**From childhood adversity to latent stress vulnerability at adulthood:**

**The mediating roles of sleep disturbances and** **HPA axis dysfunction**

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**Abstract**

Childhood adversity is a prominent predisposing risk factor for latent stress vulnerability, expressed as elevated likelihood to develop stress-related psychopathology upon subsequent exposure to trauma at adulthood. Sleep disturbances have emerged as one of the most pronounced maladaptive behavioral outcomes of childhood adversity and are also a highly prevalent core feature of stress-related psychopathology, including posttraumatic stress disorder (PTSD). After briefly reviewing the extent literature that supports these claims, the current review addresses the notion that childhood-adversity-induced sleep disturbances may play a causal role in elevating individuals’ stress vulnerability at adulthood. In support of that, sleep disturbances that predate adult trauma exposure were associated with increased likelihood to develop stress-related psychopathology post-exposure. Furthermore, novel empirical evidence suggests that sleep disturbances, including irregularity of the sleep-wake cycle, mediate the link between childhood adversity and stress vulnerability at adulthood. Cognitive and behavioral mechanisms through which such cascade may evolve are also discussed, highlighting the putative role of impaired memory consolidation and fear extinction. Next, evidence is presented to support the contribution of the hypothalamic-pituitary-adrenal (HPA) axis to these associations, stemming from its critical role in both stress and sleep regulatory pathways. Childhood adversity may yield bi-directional effects within the HPA stress and sleep axes in which sleep disturbances and HPA axis dysfunction reinforce each other, leading to elevated stress vulnerability. To conclude we postulate a conceptual path model from childhood adversity to latent stress vulnerability at adulthood and discuss the potential clinical implications of these notions, while highlighting directions for future research.

**1. Childhood adversity and** **latent stress vulnerability at adulthood**

Childhood adversity involves exposure to physical, emotional and/or sexual abuse or neglect, or to other forms of family dysfunction such as domestic violence or parental substance use, psychopathology, or death. Children exposed to such adversities are at increased risk to develop multiple health problems during childhood including asthma, infections and somatic complaints, as well as to exhibit delays in cognitive and emotional development [[1-4](#_ENREF_1)]. Exposure to childhood adversity often also carries cumulative effects, with far-reaching consequences later in life. To this end, childhood adversity is associated with elevated risk for various physical and mental health conditions at adulthood, including heart, lung and autoimmune diseases, stroke, cancer, diabetes, mood and anxiety disorders and substance use [[5-15](#_ENREF_5)]. Critically, some of the maladaptive consequences of childhood adversity may remain hidden until triggered by a second event later in life, such as in the case of exposure to subsequent psychological trauma at adulthood. In a seminal paper, Bremner and colleagues (1993) revealed that Vietnam veterans with posttraumatic stress disorder (PTSD) had almost four times higher rates of exposure to childhood physical abuse compared to Vietnam veterans without PTSD [[16](#_ENREF_16)]. Considering that many Vietnam veterans were exposed to psychological trauma at adulthood during their military service, yet only a subset of vulnerable individuals eventually developed PTSD, this study provided one of the first empirical evidence to suggest that childhood adversity may increase the likelihood to develop PTSD later in life. Since then, significant amount of evidence has accumulated to support and establish the role of prior exposure to childhood adversity as a prominent predisposing risk factor for latent stress vulnerability at adulthood (reviewed in [[17-22](#_ENREF_17)]). Such latent stress vulnerability is expressed as elevated likelihood to develop stress-related psychopathology following trauma exposure at adulthood, most commonly PTSD, in otherwise healthy adults with a history of childhood adversity. A recent epidemiological study in a large sample of adult civilians revealed that four childhood adversity types (physical and sexual abuse, neglect, parent psychopathology) are particularly associated with increased risk for developing PTSD following exposure to subsequent trauma at adulthood [[23](#_ENREF_23)]. This work further revealed that these associations are consistent across exposures to different types of traumatic events at adulthood, pointing towards generalized vulnerability to adult trauma following childhood adversity [[23](#_ENREF_23)].

