Associations of adverse childhood experiences and bullying on physical pain in the general population of Germany

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Background: Chronic pain is a frequent burden in the general population. Child maltreatment and bullying are risk factors for the development of chronic pain. Aim of this cross-sectional study was to investigate the association of child maltreatment and bullying and pain experiences in a representative sample of the general population.

Materials and methods: A total of N=2,491 people from the general population of Germany participated in the study (M_age=48.3 years [SD=18.2], 53.2 % female). Child maltreatment was assessed with the Childhood Trauma Questionnaire (CTQ), pain was rated with the Polytrauma Outcome (POLO)-physical state domain, depression scores were assessed with the Patient Health Questionnaire, and anxiety scores via the General Anxiety Disorder Questionnaire. Regression analyses were calculated to investigate the effect of bullying and child maltreatment, as well as depression, anxiety, and gender on pain experiences.

Results: A significant correlation between increasing pain levels and number of adverse childhood experiences was found. With regard to specific types of maltreatment, largest effect sizes were found for emotional abuse. Bullying was significantly, but overall rather moderately, related to pain suffering. In women, all forms of maltreatment were associated with pain, while in men only sexual and physical abuse revealed significant effects. Although depression and anxiety scores were significantly associated with the experience of current pain, they did not change the effect of child maltreatment on pain significantly.

Conclusion: In this sample of the general population, adverse childhood experiences were significantly associated with pain and showed cumulative effects, over and above depressive and anxiety symptoms.

Keywords: child maltreatment, adulthood, depression, anxiety

Introduction
Chronic pain is frequently reported in samples of the general population. In a large-scale study involving 15 European countries and Israel, around 19% of the adults reported at least a moderate to severe intensity of chronic pain. In general, pain can be perceived as the body’s warning signal when there is an imminent threat for “actual or potential tissue damage”. It is widely acknowledged that pain has somatosensory as well as affective compounds, and it has been shown that early life stressors affect neural pathways involved in the processing of acute as well as chronic pain.

The development of chronic pain in relation to childhood maltreatment may already start in childhood or adolescence, but might also lead to adult onset of chronic pain conditions. Besides clinical chronic pain conditions, participants from community
samples reporting the experience of abuse, neglect, or other traumatizing events were more likely to experience pain.10–13 Studies have also shown differential effects following diverse types of maltreatment on chronic and acute pain in different parts of the body.9,14,15 However, it has to be kept in mind that different forms of childhood maltreatment often co-occur.16,17 Therefore, several studies have focused on a “dose-response-effect,” showing a positive association of the number of reported forms of childhood maltreatment or the severity of maltreatment and the likelihood or severity of chronic pain conditions.18–21

Considering possible traumatic events throughout childhood and adolescence, bullying also has to be taken into account. It has been shown that besides childhood maltreatment by family members, bullying by peers can also lead to more experiences of physical pain (chronic and acute) later in life.22,23 Several factors may mediate the relationship between adverse childhood experiences and the development of pain. Gender can affect the hypothalamic-pituitary-adrenal axis responsiveness, rates of circuitry maturation, and neuroimmune development (for review see Ganguly and Brenhouse24), all of which are involved in the processing of stress and linked to the development of chronic pain. Several studies have also shown the involvement of neuroanatomical reorganization, neurotrophin and monoamine depletion, neuroinflammation, and changes in the endocannabinoid system to link depression to the experience of pain.25

As both childhood maltreatment and different pain conditions have been associated with depression and anxiety symptoms in several independent studies,26,27 the experience of those symptoms may have had a mediating effect on the results of the current study. Therefore, analyses were controlled for both, the experience of depression and anxiety symptoms.

To our knowledge, the current study is the first to assess the cumulative effect of childhood maltreatment on the experience of bodily pain in the general population of Germany, disentangling the effect of different forms of adverse experiences (including bullying) on different types of pain (ie, overall pain, headaches, and back/neck-pain), differentiate results by gender, and to control for depressive and anxiety symptoms.

