Early-life origin of adult insomnia: does prenatal–early-life stress play a role?

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ABSTRACT

Insomnia is very common in the adult population and it includes a wide spectrum of sequelae, that is, neuroendocrine and cardiovascular alterations as well as psychiatric and neurodegenerative disorders. According to the conceptualization of insomnia in the context of the 3-P model, the importance of predisposing, precipitating, and perpetuating factors has been stressed. Predisposing factors are present before insomnia is manifested and they are hypothesized to interact with precipitating factors, such as environmental stressful events, contributing to the onset of insomnia. Understanding the early-life origins of insomnia may be particularly useful in order to prevent and treat this costly phenomenon. Based on recent evidence, prenatal–early-life stress exposure results in a series of responses that involve the stress system in the child and could persist into adulthood. This may encompass an activation of the hypothalamic–pituitary–adrenal axis accompanied by long-lasting modifications in stress reactivity. Furthermore, early-life stress exposure might play an important role in predisposing to a vulnerability to hyperarousal reactions to negative life events in the adult contributing to the development of chronic insomnia. Epigenetic mechanisms may also be involved in the development of maladaptive stress responses in the newborn, ultimately predisposing to develop a variety of (psycho-) pathological states in adult life.

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1. Introduction

Insomnia symptoms are very common, affecting one-third of the adult population; insomnia disorder is the most prevalent among the sleep disorders afflicting approximately 6–10% of adults [1].

Experimental and epidemiological studies conducted in adults show that poor sleep and insomnia have a wide spectrum of sequelae, including neuroendocrine and cardiovascular alterations as well as psychiatric and neurodegenerative disorders [2–9]. From a life-course perspective on health, understanding the early-life origins of insomnia may be particularly useful in order to prevent and treat this disturbance, which is of high economic relevance for healthcare systems [10]. In addition, the association of insomnia with new-onset depressive disorder suggests the potential for downstream benefits of insomnia treatment with respect to prevention of psychiatric disorders [11,12]. The aim of this paper was to systematically review the evidence regarding the early-life origin of adult insomnia from prenatal to childhood origin.

2. Background of the hypothesis

2.1. Stress system and predisposition to insomnia: model of insomnia in adult and infant

A heuristic model of insomnia is the diathesis–stress model proposed by Spielman et al. [13] commonly known as the “3-P” model. The model describes predisposing, precipitating, and perpetuating factors relevant for the development and maintenance of insomnia. Predisposing factors include genetic, physiological, or psychological diatheses that confer differential susceptibility to individuals. These predisposing factors interact with precipitating factors such as physiological or environmental stressors, which lead an individual to cross a hypothetical insomnia threshold, eliciting the initial symptoms of insomnia. Perpetuating factors are proposed to play a role in the maintenance of insomnia.

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The neurocognitive model of insomnia [14] is founded on this diathesis–stress model, further integrating neurobiological and neurophysiological observations, and it proposes that insomnia leads to conditioned cortical arousal. Hyperarousal on several levels (cognitive–emotional, autonomous, and central nervous system) as such is assumed to play a central role in the development and maintenance of adult insomnia [15,16]. Buyssse et al. [17], in their neurobiological model of insomnia, hypothesized that the activation of cortico-limbic and brainstem hypothalamic centers may account for a relative increase in psychophysiological arousal observed in insomnia. The most face-valid animal model of insomnia presented by Cano et al. [18] using a cage-exchange paradigm also described insomnia as a consequence of the stressful experience of coactivation of sleep-inducing and arousing neuronal networks.

The relationships between response to a stressor and arousal deregulation have also been integrated in cognitive–psychological models of insomnia [19,20].

Roehrs et al. [21] reviewed evidence from nighttime and daytime electrophysiology, event-related brain potentials, neuroimaging, autonomic, and hypothalamic–pituitary–adrenal axis (HPA) studies that suggest insomnia is a 24-h disorder of hyperarousal. Numerous studies provide evidence for cognitive and physiological hyperarousal with an activation of the HPA in people with chronic insomnia (for an overview, see Refs. [15,16,21]). It has been hypothesized that hyperarousal may be a characteristic of individuals with elevated stress–sleep reactivity, that is, the degree of sleep disruption in response to stressful events [22–25], and that hyperarousal may constitute a premorbid characteristic of people with insomnia [22,26].