**2. Childhood adversity and sleep disturbances**

Research focusing on the behavioral consequences of childhood adversity has consistently highlighted sleep disturbances as one of the most pronounced maladaptive behavioral outcomes of adverse early exposures (reviewed in [[24-30](#_ENREF_24)]). Childhood adversity was shown to induce multiple forms of sleep disturbances, including insomnia, shorter sleep durations, difficulty falling or staying asleep, hyperarousal, irregular sleep patterns, increased awakenings during the night, greater number of body movements during sleep, parasomnia and poorer sleep quality or efficiency. Additionally, childhood adversity, particularly sexual abuse, may cause nightmares, flashbacks and intrusive memories which can interfere with sleep quality [[31-33](#_ENREF_31)]. Across studies, childhood-adversity-induced sleep disturbances were demonstrated using various assessment methods including self-report questionnaires [[34-47](#_ENREF_34)], interviews [[48](#_ENREF_48),[49](#_ENREF_49)], surveys [[50-52](#_ENREF_50)], parental reports [[53](#_ENREF_53),[54](#_ENREF_54)], case manager reports [[55](#_ENREF_55)], sleep diaries [[46](#_ENREF_46)], polysomnography and actigraphy [[33](#_ENREF_33),[56-58](#_ENREF_56)], or combinations of these methods [[59-61](#_ENREF_59)]. Similar to its lifelong impact on physical and mental health, childhood adversity was found to perturb sleep during infancy and childhood but also throughout adolescence and into adulthood and old age. Interestingly though, the range of affected individuals varied across studies, with sleep disturbances reported in anywhere between 8.7% to 59.5% of individuals exposed to childhood adversity. Such a wide range of affected individuals may stem from differences in study settings and sleep outcome measurements, as well as from differences in the type and frequency of reported adversities. Indeed, both retrospective and prospective studies demonstrated “dose-response” relationship between the severity, intensity and chronicity of childhood adversity and the extent of sleep disturbances exhibited later in life [[31-33](#_ENREF_31),[38](#_ENREF_38),[42](#_ENREF_42),[44](#_ENREF_44),[46](#_ENREF_46),[49](#_ENREF_49),[50](#_ENREF_50),[52](#_ENREF_52),[53](#_ENREF_53),[59](#_ENREF_59)].

Addressing the question of why would childhood adversity so potently impact sleep, it is important to keep in mind that many types of childhood adversities, particularly sexual abuse, often occur in bedrooms and/or at night, hence the impact of such experiences might be most prominently associated with sleep, being in bed, or being in the dark [[30](#_ENREF_30)]. The prominent “hyperarousal model of insomnia” posits that childhood adversity may lead to elevated levels of arousal or failure to downregulate arousal at night, processes that are not conducive to sleep [[28](#_ENREF_28),[30](#_ENREF_30)]. While hyperarousal or hypervigilance represent potentially adaptive behavioral tendencies under uncertain and threatening environment, their long-term consequences might be maladaptive, eventually leading to long-term reduction in sleep quality and sleep disturbances [[29](#_ENREF_29)]. Additional accounts for the impact of childhood adversity on sleep quality suggest that increased risk for early initiation of adverse health behaviors following childhood adversity, such as smoking and substance use, may negatively impact sleep [[62-64](#_ENREF_62)]. Alternatively, it has been suggested that growing up with increased family chaos and household disruption may interrupt the learning of proper sleeping habits [[38](#_ENREF_38),[56](#_ENREF_56)].

