean values (standard deviation) or percentage values are displayed for the clinical sample only. Group differences are highlighted. n, sample size; AUD, alcohol use disorder; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CSUD, cocaine and stimulant use disorders; CUD, cannabis use disorder; FTND, Fagerstrom Test for Nicotine Dependence; MACS, Mannheimer Craving Scale; SHA, sedative, hypnotics, or anxiolytic use disorders; SUD, substance use disorder; OUD, opioid use disorders; PSS, perceived stress scale.* [1,2]*Superscripted numbers describe significant group differences following post hoc tests.* [a]*Following post hoc testing including correction for multiple comparison, no statistically significant group-differences emerged.* [b]*Only administered once. Significant results are highlighted in bold.*

## Prevalence and Severity for All Sub-Types of Childhood Maltreatment With Respect to Different Kinds of Substance Use Disorders

Over all substances, prevalence rates of CM were 19.1% for sexual abuse, 19.8% for physical abuse, 24.7% for emotional abuse, 54.7% for physical neglect, and 67.9% for emotional neglect. Individuals with SUD experienced on average 1.90 (1.46) of five types CM, and significant group differences between substances emerged [$F_{(4,540)} = 4.48$, $p = 0.001$]. *Post hoc* tests indicated a significant difference in the number of CM between AUD [on average 1.71 (1.42) CM] and CUD [on average 2.38 (1.44) CM].

Within the overall sample, severity of CM [mean of sum scores (standard deviation)] resulted in 6.2 (3.5) for sexual abuse, 7.7 (4.4) for physical abuse, 8.8 (3.6) for physical neglect, 10.0 (5.4) for emotional abuse, and 13.2 (5.7) for emotional neglect. Significant group differences with respect to the main diagnosis were observed for emotional abuse [$F_{(4,622)} = 14.29$, $p < 0.001$] and physical abuse [$F_{(4,52.5)} = 5.09$, $p = 0.001$]. *Post hoc* tests

indicated significantly more severe experience of emotional abuse for CUD compared to AUD and OUD, and, additionally, of emotional neglect for CUD compared to AUD. See **Table 3** for details regarding prevalence for and severity of specific subtypes of CM in different substances.

## Sex Differences in Prevalence and Severity of Childhood Maltreatment

Over all substances, females in comparison to males reported significantly more often having experienced emotional abuse [$\chi^2(1) = 26.31$, $p < 0.001$], physical abuse [$\chi^2(1) = 9.19$, $p = 0.002$] and sexual abuse [$\chi^2(1) = 37.71$, $p < 0.001$], but not emotional neglect [$\chi^2(1) = 0.46$, $p = 0.423$] or physical neglect [$\chi^2(1) = 1.66$, $p = 0.197$]. Depending on the main diagnosis, significant sex differences to the detriment of women became apparent for alcohol and emotional abuse [$\chi^2(1) = 14.45$, $p < 0.001$], alcohol and physical abuse [$\chi^2(1) = 7.09$, $p = 0.008$], alcohol and sexual abuse [$\chi^2(1) = 12.38$, $p < 0.001$], cannabis and emotional abuse [$\chi^2(1) = 7.28$, $p = 0.007$], cannabis and physical abuse [$\chi^2(1) = 5.94$, $p = 0.015$], cannabis and sexual