Materials and methods
Using a random route procedure, a representative sample of the German population was acquired by a demographic consulting company (USUMA, Berlin, Germany) between September 2016 and November 2016. Households of every third residence in a randomly chosen geographical area were invited to participate in the study. In multi-person households, participants were randomly selected using a Kish selection grid. Inclusion criteria were a minimum age of 14 years and sufficient knowledge of the German language. Of 4,902 designated addresses, 2,510 households participated in the study. Non-participating households did not differ significantly from participating households with regard to all tested demographic variables, eg, geographical areas or composition of the household in terms of age and gender. Responses were anonymous. In a first step, sociodemographic information was gathered in an interview format by research staff. All other information was obtained via paper and pencil questionnaires, with research staff being available for questions.

The study was conducted in accordance with the Declaration of Helsinki and fulfilled the ethical guidelines of the International Code of Marketing and Social Research Practice of the International Chamber of Commerce and of the European Society of Opinion and Marketing Research. All participants (and if applicable their caregivers) gave written informed consent. The study was approved by the ethics committee of the Medical Department of the University of Leipzig.

Measures
The prevalence of five types of child maltreatment was assessed using the 28-item brief version of the Childhood Trauma Questionnaire (CTQ).28,29 The CTQ is a screening measure for the assessment of maltreatment in childhood and adolescence up to the age of 18 years. It contains five subscales, each assessed by five items: sexual, emotional and physical abuse as well as emotional and physical neglect. Additionally, three items assessed whether participants tend to trivialize problematic experiences within their family. Each item is rated on a scale from 1 (minimal) to 5 (severe). Therefore, sum scores from 5 to 25 can be reached on each subscale. Good psychometric properties of the German version of the CTQ were demonstrated by Klinitzke et al,28 with internal consistencies ranging between 0.62 and 0.96 for all subscales. The intra-class coefficient for an interval of 6 weeks was 0.77 for the overall scale and for subscales between 0.58 and 0.81. Based on norm data by Häuser et al,30 severity scores for each subscale can be calculated (based on the sum scores of each subscale), ranging from “none–minimal”, “minimal-moderate”, “moderate-severe”, to “severe-extreme”. Dichotomous scores (eg, experience of
emotional neglect: yes/no) were based on scores reaching at least moderate-severe level, as is common practice in studies using the CTQ (for details see Häuser et al30). Bullying was assessed with one question (“when you were a child, were you bullied at school?”).

Pain was assessed using the PRE-Status module of the Polytrauma Outcome Chart (POLO-Chart)31 The POLO-Chart was designed to assess level of functioning and quality of life in patients after severe physical trauma and provides a validated tool with good acceptance among patients for the assessment of pain. The PRE-Status module assesses levels of pain before the trauma; in the current study, levels of current pain were assessed. Participants rated on a scale from 0 (not at all) to 10 (unbearable) how much they had felt pain within the past 7 days in the following parts of the body: head, neck, shoulder/upper arm, elbow/lower arm, wrist/hand, fingers, chest, stomach, spine (back), pelvis, hip/thigh, knee/shin/calf, ankle/foot, and toes. In order to be able to conduct meaningful analyses, body regions were comprised and the following scales were analyzed: “any pain”=mean of all body regions, “headache”=head, “neck/back”=mean of neck and spine, “bodily pain”=mean of all body regions except head, neck, and spine.

Depressive symptoms were assessed with the German version of the screening tool Patient Health Questionnaire (PHQ-2), focusing on the depressive symptoms “low mood” and “loss of interest”. Scores can reach values from 0 to 6, with a cutoff of values higher than 3 leading to values of sensitivity of 87% and specificity of 78% for major depression.32 Anxiety symptoms were screened for using the General Anxiety Disorder Questionnaire (GAD-2). Like the PHQ-2, the questionnaire consists of two items, with possible values from 0 to 6 and a cutoff of 3. This cutoff is sensitive for screening for generalized anxiety disorders (86%), panic disorders (76%), social anxiety disorder (70%) and moderately for PTSD (59%). It is specific for all four types of anxiety disorders (81%–83%), with an internal consistency of Cronbach’s alpha=0.82.33

Participants
Of all originally included participants (N=2,510), 19 did not complete the POLO-Chart. The remaining 2,491 participants were aged M=48.3 years on average (SD=18.2, ranging from 14 to 94), and 53.2% (N=1,324) were females. Almost all participants (N=2,410, 96.7%) were of German nationality, 21.7% (N=541) had a secondary school degree qualifying to enter university (Abitur), while 2.2% (N=55) did not have a high-school degree and 5.2% (N=129) were unemployed. Around half of all participants (54.6%, N=1,360) reported to be living with a partner. There were no significant gender differences with regard to general demographic variables.

