**From childhood adversity to latent stress vulnerability in 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 an elevated likelihood of developing stress-related psychopathology upon subsequent exposure to trauma in 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 post-traumatic stress disorder (PTSD). After briefly reviewing the extensive literature supporting these claims, the current review addresses the notion that childhood adversity-induced sleep disturbances may play a causal role in elevating individuals’ stress vulnerability in adulthood. Corroborating this, sleep disturbances that predate adult trauma exposure have been associated with an increased likelihood of developing 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 in adulthood. We also discuss cognitive and behavioral mechanisms through which such a cascade may evolve, highlighting the putative role of impaired memory consolidation and fear extinction. Next, we present evidence 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 in adulthood and discuss the potential clinical implications of these notions, while highlighting directions for future research.

**1. Childhood adversity and** **latent stress vulnerability in 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 of developing multiple health problems during childhood, including asthma, infections, and somatic complaints, as well as of exhibiting 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. Thus, childhood adversity is associated with elevated risk for various physical and mental health conditions in 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 in adulthood. In a seminal paper, Bremner and colleagues (1993) revealed that Vietnam veterans with post-traumatic stress disorder (PTSD) had almost four times higher rates of exposure to childhood physical abuse than Vietnam veterans without PTSD [[16](#_ENREF_16)]. Given that many Vietnam veterans were exposed to psychological trauma in adulthood during their military service but only a subset of vulnerable individuals eventually developed PTSD, this study provided some of the first empirical evidence suggesting that childhood adversity may increase the likelihood of PTSD development later in life. Since then, a 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 in adulthood (reviewed in [[17-22](#_ENREF_17)]). Such latent stress vulnerability is expressed as an elevated likelihood of developing stress-related psychopathology following trauma exposure in 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, and parent psychopathology—are particularly associated with an increased risk of PTSD development following exposure to subsequent trauma in adulthood [[23](#_ENREF_23)]. This work further revealed that these associations are consistent across exposures to different types of traumatic events in adulthood, suggesting a 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 has been 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, a 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 that can interfere with sleep quality [[31-33](#_ENREF_31)]. Across studies, childhood adversity-induced sleep disturbances have been 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 not only during infancy and childhood, but also throughout adolescence and into adulthood and old age. Interestingly though, the range of affected individuals varies across studies, with sleep disturbances reported in between 8.7% and 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 a “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 bear 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 in uncertain and threatening environments, their long-term consequences might be maladaptive, eventually leading to a 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 the 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 in adulthood**

Sleep disturbances have also repeatedly been associated with stress vulnerability in adulthood. Perhaps the most straightforward example stems from the wealth of evidence on sleep disturbances in individuals diagnosed with stress-related psychopathologies, particularly PTSD (reviewed in [[65-71](#_ENREF_65)]). Indeed, the latest 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 in 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 have been 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 a decreased total sleep time, decreased sleep efficiency, and increased awakenings after sleep onset [[65-71](#_ENREF_65)]. In addition to relying on subjective reports, a wealth of polysomnographic studies have examined specific objective measures of sleep abnormalities in PTSD patients in laboratory settings and in the natural home environment [[70](#_ENREF_70),[75](#_ENREF_75)]. Most evidence seems to support alterations of sleep architecture, elevated nocturnal autonomic nervous system 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 have also emerged between subjective measures of sleep disturbances and PTSD symptom severity in veterans, civilians, and assault survivors with PTSD. For example, the magnitude of subjective sleep disturbances, based on the Pittsburgh Sleep Quality Index (PSQI), has been positively associated with PTSD symptom severity among women with PTSD related to sexual or physical assault [[76](#_ENREF_76)]. Similar associations have 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 inconsistent results may be related to the potential non-linearity of the associations because, for example, both a very short sleep duration (≤ 5 h of sleep) and long sleep duration (≥ 9 h) have been 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 of psychopathology development in response to psychological trauma. The existing literature seems to support both scenarios, pointing toward 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, a vast amount of evidence clearly indicates that sleep disturbances that predate adult trauma exposure significantly increase the likelihood of the subsequent development of psychopathology, suggesting a causal role of sleep disturbances in stress vulnerability. For example, a prospective study among military personnel revealed that insomnia symptoms and a 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 4 months post-deployment was a significant predictor of PTSD symptoms 1 year post-deployment, whereas PTSD symptoms at 4 months did not predict insomnia at 1 year [[89](#_ENREF_89)]. Among soldiers deployed in Iraq or Afghanistan, pre-deployment insomnia and sleep disturbances predicted PTSD and depression symptom severity at 3, 6, and 9 months and up to 2 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 2 weeks preceding the trauma increased the risk for PTSD diagnosis 3 [[93](#_ENREF_93)] and 6 [[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 most of the studies cited above, findings were obtained while controlling for the putative effects of age, sex, type, and severity of the trauma and prior psychiatric disorders, indicating that preexisting sleep disturbances may predispose vulnerability to stress following trauma exposure in adulthood above and beyond the potential contribution of these additional factors.

