Trust, Inflammatory Biomarkers, and Adversity: A Novel Investigation & Clinical Implications

Journal:	*British Journal of Guidance and Counselling*
Manuscript ID	CBJG-2020-0139.R3
Manuscript Type:	Research Article
Keywords:	Counselling psychology, Person-centred therapy, Positive psychology, Qualitative methods, Research

Title

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Abstract

Survivors of adversity and trauma experience high levels of distress, interpersonal challenges and poor physical health. We investigated the role of trust in trauma -related psychological and physiological responses. Serum concentrations of C-Reactive Protein, Cortisol, Tumour Necrosis Factor-alpha, and Interleukin-8 from 25 participants in Scotland were measured. Trauma history and experience was assessed using the Childhood Trauma Questionnaire and Life Events Checklist. Trauma symptomatology was measured by the Impact of Event Scale. Interpersonal trust was measured using the Trust Scale. Trauma history and inflammatory biomarker concentrations were significant predictors of trauma symptomatology with trust as a covariate. Psychological and

physiological responses after trauma seem strongly linked. Trust can mediate distress and physiology in adversity.

Key words: Interpersonal trust, inflammation, adversity, psychological trauma, health, relational variables

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Introduction

Psychological Trauma: Prevalence and Definitions

The lifetime prevalence of potential psychological traumas is shown to be as high as 80.7%, and the lifetime prevalence of PTSD 7.4% (deVries & Olff, 2008). Significant previous evidence suggests that there is a connection between experiencing psychological trauma, and the physiological stress response (Lagraauw *et al*., 2015). Further studies have found a connection between the psychological and physiological responses to trauma (Ippoliti *et al*., 2013). Psychological trauma refers to a broader range of experiences than posttraumatic stress

disorder (PTSD). It includes the concept of complex/relational trauma, which allows for consideration of several manifestations not necessarily included in the diagnosis of PTSD. For example, the duration and frequency of the trauma, the age of the individual when the trauma began, and whether it was interpersonal or not are all considered as part of a complex trauma diagnosis (Wamser-Nanney & Vandenberg, 2013). Interpersonal traumas are those that result from the deliberate actions of another individual, and therefore perceptions of safety and trust are often negatively affected in survivors (Wamser-Nanney & Vandenberg, 2013). Complex/interpersonal trauma is also highly prevalent with nearly a quarter of young adults (24.1%) having experienced sexual abuse alone in the UK (Radford et al., 2011). In this paper, we will often utilise the term 'adversity' as a more inclusive concept to refer to traumatogenic experiences, such as complex/relational trauma, life events, and psychological trauma symptomatology, as measured in the present study.

Chronic Distress, Psychological Trauma and Physiological Responses

The interlink between the brain and the immune system (or 'body – mind', as it is more widely known) has been dominating the field of psychoneuroimmunology for decades. What we know so far about these mechanisms is summarised succinctly by Mariotti (2015). Such research has been focusing largely on Hormonal Pituitary Adrenal (HPA)- axis dys-regulation. The understanding of the molecular mechanisms that underlie brain architectural changes and medical conditions linked to chronic stress seems to be just at the beginning. Research has centred primarily on the signalling functions of those molecules that are directly induced by stress through the activation of the sympathetic-adrenal-medullary and HPA networks (Mariotti, 2015). There is certainly consensus that psychological stress can induce the acute phase response commonly associated with infections (due to pathogens, i.re viruses and bacteria) and tissue damage and increase the levels of circulating cytokines and of various

biomarkers of inflammation (Black, 2002). The interlink between the stress response and inflammation (i.e. the body's defence response to threat) elicited by the immune system can be explained from an evolutionary perspective (Mariotti, 2015). In specific, the stress response is an adaptive process developed by co-opting the immune system mechanisms of defence (Maier & Watkins, 1998). In this context, a psychological stressor, is perceived as a threat, which is potentially harming. Consequently, the threat perception sets in motion a neuroimmune circuit that stimulates the immune system to mount a protective reaction. Such reaction intends to prevent damage, repair it and restore homeostasis. This neuroimmune communication is bidirectional. Cytokines, which are substances produced by stress-stimulated response, also convey feedback to the nervous system, thus further modulating the release of stress hormones. Brain activity that regulates behaviour, cognitive and emotional functions is also further stimulated. In brief, in a situation of chronic stress and potential (complex) psychological trauma, the neuroimmune axis can be overstimulated (Mariott, 2015). It consequently can break down, thus causing neuroendocrine/immune imbalances, which establish a negative loop, that is, a state of chronic low-grade inflammation, a possible prelude to illness processes and various -often chronic -conditions (Maier & Watkins, 1998). Diseases whose development has been linked to both stress and inflammation include cardiovascular dysfunctions, diabetes, cancer, autoimmune conditions, and mental illnesses, such as depression and anxiety disorders (Dantzer et al., 2008), all of which have been becoming prevalent.

These mechanisms are more evident and clear in the case of illnesses caused by psychosocial triggers such as power imbalances in relationships, such as occupational health. In these cases research has shown that priority should be given to creating and maintaining psychosocial conditions respectful of human physiological, emotional and social needs: in other words, the psychological environments we live and function in should stimulate safety and growth, while supporting individuals and teams through challenges. Elements like unbalanced interactions,

unequal power dynamics and imposed demands, that are quite common competitive and even abusive environments, can sharpen tensions and exaggerate the psychosocial strain to the point of causing illness, yet they usually remain overlooked and uncontrolled (Rosenthal & Alter, 2012). Despite the compelling evidence so far, the links between relational and psychosocial variables in relation to distress, and physiological health still remain under-researched. Furthermore, although we understand more about the links between distress and illness, a focus on psychological trauma and illness processes is definitely required. Limited existing evidence is compelling and is summarised below.

