Child maltreatment and telomere length in middle and older age: A retrospective cohort study of 141,748 participants in UK Biobank

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Abstract

Background and Aims: There was evidence that child maltreatment is associated with shorter telomere length (TL) in early life. This study aims to examine if child maltreatment is associated with TL in middle- and older-age adults.

Methods: This was a retrospective cohort study of 141,748 UK Biobank participants aged 37-73 at recruitment. Leukocyte TL measured using quantitative polymerase chain reaction and was log-transformed and scaled to have unit standard deviation. Child maltreatment was recalled by participants. Linear regression was used to analyse the association.

Results: After adjusting for sociodemographic characteristics, participants with ≥3 types of maltreatment presented with the shortest TLs (β [95% CI] -0.05 [-0.07, -0.03] P < 0.0001), followed by those with 2 types of maltreatment (β [95% CI] -0.02 [-0.04, 0.00] P = 0.02), referent to those who had none. When adjusted for depression and PTSD, the TL of participants with ≥3 types of maltreatment were still shorter (β [95% CI] -0.04 [-0.07, -0.02] P = 0.0008). The TL of those who had 1 type of maltreatment were not significantly different from those who had none. When mutually adjusted, physical abuse (β [95% CI] -0.05 [-0.07, -0.03] P < 0.0001), and sexual abuse (β [95% CI] -0.02 [-0.04, 0.00] P = 0.02), were independently associated with shorter TL.

Conclusions: Our findings showed that child maltreatment is associated with shorter TL in middle- and older-aged adults, independent of sociodemographic and mental health factors.

Introduction

Adverse childhood experiences (ACEs) are a major public health issue and affect over 19.4 million children [1]. Cumulative ACEs are also a significant predisposing factor for many psychological conditions in teenagers and adults, contributing to a wide range of health issues, including cardiovascular disease (CVD), diabetes, depression, and post-traumatic stress disorders [2-4]. Among all adverse childhood experiences, child maltreatment is arguably one of the more severe components [1 4-6]. Child maltreatment broadly includes all forms of physical and/or emotional ill-treatment, sexual abuse, neglect, or negligent treatment of children under the age of 18 years [5].

The existing evidence confirms that exposure to a single or sequence of chronically traumatic events may activate the biological stress response systems [7]. Long-term exposure to early-life stress was found to trigger stress-reactive networks and stress hormones, including the hypothalamic-pituitary-adrenal axis, the central nervous system, and the endocrine and immunological systems [1 6 8-10] and cortisol and catecholamines and other stress factors, such as oxidants and cytokines [10]. These stress-response mechanisms were hypothesised to have a significant role in the progression of early adversity to disease [9] and were often indicated by telomeres shortening, a marker for biological ageing[11].

Telomeres are nucleo-protein complexes containing tandem $(TTAGGG)_n$ repeats which are required for chromosomal and genetic stability [1]. Mean telomere length (TL) acts as an indicator of biological ageing as it shortens with each DNA replication cycle in primary somatic cells due to the end replication problem. It has been reported to predict morbidity and mortality within the diseasome of ageing (including CVD, obesity, CKD and cancer [1 9 12 13]. Oxidative stress leading to macromolecular damage, is one of the factors that can influence telomere attrition, and has been shown to shorten telomeres in somatic cells, or cells that do not replicate [8]. In germline and stem cells, telomerase, a

ribonucleoprotein complex that adds TTAGGG repeats, assists in actively replenishing telomeric repeats during replication, but it is not active in most somatic cells [8]. Therefore, telomere attrition due to oxidative stress in somatic cells may serve as a cumulative marker of chronic stress and provide a link between stress and age-related psychological problems [8]. Several studies have indicated that there is a strong relationship between early-life stress and poor health outcomes associated with shortened TL [4 8].

There is some evidence of an association between child maltreatment and TL, but studies are subject to limited sample sizes and inconsistent child maltreatment measures. Some previous studies have found that children exposed to more stress have a shorter TL even at a young age with evidence of a dose-dependent association between childhood stress and TL [1 14-16]. Most of the existing studies on adverse early experiences are small with the meta-analysis including only 30,773 participants in total, with the large majority having TL measured as children, adolescents, and younger adults [1]. To our knowledge, only one study has investigated the association between adverse early experiences and telomere shortening in older people [16], but they did not include being abused or neglected in childhood as adverse events. Hence, it is currently unknown whether maltreatment in childhood is associated with TL in middle-age and older adults. This study aimed to use data on UK Biobank participants to study whether and to what extent child maltreatment was associated with TL in middle and older age.