**4. From childhood adversity to latent stress vulnerability in 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 in adulthood, and both childhood adversity and stress-related psychopathology have been independently associated with sleep disturbances. Furthermore, substantial evidence suggests that sleep disturbances that predate adult trauma exposure may lead to an elevated likelihood of developing 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 of developing stress-related psychopathology upon exposure to subsequent psychological trauma in 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 perspective, 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 have been linked to 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 for 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 throughout life [[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 be related to the vital role of sleep in the 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 have been shown to have a long-term maladaptive impact on memory and cognitive control processes, and sleep deprivation leads to elevated emotional arousal and hyper-sensitivity to stress [[124](#_ENREF_124),[125](#_ENREF_125)]. The well-documented deficits in executive functioning and emotional regulation in children [[126-130](#_ENREF_126)], adolescents [[131-134](#_ENREF_131)], and adults [[135-139](#_ENREF_135)] who were exposed to childhood adversity may therefore be the result of lifelong sleep disturbances. Indeed, 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 emotional regulation are also established risk factors for the development of stress-related psychopathology [[140-142](#_ENREF_140)] and, indeed, 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, thereby reducing individuals’ chances to successfully overcome subsequent encounters with psychological trauma in adulthood.

Sleep is one of the cognitive processes critical for memory consolidation. The changes in synaptic morphology and neural excitability that occur during sleep enable the transition of initial memory traces from the hippocampus to more permanent cortical storage sites [[145-148](#_ENREF_145)]. These mechanisms are particularly relevant here given the abundance of preclinical and clinical studies that indicate 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 impair memory consolidation processes and yield reduced fear extinction, which has also been shown in PTSD patients [[149](#_ENREF_149),[152](#_ENREF_152)]. Reduced fear extinction and impaired transition to safety have also been 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 in trauma-exposed children [[154](#_ENREF_154)]. Hence, sleep disturbances and childhood adversity have independently been 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, which reduces fear extinction capabilities. These theories 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 in adulthood is limited, although more attention has been devoted in recent years to these putative associations, yielding promising results. For example, by relying on subjective measures of sleep, the association between childhood adversity and sleep disturbances has been found to be mediated by current levels of psychological distress in both adults [[157](#_ENREF_157)] and adolescents [[158](#_ENREF_158)]. Moreover, the association between childhood adversity and poor self-reported sleep quality is mediated by the level of psychological distress that was experienced specifically during a stressful period of life (i.e., when beginning life at university) [[159](#_ENREF_159)]. A similar pattern emerged in a study that used an Actiwatch to objectively measure sleep, demonstrating that the more individuals were exposed to childhood adversity the less they slept in days on which they experienced a great number of stressors or severe stressors, and this was also related to greater 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 during a medical internship may lead to an elevated mean heart rate during sleep, but that these effects are particularly potent in individuals with a history of childhood adversity. Furthermore, childhood adversity moderated the relationship between the individual sleep heart rate 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 of childhood adversity with 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 7 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)]. The results indicated that sleep patterns fully mediated the association between childhood adversity and the 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 to the negative effects of parental conflict in adolescents [[169](#_ENREF_169)]. The novel results presented here demonstrate that inconsistencies in the sleep-wake cycle are related to the magnitude of exposure to childhood adversity in 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 in 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 the variation in sleep duration over 1 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 have been associated with amplified as well as with blunted cortisol stress reactivity patterns [[180](#_ENREF_180)]. Similar effects have 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 in individuals with a history of childhood adversity, with most of the evidence pointing toward blunted reactivity [[204-209](#_ENREF_204)]. Differences in findings highlight the importance of the time passed since the exposure to trauma or adversity, the type of the exposure, and the age and sex of participants, because all of these factors have been shown to impact cortisol response patterns. Nevertheless, across studies, the 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 critical 