The impact of psychological distress and relational variables on physiological health was shown by Epel *et al*. (2010), in research which focussed upon how empathy affected telomerase activity. The activity of telomerase, an enzyme associated with both cellular and organism aging, was significantly reduced in leukocytes following chronic relational stress in a USA sample (Epel *et al*., 2009). This translated to a reduction in the proportion of circulating leukocytes and increase in circulating neutrophils, potentially causing downstream issues within the immune response (Epel *et al*., 2010). Further USA – based research by Jacobs *et al*. (2011) investigated the influence of mindfulness on telomerase activity. Mindfulness is the act of fixing one's attention on a specific object or action in the present moment, and has been found to reduce stress levels and increase empathy. Those who were most mindful were found to have the greatest level of telomerase activity (Jacobs *et al*., 2011), therefore demonstrating the influence that relational variables can have on physiological health.

In addition to the evidence above surrounding telomerase activity, another physiological system found to be altered following adversity is the inflammatory response. Several inflammatory mediators have been investigated so far, including cortisol, C-Reactive Protein (CRP), Tumour Necrosis Factor-alpha (TNF-α), and Interleukin-8 (IL-8), which can act as

biomarkers of the physiological effects of psychological trauma (Dhabhar, 2013). An acute inflammatory response is needed following injury or infection to repair tissues and eliminate pathogens (Fay, 2010). However, chronic inflammation leads to an increased chance of developing chronic health conditions, such as cardiac disease (Ridker *et al*., 2000). Furthermore, recent evidence from the USA highlights the links between inflammation, mental health and physical health, especially so in terms of depression (Kiecolt-Glaser et al., 2015). Depression is a common comorbidity in patients with psychological trauma. This further points to potential links between psychological trauma, especially when experienced in childhood, and overactivation of inflammatory responses, which the manifests in illness process both in mental and physical health (Reus et al., 2017;Slavich & Irwin, 2014).

Cortisol is a glucocorticoid hormone which has previously been shown to suppress the inflammatory response by preventing maturation of dendritic cells and lymphocytes, and inducing apoptosis of eosinophils, basophils, and T-cells (Gu *et al*., 2012). Cortisol also causes a shift in the release of cytokines, decreasing the pro-inflammatory response and increasing the anti-inflammatory response (Calcagni & Elenkov, 2006). Evidence concerning cortisol response following traumatic experiences is somewhat contradictory, with some studies finding an increase in cortisol concentration in individuals with PTSD (Bremner *et al*., 2003; Elzinga *et al*., 2003; Lemieux & Coe, 1995). Other studies have found a decrease in cortisol concentration in PTSD patients (Glover & Poland, 2002; Thaller *et al*., 1995; Yehuda *et al*., 2000).

TNF-α is a pro-inflammatory cytokine, produced mainly by T-cells and macrophages as part of the inflammatory response, which plays a role in inducing a fever, regulating blood coagulation, and promoting the adhesion of leukocytes (Zelová & Hošek, 2013). TNF-α concentration was found to be significantly increased in PTSD patients, when compared with

healthy individuals. Individuals living in lower socioeconomic status (SES) groups are likely to be exposed to greater levels of trauma due to increased exposure to crime and poverty levels. TNF-α concentration was found to be greater in those living in lower SES groups (Steptoe *et al.*, 2002; Taylor *et al*., 2006).

IL-8 is also a pro-inflammatory cytokine produced by macrophages during the inflammatory response in order to amplify the response via the recruitment and activation of polymorphonuclear leukocytes (PMNs) (Elenkov, 2008). In PTSD patients, IL-8 concentration was found to be significantly lower than that in healthy individuals (Song *et al*., 2007). This suggests that an unregulated glucocorticoid response had caused cortisol concentration to rise, which in turn led to the suppression of IL-8 release as it is a pro-inflammatory cytokine (Calcagni & Elenkov, 2006).

CRP is an acute phase protein, which is released by the Kupffer cells in the liver. Interleukin-6 (IL-6) is responsible for initiating CRP production (Calcagni & Elenkov, 2006). CRP has a pro-inflammatory effect via activation of the classical complement pathway, which in turn enhances the permeability of blood vessels and the extravasation of leukocytes, and the stimulation of cytokine release from macrophages (Sproston & Ashworth, 2018). Additionally, the release of IL-8 from peripheral blood mononuclear cells (PBMCs) is also stimulated by the classical complement pathway (Markiewski & Lambris, 2007). The aforementioned studies by Steptoe *et al*. (2002) and Taylor *et al*. (2006) also measured CRP concentration in individuals living in lower SES groups, which was found to be greater than those living in higher SES groups. Copeland *et al*. (2014) measured CRP concentration in survivors of childhood bullying. The results showed increased CRP concentrations in those who had experienced bullying compared to those that had not. This observation was still evident into adulthood.

Trust and Trauma: Psychological and Physiological Responses

Trust is a relational variable which has been defined as "a psychological state comprising the intention to accept vulnerability based upon the positive expectations of the intentions or behaviour of another" (Rousseau *et al*., 1998). Experiencing complex trauma, particularly episodes of interpersonal complex trauma, has a negative impact on psychological and physical health and wellness. Survivors of such trauma tend to present with high level of psychological distress and pathology, including depression, anxiety, low self -esteem and relational difficulties, as well as poor physical health, functional disability and even inflammatory conditions (Leserman, 2005; Cohen et al., 2008). Interpersonal trauma ruptures basic assumptions of trust, safety and intimacy (Foy *et al.*, 2001; Ratcliffe *et al*., 2014). In addition, rebuilding trust has been found to act as an important factor in psychosocial recovery of survivors (Chouliara *et al*., 2011;2014;2017; Chouliara & Narang, 2017), thus highlighting a link between interpersonal trust and psychological response to adversity. Interestingly recent research in Hong Kong investigated trust within intimate relationships in association with a history of childhood sexual abuse (CSA), depression and pro-inflammatory biomarkers. CSA and trust of partners were revealed to have significant associations with IL-6 level in adulthood. Trust played a significant mediating role between CSA and adulthood levels of IL-6. These findings are very promising about the potential role of trust in physical health and illness process in adult survivors of CSA (Leng et al., 2020).

