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Review

The importance of friendships in reducing brain responses to stress in adolescents exposed to childhood adversity: a preregistered systematic review

Maximilian Scheuplein^{a,b} and Anne-Laura van Harmelen^{a,b}**Abstract**

Up to 50% of all children and adolescents growing up worldwide are exposed to at least one form of childhood adversity (CA), which is one of the strongest predictors for later life psychopathology. One way through which CA confers such vulnerability in later life is through increased sensitivity to and likelihood of social stress. A growing body of research demonstrates the positive impact of adolescent friendship support on mental well-being after CA; however, the mechanisms that may underlie this relationship are unknown. Neurobiological models of social buffering suggest that social support can reduce perceptions, reactions, and physiological responses to and after stress. Therefore, this preregistered, systematic literature search examined whether friendships reduce neural stress responses in adolescents with CA.

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adversity (CA) (e.g., abuse, neglect, bullying, or poverty) [1,2]. CA is a strong predictor of later life mental health and interpersonal problems. One way through which CA confers such vulnerability is through increased sensitivity to and likelihood of interpersonal stress (e.g., peer relationship problems) [3–5]. As such, to improve well-being, it is imperative that stress vulnerability is reduced in young people with CA.

Safe, stable, and nurturing social relationships can help reduce perceptions, reactions, and physiological responses to and after stress [6]. Friendships may be a particularly important support source in adolescence, as this is a time when young people start to form more stable, intimate, and reciprocal peer relationships [7]. Friendship support has indeed been found to improve mental well-being in young people with CA [5,8]. However, it is unknown whether friendship support aids mental well-being through reducing stress responses in these individuals. Therefore, we performed a preregistered, systematic literature search to examine whether friendship support reduces brain responses to stress in adolescents with CA (see Figure 1).

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<https://doi.org/10.1016/j.copsyc.2022.101310>2352-250X/© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).**Keywords**

Friendship buffering, Social support, Neural stress mechanisms, Childhood adversity, Adolescence, Systematic review.

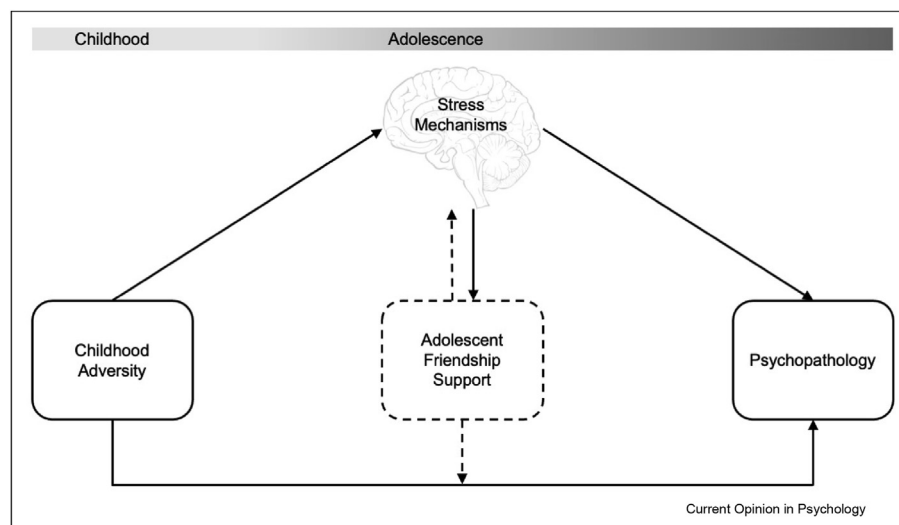
Introduction

Up to 50% of all children and adolescents growing up worldwide are exposed to at least one form of childhood

Neurobiological stress mechanisms linking CA and psychopathology

Prolonged stress exposure early in life can disrupt the development of psychological and neurobiological processes and thereby increase vulnerability to psychopathology [9]. In humans, CA can impair the responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis, a key stress response system that gets activated when homeostasis (i.e. the body's tendency to maintain a stable internal environment) is threatened. The HPA axis is responsible for producing stress hormones (e.g. cortisol), also known as glucocorticoids [10,11]. Glucocorticoids are potent anti-inflammatory as well as immunosuppressive agents and are important for healthy brain development due to their involvement in neural maturation, myelination, and neurogenesis [11,12]. In the context of CA, sustained HPA axis activation can lead to chronically elevated levels of glucocorticoids in the brain and altered frontolimbic development and functioning [13,14].