Sleep disturbances are common in infants and are a normal part of development that affects 20–33% of individuals; about half of these develop persistent sleep problems [27–29]. Infant sleep disorders, if not treated, may be quite persistent during childhood [28,29] and through adulthood [30–32].

Sleep in the infant has been hypothesized to be influenced by a combination of processes including genetics and environmental factors [33]. A theoretical model of infant sleep regulation integrating multiple environmental systems was developed in 1993 [34] and revised in 2009 (for an overview, see Ref. [35]). This integrative model emphasizes the role of postnatal environmental stressors in developing infant insomnia [35].

Postnatal–childhood stressful experiences have been associated with lifelong consequences in response to stressful events later in life [36–39] leading to a variety of negative health outcomes into adulthood [38,40,41] including increased reactivity to stress [42] and insomnia [31].

Emerging data from both animals and humans indicate that environmental influences contributing to the development of insomnia may not be restricted to periods of postnatal development but may have origins in prenatal life: prenatal stress may contribute to a predisposition for insomnia in animals and humans [43–52].

2.2. Prenatal–early-life stress and stress system: implications for insomnia

Prenatal and postnatal periods are the most important and sensitive periods during the development of an individual [53,54]. Evidence from preclinical studies indicates that the brain is particularly sensitive to remodeling by environmental factors: adverse early-life experiences, such as stress exposure or suboptimal maternal care, can have long-lasting negative consequences leading to “early-life programming” of individual health and diseases [55].

Although knowledge on the possible mechanisms underlying relations between early-life programming and risk of disorders is limited, there is evidence for impaired glucocorticoid negative-feedback control of the HPA axis, altered glutamatergic neurotransmission, and reduced hippocampal neurogenesis in both prenatally and postnatally stressed rats (for an overview, see Ref. [54]).

The HPA axis appears to be particularly sensitive to the effects of early-life stress [37,54,56–59]. Preclinical and clinical studies show the most often proposed mechanism underlying the “early-life programming” of diseases is that involving the HPA axis and cortisol [54,60–62]. A general pattern, observed in rats and nonhuman primates, is that early-stressed offspring tend to show higher basal activity of the HPA axis, as well as potentiated and prolonged HPA responses to stressors with a consistent tendency towards hyperresponsivity (for an overview, see Refs. [54,62–64]). Decreased feedback inhibition of corticotropin-releasing hormone (CRH) and prolonged elevation of plasma glucocorticoids in response to stress have also been described. Prenatally stressed rats have higher levels of CRH in the amygdala and lower hippocampal levels of both glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) [57,63,65,66]. These findings have been integrated within the framework of the life history theory [67]. High stress responsivity can be adaptive in its nature, may be considered to be predictive for adaptations that serve to improve survival, and prepares the organism for a particular range of postnatal unpredictable environments [68]. Enhanced behavioral and neuroendocrine responses to stress may reflect greater vigilance to environmental threats, which may promote survival even if this has a long-term cost of adaptation [69,70]. Accordingly, some theorists have suggested that a hyperresponsive HPA axis may have been adaptive during evolution at the cost of vulnerability for various disorders, and it may no longer be adaptive – even becoming maladaptive or disadvantageous [69–71].

Although many individuals experiencing stressful events do not develop pathologies, chronic stress seems to be a triggering factor in those individuals who are particularly vulnerable. This vulnerability may in turn depend upon a permanent increase in the activation of the HPA axis. This can increase the susceptibility of the offspring to various stress-related diseases.

In fact, there is evidence to suggest that early-life stress has been associated with a wide range of health problems later in life such as increased reactivity to stress, and psychiatric and behavioral disorders [38,42,63,65,71–74].

Sleep is also one of many outcomes causally linked with early life in the animal literature, showing some changes in sleep architecture and more fragmented sleep related to early-life stress [43,46,47,75–78].