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)]. Indeed, a blunted cortisol response to acute stress has been found to be more pronounced in adults with a history of childhood adversity than in children and adolescents [[207](#_ENREF_207)], potentially indicating 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, which is considered the pacemaking “master clock” of the brain [[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 a 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, for instance, adversely impact circadian rhythms because cortisol hinders the production of melatonin, which supports sleep onset, thereby 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, contributing to the allostatic load [[106](#_ENREF_106),[228](#_ENREF_228)]. For example, sleep deprivation, shorter sleep duration, and poorer sleep quality have all been associated with increased HPA reactivity to acute stress and alterations in the cortisol awakening response in children and adults [[229-232](#_ENREF_229)], which in turn has been 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 worth mentioning here is related 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 enhance and impair, respectively, the 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 in the associations discussed 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 an elevated likelihood of developing stress-related psychopathology upon subsequent exposure to psychological trauma in adulthood. Based on ample evidence from clinical studies of healthy and psychopathological populations that link both childhood adversity and stress-related psychopathology to sleep disturbances, we postulate that childhood adversity-induced sleep disturbances may represent a behavioral predisposing marker for stress vulnerability. Substantiating this, sleep disturbances that predate adult trauma exposure increase the likelihood of developing stress-related psychopathology post-exposure. Furthermore, 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. Lifelong sleep disturbances that develop during childhood in response to adversity may reduce individuals’ chances to overcome an encounter with a subsequent psychological trauma in adulthood, potentially because sleep disturbances may impair memory consolidation and fear extinction capabilities. At the physiological level, the 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 in 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 relationship among childhood adversity, sleep disturbances, HPA axis dysfunction, reduced fear extinction, and elevated stress vulnerability, which may lead to stress-related psychopathology upon an encounter with subsequent psychological trauma in adulthood.

Childhood adversity is, unfortunately, a common phenomenon, with detrimental impact on physical and mental health throughout life. Nevertheless, not everyone that experiences childhood adversity develops psychopathology, not even after exposure to subsequent psychological trauma in adulthood. Thus, the identification of markers for elevated stress vulnerability in healthy adult individuals with a history of childhood adversity has substantial clinical and societal implications [[236](#_ENREF_236)]. It has already been suggested that the early treatment of sleep problems may mitigate some of the long-term adverse impacts of childhood adversity [[25](#_ENREF_25),[29](#_ENREF_29)]. The targeting of childhood adversity-induced sleep disturbances may be particularly useful in preventing stress-related psychopathology because 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 toward 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 a 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 of developing 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 among 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 the HPA stress response axis has been found to be influenced by genetic dispositions and epigenetic processes as well as inflammatory and neural pathways [[245-251](#_ENREF_245)]. Furthermore, 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 the 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, most neural models of stress responsivity and psychopathology lack explicit reference to the hypothalamus, potentially because its size and location 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 strongly support all of the major pathways described above, including: a) an increased likelihood of acute stress in adulthood in rats exposed to childhood adversity (most commonly referred to as juvenile 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)]; and 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. The 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. Indeed, 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 used [[74](#_ENREF_74)]. Therefore, the use of a unified multimethod approach to quantify sleep is vital 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. The implementation of these measures in sleep research may help to substantially increase the translational validity of future findings. For example, the measurement of sleep over long periods of time and in natural settings could provide valuable insights into the typically overlooked construct of intra-individual variability in the 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)]. The real-time measurement of childhood adversity 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, subjective retrospective reports of childhood adversity have been associated with elevated psychopathology rates in adulthood, unlike objective measures [[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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