Figure 1



Friendship buffering effects on brain responses to stress in adolescents with childhood adversity. *Note.* Adolescent friendship support may help reduce (or buffer) neural stress responses (dashed lines) that are thought to aid psychopathology in young people with CA (solid lines).

Due to their dense innervation with glucocorticoid receptors, brain regions like the hippocampus, amygdala, anterior cingulate cortex, or prefrontal cortex may be particularly impacted resulting, for example, in dysfunctional social information and emotional processing [15–17]. According to the theory of latent vulnerability, alterations to these mechanisms may be adaptive in the short term to support survival in highly stressful and threatening environments. However, in the long term, such recalibration of the stress system can become maladaptive [18]. For example, in the context of an abusive home environment, it may be adaptive to rapidly detect threats (e.g. angry facial expressions). However, in less threatening environments, this amygdala-supported attentional bias to threat may aid an overattribution of hostile intentions to others' action, possibly eliciting preemptive (aggressive or avoidance) behavior [19,20]. Indeed, such attentional biases were predictive of future onset of internalizing and externalizing problems in young people with CA [21] and were linked to reduced social interactions and greater difficulties with peers [3]. Forming and maintaining friendships, defined as voluntary, reciprocal, and nurturing relationships, requires social–emotional competence [18], which relies in part on neurocognitive mechanisms (e.g. emotion perception and regulation) known to be altered in adolescents with CA [18,22]. Consequently, through this mechanism, young people with CA may be more vulnerable and more likely to experience social stress (i.e. stress generation; [18]). CA is therefore thought to shape neurodevelopment in a way that increases vulnerability to social stress [16,18,23].

Social buffering of neurobiological stress responses across development

Social buffering describes the phenomenon in which a social partner can attenuate acute physiological stress responses [6]. This leads to a reduction in the release of glucocorticoids and pro-inflammatory markers into the bloodstream [24,25]. In humans, this decreased allostatic load (i.e. the physiological impact of stress on the body) may help protect against the emergence of psychopathology [16,26]. Indeed, trauma-exposed young people with high levels of social support are less likely to develop psychopathology [27].

Social buffering occurs throughout the life span and its effectiveness is influenced by previous social experiences, as well as the developmental stage of the recipient [28]. During early childhood, the caregiver is the most potent stress buffer. Animal models have demonstrated that maternal presence can attenuate glucocorticoid release and block amygdala-dependent threat learning in rodent pups [25,29]. Similarly, in humans, maternal availability after a social evaluative performance stressor was found to facilitate greater oxytocin release, a neuropeptide capable of inhibiting glucocorticoid secretion in response to stress, as well as a more rapid decrease and lower levels of peak cortisol in children [30]. Across social species, high-quality caregiving, characterized by predictable caregiving that signals safety, can improve the effectiveness of social buffering [31,32]. In humans, high-quality caregiving modulates children's frontolimbic circuitry and contributes to healthy socioemotional functioning [32]. For example, greater feelings of child-reported security in the

caregiver–child attachment relationship buffers amygdala reactivity and enhances affective behavior and mental health [33,34].

While caregivers remain potent stress buffers throughout childhood, evidence suggests that their effectiveness diminishes with the transition to adolescence [34,35]. One potential mechanism proposes that with the maturation of frontolimbic circuitry, caregivers lose their active role in facilitating emotion regulation and buffering amygdala reactivity [32,34,35]. This makes space for other attachment figures to take over the stress-alleviating role of social support. At the same time, adolescents learn to navigate the world more independently and start to increasingly form and maintain emotionally intimate peer relationships [7]. Hence, peers take on a more central role in social–emotional buffering [32].