**3. Sleep disturbances and stress vulnerability at adulthood**

Sleep disturbances were also repeatedly associated with stress vulnerability at adulthood. Perhaps the most straightforward example stems from the wealth of evidence on sleep disturbances among individuals diagnosed with stress-related psychopathologies, particularly PTSD (reviewed in [[65-71](#_ENREF_65)]). In fact, current epidemiological studies suggest that over 90% of adult patients with PTSD suffer from clinically relevant sleep disorders [[72](#_ENREF_72)]. Sleep disruption is so prevalent among PTSD patients that it is intertwined with PTSD etiology, and is considered a core feature of the disorder and a diagnostic criterion for it, as well as for additional stress-related psychopathologies [[73](#_ENREF_73)]. Importantly, sleep disturbances were consistently reported in PTSD samples across diverse adult trauma types, including veterans, sexual assault survivors and mixed trauma samples [[74](#_ENREF_74)]. Across these samples, difficulties falling and staying asleep and nightmares were most commonly reported, yielding decreased total sleep time, decreased sleep efficiency and increased awakenings after sleep onset [[65-71](#_ENREF_65)]. In addition to relying on subjective reports, wealth of polysomnographic (PSG) studies examined specific objective measures of sleep abnormalities in PTSD patients in laboratory settings and in natural home environment [[70](#_ENREF_70),[75](#_ENREF_75)]. The majority of evidence seems to support alterations of sleep architecture, elevated nocturnal autonomic nervous system (ANS) arousal and fragmentation of rapid eye movement (REM) sleep. Similar to the “dose-response” relationship between childhood adversity and sleep disturbances, small to moderate associations also emerged between subjective measures of sleep disturbances and PTSD symptom severity among veterans, civilians, and assault survivors with PTSD. For example, the magnitude of subjective sleep disturbances, based on the Pittsburgh Sleep Quality Index (PSQI) was positively associated with PTSD symptom severity among females with PTSD related to sexual or physical assault [[76](#_ENREF_76)]. Similar associations also emerged in combat veterans with PTSD, which in turn contributed to their deficits in neuropsychological functioning [[77](#_ENREF_77)], as well in utility workers who were deployed at the World Trade Center site in the aftermath of the 9/11 attack [[78](#_ENREF_78)], and in individuals exhibiting PTSD symptoms after acute coronary syndrome [[79](#_ENREF_79)]. Interestingly however, some studies reported no association between PSQI based sleep disturbances and PTSD severity [[80](#_ENREF_80),[81](#_ENREF_81)]. Some of the inconsistencies in results may relate to the potential non-linearity of the associations, as for example both very short sleep duration (≤ 5 h of sleep) and long sleep duration (≥ 9 h) were associated with increased odds of current PTSD [[82](#_ENREF_82)]. Indeed, studies implementing objective sleep measures mostly did not report on linear associations between sleep disturbances and PTSD symptom severity [[74](#_ENREF_74)].

A highly relevant debate in the context of the current review is whether the abundant sleep disturbances in PTSD patients are consequences of the exposure to trauma and the subsequent development of psychopathology, or whether preexisting sleep disturbances may increase the risk to develop psychopathology in response to psychological trauma. Existing literature seems to support both scenarios, pointing towards reciprocal relations between sleep disturbances and stress vulnerability (reviewed in [[83-87](#_ENREF_83)]). On the one hand, trauma exposure can induce sleep problems, most probably insomnia and/or nightmares. On the other hand, however, vast amount of evidence clearly indicates that sleep disturbances that predate adult trauma exposure significantly increase the likelihood to subsequently develop psychopathology, pointing towards a causal role of sleep disturbances in stress vulnerability. For example, a prospective study among military personnel revealed that insomnia symptoms and short sleep duration pre-deployment to combat were significantly associated with higher odds of developing PTSD, depression, and anxiety post-deployment [[88](#_ENREF_88)]. In another study, insomnia at four months post-deployment was a significant predictor of PTSD symptoms one-year post-deployment, whereas PTSD symptoms at four months did not predict insomnia at one-year [[89](#_ENREF_89)]. Among soldiers deployed in Iraq or Afghanistan, pre-deployment insomnia and sleep disturbances predicted PTSD and depression symptom severity at three, six and nine months and up to two years post-deployment [[90-92](#_ENREF_90)]. Similar patterns emerged among civilian cohorts. For example, in civilians assessed during hospital admission, self-reported sleep disturbance in the two weeks that preceded the trauma increased the risk for PTSD diagnosis three [[93](#_ENREF_93)], and six [[94](#_ENREF_94)] months later. In other studies, pre-trauma sleep disturbances predicted PTSD severity following the 2008 Wenchuan earthquake [[95](#_ENREF_95)] and the COVID-19 pandemic [[96](#_ENREF_96)] in China. Finally, insomnia as a predictor of PTSD was also recently demonstrated in a series of studies that examined the associations between sleep disturbances and PTSD symptoms on a daily basis and in natural settings, using ecological momentary assessment (EMA) [[97-101](#_ENREF_97)]. Across these studies, daily insomnia symptoms or other aspects of sleep disruptions were found to predict next-day PTSD symptoms, yet PTSD symptoms did not predict subsequent sleep problems in the reverse direction, suggesting that sleep disturbances predate exacerbation of daily PTSD symptomatology. Importantly, across majority of studies cited above, findings were obtained while controlling for the putative effects of age, gender, type and severity of the trauma and prior psychiatric disorders, indicating that pre-existing sleep disturbances may predispose to stress vulnerability following trauma exposure at adulthood above and beyond the potential contribution of these additional factors.