Methods

Study design and participants

This is a retrospective cohort study. Between 2007 and 2010, UK Biobank recruited 502,488 participants from the general population. The participants attended one of 22 assessment centres

across England, Scotland, and Wales where they completed a computer questionnaire and underwent a personal interview. The information collected at baseline included household data (postcode, rented/owned, number of people in household), socio-demographic information (age, sex, highest educational level, employment status, car ownership, and ethnic group) as well as lifestyle information (tobacco and alcohol consumption, and completion of the standard Physical Activity Questionnaire). Postcode was used to obtain Townsend area deprivation indices for the participants; a composite area-based measure derived from unemployment, car ownership, household overcrowding, and owner occupation, with higher scores indicating higher levels of deprivation [17 18].

Child maltreatment and mental health

Participants were invited to complete an online mental health questionnaire [19]. Overall, 157,348 (31.3%) of participants completed this but 5,308 were excluded for incomplete data resulting in 152,040 usable responses. The online questionnaire measured current symptoms of depression and post-traumatic stress disorder (PTSD), using two well-established tools: the Patient Health Questionnaire-9 (PHQ-9), and Post-traumatic stress disorder Check List – civilian Short version (PCL-S). Specifically, PHQ-9 measures depression severity from the frequency of nine items, ranging from 0 (not at all) to 3 (nearly every day). All items were summated to provide a total score of depression severity, with higher scores indicating more symptoms. Previous work has demonstrated the validity and reliability of the use of this scale in UK Biobank [20]. PCL-S consists of five items that map onto the DSM-IV criteria [21].

The mental health questionnaire also included assessment of child maltreatment using the Childhood Trauma Screener (CTS)[4]; a shortened version of the Childhood Trauma Questionnaire (CTQ). It consists

of one 5-point Likert scale item for each of five types of child maltreatment - physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse - and has been validated against the CTQ with good overall (r=0.88) and satisfactory type-specific (r=0.55-0.87) correlations [4]. The CTQ is a widely used instrument for measuring child maltreatment and has been validated against actual records of abuse and neglect, and threshold values on the Likert scale derived from the validation study [22] were used to define the presence or absence of each type of child maltreatment. In this study, the primary exposure variable was the number of types of child maltreatment (range 0-5) as it reflects the dimensions of maltreatment.

Telomere length

Detailed information on measurement of TL in UKB has been provided elsewhere [23]. Briefly, DNA was extracted from peripheral blood leukocytes. TL was assayed using the quantitative polymerase chain reaction (qPCR). The assay results were presented as a relative ratio of the telomere repeat copy number (T) to a single-copy gene (S). The calculated T/S ratios were then adjusted for technical variation, log-transformed and Z-standardised so that they approximated to a normal distribution with mean of 0 and SD of 1.

Statistical analyses

Multivariable linear regression was used to study the association between frequency and types of maltreatment and TL. We first examined the association between maltreatment frequency and TL by using the count of types of maltreatment (0, 1, 2, or ≥3) and the presence or absence (yes/no) of each of the five types of maltreatment (physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect) mutually adjusted. For each of the outcomes, we adjusted for age,

sex, ethnicity, deprivation, and educational attainment, as these likely to have affected the exposure and the recall of) child maltreatment as well as TL.

Three additional analyses were undertaken. Firstly, the models were then re-run also adjusting for symptoms of depression and PTSD. These were not included as the main analysis because they could be mediators. Secondly, the frequency of maltreatment was categorised as rarely, sometimes, or often/very to examine the dose-response relationship. Thirdly, moderator analyses were conducted on the main model to investigate whether the association between child maltreatment and TL varied by age (<60 vs ≥60 years), sex (male vs female), able to confide (none vs any), social visits (none vs any), alcohol drinking (≥ vs < 14 units/week), depression (yes vs no), and PTSD (yes vs no). These moderators were analysed separately to avoid dimensionality problem, and were selected as there were prior evidence showing the effect of trauma on health could differ by these variables[24 25].