**TABLE 3 |** Severity of childhood maltreatment.

| | AUD | CUD | CSUD | SHA | OUD + OMT | Statistics |
|---|---|---|---|---|---|---|
| N | 364 | 118 | 43 | 12 | 118 | 655 |
| CTQ sum score | **43.2 (16.6)[1]** | **51.4 (17.5)[1]** | 43.7 (15.2) | 42.6 (13.7) | 46.9 (17.7) | **$F_{(4,539)}$ = 4.96, $p$ = 0.001** |
| Number of types of CM | **1.71 (1.42)[1]** | **2.38 (1.44)[1]** | 1.70 (1.41) | 1.71 (1.98) | 1.99 (1.48) | **$F_{(4,540)}$ = 4.48, $p$ = 0.001** |
| CTQ emotional abuse | **9.2 (5.2)[1]** | **12.8 (6.0)[1,2]** | 10.4 (5.2) | 9.4 (3.9) | 9.5 (4.7)[2] | **$F_{(4,622)}$ = 14.29, $p$ < 0.001** |
| Prevalence (yes, %) | 19% | 47% | 28% | 25% | 19% | **$\chi^2_{(4)}$ = 35.18, $p$ < 0.001[a]** |
| CTQ emotional neglect | 12.7 (5.6)[1] | 14.5 (5.6)[1] | 13.0 (6.1) | 12.7 (5.7) | 13.5 (5.9) | $F_{(4,625)}$ = 2.16, $p$ = 0.072 |
| Prevalence (yes, %) | 65% | 78% | 62% | 50% | 70% | $\chi^2_{(4)}$ = 6.48, $p$ = 0.166 |
| CTQ physical abuse | 7.3 (4.0) | **8.2 (5.6)[1]** | 7.9 (4.3) | **6.0 (1.5)[1,2]** | 8.7 (5.2)[2] | **$F_{(4,52.5)}$ = 5.09, $p$ = 0.001** |
| Prevalence (yes, %) | 16% | 24% | 26% | 8% | 27% | **$\chi^2_{(4)}$ = 10.58, $p$ = 0.032[a]** |
| CTQ physical neglect | 8.7 (3.4) | 9.2 (4.0) | 8.0 (3.1) | 8.6 (2.8) | 9.1 (3.8) | $F_{(3,627)}$ = 1.37, $p$ = 0.241 |
| Prevalence (yes, %) | 54% | 58% | 47% | 50% | 56% | $\chi^2_{(4)}$ = 2.413, $p$ = 0.660 |
| CTQ sexual abuse | 6.0 (3.3) | 6.6 (4.0) | 5.5 (1.5) | 6.5 (3.7) | 6.7 (4.0) | $F_{(4,617)}$ = 1.72, $p$ = 0.144 |
| Prevalence (yes, %) | 15% | 28% | 12% | 25% | 25% | **$\chi^2_{(4)}$ = 13.093, $p$ = 0.011[a]** |

*Mean values (standard deviation) or percentage values are displayed. Group differences are highlighted in bold. n, sample size; AUD, alcohol use disorder; CSUD, cocaine and stimulant use disorders; CTQ, Childhood Trauma Questionnaire; CUD, cannabis use disorder; SHA, sedative, hypnotics, or anxiolytic use disorders; OUD, opioids use disorders + opioid maintenance treatment. Prevalence numbers and the number of types of CM are reported for the dichotomized item "having experiences CM" coding "yes" for at least moderate experience of the respective subscale of CM. [1,2]Superscripted numbers describe significant group differences following post hoc tests. [a]Following post hoc testing including correction for multiple comparison, no statistically significant group-differences emerged.*

abuse [$\chi^2_{(1)}$ = 11.15, $p$ = 0.001] and opioids and sexual abuse [$\chi^2_{(1)}$ = 9.09, $p$ = 0.003].

Over all substances, females reported more severe experiences of CM compared to men, resulting in significant sex differences for emotional abuse [$t_{(242.3)}$ = −4.14, $p$ < 0.001] and sexual abuse [$t_{(196.3)}$ = −4.46, $p$ < 0.001] (**Figure 1**). Sex differences regarding emotional neglect [$t_{(628)}$ = −2.16, $p$ = 0.034] did not survive correction for multiple testing. Within each main diagnosis, significant sex differences to the detriment of women became apparent following two-sided $t$-tests for alcohol and emotional abuse [$t_{(123.0)}$ = −3.05, $p$ = 0.003], alcohol and sexual abuse [$t_{(100.75)}$ = −2.77, $p$ = 0.007], alcohol and emotional neglect [$t_{(155.49)}$ = −2.24, $p$ = 0.026], cannabis and emotional