2.3. Epigenetic programming of the stress system: implications for insomnia

In the last decade, there has been increasing evidence that epigenetic mechanisms are likely to play a major role in the molecular mechanisms underlying the long-lasting effect of early-life stress on adult health. The early-life years represent a period of particular susceptibility to epigenetic alteration, as active changes in DNA methylation and histone marks occur as part of developmental programs and in response to environmental cues (for an overview, see Ref. [79]). Epigenetic mechanisms have been hypothesized to shape the responsiveness of the HPA axis to subsequent early-life stressors, thus substantially contributing to the development of stable individual differences in HPA hyperresponsivity to stressful stimuli [80–83]. The most investigated hypothesis on how early-life stress can alter the child’s development in utero and postnatally is that this is mediated by long-term effects on the function/activity of genes involved in the regulation of the HPA axis.

A number of studies have shown that induction of early-life stress can lead to epigenetic changes in key regulators of the stress response. This impairs negative HPA axis feedback by, for example,
inducing DNA demethylation of the \textit{FKBP5} gene, thus reducing GR sensitivity, which prolongs the cortisol response \cite{84,85}.

Recently, an epigenetic model of insomnia has been proposed \cite{86}. While a genetic susceptibility may modulate the impact of stress on the brain, this finding does not provide a complete understanding of the underlying pathophysiology whereby stress produces long-lasting perturbations of brain and behavior leading to chronic insomnia: stress response-related brain plasticity might be epigenetically controlled starting from early life \cite{86}.

### 2.4. Hypothesis of the review

In this scenario, prenatal/early-life stressors might contribute to an "early-life programming" of the HPA axis and the stress system, which may predispose to the development of insomnia in later life. We hypothesize a consistent tendency towards stress system hyperresponsivity in subjects who may be predisposed to develop insomnia: a vulnerability to hyperarousal reactions to life events in the adult may predispose to the development of insomnia. An epigenetic early-life shaping of the HPA axis and of the stress system may be implied in the "early-life programming" of the vulnerability to develop insomnia.

To this aim, we systematically review the evidence on prenatal and early-life distress and predisposition to adult insomnia. We then review the hypothesis of its epigenetic programming.

### 3. Methods

#### 3.1. Search strategy

We performed a systematic search of Medline, Embase, and PsycINFO. The initial search was conducted in November 2013 with a final search in April 2014. The search strategies included the use of Medical Search Headings (MeSH) headings and keywords for "prenatal stress" or "antenatal stress" or "childhood stress" and "insomnia" or "adult insomnia" or "sleep disorder" and "epigenetic."

#### 3.2. Inclusion and exclusion criteria

Studies were included if they satisfied the following criteria: (1) studies involving animal subjects or human participants; (2) longitudinal, observational, case–control, or cross-sectional studies; (3) studies analyzing the effect of prenatal or postnatal childhood stress on the development of adult insomnia; (4) studies published between 1 January 1960 and April 2014.

Studies were excluded if they: (1) were not available in full text or (2) were not available in English.

### 4. Results

Ninety articles were retrieved; of these, 77 were excluded after detailed review as they did not meet the inclusion criteria. Twenty-four papers were included and their data retrieved. The flow diagram reporting the inclusion and exclusion process through the different phases of the systematic review is presented in Fig. 1.

#### 4.1. Prenatal origin of adult insomnia

Emerging data from both humans and animals indicate that environmental influences contributing to the development of insomnia may have origins in prenatal life: prenatal response to stress may contribute towards a predisposition for insomnia. Prenatal stress may contribute in predisposing to insomnia in humans and animals \cite{43-51}.

![Fig. 1. Flow diagram reporting the flow of information through the different phases of the systematic review.](image-url)
newborns had more sleep disturbances including less time in deep sleep and more time in indeterminate (disorganized) sleep, and they were more active and cried/fussed more.

In a longitudinal, prospective study of 14,541 pregnancies, O’Connor et al. [50] reported that higher levels of prenatal maternal anxiety and depression predicted reduced sleep duration and more disturbed sleep due to infant night wakings in newborns at 18 and 30 months after controlling for postnatal mood and obstetric and psychosocial covariates. A delayed onset of consolidated sleep at 18 and 30 months has also been described.

In a study from Baird et al. [51], a total of 874 women from the Southampton Women’s Survey were recruited between 20 and 34 years of age and followed up through their subsequent pregnancies and beyond. Prenatal psychological distress was measured with the General Health Questionnaire and was considered a strong predictor of infant night wakings at bedtime and 6 months and 30 months of age, independent of the effects of postnatal depression, birth weight, and other confounding factors. The authors concluded that women with prenatal psychological distress are more likely to have babies with longer night wakings during infancy, independent of whether they suffered from postnatal depression.