Statistical analyses
Statistical analyses were performed using SPSS version 21. Gender differences regarding pain scores and adverse childhood experiences were calculated using t-tests and chi²-tests. In order to analyze the cumulative effect of child maltreatment on pain, Pearson correlations were calculated. Differential effects of different types of child maltreatment and bullying on different types of pain (eg, head/neck pain, bodily pain) were analyzed using separate t-tests and effect sizes (Cohen’s d) were calculated (d≥0.2 small effect, d≥0.5 medium effect, d≥0.8 large effect). All variables assessing child maltreatment and bullying were entered into a regression model. Scores of the GAD-2, PHQ-2, as well as age and gender were entered as covariates to the model in order to differentiate the effect of different types of maltreatment and bullying, and to control for depressive and anxiety symptoms, age, and gender. Subsequently, in order to differentiate results by gender, separate regression analyses by gender (including the same variables as already mentioned) were calculated and presented in a separate table.

Results
Overall levels of pain were rather low (M=0.82, SD=1.07), given a possible range of 0–10. Relatively speaking, levels of pain were highest in neck/back or headaches. Concerning adverse childhood experiences, physical and emotional neglect were endorsed most often (22.4% and 13.1%, respectively), while having been bullied at school was least common (10.9%). Over 30% of the overall sample reported at least one form of maltreatment or neglect of moderate to severe level, and 1.2% reported all five forms of abuse and neglect (for further details see Table 1).

Cumulative effect of childhood abuse and neglect
The number of experienced forms of childhood abuse and neglect was significantly correlated with overall pain scores (r=0.32, P<0.001, Figure 1). This effect was also significant for bodily pain (r=0.33, P<0.001), back/neck pain (r=0.22, P<0.001), and headaches (r=0.16, P<0.001).

Differential effects of different adverse childhood experiences
Results were significant for all forms of childhood abuse and neglect and for having been bullied by peers. This was true for
overall pain, as well as bodily pain, headaches, and back/neck pain (Table 2). Large effects were seen for emotional abuse on all types of pain, and for physical and sexual abuse on overall pain and bodily pain. Small effects were found for emotional and physical neglect on headaches and back/neck pain, while all other effects were in a medium range (for details see Table 2).
Table 2  Differential associations of forms of adverse childhood experiences with different types of pain