**FIGURE 1 |** Significant sex differences for the overall sample regarding mean values of the sum scores per subscale of the CTQ. Females (red) reported significantly more severe CM for emotional and sexual abuse than males (blue). CTQ, Childhood Trauma Questionnaire; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect. Error bars are displayed at a 95% confidence interval. *Significant sex difference.
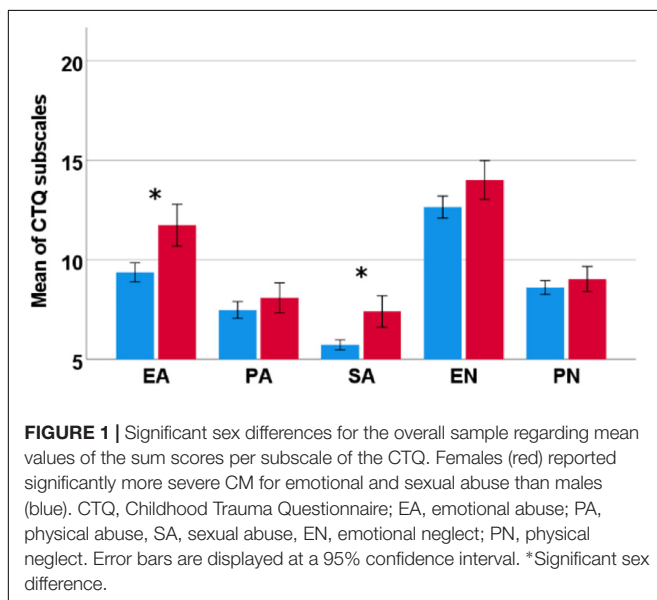
abuse [$t_{(46.50)}$ = −3.31, $p$ = 0.002] and cannabis and sexual abuse [$t_{(33.40)}$ = 2.54, $p$ < 0.001]. Sex differences for physical neglect in individuals with CUD [$t_{(38.22)}$ = −2.24, $p$ = 0.031] did not survive correction for multiple testing. See **Figure 2** for more details.

## Severity of Childhood Maltreatment in Relation to Symptoms of Anxiety, Depressiveness, and Perceived Stress in the Overall Patient Sample

Statistically significant positive correlations between the severity of CM (CTQ sum score) and affective symptoms were observed in the overall sample. See **Figure 3** for more details. A positive correlation between the severity of CM and BDI sum score at admission was observed for males and females (males r = 0.241, $p$ < 0.001; females r = 0.251, $p$ = 0.012). The correlation between severity of CM and BAI sum score at admission and PSS sum score were significant for males (BAI r = 0.248, $p$ < 0.001; PSS r = 0.207, $p$ = 0.012), but not females (BAI r = 0.188, $p$ = 0.062; PSS r = 0.044, $p$ = 0.679). See **Table 4** for more details.

## The Influences of Different Types of Childhood Maltreatment on Substance Craving at Admission With Respect to Main Diagnosis and Sex

Craving at T01 (MACS T01) differed statistically significant for the different substance groups [$F_{(4,381)}$ = 2.622, $p$ = 0.035, $\eta^2$ = 0.027], and sex [$F_{(1,381)}$ = 6.771, $p$ = 0.010, $\eta^2$ = 0.017] after adjusting for all five subscores of the CTQ and age. Severity of emotional abuse [$F_{(1,381)}$ = 17.353, $p$ < 0.001, $\eta^2$ = 0.044] but none of the other subscales of CM or age did show a significant influence. After adjusting for before-mentioned covariates, Bonferroni-corrected *post hoc* tests revealed significantly more severe craving for women ($p$ = 0.010, $M_{Diff}$ = 2.92, 95% CI [0.71,