Adolescent friendship support is a potent protective factor, capable of buffering threat-related processing (see the review by Gunnar [6]). Specifically, adolescents with heightened levels of perceived social support (e.g. measured through the time spent interacting with friends) had diminished cortisol responses and lower neural activity in brain regions commonly associated with social distress following social exclusion [36,37], providing initial evidence that adolescent friendships may buffer neural stress responses in young people without CA [36]. However, it is yet unknown whether friendship support similarly buffers neural stress responses in vulnerable adolescents with CA.

Do friendships reduce neural stress responses in adolescents with CA?

While there is a growing body of research demonstrating the positive impact of adolescent friendship support on mental well-being after CA [5,8,38], very little is known about the neural mechanisms that aid this relationship. Therefore, we performed a preregistered, systematic literature review to examine whether friendship support buffers neural stress responsivity in adolescents with CA (Prospero: CRD42021233949).

Systematic review: study selection and data extraction

In accordance with the PRISMA guidelines [39], we searched for empirical studies (peer-reviewed articles, proceedings papers, and conference papers) published in English and involving human subjects by using internet databases (Web of Science Core Collection, PubMed, and PsycINFO) through December 2021.

We included studies assessing friendships and neural stress responses in adolescents with CA. Specifically, we

included studies in which at least a portion of the adolescent sample (sample mean age 10–24) had experienced or reported a history of CA. CA was defined as any event assessed prior to the age of 18, which is ‘likely to require significant adaptation by an average child and that represent[s] a deviation from the expectable environment’ [2], such as abuse, neglect, or bullying. Friendships had to be assessed between the (sample mean) age of 10 and 24 and were defined as self- or other-reported, subjective or objective peer relationships, excluding support from family, pets, community ties, or coworkers. Measures of neural stress responses needed to be induced (e.g. stress exposure or negative feedback) in the lab and assessed using neuroimaging techniques (e.g. functional magnetic resonance imaging (fMRI) or electroencephalography (EEG)).

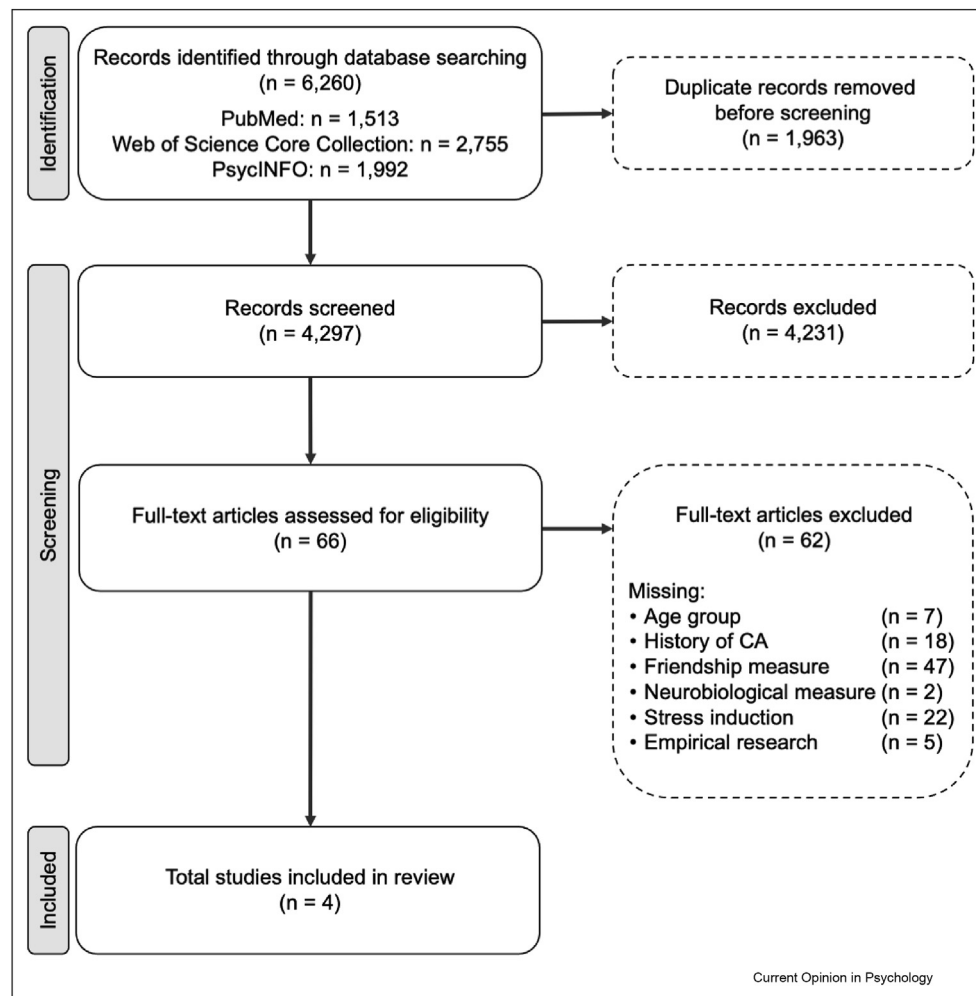
These categories were included in search terms encompassing friendship support, study population, neural domains, CA, and stress exposure (see Table S1 for all search terms used). To identify studies missed in this targeted search, we performed backward reference searches and used Google Scholar for forward searching.