The Present Study: Scope and Rationale

The present study aimed to investigate the potential role of interpersonal trust in the relationship between experiencing psychological complex trauma and the physiological inflammatory response. The study focused on the inflammatory response following complex trauma, rather than PTSD, as only very limited evidence exists in this area.

In short, inflammation is considered to be the body's response to a threat. Interpersonal trust is likely to be a mechanism for regulating and responding to emotional threat, and managing anxiety

levels. We are putting trust forward as a relational factor that mediates adversity and illness processes, that is, the relational factor that mediates psychological and physiological processes. It is therefore hypothesised that those who have experienced the greatest level of trauma will have the lowest levels of trust, and also decreased cortisol concentrations due to a deregulated glucocorticoid response. This decrease in cortisol concentration is expected to cause an increase in pro-inflammatory cytokine release, leading to an increase in TNF-α, IL-8, and CRP concentrations in survivors of complex trauma. Finally, it is anticipated that low levels of trust will correlate with higher levels of trauma exposure and more negative psychological symptoms. Therefore, it is expected that trauma history and inflammatory biomarker concentrations will be able to significantly predict severity of psychological trauma symptoms, and that interpersonal trust will act as a mediating factor in this prediction.

Research Hypotheses

The following hypotheses are investigated in this study:

1. Levels of trust will be lower in those who have experienced more traumas and or present with higher levels of posttraumatic symptoms.

2. Complex/relational trauma will cause deregulation of the HPA-axis, leading to a decrease in cortisol concentration.

3. Decreased cortisol concentrations will cause an increase in Th1 cytokine secretion, and therefore concentrations of TNF-α, IL-8 and CRP will be higher in those who have experienced complex/relational trauma.

4. Low levels of trust will correlate with a high amount of complex trauma experienced and an increased inflammatory response.

Methodology

Sample and Procedure

A total of 30 volunteers, university staff and students, who had not been diagnosed with any mental health or inflammatory or chronic pathological medical condition at the time of testing, aged between 19 and 62 years were asked to complete four standardised psychological questionnaires. The study cohort consisted of 9 males and 21 females. A venous blood sample was obtained from 25 participants. Venepuncture was unsuccessful on the remaining 5 participants because they did not attend the appointment for blood sample. Any prescription medication being taken by volunteers was disclosed at the time of participation. Any volunteers who were taking medication for inflammatory conditions were excluded from participating in the study. Ethical approval was granted by a university in Scotland. Testing was tolerated well by all participants and no incidents of psychological or physiological distress were recorded. For a sample size of 30 participants when only psychological variables were analysed, and a significance level of 5%, the observed power for multiple regression analyses with five predictors was 0.60 (Soper, 2015). For regression analyses when physiological variables were included, the sample size decreased to 25. These tests utilised nine predictors and the statistical power was 0.30 (Soper, 2015).

Psychological Measures

We utilised a battery of widely used scales shown to have good psychometric properties:

1. The Childhood Trauma Questionnaire (CTQ) (Pennebaker & Susman, 2013), consisting of the Childhood Traumatic Events (CTE) scale and the Recent Traumatic Events (RTE) scale. The CTQ is a brief survey of six early traumatic experiences (i.e. death of loved one, divorce, violence, sexual abuse, illness or other), and assesses individual's understanding and experiencing of these traumas in childhood and in adulthood (within the last three years prior to assessment).

2. The Life Events Checklist (LEC) (Blake *et al*., 1995) is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. It assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items. Items/events included: Natural disaster, Fire/explosion, Car accident, Other serious accident, Exposure to toxic substance, Physical assault, Assault with weapon, Sexual assault, Other unwanted sexual experience, Combat, Captivity, Life-threatening injury/illness, Severe human suffering, Witness violent death, Sudden, unexpected death of loved one, Caused serious injury/death of another, Other very stressful event. The LEC was scored using a 5-point scale to allow for consideration of the self - reported severity as well as typology of each participants' trauma exposure, that is, whether they had ranked each scenario as "happened to me", "witnessed it happening to someone else", "does not apply" etc. This scale is usually scored as a checklist by listing the number and type of life events experienced. However, in our study self -reported severity of impact and closeness to the experience was as important as the events experienced, because of the trauma specific focus and its potential impact on immunological processes. For this reason, we utilised a Likert – type scale to cover as much of the variance as possible.
3. The Impact of Event Scale (IES-R) (Weiss & Marmar, 1995), comprising the avoidance, intrusions, and hyperarousal subscales, which is a scale measuring psychological trauma symptomatology. The IES-R is a 22-item self-report measure (for DSM-IV) that assesses subjective distress caused by traumatic events. It is a revised version of the older version, the 15-item IES (Horowitz et al., 1979). The IES-R contains 7 additional items related to the hyperarousal symptoms of PTSD, which were not included in the original IES. Respondents are asked to identify a specific stressful life event and then indicate how much they were distressed or bothered during the past seven days by each "difficulty" listed.