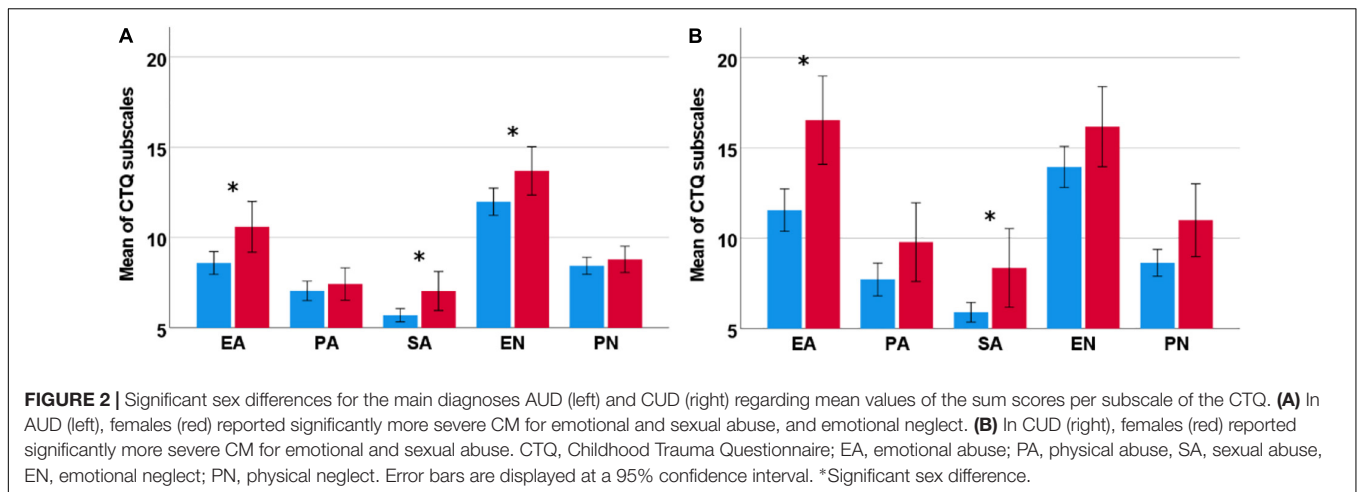**FIGURE 2 |** Significant sex differences for the main diagnoses AUD (left) and CUD (right) regarding mean values of the sum scores per subscale of the CTQ. **(A)** In AUD (left), females (red) reported significantly more severe CM for emotional and sexual abuse, and emotional neglect. **(B)** In CUD (right), females (red) reported significantly more severe CM for emotional and sexual abuse. CTQ, Childhood Trauma Questionnaire; EA, emotional abuse; PA, physical abuse, SA, sexual abuse, EN, emotional neglect; PN, physical neglect. Error bars are displayed at a 95% confidence interval. *Significant sex difference.

**TABLE 4 |** Severity of childhood maltreatment in relation to symptoms of anxiety, depressiveness, and perceived stress for the overall patient group, and separately by sex.

|  | BDI T01 | BAI T01 | PSS |
|---|---|---|---|
|  | Corr. Coeff. \| $p$-value \| $1-\beta$ \| $N$ | Corr. Coeff. \| $p$-value \| $1-\beta$ \| $N$ | Corr. Coeff. \| $p$-value \| $1-\beta$ \| $N$ |
| **CTQ** |  |  |  |
| All | **0.277 \| <0.001 \| >0.9999 \| 391** | **0.259 \| <0.001 \| >0.9961 \| 388** | **0.191 \| <0.001 \| >0.8393 \| 351** |
| Males | **0.241 \| <0.001 \| >0.9023 \| 291** | **0.248 \| <0.001 \| >0.8981 \| 288** | **0.207 \| <0.001 \| >0.8641 \| 261** |
| Females | **0.251 \| <0.012 \| >0.3254 \| 100** | 0.188 \| >0.062 \| – \| 100 | 0.044 \| <0.679 \| – \| 90 |

*Pearson correlation coefficients, p-values (two-sided), and power estimates are displayed. Significant correlations are highlighted in bold. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire, sum score; PSS, Perceived Stress Scale. All significant results survived correction for multiple testing (p > 0.05). Post hoc power calculations were performed in G\*Power (57).*

5.12]). *Post hoc* tests regarding substance group did not yield significant results following Bonferroni correction.

After adjusting for all five subscores of the CTQ and age but also PSS, BDI (T01) and BAI (T01) sum scores, craving at T01 (MACS T01) did no longer differ statistically significant between the different substance groups [$F(4,282) = 2.516$, $p = 0.107$, $\eta^2 = 0.027$] or sex [$F(1,282) = 2.516$, $p = 0.114$, $\eta^2 = 0.009$]. Severity of emotional abuse [$F(1,282) = 1.282$, $p = 0.258$, $\eta^2 = 0.005$] did no longer show a significant influence, neither did the PSS sum score [$F(1,282) = 0.735$, $p = 0.392$, $\eta^2 = 0.003$]. BDI and BAI sum scores at admission, however, did show a significant influence [$F(1,282) = 43.637$, $p < 0.001$, $\eta^2 = 0.134$; $F(1,282) = 15.360$, $p < 0.001$, $\eta^2 = 0.052$].