Ethics approval

UK Biobank received ethics approval from the Northwest Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki. Direct dissemination of the results to participants is not possible/applicable.

Results

Of the 153,623 UK Biobank participants who completed the mental health questionnaire, 8,595 (5.6%) and 3,280 (2.1%) were excluded due to no valid TL and covariate data respectively. Therefore, the sample size was 141,748 (Supplementary Figure 1).

Table 1 shows the participants' characteristics broken down by child maltreatment frequency. Both any type of child maltreatment and multiple types of child maltreatment were more commonly reported by female, Black and South Asian participants, those who lived in more deprived areas, those who did not have a university degree, and those who reported more symptoms of depression and PTSD. There was no association between child maltreatment and TL in univariate analysis (Table 1).

After adjusting for sociodemographic characteristics, participants with ≥3 types of maltreatment presented with the shortest TLs (β [95% CI] -0.05 [-0.07, -0.03] *P* < 0.0001), followed by those with 2 types of maltreatment (β [95% CI] -0.02 [-0.04, 0.00] *P* = 0.02), referent to those who had none (Figure 1). The TL of those who had 1 type of maltreatment were not significantly different from those who had none. When mutually adjusted, physical abuse (β [95% CI] -0.05 [-0.07, -0.03] *P* < 0.0001), and sexual abuse (β [95% CI] -0.02 [-0.04, 0.00] *P* = 0.02), were independently associated with shorter TL. When adjusted for depression and PTSD, the TL of participants with ≥3 types of maltreatment were still significantly shorter (β [95% CI] -0.04 [-0.07, -0.02] P = 0.0008) and that with physical abuse remained significant (β [95% CI] -0.05 [-0.07, -0.03] P < 0.0001). (Supplementary Figure 2). Dose-response relationships were observed by frequency of physical and sexual abuse (Table 2).

Table 3 shows the moderation analysis results. The associations between child maltreatment and TL were generally consistent across subgroups except for age where the association was weaker in older people ($\beta_{interaction}$ [95% CI] 0.01 [0.00, 0.03], P = 0.04).

Discussion

Our study demonstrates that child maltreatment was associated with TL in middle and older-aged adults. The associations were strongest for physical and sexual abuse and there was also evidence of

dose-response relationships for these two types of abuses. Depression and PTSD appeared to partially explain some of the association. These findings echoes previous studies in physical [26] and mental [27] health outcomes.

Strengths and Weaknesses

One of the strengths of using UK Biobank was a large sample size (*N* = 141,748) of middle and older age adults, providing sufficient power to detect differences, even by sub-group. Additionally, we were able to explore the association with TL of both the frequency and types of maltreatment, and therefore, demonstrate a dose-response relationship for both physical and sexual abuses. Some limitations and considerations should be acknowledged. We hypothesised the number of types of maltreatment indicate cumulative association regardless of the combination, but we were not able to provide such evidence in this study. There were small number of cases in each of the combinations of the maltreatment types. There could be residual confounding in this study, e.g. we did not adjust for antidepressant use. Child maltreatment was recalled by participants rather than having it recorded prospectively, a common disadvantage of the long-term outcomes of childhood exposures. This could have led to recall bias if attribution of childhood events is associated with mental health problems. Another limitation was that child maltreatment information was limited to type and frequency and the temporality of the exposure was not measured. Last but not least, the potential mechanism between child maltreatment and TL were not examined, which warrants future studies.

Comparison with existing literature

In this study, we found associations between childhood maltreatment and TL in middle- and older-aged adults, which meaningfully extends the literature. While previous studies reported similar findings in children, young adults, middle-aged women and older adults [1 14 15 28], the sample sizes were

small and very often not sampled from the general population [1]. In the Nurses' Health Study II [15], presence of abuse was associated with shorter TL even though no graded association by severity was observed. This was in contrast to our findings that both number of types and frequency of maltreatment had dose-response associations with TL.

Interestingly, the association between maltreatment and TL was slightly weaker in older individuals, which is in contrast to a previous study that child maltreatment is directly correlated with the rate of telomere attrition [29]. However, we should note that our findings might be subject to survival bias, as people who had maltreatment could die earlier and might not be included in UK Biobank [30] or reflect exposome differences [12].