**4. From childhood adversity to latent stress vulnerability at adulthood**: **The mediating role of sleep disturbances**

Taken together, childhood adversity has been established as a potent predisposing risk factor for stress-related psychopathology following subsequent trauma exposure at adulthood, and both childhood adversity and stress-related psychopathology were independently associated with sleep disturbances. Furthermore, substantial evidence seems to suggest that sleep disturbances that predate adult trauma exposure may lead to elevated likelihood to develop stress-related psychopathology post-exposure. This in turn raises the question of whether sleep disturbances that stem from childhood adversity play a causal role in stress vulnerability, by increasing the risk to develop stress-related psychopathology upon exposure to subsequent psychological trauma at adulthood. In other words, childhood-adversity-induced sleep disturbances may represent a behavioral predisposing marker for latent stress vulnerability. Several independent lines of research support this scenario. In a broad prospective, efficient sleep is a critical factor for optimal physiological functioning in general, while sleep disturbances produce allostatic overload that can have deleterious physiological and psychological consequences [[102-106](#_ENREF_102)]. Indeed, sleep disturbances were linked with multiple mental and physical disorders including cardiovascular diseases, obesity, hypertension, neurocognitive deficits and mood disorders, in children, adolescents and adults [[107-111](#_ENREF_107)]. The destructive impact of sleep disturbances on bodily systems might be particularly potent if these disturbances occur during developmental periods, such as the case in childhood adversity [[112](#_ENREF_112)]. Accordingly, sleep disturbances may be a critical behavioral health risk factor that mediates the robust associations between childhood adversity and overall poor mental and physical health across the lifespan [[25](#_ENREF_25),[27](#_ENREF_27),[112](#_ENREF_112),[113](#_ENREF_113)].

A more direct pathway through which sleep disturbances could specifically lead to elevated stress vulnerability may relate to the vital role of sleep in adaptive modulation, regulation, and even preparation of cognitive and emotional functions [[114-119](#_ENREF_114)], potentially even more so in children and adolescents [[120](#_ENREF_120),[121](#_ENREF_121)]. Two sleep states, REM sleep and slow-wave sleep are critical for efficient cognitive and emotional processes, by enabling plasticity-related mechanisms that reactivate, stabilize and store memory traces, including emotional memories, as well as integrate memories with preexisting knowledge [[114-119](#_ENREF_114)]. These processes also enable the forgetting of information that may no longer be relevant, thus avoiding saturation [[122](#_ENREF_122),[123](#_ENREF_123)]. Along these lines, sleep disturbances were shown to have long-term maladaptive impact on memory and cognitive control processes, and sleep deprivation led to elevated emotional arousal and hyper-sensitivity to stress [[124](#_ENREF_124),[125](#_ENREF_125)]. The well-documented deficits in executive functioning and in emotional regulation among children [[126-130](#_ENREF_126)], adolescents [[131-134](#_ENREF_131)] and adults [[135-139](#_ENREF_135)] that were exposed to childhood adversity may therefore be the result of life-long sleep disturbances. In support of that, difficulties in emotional regulation were recently shown to mediate the relationship between childhood abuse and pre-sleep arousal [[138](#_ENREF_138)]. Critically, deficits in executive functioning and in emotional regulation are also established risk factors the development of stress-related psychopathology [[140-142](#_ENREF_140)], and in fact the association between childhood adversity and adult psychopathology was found to be mediated by emotional dysregulation [[143](#_ENREF_143),[144](#_ENREF_144)]. Childhood-adversity-induced sleep disturbances may therefore result in limited emotional and cognitive resources, hence reducing individuals’ chances to successfully overcome subsequent encounters with psychological trauma at adulthood.

Among cognitive processes, sleep has been shown to be critical for memory consolidation. Changes in synaptic morphology and neural excitability that occur during sleep enable transition of initial memory traces from the hippocampus to more permanent cortical storage sites [[145-148](#_ENREF_145)]. These notions are particularly relevant here given abundant preclinical and clinical studies that point towards the role of memory consolidation during sleep in the strengthening and generalization of fear extinction (reviewed in [[149-151](#_ENREF_149)]). Along these lines, sleep disturbances were shown to impair memory consolidation processes and to yield reduced extinction of fear, including among PTSD patients [[149](#_ENREF_149),[152](#_ENREF_152)]. Reduced fear extinction and impaired transition to safety were also repeatedly demonstrated in children and adults exposed to childhood adversity [[153](#_ENREF_153)]. For example, a recent study uncovered poor differentiation between threat and safety cues following fear extinction among trauma-exposed children [[154](#_ENREF_154)]. Hence, sleep disturbances and childhood adversity were independently shown to yield reduced fear extinction, which by itself is a potent predisposing risk factor for PTSD [[155](#_ENREF_155)]. Taken together, childhood adversity may lead to stress vulnerability by impairing sleep-related memory consolidation processes yielding reduced fear extinction capabilities. These ideas should be considered alongside the recently suggested notion that insomnia reflects a fear-related evolutionary survival mechanism following trauma exposure, which becomes persistent in some vulnerable individuals due to failure of the fear extinction function [[156](#_ENREF_156)]. If so, these processes may form a cycle that promotes the mutual development of sleep disturbances and impaired fear extinction.