## The Influences of Different Types of Childhood Maltreatment on the Reduction of Substance Craving During the First 2 Weeks of Treatment With Respect to Main Diagnosis and Sex
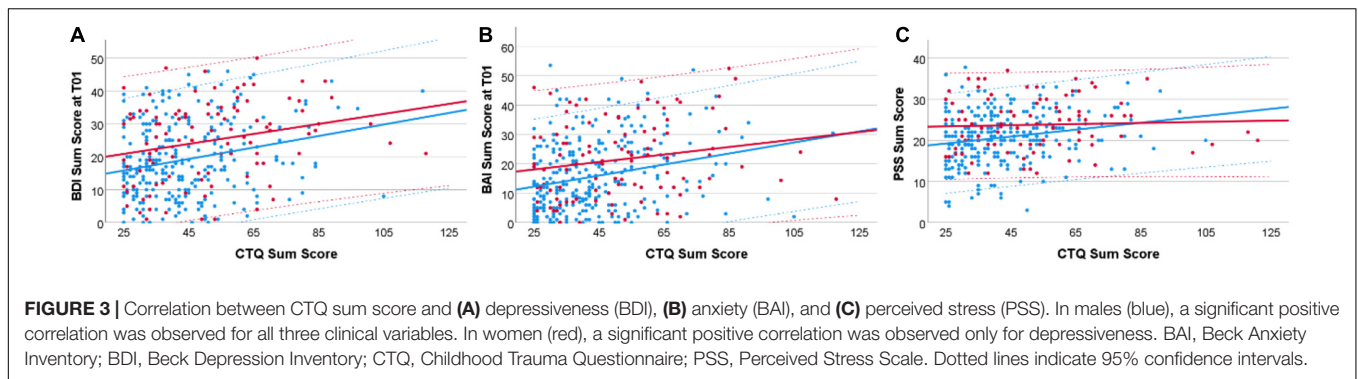
Over all substances, craving diminished from 18.0 (10.0) at T01 to 11.0 (8.3) at T14 in the MACS questionnaire. However, no significant effect of substance group [$F(4,306) = 0.836$, $p = 0.503$, $\eta^2 = 0.011$] or sex [$F(1,306) = 3.516$, $p = 0.062$, $\eta^2 = 0.011$] was observed after adjusting for age and all five subscores of CM. There was no significant influence regarding all subscores of CM. Including PSS, BDI (T01) and BAI (T01), no

significant effect of substance group [$F(4,282) = 0.341$, $p = 0.850$, $\eta^2 = 0.005$] or sex [$F(1,282) = 0.513$, $p = 0.475$, $\eta^2 = 0.002$] did emerge either. However, PSS and BDI (T01) sum scores excerpted a significant influence [$F(1,282) = 14.433$, $p < 0.001$, $\eta^2 = 0.049$; $F(1,282) = 21.050$, $p < 0.001$, $\eta^2 = 0.069$], so did age [$F(1,282) = 5.095$, $p = 0.025$, $\eta^2 = 0.018$], but not the BAI (T01) sum score [$F(1,282) = 2.807$, $p = 0.095$, $\eta^2 = 0.010$].

## DISCUSSION

To our knowledge, this study is the first to examine a broad range of CM, namely emotional and physical abuse, emotional and physical neglect as well as sexual abuse in patients undergoing treatment for SUD while including several substances, such as alcohol, cannabis, cocaine and stimulant, opioid and sedative use disorders. The most salient finding of the present study was the high prevalence and severity of experienced CM in patients with CUD compared to other SUDs and especially compared to AUD. This study expands previous work on the relevance of psychosocial and biographical aspects regarding SUD.