Nevarez et al. [52] studied 1676 mother–infant pairs in a prebirth cohort study. Maternal prenatal depression was associated with shorter sleep durations in the infant at both 1 and 2 years of age. Sleep durations were estimated to be 0.36 fewer hours of sleep in the first two years of life of the infant for maternal prenatal depression. The authors concluded that maternal depression during pregnancy to be associated with shorter infant sleep duration.

Although the mechanisms relating maternal prenatal stress, mood disturbance, and infant sleep have yet to be fully understood, authors suggested that prenatal maternal anxiety, anger, and depression may be associated with increased prenatal stress leading to elevated glucocorticoid secretion. Subsequent to experienced maternal stress, an increased activity in the maternal HPA axis and in consequence increased cortisol levels have been observed: it probably also accesses the fetal–placental unit [63, 87–89] resulting in fetal glucocorticoid hyper-exposure [90].

The hypothesized mechanism is that elevated prenatal exposure to glucocorticoids disrupts or programs the fetus’ HPA axis and its diurnal pattern toward a hyperactivation [48–50, 52]. A link between the establishment of a diurnal pattern in cortisol and sleeping through the night in infancy has been reported [91]. Exposure to prenatal maternal anger/anxiety/depression and the implied associated increased exposure to glucocorticoids [90] may disrupt the onset of cortisol normal diurnal pattern and of a normal sleep cycle in the child. The view hypothesized in human subjects is supported by experimental studies in animals as the vast majority of human studies is, by necessity, descriptive and therefore cannot demonstrate causality or identify the basic mechanisms that underlie pathophysiological processes during development or in adulthood. In addition, most of the studies in human subjects measure sleep in young infants and they do not allow to follow the offspring once they have reached adulthood.

4.1.2. Clinical and psychobiological hypothesis in animals

In order to study the response to stress during prenatal life, different animal models of perinatal stress have been developed since 1957 (for an overview, see Ref. [81]). The sleep–wake cycle has been described to be modified by prenatal stress and significant phase advances have also been observed in the circadian rhythms of locomotor activity relative to the entrained light/dark cycle [43–47].

Dugovic et al. [43] hypothesized that prenatal restraint stress predisposes rats to long-lasting disturbances that persist throughout adulthood. The authors studied sleep–wake parameters in control and prenatally stressed adult rats (3–4 months old) and examined possible relationships with their corticosterone levels (determined at two months of age). Under baseline conditions, prenatally stressed rats showed increased amounts of paradoxical sleep, which were positively associated with plasma corticosterone levels.

Koehl et al. [44] studied the effects of prenatal stress on the daily pattern of corticosterone secretion in male and female rats once they had reached adulthood. The results demonstrated that prenatally stressed rats exhibit an altered temporal functioning of the HPA axis with increased basal levels of corticosterone particularly at the end of the light phase or resting phase.

Rao et al. [45] studied adult male rats that had been exposed to stress in utero and showed that prenatally stressed animals as compared to non-stressed controls had reduced amount of slow-wave sleep and reduced latency to the onset of rapid eye movement (REM) sleep with a prolongation of the first REM episode.

Prenatal stress in animal models has been shown to alter the re-active adaptation of the offspring. Investigations have demonstrated that early experiences influence the development of the 24-h diurnal pattern of the HPA system [92]. Exposure to prenatal restraint stress has been shown to result in increased responsiveness of the HPA axis to stress [75, 93]. Prolonged restraint stress can induce decreased feedback inhibition of the CHR by increasing circulating glucocorticoids; prolonged corticosterone secretion has been shown in prenatally stressed rats [93, 94]. In addition, prenatal stress exposure results in reduced expression of both GR [95] and MR.
in the hippocampus of the adult offspring [75], revealing a possible mechanism for the deficit of HPA axis feedback processes [46, 57, 65, 66, 93]. The sleep–wake cycle modification in animal models of prenatally stressed rats has been related to alteration in circulating glucocorticoids [43, 46, 47].