Empirical evidence to support the mediating role of sleep disturbances in the association between childhood adversity and stress vulnerability at adulthood is limited; though in recent years more attention has been devoted to these putative associations, yielding promising results. For example, by relying on subjective measures of sleep, the association between childhood adversity and sleep disturbances was found to be mediated by current levels of psychological distress in both adults [[157](#_ENREF_157)] and adolescents [[158](#_ENREF_158)]. Even further, the association between childhood adversity and poor self-reported sleep quality was mediated by the level of psychological distress that was experienced specifically during a stressful period of life (i.e., beginning life at university) [[159](#_ENREF_159)]. A similar pattern emerged in a study that implemented Actiwatch to objectively measure sleep, demonstrating that the more individuals were exposed to childhood adversity the less they slept in days in which they experienced great number of stressors or severe stressors, and this was also related to more cortisol secretion during these stressful days [[160](#_ENREF_160)]. More recently, using a wearable sensor it was found that periods of prolonged stress such as medical internship may lead to elevation in mean heart rate (HR) during sleep, yet that these effects are particularly potent among individuals with a history of childhood adversity. Further, childhood adversity moderated the relation between individual sleep HR increase and the development of anxiety during that stressful period [[161](#_ENREF_161)]. These results are also in line with previous findings highlighting poor sleep quality as a mediator in the association between childhood adversity and anxiety and depression symptom severity in adulthood [[47](#_ENREF_47),[162](#_ENREF_162)].

We recently addressed these putative associations by tracking sleep patterns in natural settings using wearable sensors [[163](#_ENREF_163)]. Specifically, 96 healthy adult female participants completed the well-established childhood trauma questionnaire (CTQ) before wearing a wearable sensor for seven consecutive days and nights and while fully maintaining their daily routine. Immediately following the measurement period, participants underwent an acute laboratory stress induction procedure using a modified version of the Maastricht Acute Stress Task [MAST][[164](#_ENREF_164)], to produce a robust and prolonged acute stress response [[165](#_ENREF_165)]. Results indicate that sleep patterns fully mediated the association between childhood adversity and psychological response to acute stress in adulthood. Specifically, elevated levels of childhood trauma were associated with inconsistent sleep patterns across the recording period, which in turn was associated with higher stress-induced negative affect (**Figure 1**). These findings are in line with previous demonstrations that high day-to-day variability in sleep duration, but not average sleep duration, is related to reduced subjective sleep quality and poorer well-being [[166](#_ENREF_166)]. High intra-individual day-to-day variability in sleep duration was also related to more stressful life events and more negative affect in adults [[167](#_ENREF_167)], greater perceived stress in young adults [[168](#_ENREF_168)], and increased vulnerability towards the negative effects of parental conflict in adolescents [[169](#_ENREF_169)]. The novel results presented here demonstrate that inconsistencies in sleep-wake cycle are related to the magnitude of exposure to childhood adversity among healthy adults, as well as to their level of affective responsivity to stress. Irregularity of the sleep-wake cycle may therefore represent a marker of sleep disturbances that mediates the association between childhood adversity and heightened stress reactivity at adulthood.

**Figure 1**

**Figure 1.** Structural equation mediation model depicting how the association between childhood adversity and stress-induced negative affect is fully mediated by variation in sleep duration over one week of measurement in natural settings. Coefficient values are standardized. (\* p < 0.01, \*\* p < 0.001).