The association between CM and SUD is well known in literature (12–21). The prevalence of moderate to extreme CM in our sample exceeded a previous estimation for the general German population ranging between 6.5% for emotional abuse and 22.4% for physical neglect (11). Similarly to the general population (11), women with SUD also reported higher

**FIGURE 3 |** Correlation between CTQ sum score and **(A)** depressiveness (BDI), **(B)** anxiety (BAI), and **(C)** perceived stress (PSS). In males (blue), a significant positive correlation was observed for all three clinical variables. In women (red), a significant positive correlation was observed only for depressiveness. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire; PSS, Perceived Stress Scale. Dotted lines indicate 95% confidence intervals.

prevalence rates for abuse but not neglect. Also, individuals with SUD suffered from significantly more severe experiences of CM for all subscales compared to the general German population (22). Our findings are consistent with previous studies, reporting a high prevalence and strong severity of CM in individuals with SUD (12, 15, 23, 58). Compared to a previous study on the severity of CM in individuals with SUD (23), we observed significantly less severe experiences of all forms of abuse but a more severe experience of physical neglect. A higher percentage of women in the previously reported SUD sample (41.3 vs. 27%) might contribute to these differences, since women are known to report higher severities of CM, which was also observed in our sample regarding emotional and sexual abuse. Also, Wingenfeld et al. (23) did not report on different substances. Depending on the composition of SUDs, group differences as we observed here might also contribute to the diverging observations.

Contrary to our hypothesis, individuals with OUD were not the most severely affected substance user group by CM in comparison to other SUD – although prevalence rates of OUD were comparable to previous studies (15, 58). This opposes previous research showing that individuals with OUD were more likely to report ACE in comparison to individuals with tobacco or cocaine use disorder (59). Others observed similar prevalence numbers of CM in both, individuals with OUD and matched controls, which was explained by the control group also containing individuals with other SUD. Still, males with OUD experienced significantly more physical and emotional abuse than controls, and females sexual abuse, respectively (60).

In our sample, patients with CUD showed both higher prevalence and more severe experiences of several subtypes of CM. Emotional abuse was significantly more severe in CUD compared to AUD. However, CUD compared to OUD did not reach significance. Individuals with CUD were similarly affected by comorbid mental disorders, i.e., schizophrenia, schizotypal and delusional disorders (F2), affective (F3), or neurotic, stress-related and somatoform disorders (F4) as AUD. *Post hoc* analyses (see **Supplementary Material**) for CUD and AUD did not yield significant group differences. However, individuals with CUD were diagnosed with more comorbid SUD compared to individuals with AUD. An explanation for our observation with respect to individuals with OUD might be three-fold. Firstly, an age effect cannot be ruled out regarding patients with CUD, since they were significantly younger. *Post hoc* analyses

(see **Supplementary Material**) revealed a negative correlation between age and overall CM severity. However, within each substance group, including CUD, this correlation did not reach significance. Discussing generational aspect when it comes to (not) reporting CM are relevant, but beyond the scope of this retrospective, observational study. Secondly, CM data for OUD mainly derived from OMT patients. In contrast to the other SUD patients of our study, OMT patients were not abstinent, but continuously treated with opioids. Therefore the daily opioid treatment may have an acute effect and memories of CM might be suppressed to a certain extent. This could have led to an underreporting of prevalence and severity of CM. Opposing to this and besides psychobiological mechanism of withdrawal, in-house patients might find themselves strongly confronted with current problematic psychosocial factors during our treatment. They might increase attention toward traumatic events as one potential factor within the biopsychosocial model of addiction that is regularly discussed during medical and psychotherapeutic treatment of SUD. Thirdly, endocannabinoids mediate the extinction of aversive memories and regulate fear, anxiety and stress. External cannabis might enhance these effects, and thus might be consumed as a self-medication (61, 62). A systematic review of cannabis use motives identified negative life events, trauma, and maladaptive coping being related to consumption (63). This was also confirmed for CM as origin of negative stress and influenced by impairments in emotion regulation, e.g., negative mood (64). Cannabinoids are discussed as medical intervention for several anxiety- and trauma-related disorders by reason of their neuromodulator capacities in brain regions relevant for emotion and stress regulation (65, 66). Further research examined the hypothesis of a self-medication model of cannabis in posttraumatic stress disorder and revealed an acute, dose-dependent cannabis effect of a 51–67% symptom relief in more than 92% of cannabis users. However, a development of tolerance and therefore limited effects were observed (67).