A total of 6260 articles were identified. After removing duplicates, two independent reviewers screened titles, abstracts, and keywords of 4297 articles based on the PI(C)OS concept: population (P; adolescents between the age of 10 and 24 (sample mean age) with CA (assessed prior to the age of 18)), intervention (I; friendships assessed between the age of 10–24 (sample mean age)), outcome (O; neural stress mechanisms), and study design (S; empirical study) [40]. This screening resulted in adequate inter-rater reliability of kappa = 0.58, and disagreement was resolved through discussion. Next, 66 full-text articles were selected and subsequently assessed for eligibility; however, only two articles matched all search criteria (kappa = 0.79) (Figure 2). Therefore, we allowed stress responses in any neurobiological system (including endocrine and sympathetic nervous system) and included two additional studies. For a detailed summary of all excluded studies, see Tables S2–6. Risk of bias (quality) assessments were performed for the four included studies, in which studies could score one point for each quality marker they met (e.g. ‘Is the sample representative of the defined population?’). The overall quality score (QA score) for each study was calculated by adding up all nine items (see Table S7 for all assessment questions).

Results

This preregistered, systematic review identified four eligible studies [38,41–43] (see Table 1 and Figure 2).

Figure 2



PRISMA flow diagram. Note. Following the reporting guidelines for systematic reviews as detailed by Page et al. [39].

Only two of those studies did directly test whether friendships buffer neurobiological stress responses in adolescents with CA [38,43]. Tang et al. [43] showed that high-quality friendships at age 12 can buffer the indirect effect of maladaptive stress physiology (blunted sympathetic nervous system reactivity to social rejection feedback) on peer problems at age 16 in 217 adolescents (136 with CA) who had been institutionalized. In contrast, Fritz et al. [38] found that friendship support at ages 14 or 17 was not associated with affective behavioral or neural responses to social rejection at age 18 in a small sample of 55 adolescents (26 with CA). However, adolescents with CA reported more friendship support at age 14, suggesting a particularly well-functioning sample with possibly normalized stress responses. Indeed, Schweizer et al. [44] reported enhanced emotion regulation capacity in the same

cohort of adolescents with CA, perhaps obscuring the ability to comprehensively examine friendship stress buffering effects.