While it is not entirely clear how child maltreatment could accelerate telomere shortening, psychological stress is a potential mechanism [31]. It has been consistently shown that child maltreatment sometimes leads to a traumatic stress response, which could alter the victim's long term response to stress [32]. Cumulative chronic stress could induce higher oxidative stress levels [33], which accelerate telomere attrition [34], and lower telomerase activity [35], which inhibits telomere maintenance[31]. These ultimately manifest as a measurable difference in TL in later life.

Implications

It is still under debate whether TL is a causal agent for clinical diseases [36]. TL remains a modest marker of biological ageing with significant inter-individual variability [37]. Even though genetically predicted shorter TL has been associated with higher risk of cardiovascular disease [38], cardiovascular disease [39] is not a common complication of dyskeratosis congenita, a genetic disorder resulting in critically short TL. Regardless of the biological role of telomeres, the association we have shown in this study indicated that individuals suffering maltreatment in childhood are likely to suffer from shorter telomere length, possibly an indicator of biological ageing. This may be able to explain why

victims of child maltreatment experience multitudes of mortality and morbidity risks [26 27 40 41] – the elevation in risk is simply a reflection of the victims 'true' biological age [42 43]. If this hypothesis is true, interventions that could reduce the telomere shortening process (e.g. by reducing chronic perceived stress [32]) among maltreatment victims might be effective in preventing multiple conditions.

Conclusions

Our findings showed that child maltreatment is associated with shorter TL in middle- and older-aged adults, independent of sociodemographic and mental health factors.

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Declaration of Interest:

None

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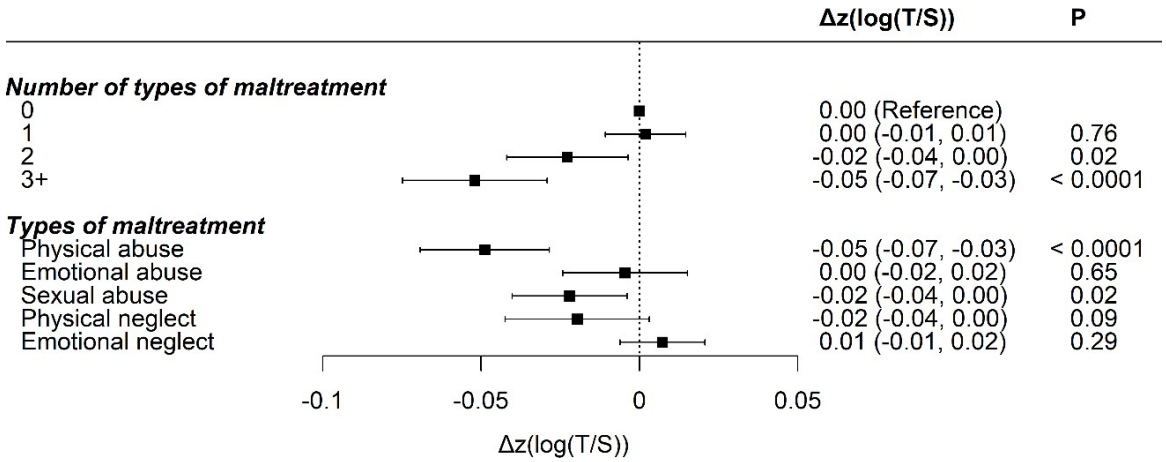
Author contribution

Ziyi Zhou wrote the first draft of the paper and analysed the data. Camilla K M Lo, Ko Ling Chan, Rachel S Y Chung, Jill P Pell, Helen Minnis, and Paul G Shiels interpreted the data and critically revised the manuscript. Patrick Ip conceptualised this study, interpreted the data, and critically revised the manuscript. Frederick K Ho conceptualised this study, analysed the data, and critically revised the manuscript. All authors approved the final submitted manuscript.