Named considerations evoke the question of a causal origin of the association, namely whether CM is more frequent in SUD compared to the general population, because CM leads to SUD. Our analyses highlighted association between CM and SUD rather than causation. However, mechanisms identified in basic and animal research include a long lasting altered stress response after early life adversity. Further, perturbation of numerous neurodevelopmental processes, including the development and

maturation of brain circuits involved in cognition and emotion, finally result in diminished cognitive control and increased desire for drug effects, i.e., memory extinction and relief from negative affect. Mechanisms are reviewed in Al'absi et al. (68) and Levis et al. (69). Recent basic research supported the contribution of CM to an increase in vulnerability for opioid addiction (Sophia C. (70)), possibly mediated by the endogenous opioid system which is involved in pro-social behavior in mammals, including humans (71). A recent review proposes "[...] based upon recent findings of opioid modulation of human social learning, bonding and empathy in relation to affiliative and protective tendencies. Fundamental to the model is that the mu-opioid system reinforces socially affiliative or protective behavior in response to positive and negative social experiences with long-term consequences for social behavior and health" (72). Lacking of pro-social touch, caring and protective behavior in childhood is a key feature of CM and may result in a long-term modification of the endogenous opioid system. On the emotional level this might result in an enhanced desire for social attachment and the pro-social effects of endogenous or external opioids. Not only opioids but all addictive substances share an activation of the opioid system, either by releasing endogenous opioids (alcohol, cannabis, amphetamines, and cocaine) or by direct activation of opioid receptors (heroin and synthetic opioids) (73–76). Therefore, this opioid pathway also increases the risk for non-opioid SUD in individuals having experienced CM.

In our sample, a positive relation between the severity of the overall CM and depressiveness, anxiety and perceived stress was observed for males. However, in women, current perceived stress did not relate to a history of CM. The relation between ACE such as CM and a later SUD has been observed to be party mediated by mood and anxiety disorders (33).

The influence of sex with regard to outcomes of CM has been discussed previously (77) and sex differences are commonly accepted. However, White and Kaffman (77) argued that despite similar presentation, underlying mechanisms might differ. Also, impairments in mental health following CM are subject to effects of gender and CM subtype (78). Potentially, physical abuse is more often related to internalizing mental disorders (e.g., affective disorders) in females subjects whereas in males physical abuse more often related to externalizing mental disorders (e.g., SUD) (79). For women, but not men, several subtypes of CM were associated with an increased risk for cocaine relapse (80). In cocaine, CM might increase the risk for relapses due to an increased appetitive anticipatory response to drug cues. Further, regulatory and control mechanism regarding stress- and cocaine-induces craving might be reduced following CM (81).

Substance craving refers to a multifaceted construct, including internal and external factors as well as corresponding interactions, that results in the desire or urge for consumption (82). Further, within the diagnosis of SUD, craving is listed as a relevant item (43). In our sample, substance craving at admission to treatment differed between sex and substance group and was influenced by emotional abuse, but not other types of CM. Higher craving at admission to SUD treatment was previously related to relapse, i.e., in individuals with AUD (35, 83), indicating the importance of monitoring craving and examining influencing

factors. Regarding a diverging influence of specific subtypes of CM, physical and emotional abuse, as well as emotional neglect were previously associated with drug use (84) and emotional abuse, followed by physical abuse, were the strongest predictors for the severity of AUD (31). However, depressiveness as a current affective state exerted a strong influence on craving at admission and on craving reduction over the course of treatment. The influence of anxiety on craving became apparent only at admission, whereas perceived stress significantly contributed to craving reduction. Within our sample, a positive correlations between CM and symptoms of depressiveness, anxiety, and perceived stress have been observed. Individuals with CM are at higher risk for psychopathologies related to anxiety and depressiveness (4). At the same time, symptoms of depressiveness and anxiety are common for individuals entering treatment for SUD and negatively influence treatment outcome, i.e., increased risk for relapse (85). In AUD, inefficient emotion regulation is associated with increased alcohol craving and use (86). A history of CM was related to alcohol craving as a response to traumatic stimuli in healthy males. Further, physiological markers, such as cortisol reactivity, heart rate or skin conductance were also related to alcohol craving, CM or both (87).