The remaining two studies included in the review did not directly test the model of interest [41,42]. Kelly et al. [41] found that adolescents (aged 10–14) with documented maltreatment experiences displayed increased emotional reactivity, an attentional bias away from threat, and reduced gray matter volume (GMV) in the left medial orbitofrontal cortex (mOFC), a brain region implicated in empathic, social functioning. In addition, reduced GMV in the left mOFC mediated the relationship between maltreatment and peer relationship problems providing support for neural stress generation and mechanisms in adolescents with CA. Similarly, Negri et al. [42] found that 10-year-old

Table 1**Summary of studies included in the systematic review.**

Paper	N	Age (years)	Adversity	Friendship Support	Neurobiology	Stress	Main Findings	QA Score
Fritz et al., 2020 [38]	Total: 55 CA: 26 Control: 29	Three time points: 14, 17, 18 <i>Scanning at T₃</i>	Intrafamily adverse events CAMEEI performed with primary caregiver	Perceived friendship support CFQ	Brain function	Social feedback task	CA predicted higher levels of perceived friendship support at age 14, which was associated with perceived friendship support at age 17. However, friendship support at either age did not mediate the link between CA and affective behavioral or neural (AI and dACC) responses to social rejection.	7
Kelly et al., 2015 [41]	Total: 122 CA: 62 Control: 60	10–14	Maltreatment Child Protection Service records	Perceived access of support from others Perceived sense of relatedness scale of the RSCA	Brain structure	Threat processing task	Maltreated adolescents showed increased behavioral threat reactivity, greater peer problems, which were partly mediated by reduced GMV in the left mOFC as well as no group specific differences in perceived friendship support. However, it was not specifically tested whether friendship support was associated with reduced mOFC GMV, emotional reactivity, or changes in attentional threat bias in this sample.	6
Negriff et al., 2020 [42]	Total: 303 CA: 303 Control: 151	Four time points: 10, 12, 14, 18	Maltreatment Child Protection Service records	Perceived social support (incl. friendships) Social Network Interview; CSSQ; MOS-SS	Salivary cortisol, salivary alpha amylase	TSST	At age 10, maltreated adolescents not only reported a smaller perceived friendship support network, compared to the age-matched non-maltreated comparison group, they also showed a blunted cortisol response to social stress, which was especially pronounced for adolescents, who experienced physical or sexual abuse. However, it was not specifically investigated whether the size and interconnections of the friendship support network were associated with lower cortisol responses to social stress.	5
Tang et al., 2021 [43]	Total: 217 CA: 136 Control: 135	Two time points: 12, 16	Institutional rearing Bucharest Early Intervention Project	Friendship quality	Sympathetic nervous system reactivity	Social evaluation task	High-quality friendships at age 12 can buffer the indirect effect of blunted SNS reactivity to social rejection feedback on peer problems at age 16 following early institutionalization.	8

Note. Summary of four studies included in the systematic review. Abbreviations: CAMEEI = cambridge early experiences interview; CFQ = cambridge friendship questionnaire; CA = childhood adversity; AI = anterior insula; (d)AAC = (dorsal) anterior cingulate cortex; QA Score = quality assessment score; RSCA = resiliency scale for children and adolescents; GMV = gray matter volume; (m)OFC = (medial) orbitofrontal cortex; CSSQ = child social support questionnaire; MOS-SS = MOS social support survey; TSST = trier social stress test; T₃ = Time point three; SNS = sympathetic nervous system.

adolescents with CA reported a smaller perceived friendship support network and showed blunted cortisol responses to social stress. However, in both studies, it was not specifically tested whether friendship support or network characteristics (size or interconnections) were associated with reduced neurobiological stress responses.

These findings add to studies that were excluded from the current review due to missing search criteria (summarized in [Tables S2–6](#)). For example, studies investigating friendship stress buffering in individuals without CA demonstrated that adolescents who spent more time with friends showed reduced neural activity (dACC and anterior insula) during social exclusion [37]. Whereas adults with below-average levels of perceived social support showed a positive correlation between threat-related amygdala reactivity and trait anxiety [45].