Although much of the animal literature on prenatal stress has focused on the HPA axis activity, some authors suggested that prenatally stressed animals may have higher sympathetic reactivity into adulthood. In a study by Weinstock et al. [96], prenatally stressed mice displayed a stronger noradrenaline response upon transfer to a novel environment.

Dugovic et al. (1999) hypothesized that, in addition to glucocorticoids, other factors may be involved in the long-term effects of prenatal stress on sleep [43]. As CRH is involved in the regulation of physiological waking by promoting it under both baseline conditions [97] and stress conditions, CRH may act in inducing an increase in the activity of noradrenergic neurons in the locus coeruleus [98, 99]. Thus, permanent neurochemical changes in the activity of the noradrenergic systems might participate in sleep modifications found in prenatally stressed rats.

Prenatal life experiences are thus associated with persistent changes in both the modulation of HPA axis activity and the HPA axis-mediated response to stress with a tendency towards hyperactivity; these experiences may be involved in the predisposition to develop hyperarousal and overstress reactivity in adult life leading to the development of insomnia. Indeed, other neurochemical changes that have been described to activate the arousal system may be involved as well.

A large body of evidence demonstrates that stress, via elevated levels of glucocorticoids, affects both the hippocampal structure and function [70, 71, 100]. Functionally, chronic stress is generally associated with reductions in hippocampal excitability; long-term potentiation and morphological consequences of chronic stress include volume reductions and suppressed rates of adult neurogenesis [70, 71, 100].

Prenatal stress is also associated with a decrease in various stages of adult hippocampal neurogenesis in a lasting manner that persist into adulthood (for an overview, see Refs. [53, 81, 101]). It has been shown to impair the morphological and functional maturation of hippocampal granule cells in adult offspring via the downregulated expression of MRs [102]. Rats exposed to some form of prenatal stress seem no longer plastic and they are unable to react to experiences that are known to modulate neurogenesis under control conditions, such as learning and stress [101].

A growing number of preclinical studies have shown that prolonged disruption of sleep in rats results in a decrease in neurogenesis and hippocampal cell survival (for a review, see Ref. [103]). Recently, hippocampal subfield atrophy has been demonstrated in chronic insomnia, suggesting a reduced neurogenesis in the dentate gyrus and neuronal loss in the cornu ammonis subfields in conditions of sleep fragmentation and related chronic stress condition [104].

We may hypothesize prenatal stress to alter hippocampal neurogenesis in the offspring, which may persist into adulthood and be related to insomnia development.

4.1.3. Prenatal life and epigenetic programming of the stress system: implications for developing insomnia

Epigenetic modification of gene function may be one mechanism by which prenatal stress may affect the development of the brain and may account for the long-lasting effect into adulthood contributing to persisting changes in stress reactivity [63, 79, 105, 106]. DNA methylation could be modulated by exposure to a variety of maternal experiences and might participate in processes that “adapt” the genome to stress. Prenatal exposure to stress conditions has been hypothesized to affect the differentiation of hippocampal neurons and it alters hippocampal GR gene expression by reduction [80, 82, 83].

Human infants of mothers with high levels of depression and anxiety during the third trimester have been shown to exhibit increased DNA methylation of the Nr3c1 gene promoter, which may lead to an impaired negative feedback by reducing GR levels (for an overview, see Ref. [105]). Knowledge of very important roles of placenta in the fetal brain development has been increasing. Stress during pregnancy may affect the expression of a number of key genes that may alter the permeability of the placenta to glucocorticoids. It possibly happens through alteration of the function of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which further increases glucocorticoid levels in the fetus and leads to long-term changes in stress hormone regulation. Studies indicate that maternal stress during the prenatal period can lead to a downregulation of this enzyme: DNA methylation has been hypothesized as a mechanism by which prenatal stress alters HSD11B2 gene expression (for an overview, see Ref. [85]).

Prenatal stress may thus affect the expression of a number of key genes that may alter the permeability of the placenta to glucocorticoids, which further increases glucocorticoid levels in the fetus and leads to long-term changes in neurodevelopment. In addition, prenatal stress may also directly impact the function of enzymes involved in epigenetic regulation leading to epigenetic effects of prenatal stress and stress hormone regulation.