Items are rated on a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The IES-R yields a total score (ranging from 0 to 88) and subscale scores can also be calculated for the Intrusion, Avoidance, and Hyperarousal subscales. In general, the IES-R (and IES) is not used for diagnostic purposes. Having said that, cut off scores for a preliminary diagnosis of PTSD have been cited in the literature.

4. The Trust Scale (Rempel *et al*., 1985) is a 17 – item scale, designed to gauge levels of trust within close relationships. The scale comprises three subscales: predictability, dependability, and faith. Each item is answered based on a 7-point Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree). The scale is meant to focus on intimate relationships with a partner. However, we have had to adjust the instructions by saying the people could answer with any close relationship in mind so that we did not exclude those who were not in an intimate/romantic relationship at the time of assessment.

Biological Testing

A 42ml venous blood sample was taken from 25 participants; 4.8% sodium citrate (Sigma-Aldrich Ltd., Gillingham, UK) was added to the blood samples to separate the plasma, and 1M calcium chloride (Sigma-Aldrich Ltd., Gillingham, UK) was added to the plasma to form a platelet plug. The serum was then removed and frozen at -80°C. The concentration of CRP, cortisol, TNF-α, and IL-8 in the blood serum was measured using Enzyme-Linked Immunosorbent Assays (ELISA). These biomarkers were chosen for the study as they are classical mediators of the inflammatory response. Sandwich ELISA kits (Life Technologies Ltd., Paisley, UK) were used to quantify the concentrations of CRP, TNF-α, and IL-8, whereas a competitive ELISA kit (R&D Systems, Abingdon, UK) was use measure the concentration of cortisol. All ELISAs were conducted according to the manufacturer's instructions.

Results

Descriptive statistics

The mean (± standard deviation), median, and range are reported to provide an overview of the psychological and physiological profile of the study cohort and the distribution of the variables in the cohort (See Table 1)

[TABLE 1 ABOUT HERE]

Out of a maximum possible total score on the CTE scale of 114, the mean score for this cohort was 25.67 (±14.74). The maximum possible score on the RTE scale was 112, and the mean for the present study cohort was 22.00 (± 9.90). The LEC had a maximum possible score of 80 and the mean score was 40.87 (± 13.82). The mean score on the IES was 4.09 (± 2.84), out of a maximum possible score of 88. The mean trust score was 19.70 (±8.40), out of a maximum possible score of 119. The mean concentration of CRP was $1.49x10^{-3}$ mg/ml and for cortisol was 59.35 ng/ml. TNF-α had a mean concentration of 19.22 pg/ml in this cohort and the mean concentration of IL-8 was 4.01 pg/ml.

Interactions between Psychological Trauma History and Symptoms, Interpersonal Trust and Biomarkers

A hierarchical regression was conducted to identify whether trust acts as a mediating factor (covariate) when using exposure to traumatic events (predictor/independent variable) to predict psychological trauma symptomatology, and also when using inflammatory biomarker concentration (predictor/independent variable) to predict trauma symptomatology (dependent variable/outcome variable). Therefore, traumatic symptomatology was the outcome variable, traumatic exposure and inflammatory biomarkers were predictors and trust was the mediator in the regression analysis. Measures of trauma history were analysed individually, and also

combined, to provide a composite variable representing an overview of traumatic experience. Similarly, concentrations of each inflammatory biomarker were analysed separately as individual predictors, and also as a composite measure of inflammation. Variables were combined due to lack of previous evidence, which could inform prediction models. Furthermore, trauma is a spectrum which comprised exposure, experience and types of traumatic events. On the other hand, we do not have clear understanding how inflammatory biomarkers might be interacting. We do know that their dynamic interaction might be leading to illness processes. Hence the utilisation of composite variables. Trust was included as a covariate in all analyses. Table 2 shows the results.

[TABLE 2 ABOUT HERE]

CTE, RTE, and LEC individually were not found to be significant predictors of trauma history and trauma symptomatology. However, a significant predictor was found when trust was introduced as a covariate between combined psychological trauma exposure and psychological trauma symptomatology (p=0.013). The trauma measure that had the largest weights in this prediction was RTE (Beta = 0.317).

Individual inflammatory biomarkers also showed no significant predictive power on trauma symptomatology. Conversely, when a combined overview of inflammation (i.e. composite of CRP, cortisol, TNF-α, and IL-8 concentrations) was considered, biomarker concentration was found to be a statistically significant predictor of psychological trauma symptoms, when including trust as a covariate (p=0.001). The inflammatory biomarker which had the strongest influence in this prediction was TNF-α (Beta = -0.113). Creating a combined variable for inflammatory biomarkers by adding all biomarkers variables together was deemed necessary and justified. This is because we have no limited previous evidence to indicate a conclusive pattern of interaction of all these biomarkers which we could use to inform a regression model.

There is however indirect evidence to indicate synergistic action of these biomarkers which may, in turn, indicate a link with distress and health via illness processes.

The application of hierarchical regression in psychological and psychotherapy/counselling research presents with challenges (Petrocelli et al., 2003). These include small samples sizes and nonlinearity. Our study is not an exception. We did not specifically check for homoscedasticity. A small number of participants with chronic inflammatory conditions were excluded from the sample, so the likelihood of presence of outliers in inflammatory biomarker variables would have been minimised, thus providing support towards linearity. There was no multicollinearity in the data. A correlation matrix was conducted and no correlation above 0.8 were identified. The Durbin-Watson statistic was not run. We did not check homoscedasticity by plotting standard residuals. We did not run P-P plots to check for normality of residuals and we did not conduct Cook Distance values. Some of these assumptions would have been more relevant if we were testing the 'fit' of a particular regression model based on previous evidence. This was not the case here.