<table>
<thead>
<tr>
<th>Adverse childhood experience</th>
<th>Any pain M (SD)</th>
<th>T (df)</th>
<th>Cohen’s d</th>
<th>Bodily pain M (SD)</th>
<th>T (df)</th>
<th>Cohen’s d</th>
<th>Headache M (SD)</th>
<th>T (df)</th>
<th>Cohen’s d</th>
<th>Back/neck pain M (SD)</th>
<th>T (df)</th>
<th>Cohen’s d</th>
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<tr>
<td>Bullying</td>
<td>9.2 (2,476)***</td>
<td>0.67</td>
<td></td>
<td>7.9 (2,476)***</td>
<td>0.52</td>
<td></td>
<td>7.2 (2,476)***</td>
<td>0.47</td>
<td></td>
<td>8.0 (2,476)***</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Yes (N=270)</td>
<td>1.37 (1.4)</td>
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<td></td>
<td>1.05 (1.3)</td>
<td></td>
<td></td>
<td>2.67 (2.7)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No (N=2,208)</td>
<td>0.74 (1.0)</td>
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<td>0.55 (0.9)</td>
<td></td>
<td></td>
<td>1.56 (2.3)</td>
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<td></td>
<td>1.43 (1.9)</td>
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<tr>
<td>Emotional abuse</td>
<td>14.4 (2,475)***</td>
<td>1.23</td>
<td></td>
<td>13.5 (2,475)***</td>
<td>1.13</td>
<td></td>
<td>9.5 (2,475)***</td>
<td>0.77</td>
<td></td>
<td>9.7 (2,475)***</td>
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<tr>
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<td>1.59 (1.7)</td>
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<td>3.40 (2.9)</td>
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<tr>
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<td>0.53 (0.9)</td>
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<td>1.57 (2.3)</td>
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<td>1.44 (1.9)</td>
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<tr>
<td>Physical abuse</td>
<td>12.5 (2,480)***</td>
<td>1.04</td>
<td></td>
<td>12.7 (2,480)***</td>
<td>1.04</td>
<td></td>
<td>5.3 (2,480)***</td>
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<td>8.7 (2,480)***</td>
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<td>1.53 (1.6)</td>
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<td></td>
<td>2.65 (2.8)</td>
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<td>2.81 (2.4)</td>
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<tr>
<td>No (N=2,173)</td>
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<td></td>
<td></td>
<td>0.53 (0.9)</td>
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<td>1.45 (1.9)</td>
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<td>Sexual abuse</td>
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<td>0.84</td>
<td></td>
<td>11.9 (2,481)***</td>
<td>0.93</td>
<td></td>
<td>7.8 (2,481)***</td>
<td>0.58</td>
<td></td>
<td>6.5 (2,481)***</td>
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<td>Yes (N=343)</td>
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<td></td>
<td>1.42 (1.6)</td>
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<td>3.00 (2.7)</td>
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<td>1.47 (1.9)</td>
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</tr>
<tr>
<td>No (N=2,140)</td>
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<td></td>
<td></td>
<td>0.53 (0.9)</td>
<td></td>
<td></td>
<td>1.58 (2.4)</td>
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<td>2.44 (2.4)</td>
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<tr>
<td>Emotional neglect</td>
<td>9.4 (2,445)***</td>
<td>0.60</td>
<td></td>
<td>9.2 (2,445)***</td>
<td>0.61</td>
<td></td>
<td>4.6 (2,445)***</td>
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<td>6.7 (2,445)***</td>
<td>0.40</td>
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<td></td>
<td>1.07 (1.4)</td>
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<td>2.26 (2.6)</td>
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<td>2.21 (2.3)</td>
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<tr>
<td>No (N=1,420)</td>
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<td>0.5 (0.9)</td>
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<td></td>
<td>1.60 (2.4)</td>
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<tr>
<td>Physical neglect</td>
<td>10.6 (2,475)***</td>
<td>0.51</td>
<td></td>
<td>11.0 (2,475)***</td>
<td>0.53</td>
<td></td>
<td>2.6 (2,475)*</td>
<td>0.12</td>
<td></td>
<td>7.49 (2,475)***</td>
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<td>Yes (N=1,028)</td>
<td>1.22 (1.4)</td>
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<td>0.99 (1.3)</td>
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<td>2.08 (2.2)</td>
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<tr>
<td>No (N=1,449)</td>
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<td></td>
<td></td>
<td>0.48 (0.8)</td>
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<td>1.62 (2.4)</td>
<td></td>
<td></td>
<td>1.39 (1.8)</td>
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</tr>
</tbody>
</table>

Note: *P<0.05, ***P<0.001; pain as measured by the POlO pain scale.
Abbreviations: Cohen’s d, effect size; M, mean; N, number of participants; POlO, Polytrauma Outcome; T, t-test value; df, degrees of freedom.
Effect of childhood abuse, neglect, and peer bullying controlled for current symptoms of anxiety and depression, gender, and age

A regression model including all five forms of maltreatment as measured dimensionally by the CTQ, bullying by peers (dichotomous), current anxiety and depression symptoms (as measured by the PHQ-2 and the GAD-2), age, and gender explained 28.6% of the variance of the POLO-physical state domain for pain (adjusted $R^2=0.286$). All types of abuse, physical neglect, and bullying were positively associated with the experience of pain (Table 3), while emotional neglect was not. Even though depression/anxiety scores alone explained 10.5% of the variance and had the largest association overall, they did not significantly affect the impact of adverse childhood experiences on the experience of pain.

The significantly negative association of emotional neglect might be due to other variables explaining much more variance in the regression model, as $t$-tests showed enhanced pain levels in those participants reporting emotional neglect (Table 2), and an additional regression analysis performed only with participants who had only experienced emotional neglect (N=48) showed a positive (standardized B=0.17) but non-significant ($P=0.29$) association with pain levels.