Data availability

The data that support the findings of this study can be requested from the UK Biobank: https://www.ukbiobank.ac.uk/

Figure 1. Association between maltreatment frequency and telomere length



Adjusted for age, sex, ethnicity, deprivation, and education attainment

Table 1. Participant characteristics

	Number of maltreatment types				
	0	**1**	**2**	**3+**	**P-value**
Total n	94,932	28,682	10,755	7,379	
Age, mean (SD)	56.11 (7.71)	55.78 (7.73)	55.23 (7.79)	54.12 (7.71)	< 0.0001
Male	42,809 (45.1)	12,880 (44.9)	4238 (39.4)	2349 (31.8)	< 0.0001
Ethnicity					< 0.0001
White	93,090 (98.1)	27,705 (96.6)	10,251 (95.3)	6818 (92.4)	
South Asian	600 (0.6)	295 (1.0)	130 (1.2)	109 (1.5)	
Black	395 (0.4)	210 (0.7)	137 (1.3)	193 (2.6)	
Chinese	129 (0.1)	101 (0.4)	49 (0.5)	41 (0.6)	
Mixed	336 (0.4)	186 (0.6)	92 (0.9)	120 (1.6)	
Any other	382 (0.4)	185 (0.6)	96 (0.9)	98 (1.3)	
Deprivation index, mean (SD)	-1.90 (2.72)	-1.56 (2.88)	-1.29 (3.02)	-0.80 (3.25)	< 0.0001
College or University degree	44577 (47.0)	12915 (45.0)	4585 (42.6)	2972 (40.3)	< 0.0001
PHQ-9, mean (SD)	2.20 (3.05)	3.23 (3.86)	4.22 (4.65)	5.45 (5.70)	< 0.0001
PCL-S, mean (SD)	1.23 (2.19)	2.02 (2.92)	2.97 (3.56)	4.38 (4.39)	< 0.0001
Log(T/S ratio), z-score, mean (SD)	0.05 (0.99)	0.06 (1.00)	0.06 (1.00)	0.07 (0.98)	0.16

Numbers presented are mean (SD) unless otherwise specified.

Table 2. Association between child maltreatment frequency and telomere length

	Rarely true		**Sometimes true**		**Often/very often true**	
	β (95% CI)	**P**	**β (95% CI)**	**P**	**β (95% CI)**	**P**
Physical abuse	**-0.02 (-0.04, 0.00)**	**0.01**	**-0.05 (-0.07, -0.03)**	**<0.0001**	**-0.08 (-0.12, -0.03)**	**0.0004**
Emotional abuse	-0.01 (-0.03, 0.01)	0.24	**-0.03 (-0.05, -0.01)**	**0.008**	-0.02 (-0.05, 0.01)	0.29
Sexual abuse	-0.01 (-0.03, 0.01)	0.40	**-0.04 (-0.07, -0.02)**	**0.002**	**-0.07 (-0.12, -0.02)**	**0.006**
Physical neglect	-0.03 (-0.09, 0.04)	0.44	0.00 (-0.04, 0.05)	0.85	0.03 (-0.01, 0.06)	0.10
Emotional neglect	-0.01 (-0.06, 0.04)	0.75	0.02 (-0.03, 0.06)	0.40	0.02 (-0.02, 0.06)	0.37

Adjusted for age, sex, ethnicity, deprivation, and education attainment.