**5. The role of the HPA axis in stress and sleep**

A detailed account of the physiological mechanisms of stress and sleep is beyond the scope of the current review. Here we focus on the hypothalamic-pituitary-adrenal (HPA) axis due to its critical role in both stress and sleep regulatory pathways. The paraventricular nucleus (PVN) of the hypothalamus is the starting point of the HPA stress response axis, a major neuroendocrine stress responsivity pathway that regulates cortisol secretion and suppression [[170-174](#_ENREF_170)]. As such, it comes as no surprise that PTSD and additional stress-related psychopathologies are associated with aberrant HPA activity at baseline and in response to stress (reviewed in [[175-179](#_ENREF_175)]). Interestingly, more severe PTSD symptoms were associated with amplified as well as with blunted cortisol stress reactivity patterns [[180](#_ENREF_180)]. Similar effects emerged in studies of childhood adversity. Here as well, both increased [[181-189](#_ENREF_181)] and decreased [[190-203](#_ENREF_190)] cortisol baseline and stress reactivity levels were documented among individuals with a history of childhood adversity, with the majority of evidence pointing towards blunted reactivity [[204-209](#_ENREF_204)]. Differences in findings highlight the importance of the time that passed since the exposure to trauma or adversity, the type of the exposure and the age and gender of participants, as all of these factors were shown to impact cortisol response patterns. Nevertheless, across studies results clearly indicate that HPA dysfunction is highly prevalent in both stress-related psychopathology and childhood adversity cohorts. In fact, dysregulation of the HPA stress response axis is considered one of the most key neuroendocrine mechanisms through which childhood adversity may confer stress vulnerability [[17](#_ENREF_17),[207](#_ENREF_207),[210-213](#_ENREF_210)]. Given that the HPA stress response axis undergoes maturational changes throughout childhood and adolescence, it may be particularly sensitive to childhood adversity, yielding long-term and persistent dysregulation of the HPA pathway [[206](#_ENREF_206),[210](#_ENREF_210),[214](#_ENREF_214),[215](#_ENREF_215)]. Specifically, blunted cortisol levels (e.g., hypocortisolism) may develop as an adaptation of the HPA axis to constant or repeated activation during sensitive developmental periods, such as in the case of childhood adversity [[216](#_ENREF_216),[217](#_ENREF_217)]. In support of that, blunted cortisol response to acute stress was found to be more pronounced in adults with a history of childhood adversity compared to children and adolescents [[207](#_ENREF_207)], potentially indicating on long-term cumulative effects.

The HPA axis also plays a key role in regulating sleep-wake cycles, by controlling diurnal rhythms of cortisol secretion. The diurnal rhythm is primarily controlled by the suprachiasmic nucleus (SCN) of the hypothalamus that is considered the brain’s pacemaking ‘master clock’ [[218](#_ENREF_218),[219](#_ENREF_219)]. With input from the SCN through the PVN, the HPA axis secretes cortisol in a pulsatile manner throughout the day, with greater secretion occurring during the transition from sleep to waking [[220](#_ENREF_220)]. Similar to the HPA stress response pathway, the HPA endogenous circadian rhythm mechanism also demonstrates significant functional changes throughout development [[221](#_ENREF_221),[222](#_ENREF_222)]. Such mutual dependence of stress and sleep regulatory pathways on the HPA axis may set the stage for the bi-directional causal relationship between stress exposure and sleep disturbances [[223-226](#_ENREF_223)]. On the one hand, HPA stress response hyper-reactivity may adversely impact circadian rhythms, for instance because cortisol hinders the production of melatonin which supports falling asleep, hence leading to sleep disturbances [[227](#_ENREF_227)]. On the other hand, sleep disturbances may alter the physiological neuroendocrine stress response pathway by increasing sympathetic tone and HPA stress reactivity, thus contributing to allostatic load [[106](#_ENREF_106),[228](#_ENREF_228)]. For example, sleep deprivation, shorter sleep duration and poorer sleep quality were all associated with increased HPA reactivity to acute stress and alterations in the cortisol awakening response among children and adults [[229-232](#_ENREF_229)], which in turn was associated with elevated depressive symptoms [[229](#_ENREF_229)]. Together, these bi-directional effects within the HPA stress and sleep axes may yield a vicious cycle in which sleep disturbances and HPA axis dysfunction reinforce each other, leading to elevated stress vulnerability.

Another highly relevant pathway that is noteworthy mentioning here relates to the well-documented impact of cortisol on different phases of memory formation [[145](#_ENREF_145)]. To this end, elevated levels of cortisol during learning and during retrieval were shown to enhance and impair, respectively, retention of emotional, but not neutral, memories [[233](#_ENREF_233),[234](#_ENREF_234)]. Given the notion that impaired memory consolidation and fear extinction processes represent maladaptive consequences of childhood adversity, as discussed above, the impact of cortisol levels on memory processes represents a critical pathway through which HPA dysfunction may further contribute to stress vulnerability. Interestingly, and perhaps not surprisingly, cortisol levels differently impact memory consolidation during sleep and during wakefulness [[235](#_ENREF_235)], further supporting the relevance of this pathway to the associations discussed in here.