In order to test for a possible cumulative effect of experiencing different types of childhood maltreatment, but to reduce multicollinearity, a separate regression model including the number of experienced maltreatment categories was performed. The linear regression model further included a variable containing the numbers of categories met in the CTQ (at least moderate to severe), instead of individual CTQ categories, as well as bullying by peers, current anxiety and depression symptoms, age, and gender, explained 26.9% of the variance of the POLO-physical state domain for pain (adjusted $R^2=0.269$). In this model, all entered variables were significantly positively associated with pain scores (numbers of categories met in the CTQ: standardized B=0.16, $P<0.001$, $t=8.77$; bullying: standardized B=0.08, $P<0.001$, $t=4.29$).

Differential effects by gender

Generally, women reported significantly higher levels of pain and higher levels of emotional abuse and sexual abuse than men, but not for other types of abuse. Women also stated to have been bullied slightly more often than men and reported significantly higher levels of anxiety and depression (for details see Table 1). Therefore, two separate linear regression models were entered for male and female participants. The same variables as for the overall sample were entered. While in women emotional abuse, physical abuse, sexual abuse, physical neglect, and bullying were positively associated with the experience of pain, only physical and sexual abuse were significantly predictive in men (Table 4). Again, the significantly negative association of emotional neglect in women might be due to other variables explaining much more variance in the regression model.

In order to test for a possible cumulative effect of experiencing different types of childhood maltreatment, but to reduce multicollinearity, separate regression models including the number of experienced maltreatment categories were performed (for a more extensive description see above). In both, men and women, number of experienced types of childhood maltreatment were significantly associated with levels of pain (standardized $B_{\text{males}}=0.17$, $P<0.001$, $t=6.14$; standardized $B_{\text{females}}=0.16$, $P<0.001$, $t=6.09$). However, while bullying was still significantly associated with pain in women (standardized $B_{\text{females}}=0.10$, $P<0.001$, $t=4.04$), it was not in men (standardized $B_{\text{males}}=0.04$, $P=0.16$, $t=1.42$).

Discussion

In this study based on a representative sample of the German population, adverse childhood experiences were significantly linked to the experience of pain in adulthood. As most studies so far have been investigating this relationship in clinical samples, or populations with a history of abuse, the current study adds to the literature by providing data from the general population, on participants with mainly non-clinical levels of pain. Interestingly, adverse childhood experiences still were significantly associated with experiences of pain over and above current symptoms of depression and anxiety. However, depression and anxiety scores were associated significantly with pain experiences. These results are in line
with results from a sample of the general population from the US (N=1,727), describing sexual and physical abuse, as well as symptoms of depression to be significantly, but independently, associated with experiences of pain\textsuperscript{10} and a study including German patients with fibromyalgia syndrome only finding partially mediating effects of depression and childhood maltreatment.\textsuperscript{34} Furthermore, the relationship between finding partially mediating effects of depression and childhood maltreatment,\textsuperscript{20} we found significant associations

 Pain can lead to the development of depressive and anxiety symptoms, but can also represent an affective component and is therefore likely to be influenced by depressive and anxiety symptoms vice versa.

 Comparable to another study using the CTQ to measure childhood maltreatment,\textsuperscript{20} we found significant associations between the number of forms of childhood maltreatment and severity of pain. Interestingly, a regression model containing all different types of maltreatment explained a similar part of the variance of scores on the POLO pain scale as a regression model only containing the number of different types of childhood maltreatment experienced. These results underline a dose-response effect of childhood maltreatment, as found in previous studies.\textsuperscript{9,18,20,21} This effect might be due to an additive effect of stress related to several adverse childhood experiences, thus leading to an even more pronounced detrimental effect on the developing brain and associated neurophysiological mechanisms.\textsuperscript{35}

 While physical and sexual abuse, physical neglect, and bullying were significantly associated with pain levels in the regression model, emotional abuse showed particularly high effect sizes for all types of pain (ie, bodily pain, back pain, and headaches) when comparing participants with and without specific adverse childhood experiences. Especially, the pronounced effect on headaches corresponds well to results of a study reporting specifically high prevalence rates of emotional abuse in a sample of migraine patients.\textsuperscript{15} This is a particularly interesting finding, as types of abuse involving the body (physical and sexual abuse) showed particularly high effects on bodily pain, while emotional abuse resulted in more general effects on pain across the body. Similar as in a study of a community-based sample from Japan, physical abuse had a significant effect on bodily and back/neck pain, while sexual abuse was rather associated with any pain than back/neck pain.\textsuperscript{9}