Moreover, three excluded studies supported the notion of friendship buffering on neurobiological mechanisms, despite not investigating stress responses [46–48]. First, Reid et al. [48] found that the quality of social support, but not previous institutionalization experiences, predicted changes in diurnal cortisol patterns across early adolescence. Specifically, higher levels of social support were associated with lower bedtime cortisol levels. Second, Gu et al. [46] tested adolescents orphaned by parental HIV/AIDS who displayed decreased cortical resting state activity (elevated theta-beta ratio) in frontocentral regions, which was also associated with greater learning and behavioral problems as well as difficulties making friends. Similarly, Malhi et al. [47] showed that adolescents (12–18 years) with severe emotional trauma had smaller left hippocampal volumes as well as less perceived social support from friends, family, and significant others, compared to individuals with minimal trauma exposure. In addition, the former two studies [46,47] lend further support to the stress generation idea through which friendship support may also be less available to young people with CA.

Discussion

This preregistered, systematic review identified only four studies that could have examined whether friendship support buffers neurobiological stress responses in adolescents with CA [38,41–43]. One study found support for friendship stress buffering in a large sample of previously institutionalized adolescents [43], whereas two studies did not directly test this model [41,42], and another was limited by an underpowered sample of well-functioning adolescents with mild to moderate CA [38]. Previous research (including the study by Negri et al. [42]) classified individuals with CA exposure as more sensitive and likely to experience

interpersonal stress due to compromised social-emotional functioning [3,18,22,41]. Through this mechanism, it is suggested that friendship support may also be less available to young people with CA. However, Kelly et al. [41] and Fritz et al. [38] demonstrated that adolescents with CA can have normative or even increased levels of friendships support. This is promising, considering that greater friendship support has been proven to promote mental well-being in this population [8] as well as reduce neurobiological responses to social stress in adolescents without CA [36,37]. Given that friendship stress buffering was only studied in two samples, future research is clearly needed to investigate whether friendships aid mental well-being through reducing neurobiological stress responses in adolescents with CA.

Future research should explore the heterogeneity in CA exposure as well as the types of assessment. For example, a dimensional approach could be used to conceptualize complex CA experiences along distinct dimensions of threat and deprivation in order to capture their impact on neurobiological stress mechanisms [49]. However, whether this approach allows the field to ultimately advance from cumulative measures of risk remains to be further investigated (see Pollak and Smith [50]). Furthermore, previous empirical and meta-analytic evidence has confirmed that prospective documentation (objective) and retrospective self-report (subjective) measures of CA identify individuals with differential neural outcomes and psychopathological risk trajectories [51,52]. Specifically, understanding and measuring variability in subjective life experiences appears crucial for identifying maladaptive neurobiological stress mechanisms linking CA exposure and risk of psychopathology.

Differential dimensions of friendships (e.g. intimacy or support network size) as well as developmental differences should also be considered. For example, Smith et al. [53] showed that the degree of psychological closeness between same-sex adolescent stranger pairs modulates cortisol responses during a social stress task. Moreover, Hostinar et al. [35] showed that parental support becomes less effective in reducing cortisol stress responses (i.e., HPA reactivity) from childhood to adolescence. Hence, future studies should include well-powered samples to allow for the investigation of heterogeneity of CA and its assessments as well as friendship dimensions and developmental timing on friendship stress buffering in young people with CA.

In sum, this systematic review identified only two studies that specifically tested whether friendship support buffers neural stress responses in adolescents with CA. Both studies provided divergent evidence for the stress buffering role of friendship support, which is

why future research is clearly needed to investigate whether friendships reduce stress vulnerability in young people with CA.

Author contributions

Maximilian Scheuplein: Conceptualization, Methodology, Validation, Investigation, Data Curation, Visualization, Writing - Original draft preparation. **Anne-Laura van Harmelen:** Supervision, Conceptualization, Methodology, Writing - Reviewing and editing.

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Pre-registration

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Conflict of interest statement

Nothing declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.copsyc.2022.101310>.

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