**6. Conclusions, implications and future directions**

The current review focuses on stress vulnerability as a prominent maladaptive consequence of childhood adversity, expressed in the form of elevated likelihood to develop stress-related psychopathology upon subsequent exposure to psychological trauma in adulthood. Based on ample evidence from clinical studies among healthy and psychopathological populations that link both childhood adversity and stress-related psychopathology with sleep disturbances, we postulate that childhood-adversity-induced sleep disturbances may represent a behavioral predisposing marker for stress vulnerability. In support of that, sleep disturbances that predate adult trauma exposure increase the likelihood of developing stress-related psychopathology post-exposure. Further, novel empirical evidence suggests that sleep disturbances, including irregularity of the sleep-wake cycle, mediate the association between childhood adversity and heightened stress reactivity in adulthood. Life-long sleep disturbances that develop during childhood in response to adversity may reduce individuals’ chances to overcome encounter with subsequent psychological trauma at adulthood, potentially because sleep disturbances may impair memory consolidation and fear extinction capabilities. At the physiological level, mutual dependence of stress and sleep regulatory pathways on the HPA axis may produce a vicious cycle in which sleep disturbances and HPA axis dysfunction reinforce each other, leading to elevated stress vulnerability. **Figure 2** depicts a conceptual path model from childhood adversity to stress-related psychopathology, highlighting the mediating roles of sleep disturbances and HPA axis dysfunction. This model resembles the broad concept of the “two hit model for psychopathology” where childhood adversity is the first hit and subsequent trauma exposure at adulthood is the second hit. In this respect, HPA axis dysfunction, sleep disturbances and reduced fear extinction capability are the physiological, behavioral and cognitive “scars”, respectively, of the first hit that together yield predisposed stress vulnerability. Such vulnerability, in turn, is carried into the second hit, exaggerating its impact on mental health, and increasing the likelihood of developing stress-related psychopathology.

**Figure 2**

**Figure 2.** A conceptual path model of the causal relations between childhood adversity, sleep disturbances, HPA axis dysfunction, reduced fear extinction and elevated stress vulnerability, which upon encounter with subsequent psychological trauma at adulthood may yield stress-related psychopathology.

Childhood adversity is, unfortunately, a common phenomenon, with detrimental impact on physical and mental health throughout the life course. Nevertheless, not everyone that experiences childhood adversity develops psychopathology, not even after exposure to subsequent psychological trauma in adulthood. Thus, identifying markers for elevated stress vulnerability among healthy adult individuals with a history of childhood adversity carries substantial clinical and societal implications [[236](#_ENREF_236)]. It has already been suggested that early treatment of sleep problems may mitigate some of the long-term adverse impacts of childhood adversity [[25](#_ENREF_25),[29](#_ENREF_29)]. Targeting childhood-adversity-induced sleep disturbances may be particularly useful in preventing stress-related psychopathology, as one of the beneficial outcomes of such early treatments could be increased resilience to subsequent stress and trauma exposure. Promising results from recent studies demonstrate that even a short sleep period after experimental trauma, as long as it contains REM sleep, plays a protective role in trauma memory formation [[237](#_ENREF_237)], and contributes to adaptive reconsolidation of aversive autobiographical memories [[238](#_ENREF_238)]. In another study, normal sleep following experimental trauma led to higher explicit memory for potential trauma reminders and fewer intrusions after sleep, compared to partial sleep deprivation, again supporting the protective role of sleep in trauma memory [[239](#_ENREF_239)]. This is also in line with extensive literature on stress resilience among healthy adults that points towards strong positive associations between stress resilience and sleep duration and sleep quality [[240](#_ENREF_240)]. Another potential therapeutic avenue may involve treatments during sleep. This option builds upon promising results that fear memories can be extinguished during sleep using targeted memory reactivation [[241](#_ENREF_241),[242](#_ENREF_242)]. The implantation of such novel treatment procedure could be particularly beneficial for children who might be overwhelmed by conventional exposure therapy or reluctant to participate. Together, these results suggest that interventions aimed at reducing sleep disturbance in children exposed to adversity or in healthy adults with a history of childhood adversity may reduce their likelihood to develop stress-related psychopathology upon subsequent exposure to trauma, or even prevent it altogether. These interventions may gradually become more and more effective as we learn how to experimentally manipulate which memory traces are reactivated during sleep [[118](#_ENREF_118)], or how to pharmacologically boost memory consolidation and fear extinction processes following successful treatment sessions [[243](#_ENREF_243),[244](#_ENREF_244)].