 While most studies have so far focused on maltreatment by family members, our study also showed adverse effects of being bullied by peers. This form of interpersonal violence was therefore significantly related to pain independently of family-related adverse experiences. A longitudinal study showed significant effects of being bullied as an adolescent on the experience of pain in young adulthood;\textsuperscript{23} however, those results were not controlled for adverse experiences within the family. As a Dutch study found significant results of bullying on the experience of chronic pain in adolescents who were independent of parental physical and sexual abuse,\textsuperscript{22} our study adds on to those findings by extending the effect to adulthood and by also showing an independent effect besides emotional abuse and neglect by family members. Interestingly, the effect of bullying on pain was independent from adverse experiences within the family in women, but not in men. This is in line with studies investigating adverse psychosocial outcomes of being bullied, finding stronger effects in girls than in boys,\textsuperscript{36} even lasting into adulthood.\textsuperscript{37} Reasons for those differences might be that girls are more often victims of relational bullying (such as ostracism), while boys are more often victims of direct, physical forms of bullying. As relational bullying seems to have generally more

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female (adjusted $R^2$=0.30; N=1,309)</th>
<th>Male (adjusted $R^2$=0.23; N=1,152)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized B</td>
<td>T</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>0.15</td>
<td>4.08</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>0.08</td>
<td>2.52</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>0.08</td>
<td>2.93</td>
</tr>
<tr>
<td>Physical neglect</td>
<td>–0.14</td>
<td>–4.16</td>
</tr>
<tr>
<td>Bullying</td>
<td>0.10</td>
<td>2.84</td>
</tr>
<tr>
<td>Anxiety scores</td>
<td>0.20</td>
<td>5.30</td>
</tr>
<tr>
<td>Depression scores</td>
<td>0.20</td>
<td>5.28</td>
</tr>
<tr>
<td>Age</td>
<td>0.14</td>
<td>5.63</td>
</tr>
</tbody>
</table>

Notes: Standardized B, standardized regression coefficient. Bold values are significant results regarding childhood maltreatment.

Abbreviations: POLO, Polytrauma Outcome; T, t-test value.
Limitations of the study

Since this was a cross-sectional study, no interpretations on causality can be made. As in all retrospective studies, results of this study may have been biased by recall biases with regard to reports on childhood maltreatment and bullying. However, results measured by the CTQ in representative samples of the German population seem to be rather reliable, as shown in a recent study comparing two samples from 2011 and 2016.\(^{43}\) Bullying was only assessed by one question, which did not specify the age in which bullying occurred during childhood and what type of bullying was experienced. Therefore, results on bullying need to be interpreted with care, as the validity of this question is not known. Furthermore, levels of pain in this non-clinical sample were expectedly rather low (around 1 on a scale from 0 to 10), thus possibly not providing a large enough variance in data to detect all possible effects. Pain and bullying were administered by scales without previously published psychometric properties. No differentiation between the experience of acute and chronic pain in participants can be made, as they were asked to indicate their experiences with pain within the past 7 days (which may have been chronic or acute). Therefore, effects found in this study have to be interpreted with care concerning the state-dependency of reported levels of pain. As this was a study including a large sample and focusing on psychological measures, no funds were available to collect neurobiological data. Despite these limitations, effect sizes found in this study were rather large.

Conclusion

Adverse childhood experience seems to have a long-lasting effect on the experience of pain in the general population in Germany. This was specifically true for emotional, physical, and sexual abuse. Apart from maltreatment by family members, bullying by peers during childhood was also significantly related to pain. While symptoms of depression and anxiety were strongly related to the experience of pain, they did not affect the relationship between adverse childhood experiences and pain. These results underline the necessity of prevention of childhood maltreatment and bullying, as adverse long-term effects can not only be seen in clinical samples but even in the general population.

Author contributions

RCB and PLP take responsibility for the integrity of the work as a whole, from inception to published article. PLP, MHL, and JMF designed the study; JMF and EB acquired the data; and RCB analyzed and interpreted the data. RCB and PLP drafted the manuscript, and all the authors revised it critically.
for important intellectual content. All the authors approved the final version to be published. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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