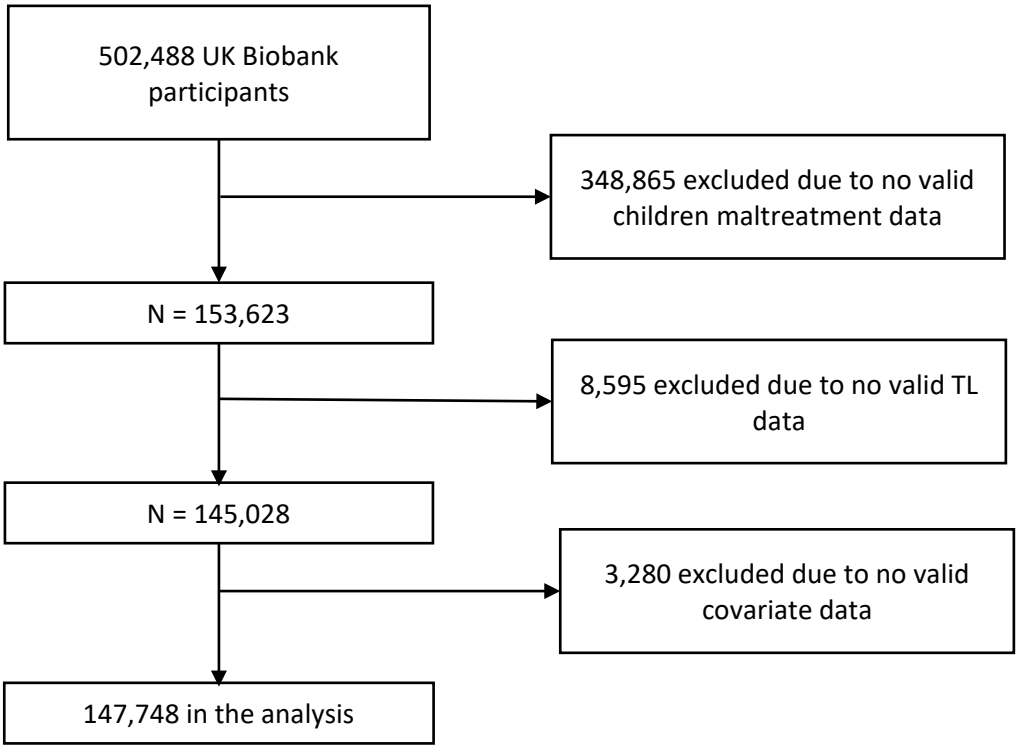
Table 3. Moderation analysis for the association between child maltreatment and telomere length

	$\beta_{interaction}$ (95% CI)	**P**
Age≥60 years	**0.01 (0.00, 0.03)**	**0.04**
Male	0.01 (0.00, 0.02)	0.09
Able to confide	0.01 (-0.01, 0.02)	0.35
Social visits	0.03 (-0.08, 0.14)	0.64
Alcohol drinking	0.01 (0.00, 0.02)	0.19
Depression	-0.01 (-0.02, 0.01)	0.28
PTSD	-0.01 (-0.02, 0.00)	0.18

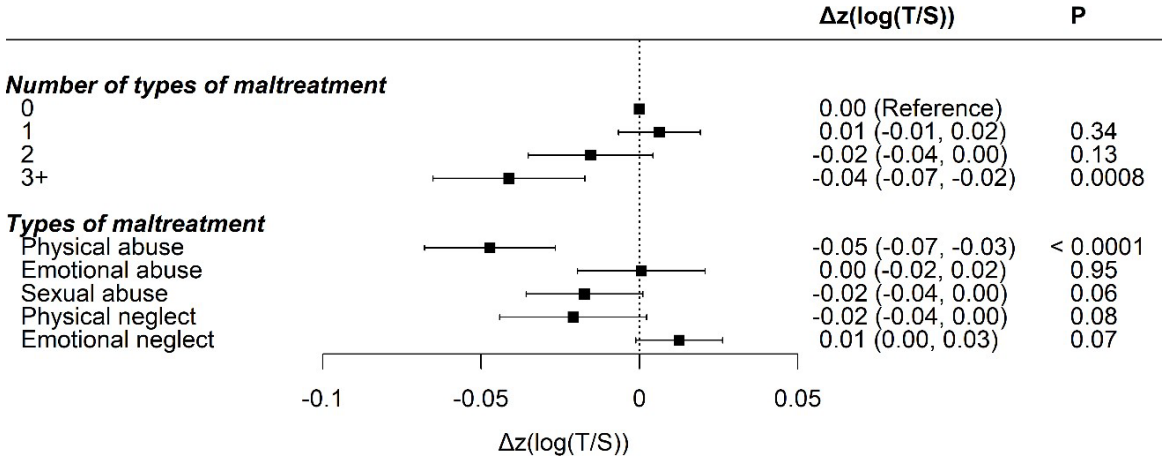
Adjusted for age, sex, ethnicity, deprivation, and education attainment.

Supplementary materials

Supplementary Figure 1. Participant flowchart



Supplementary Figure 2. Association between maltreatment frequency and telomere length independent of depression and PTSD



Adjusted for age, sex, ethnicity, deprivation, education attainment, depressive symptoms, and PTSD symptoms