While supported by vast literature, it is critical to acknowledge that the suggested conceptual model represents a clear simplification of the associations between the discussed factors. Furthermore, the model omits many additional factors and pathways that are also highly involved in the path from childhood adversity to stress-related psychopathology. For example, the interaction between childhood adversity and HPA stress response axis was found to be influenced by genetic dispositions and epigenetic processes as well as inflammatory and neural pathways [[245-251](#_ENREF_245)]. Further, while the current review focuses on the hypothalamus due to its critical role in HPA stress and sleep regulatory axes, additional neural structures and networks are tightly involved in regulating, and are impacted by, stress and sleep. The most frequently reported brain regions are the limbic structures amygdala and hippocampus as well as the prefrontal cortex (PFC), all of which are implicated in executive functioning, emotional regulation and fear extinction, with the PFC also highly relevant in the context of childhood adversity due to its susceptibility to stress during development [[252-259](#_ENREF_252)]. In fact, the majority of neural models of stress responsivity and psychopathology lack explicit reference to the hypothalamus, potentially due to its size and location that pose a challenge for neuroimaging studies. While no study can include all relevant factors, incorporation of multiple pathways and systems by future studies may further improve our understanding of the complex multilayer interactions between childhood adversity and stress vulnerability. Models that incorporate evidence from animal studies may prove to be particularly valuable given that in animal models childhood adversity can be induced and followed throughout animals’ lifespan, allowing causal inferences. Indeed, studies in animals provide strong support to all the major paths described above, including: A) Increased likelihood to be affected by acute stress in adulthood for rats that underwent childhood adversity (most commonly referred to as juvenile stress or early-life stress) [[260](#_ENREF_260)]; B) Childhood-adversity induced sleep disturbances that last into adulthood [[223](#_ENREF_223)]; C) Specific sleep patterns before exposure to stress that predict animals’ resilience vs. vulnerability post-exposure [[261](#_ENREF_261),[262](#_ENREF_262)]; D) Advantages of sleep for memory consolidation processes [[263](#_ENREF_263)].

Future progress may also be achieved by implementing unified designs and terminology, and harnessing technological advances, particularly as it comes to sleep measures. Studies covered in this review considerably varied with respect to their subjective and objective measures of sleep efficacy and/or disturbance. Such heterogeneity of sleep outcome variables significantly limits comparisons across studies and may contribute to some of the inconsistencies in results. In fact, previous research suggests that objective and subjective measures of sleep are often discrepant in both healthy and clinical samples, with the degree of discrepancy between objective and subjective sleep being dependent on the measures utilized [[74](#_ENREF_74)]. Therefore, utilizing a unified multimethod approach to quantify sleep is vital in order to fully understand the role of sleep disturbances in the path from childhood adversity to stress vulnerability. Also important in this regard, many sleep studies relied on single-night measurements in artificial laboratory settings and/or self-reported diaries. Recent advances in wearable technology enable accurate estimation of multiple objective sleep measures in real-life settings and over long time periods. Implementing these measures in sleep research may aid to substantially increase the translational validity of future findings. For example, measuring sleep over long period of time and in natural settings could provide valuable insights regarding the typically overlooked construct of intra-individual variability in sleep-wake cycle which is a highly relevant factor in the context of childhood adversity and stress reactivity, as suggested above and in prior studies [[166-169](#_ENREF_166),[264](#_ENREF_264),[265](#_ENREF_265)]. Measuring childhood adversity in real-time is obviously much more challenging and indeed must typically rely on retrospective self- or parent- reports that are prone to recall bias. An alternative approach could be to rely on more objective official court or child protection records, wherever feasible. Interestingly enough, subjective retrospective reports of childhood adversity were associated with elevated psychopathology rates at adulthood while objective measure were not [[266](#_ENREF_266)]. With increased efforts to integrate multiple response domains and to rely on objective valid measures of sleep over long time periods, future studies may continue to uncover the impact of childhood adversity on physiology, sleep and behavior, and consequently, on lifelong physical and mental health.

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L.S and R.A jointly wrote the paper.

**7. References**

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