In summary:

Hypothesis 1 was confirmed: Levels of trust were positively associated with levels of traumatic symptomatology.

Hypothesis 2 was partly confirmed: Childhood trauma, recent traumatic events and life events were not significant predictors of trauma symptomatology. However, recent traumas on adulthood did significantly predict traumatic symptomatology when trust mediated.

Hypotheses 3 and 4 were partly conformed: Proinflammatory biomarkers were not found significant predictors of trauma symptomatology as individual predictors. However, with trust as a covariate the composite variable of all proinflammatory biomarkers was a significant

predictor of trauma symptomatology. TNF-A was the most powerful predictor of all biomarkers tested.

Discussion

Psychological and physiological profile of participants

The mean scores on the CTE and RTE scales of the CTQ were 25.67 and 22.00 respectively. Since no standard scoring protocol was available for the CTQ, these results are not easily comparable to the findings of previous studies. However, although comparisons cannot be easily made to previous studies, CTQ scores can still be compared between individuals within the present study, and the results can be used to correlate childhood trauma with biomarker concentration. The mean LEC score for the present cohort was 40.87. Once again, since the present study opted to score the LEC on a 5-point scale, as opposed to simply counting how many events that the participants had experienced, the results are not directly comparable with previous research. As with the CTQ results, comparison between individuals within the present study is still possible, and correlations between life events experienced and biomarker concentrations can still be made. The mean CRP concentration was $1.49x10^{-3}$ mg/ml and the results ranged from $5.00x10^{-5}$ mg/ml to $7.37x10^{-3}$ mg/ml. Previous evidence has shown the average CRP concentration in healthy individuals to be below $1.00x10^{-2}$ mg/ml (Xu *et al*., 2014). Karadag *et al*. (2008) measured CRP concentration in adults with diagnosed Chronic Obstructive Pulmonary Disease (COPD), providing an indication of the mean CRP concentration that would be expected in the presence of chronic inflammation. They found the mean CRP concentration in these patients to be $1.97x10^{-2}$ mg/ml. Since all of the measurements obtained in this study are below this value, it suggests that there is no evidence of increased inflammation within this cohort. The results do correlate with previous studies by Flock *et al*. (2014) and Hermsdorff *et al*. (2012), which found healthy adults to have a mean CRP

concentration of $5.00x10^{-4}$ mg/ml and $8.30x10^{-3}$ mg/ml respectively. The mean cortisol concentration was 59.35 ng/ml and the results ranged from 33.37 ng/ml to 82.05 ng/ml. A previous study by Konishi *et al*. (2012) showed the mean cortisol concentration in healthy individuals to be around 41.6 ng/ml. Gill *et al*. (2008) measured cortisol concentration in adults with diagnosed PTSD and the results suggested that a substantially lower mean cortisol concentration is expected in individuals with a chronic psychological stress condition (2.7 ng/ml). Since the results of the present study are significantly greater than those found in PTSD patients, there is no indication of chronic psychological stress being present in this cohort. The mean TNF-α concentration was 19.22 pg/ml and the results ranged from 9.74 pg/ml to 56.05 pg/ml. Results from previous studies show that the mean TNF-α concentration in healthy individuals is expected to be below 10 pg/ml (Derin *et al*., 2008; Goyal *et al*., 2012). Rabinovich *et al*. (2003) measured TNF-α concentration in individuals with diagnosed COPD, and found the mean TNF-α concentration to be 17pg/ml. The mean TNF-α concentration in the present study is greater than both the healthy concentration identified by Derin *et al*. (2008) and Goyal *et al*. (2012), and also the mean concentration found in a population with a chronic inflammatory disease (Rabinovich *et al*., 2003). This could suggest that inflammation is present within the current cohort. The mean IL-8 concentration was 4.01 pg/ml and the results ranged from 0 pg/ml to 13.56 pg/ml (excluding three samples that suggested a negative IL-8 concentration). Previous evidence suggests that IL-8 concentration in healthy individuals should be between 5 pg/ml and 60 pg/ml (de Lira Freire *et al*., 2004; Mikova *et al*., 2001; Arican *et al*., 2005; Sun *et al*., 2005). Ozol *et al*. (2005) found the mean IL-8 concentration in patients diagnosed with COPD to be 490 pg/ml. This demonstrates that IL-8 concentration would have been expected to be considerably greater than the mean concentration found in this cohort if life-threatening or chronic inflammation were present, which is not the case in our sample. The mean IL-8 concentration found in the present study is low compared to the

previously defined healthy range of 5 pg/ml to 60pg/ml. Three samples also returned negative IL-8 concentrations. These findings suggest that the samples were towards the limit of the detection of the assay. The lowest standard used in the assay had an IL-8 concentration of 15.60 pg/ml. Since the samples all had an IL-8 concentration of below this, questions are raised as to whether there were confounded factors could be present, which could explain these low concentrations in our sample. All of the samples returned an IL-8 concentration towards the lower limit of the detection range of the assay, suggesting that only significantly elevated concentrations of IL-8 would have been accurately detected. We should note that potential participants who declared inflammatory conditions were indeed excluded from the sample. Therefore, high levels of this biomarkers would have indeed been unlikely. There has been evidence suggesting that low levels of this biomarker are still linked to illness processes, that is occurrence of Pericardiotomy Syndrome (Jaworska-Wilczyńska et al., 2014). Previous evidence suggests that IL8 concentration measurement by ELISA can be used to identify serum samples with room temperature (RT) precentrifugation times of more than 24 h with sensitivity 97% and specificity 90% at the cutoff 125 pg/mL. IL8 concentration measurement by ELISA can also be used to identify serum samples with RT precentrifugation times of more than 48 h with sensitivity 94% and specificity 94% at the cut-off 528 pg/mL. IL8 concentration measurement by ELISA can be used to identify citrate plasma samples with RT precentrifugation times of more than 48 h with sensitivity 86% and specificity 93% at the cut-off 21.5 pg/mL (Kofanova et al., 2018). The above conditions are highly likely to have been met by the university lab that we utilised for the analysis. It cannot not however be excluded that some of these preconfingutation conditions, which have been deemed essential by previous evidence in defining specificity and sensitivity of measurements in IL-8 might have not been met at all times. This in turn might have influenced the results. In addition, we cannot exclude that levels of IL-8 might be an idiosyncratic finding, due to sample characteristics, such as