## Limitations
Limitation, that might reduce the generalizability of the results have to be mentioned. First, possible limitations include the study being based on retrospective self-report questionnaires. Especially, when retrospectively assessing CM as it is done with the CTQ, answers might be biased. When assessing CM, a great heterogeneity regarding the instruments can be observed in the literature. Second, besides using questions defined by the authors, validated questionnaires, such as the CTQ, or interviews were used. When assessing ACE, CM has to be distinguished from a dysfunctional household (including divorce, substance use, observing intimate partner violence) *per se*. CM, abuse or neglect, account primarily for negative mental health outcomes in a study that examined individuals in their early and late adolescence (3). Due to the design of the here presented analyses, we did not assess other ACE besides CM as defined by CTQ and did not collect information about income or family structures which might have added to the biographical burden that possibly contributes to the development of SUD. This hinders the integration of study results in previous literature. Third, only patients were included in the analyses. Therefore, the influence of CM on the transition from low-risk to high-risk consumption possibly leading to a substance use disorder as well as characteristics inherent to non-treatment seeking individuals with SUD could not be examined. Fourth, substances were grouped and only the main diagnosis was considered. The small sample size for individuals with OUD or SHA does not allow for a broader discussion of the influence of main diagnosis on craving at admission and the reduction of craving during treatment.

## Clinical Implications
The here observed high prevalence and severity of CM in individuals with CUD, but also recent developments in the pattern of consumption and the potency of the available

substances (88) underline the need for screening for CM both during treatment for CUD and in prevention of CUD. This is backed up by previous studies in individuals with both a history of CM and cannabis use that indicated a higher risk for psychotic symptoms in adolescents (89) and a more severe symptomatology for bipolar disorder (90). Irrespective of the substance of use, a high prevalence and severity of CM was underlining the importance of assessing CM with suitable tools in all settings of SUD prevention and treatment. If CM can be ceased and a positive environment is installed including intact social networks, positive coping, self-esteem and optimism, the neuro-adaptive capacities of the human brain might allow for a positive outcome, even following CM (91). For example, low levels of mindfulness might link CM to alcohol use (92), therefore serving as a therapeutic target. Individuals with SUD and CM might benefit from integrative psychosocial interventions targeting both, trauma-related and SUD-related symptoms (93), such as interpersonal psychotherapy (94) or trauma informed yoga (95, 96).

## CONCLUSION

Individuals with SUD experience various forms of CM more often and in a more severe manner than the general population. SUD group differences with regard to prevalence and severity of CM were observed. Sex differences to the detriment of women can be observed in several SUDs. CM, specifically emotional abuse, might be related to craving at admission to treatment. However, pathways of mediating factors, such as depressiveness, anxiety and stress still have to be examined in more depth. Also, underlying causal and explanatory mechanism such as impairments in processing of trauma history, emotional regulation, or neurobiological alterations following CM remain to be further examined. A history of CM should be assessed during treatment for SUD. A possible positive influence of trauma-related interventions during SUD treatment specifically addressing aspects of CM on treatment outcomes and relapse rates can be hypothesized.

## DATA AVAILABILITY STATEMENT

Data contains sensitive medical information and will be made available for researchers who meet the criteria for access to confidential data. The data underlying the results presented in the study are available upon reasonable request from SV-K (s.vollstaedt-klein@zi-mannheim.de).

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (approval numbers 2018-531N-MA and 2018-807R-MA). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

SG designed the current study, performed the data analysis, and drafted the manuscript. KE and NB collected the parts of the data from study 2. SH supported the data analysis. KE, DH, AK, WS, and SV-K contributed to the interpretation of the data. KE helped with the writing of the manuscript. SV-K, FK, PB, NB, DH, AK, and WS were responsible for the study designs of the original studies and helped with the recruitment. DH, FK, and WS procured the funding of the original studies. All authors revised the manuscript critically for important intellectual content and approved the final version.

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**Conflict of Interest:** DH was employed by the Therapieverbund Ludwigsmühle gGmbH.

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