In addition, there is evidence for an additional direct transmission of parental or ancestral stress through the germ line (for an overview, see Ref. [85]). This so-called transgenerational epigenetic inheritance may be responsible for the transgenerational inheritance of brain-related phenotypes and disease [107]. It was recently reported that mental stress in mouse pups (i.e., separation from the mother) not only changes the DNA methylation status in the brain of the separated pups, but these changes are also transmitted to the next generation. In the next generation, the changed status is visible in the brain of the offspring, and it is reflected by alterations in the corticotropin-releasing factor receptor 2 (Crfr2) gene expression and in the animal’s behavior [108]. Multiple perinatal factors can have a transgenerational, lifelong impact on morbidity [109].

A prenatal complex epigenetic effect may in turn modify the responsivity of the HPA axis to subsequent stressors, toward a hyperresponsivity, thus substantially contributing to the development of stable individual differences in HPA responsivity to stressful stimuli [81–83]. It may produce long-lasting modifications of the developing brain and long-term effects on the behavioral and neuroendocrine response to stressors increasing the vulnerability to stress-related disorders including insomnia [86].

4.2. Childhood origin of adult insomnia

Not only prenatal stress but also stress in the early postnatal period after birth has been associated with persistent alterations in the regulation of stress systems and changes in adult stress sensitivity [37–39]. This, in turn, may increase the risk of a variety of diseases including insomnia [31]. Several studies document the prominent role of childhood stress such as sexual, physical, or emotional abuse, emotional or physical neglect, or parental loss, in the pathogenesis of stress-related disorders including depression and insomnia [110, 111]. Twelve studies met the inclusion criteria in human subjects and four in animals.

4.2.1. Clinical and psychobiological hypotheses in humans

Twelve studies met our inclusion criteria in humans and they are summarized as shown in Table 2 [31, 78, 112–121].