fitness or interactions between biomarkers that were beyond the scope of this investigation (Leng et al., 2020). Based on our experience, counterintuitive findings are not unusual in this type of research. Further investigation to unpick the complexity of the interactions between biomarkers and psychological phenomena.

Trust as a mediator between biomarker concentration and trauma symptomatology

When we analysed overall trauma exposure, combining CTE, RTE, and LEC results, and included trust as a covariate, a significant association was found between trauma history and psychological trauma symptoms. This identifies trust as a mediating factor in the relationship between experiencing psychological trauma and the psychological symptomatology, in this cohort. To our knowledge, there have been no previous studies assessing the role of trust in this relationship. Therefore, further work is needed in order to contextualise these results. However, as discussed by Chouliara *et al.* (2014) and Chouliara and Narang (2017), trust is a key factor in, and sign of, recovering from relational adversity. Therefore, it was to be expected that trust could be linked with changes in psychological symptomatology in psychological trauma. Overall inflammatory biomarker concentration, combining CRP, cortisol, TNF-α, and IL-8 concentrations, was a significant predictor of trauma symptomatology, when we included trust as a covariate. This demonstrates that, in this study population, trust acts as a mediating factor between the physiological and psychological outcomes of experiencing adversity. Since this was the first known study of its type investigating the relationship between inflammation, psychological trauma symptoms, and trust, future research is necessary to provide context for these findings. However, based on previous studies that have examined the potential of a physiological basis for psychological conditions, an increase in pro-inflammatory cytokines has been found in individuals with depression (Zorrilla *et al.*, 2001). Since depression tends to be highly comorbid with psychological trauma, a relationship between IES scores and

inflammation was expected. Recent evidence has also found a direct link between depression and inflammation (Raggi, 2016).

Strengths and Limitations of the study

One of the study's strengths is its focus on the factor of adversity, which is much broader than just PTSD, thus recognising psychological trauma as a spectrum. We also considered the role of trust as a mediating variable, whilst examining physiological measures in relation to psychological trauma. Our findings make a case for trust - based intervention both as curative and preventative measures.

The main limitation of this research study was the small sample size, which might impact generalisability of findings. Due to the small sample size, the overall statistical power was between 30% and 60%. However, when only analysing the psychological results, such as when assessing the impact of complex trauma on trust levels, the statistical power was approximately 60%, which builds greater confidence to the results on the association between interpersonal trust and psychological response to adversity. In addition, the experimental procedures for the measurement of IL-8 concentration presented certain challenges. These challenges have been articulated in previous sections.

Our sample was characterised by a wide age range. This was not unusual for a naturalistic sample of staff and students at a HEI as opposed to a clinical sample. In addition, age was not a variable deemed important within the scope of this study. Links between age and trauma are not linear. Although age -and therefore life experience- might increase exposure to traumatogenic events and life events, other variables such as gender, social deprivation and criminal activity, might impact on both exposure to traumatic events and development of traumatic symptomatology. Given the above and our small sample size, an analysis by age group was not deemed important nor statistically justified. McCutcheon et al. (2010) tested

differences in risk as a function of age at trauma by exploring eight types of trauma in a sample of young women. Childhood sexual assault, physical abuse, and neglect were stronger predictors of PTSD onset than adolescent/early adult occurrence of these events in individual models. In a model including all traumatic events, differential risk by age remained for sexual assault and physical abuse. Early sexual assault was the strongest predictor of risk, but additional traumatic events increased risk even in its presence (McCutcheon, et al., 2010). This highlights the dynamic interaction between accumulative impact of trauma exposure, the importance of age on exposure, as well as of the type of trauma experienced. Relational traumas seem more likely to have a more negative impact and to be impacted upon by age. This dynamic complexity provided extra rationale to our choice not to analyse by age group and also to create composite trauma variable. Our sample consisted predominantly by females. The gender balance in our sample seems to reflect the gender ratio in academia in general. In addition, females tend to be more likely to participate in survey type research (Smith, 2008) and more concordant in health-related matters, as demonstrated during the COVID -19 pandemic (Bargain & Aminjonov, 2020; Gallaso et al, 2020; Garikipati & Kambhampati, 2020). Women have also been shown as more likely to be diagnosed with PTSD, although they tend to experience fewer traumatic events (Tolin & Foa, 2006; https://www.apa.org/news/press/releases/2006/11/ptsd-rates). The gender differences could be explained by differences in the expression of symptoms, by trauma measurement issues, as well as difference in types of traumas experienced by gender. In specific, women are more likely to experience sexual assaults whereas men are more likely to be exposed to violence and crime. These effects are of course mediated by sociodemographic factors. Sexual assaults and abuse also tend to be largely under-reported, which adds another dimension to rates by gender and across genders. In this study we did measure psychological trauma within the wider concept of adversity and not just PTSD and we did include lifeevents, childhood

trauma/complex trauma. Within the concept of a naturalistic small scale investigation, the vast complexities of the interplay between age, gender, social quota and trauma could not all have been addressed at the same time as we were focusing on the complexities of the interplay between relational, physical and trauma. Gender bias against women in health and medical research mainly in the form of limited inclusion of female participants has been highlighted by Holdcroft (2007). In our study this was not the case. This could be considered a strength given that some forms of trauma investigated in our study appear more prevalent in females (Torin & Foa, 2006).

Our sample consisted of staff and students. Although we did collect data at the time regarding the student-staff ratio, we chose not to report this data. Given the small sample size, the size of the organisational pool from which we were recruiting, and the gender ratio, as well as the sensitive type of the information collected, this was deemed a legitimate ethical choice to safeguard anonymity and ensure non-identification of participants. Given the evidence presented above, the ethical responsibility by far outweighed the methodological value of reporting such information.

Furthermore, although all blood samples were taken at the same time of day, participants were not asked about their eating, drinking, or sleeping patterns in the 24 hours prior to testing. No viral or bacterial screening was conducted on the blood samples prior to cytokine analysis. These factors could have introduced some confounding variables when considering the concentration of each biomarker. In order to determine whether there was any diurnal variation in biomarker concentrations in individuals who had experienced greater levels of trauma and/or those that had reduced levels of interpersonal trust, a 24-hour cytokine profile could have been obtained for each participant. Since limited evidence existed surrounding the impact of adversity on inflammatory biomarkers, there were no suggested criteria or established

framework on which to base selection of biomarkers to measure. The present study measured the concentration of a small number of inflammatory biomarkers based on findings from similar research studies. Nevertheless, there remains a large spectrum of inflammatory cytokines that could be studied in relation to psychological trauma and interpersonal trust. Including differential eosinophil counts and additional cytokine profiles in the analyses could have identified the presence of any allergic reactions, thus providing a potential explanation for an increase in the inflammatory response.

Since the cohort was not clinical, the majority of participants reported limited history of traumatic experiences and severe adversity. Targeting clinical samples already diagnosed with psychological trauma and/or who were receiving psychological treatment for psychological trauma could have potentially addressed this bias. Such design might of course present with certain ethical and methodological challenges, especially so because of the use of venepuncture. However, testing individuals who were not severely traumatised can also be considered a strength. Because significant associations were found within a non-clinical cohort small sample, the chance of a type II error occurring was reduced. Studying a non-clinical sample also allows for greater generalisations to be drawn from the findings in relation to life events/adversity, relational factors and the immune system. The nonclinical nature of the study allows for the potential of utilising our findings in future research focusing on prevention of illness processes after exposure to trauma and chronic stress. Present findings could also support the application and evaluation of relational interventions in addressing trauma symptomatology and managing physical symptoms and poor physical health in survivors of trauma.

Measuring trust is challenging especially due to issues surrounding the actual definition of interpersonal trust, as well as the lack of a ‘gold standard’ measure of trust. The present study

utilised a trust scale specifically designed to measure trust within intimate relationships, which can be a good indicator of interpersonal trust in general and is more suitable for non clinical settings. Also interpersonal trust in intimate relationships can be impacted upon due to adversity and relational trauma in particular, which was focused upon in this study. Although the majority of the items were suitable for ascertaining the level of trust present in any close interpersonal relationship, some items might have been more challenging for participants who were not in an intimate relationship. To mitigate this, participants were given written instructions to answer the questions with any close relationship(s) in their life at the time if they lacked an intimate relationship. Ongoing work to produce a clearer definition of trust within therapeutic and non – therapeutic contexts will hopefully yield the opportunity to design new measurement instruments to more accurately assess trust within interpersonal, and clinical/therapeutic contexts.

The study did not incorporate a measure of somatic symptoms. Therefore it was not possible to determine whether those with an increased inflammatory response were also experiencing physiological symptoms. A future study should include a somatic symptoms questionnaire to determine whether those with significant changes in the concentration of certain inflammatory biomarkers are also experiencing poorer physical health than those with more stable inflammatory biomarker concentrations. Establishing this link could highlight how experiencing adversity not only impacts upon objective measures of psychological symptoms and the inflammatory response, but also somatic symptomatology.

Finally, since this was an innovative study into the role of interpersonal trust in the relationship between adversity and physiological variables, to our knowledge there is no published precedence to provide context for the present results. Further work is required in this area, to enable comparisons and contextualisation of present findings.

Clinical implications

The findings highlight the potential for utilising trust-based interventions to improve psychological and physical health in survivors of adversity. Trust was found to be a mediating factor when using trauma history to predict trauma symptomatology. It could therefore be hypothesised that if trust is rebuilt, an improvement in psychological symptoms would be expected. Trust was also found to be a mediating factor when using inflammatory biomarker concentration to predict psychological trauma symptomatology. Thus trust levels might enable early identification of those at greatest risk of deterioration in their physiological and psychological health, and therefore enable early intervention. This demonstrates the potential for trust-based interventions to prevent, manage, and reduce the impact of adversity on physiological or psychological health, especially so in high-risk populations, such as the forces, emergency services, mental health clinicians, survivors of war/conflict and those living in volatile areas.

Although recent research has examined the interdependent links between inflammation, physical and mental health (Kiecolt-Glaser et al., 2015) and have also highlighted the key role of adversity in these processes (Reus et al., 2017), prior to our research relational variables have not been considered in these complex interactions. The finding of trust acting as a mediating factor when predicting psychological symptoms based on trauma history also shows the potential for the use of trust-based 'psychological vaccines' (Friedman *et al*., 2004), to prevent re-victimisation and re-traumatisation of individuals, both of which are key in morbidity and comorbidity in psychological trauma. In specific, if the general population, particularly those at greatest risk of experiencing complex trauma, were exposed to trust-based interventions and provided with strategies to enhance levels of interpersonal trust, resilience could be strengthened, thus improving psychological and physiological outcomes.

Furthermore, recent research on complex trauma, which has led to the inclusion of CPTSD in the ICD 11 (Knefel et al., 2019), has acknowledged the inadequacy of standard trauma treatments to respond to the needs of clients with complex trauma (Karatzias et al., 2018). The importance of developing treatments that better respond to the distinguished features of complex trauma, which are deeply relational (i.e. disorganisarion of self (DOS), prevailing low self-worth/shame, poor emotional regulation, and relational sensitivity) is now more widely recognised (Karatzias et al., 2018). Our sample reported relatively low levels of trauma in general including complex traumas, as measured by LEC and CTQ. We did not include a CPTSD specific scale as at the time the study was designed the ICD 11 CPTSD scale was not fully developed. We also wanted to increase generalisability and facilitate discussion of our findings across disciplines and approaches. We needed to factor in that psychological trauma – especially so some complex traumas, such as child abuse- are largely under-reported, heavily due to social stigma and stereotypes. In addition, a distinctive manifestation of complex trauma is the presence of somatic symptomatology often accompanies by poor physical health and frequent use of medical services for medically unexplained symptoms (MUS) or subclinical presentations. It is the very link between the physical/somatic and the psychological aspects of our study, which highlights its relevance for complex trauma. Our findings bring relational variables and trust in the centre of working with complex trauma. At the same time the importance of humanistic/relational variables, as valid therapeutic goals in complex trauma, is more widely recognised than ever before (Karatzias et al., 2018). This is especially so because relational/humanistic approaches are likely to address disengagement and drop out with psychological treatment, which are key challenges for survivors of complex trauma (Schottenbauer et al., 2008; Imel et al., 2013). In this context the development of trust -based interventions would be well placed, timely and justified for the whole spectrum of adversity, even more so complex trauma presentations.

Conclusion

The results from our study suggest that experiencing adversity within the past three years may lead to significantly poorer psychological health, according to IES scores. For this cohort, interpersonal trust was found to play a mediating role between experience of adversity, especially so for psychological/complex trauma and psychological distress. Interpersonal trust was also found to be a mediating factor when predicting psychological symptoms, following adversity, based on the individuals' inflammatory profile. These findings have important implications for clinical practice, as they highlight the potential of using preventative and therapeutic trust-based interventions to improve both the psychological and physiological outcomes in survivors of adversity and trauma, and those at high risk of experiencing adversity. The findings can contribute to the field of mental health, particularly the conversations around adverse childhood experiences and the long-term effect that carry into adulthood. As we live in an increasingly traumatogenic world, these findings can be particularly decisive in rethinking our means of managing adversity, preventing further morbidity and promoting better wellbeing in survivors of trauma and adversity.

Data Availability Statement

Data not available due to ethical/legal restrictions Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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Table 1. Descriptive Statistics for Psychological and Physiological Variables.

Psychological Variables

Variable	*N*	Mean (± SD)	Median	Actual Range	Theoretical Range
CTE	30	25.67 (± 14.74)	23.50	6 – 58	1-114
RTE	30	22.00 (± 9.90)	20.00	7 – 45	1-112
LEC	30	40.87(± 13.82)	42.00	17 – 73	0-80
IES	30	4.09 (± 2.84)	4.00	0 – 10.11	0-88
Trust	30	19.70 (± 8.40)	21.00	67 – 99	0-119

Physiological Variables

Variable	*N*	Mean (± SD)	Median	Range	Expected concentration in healthy individuals	
CRP (mg/ml)	25	$1.49x10^{-3}$ (± $1.91x10^{-3}$)	$8.44x10^{-4}$	$5.28x10^{-5}$– $7.37x10^{-3}$	$<1.00x10^{-2}$	
Cortisol (ng/ml)	25	59.35 (± 13.39)	59.56	33.37 – 82.05	41.60	
TNF-α (pg/ml)	25	19.22 (± 8.81)	18.54	9.74 – 56.05	<10	
IL-8 (pg/ml)	25	4.01 (± 3.55)	4.38	-2.44 – 13.56	5 - 60	

CTE = Childhood Traumatic Events; RTE = Recent Traumatic Events; LEC = Life Events Checklist; IES = Impact of Event Scale; CRP = C-Reactive Protein; TNF-α = Tumour Necrosis Factor-alpha; IL-8 = Interleukin-8. Expected values are based on the findings of previous studies which measured the concentration of each biomarker in healthy individuals (Xu et al., 2014; Konishi et al., 2012; Derin et al., 2008; de Lira Freire et al., 2004).

Table 2. Hierarchical Regression Results: Trust as a Covariate, Trauma History or Biomarker Concentrations as Predictors, and Trauma Symptomatology as the Outcome Variable (*n*=25).

Measure	*Beta*	*p*	Degrees of freedom
Combined trauma history		0.013*	4
CTE	0.266	0.136	4
RTE	0.317	0.071	4
LEC	-0.030	0.863	4
Combined biomarker concentrations		0.001*	5
CRP	-0.029	0.884	5
Cortisol	0.002	0.991	5
TNF-α	-0.133	0.487	5
IL-8	-0.032	0.870	5

CTE = Childhood Traumatic Events; RTE = Recent Traumatic Events; LEC = Life Events Checklist; CRP = C-Reactive Protein; TNF-α = Tumour Necrosis Factor-alpha; IL-8 = Interleukin-8. Combined trauma history = CTE, RTE, and LEC results. Combined biomarker concentrations = CRP, cortisol, TNF-α, and IL-8 concentrations.

* denotes a significant result ($p<0.05$).