In a study by Gregory et al. [31], family conflict at age 7–15 years predicted the development of insomnia at age 18 (odds ratio,
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Study population</th>
<th>Measure of stress</th>
<th>Sleep evaluation</th>
<th>Main findings in adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gregory et al.</td>
<td>Longitudinal</td>
<td>137 subjects, age 18 years New Zealand</td>
<td>FES family conflict</td>
<td>Clinical interview</td>
<td>Family conflict at age 7–15 years predicted insomnia at 18 years OR 1.42 (1.17–1.73)</td>
</tr>
<tr>
<td>Noll et al. [112]</td>
<td>Cross-sectional</td>
<td>147 females of adolescent age USA</td>
<td>Self-report for depression, lifetime ACE, PTSD</td>
<td>Self-report questionnaire for sleep pattern</td>
<td>Sexually abused showed greater rates of sleep disturbances than independently from depression of PTSD.</td>
</tr>
<tr>
<td>Bader et al. [113]</td>
<td>Cross-sectional</td>
<td>39 primary insomniacs aged 21–55 years Germany</td>
<td>Self-report questionnaire for ACE, current level of stress, arousability, depression</td>
<td>Actigraphy</td>
<td>ACE is an important predictors of sleep onset latency, sleep efficiency, number of body movements, and moving time</td>
</tr>
<tr>
<td>Bader et al.</td>
<td>Cross-sectional</td>
<td>51 primary insomniacs aged 21–55 years Germany</td>
<td>CTQ</td>
<td>Actigraphy polysomnography</td>
<td>46% reported moderate to severe ACE. They show a greater number of awakenings and arousals compared to low or no reports of ACE.</td>
</tr>
<tr>
<td>Bernert et al.</td>
<td>Cross-sectional</td>
<td>115 subjects, aged 17–22 years Germany</td>
<td>NLEQ BDI</td>
<td>ISI</td>
<td>Family life stress was significantly associated with increased insomnia symptomatology, even after controlling for depression.</td>
</tr>
<tr>
<td>Koskenvuo et al.</td>
<td>Population-based</td>
<td>25,605 subjects, 20–54 years, Finland</td>
<td>Self-report questionnaire for ACE child–father and mother relationships BDI</td>
<td>Self-report questionnaire for sleep quality</td>
<td>Poor sleep quality was related to multiple childhood adversities OR 3.64 (2.94–4.50) for poor child–mother relationships OR 10.4 (6.73–16.07) for poor child–father relationships OR 5.4 (3.89–7.50)</td>
</tr>
<tr>
<td>Greenfield et al.</td>
<td>Cross-sectional</td>
<td>835 subjects (MIDUS), mean age 54 years USA</td>
<td>CTQ</td>
<td>PSQI</td>
<td>Physical, emotional and sexual abuse are risk factors for global sleep pathology OR 3.65 (1.75–7.60) for poorer sleep quality OR 2.58 (1.34–4.96) for greater sleep disturbances OR 3.51 (1.80–6.86) for greater use of sleep medication OR 2.49 (1.28–4.86) for greater daytime dysfunction OR 2.61 (1.38–4.93).</td>
</tr>
<tr>
<td>Chapman et al.</td>
<td>Retrospective</td>
<td>17,337 subjects, aged &gt;18 years USA</td>
<td>CTS</td>
<td>Self-report questionnaire</td>
<td>All ACE categories were associated with increased sleep disturbances ((p &lt; 0.05)), Subject with ACE reported: OR 2.1 (1.8–2.4) for trouble falling or staying asleep OR 2.0 (1.7–2.3) for feeling tired even after a good night’s sleep</td>
</tr>
<tr>
<td>Ramsawh et al.</td>
<td>Cross-sectional</td>
<td>327 subjects, mean age 18.9 years USA</td>
<td>Self-report questionnaire</td>
<td>Self-report questionnaire</td>
<td>Strong significant relationship between childhood adversity and adult sleep quality All ACE categories were associated with increased insufficient sleep ((p &lt; 0.05)), Subject with ACE reported: OR 2.5 (2.1–3.1) for insufficient sleep</td>
</tr>
<tr>
<td>Chapman et al.</td>
<td>Retrospective</td>
<td>25,810 subjects, aged &gt;18 years USA</td>
<td>CTS</td>
<td>Self-report questionnaire</td>
<td>All ACE categories were associated with increased insufficient sleep ((p &lt; 0.05)), Subject with ACE reported: OR 2.5 (2.1–3.1) for insufficient sleep</td>
</tr>
<tr>
<td>Gress-Smith et al.</td>
<td>Cross-sectional</td>
<td>447 subjects, 18–23 years</td>
<td>NSLUJHS PSS CES-D</td>
<td>ISI</td>
<td>ACE is significantly related to insomnia in undergraduate students. Perceived stress may partially explain the relation</td>
</tr>
<tr>
<td>Bader et al.</td>
<td>Cross-sectional</td>
<td>45 primary insomniacs aged 21–55 years Germany</td>
<td>CTQ DSM-IV interview for anxiety, depression and sleep disorders</td>
<td>PSQI polysomnography</td>
<td>Significant association between history of childhood maltreatment and increased beta EEG activity during NREM. It may reflect heightened arousal during sleep</td>
</tr>
</tbody>
</table>

**Footnotes:** FES: Moos Family Environment Scale; ACE: adverse childhood experiences; PTSD: post-traumatic stress disorder; CTQ: Childhood Trauma Questionnaire; NLEQ: Negative Life Events Questionnaire; BDI: Beck Depression Inventory; CTS: conflict tactics scale; PSQI: Pittsburgh Sleep Quality Index; MIDUS: National Survey of Midlife Development USA; NSLUJHS: Trauma History Checklist and Interview; PSS: Perceived Stress Scale; CES-D: Center for Epidemiological Studies Depression Scale; ISI: Insomnia Severity Index; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); NREM: non-rapid eye movement sleep.
Study showed physical, emotional, and sexual abuse to be risk factors for sleep disturbance and poor sleep quality in the adult. Ramsawh et al. [118] confirmed these data in a population of 327 subjects aged 18 years. This evidence has also been confirmed in other studies: in a retrospective cohort study of 25,810 adult subjects [78] and in a cross-sectional study of 447 adult subjects [119]. Finally, Bader et al. [120] studied 45 primary insomniacs showing a significant association between a history of childhood maltreatment and increased beta EEG activity during non-rapid eye movement (NREM) sleep.

Stress that is experienced early in life and during sensitive periods of development – such as abuse, neglect, parental separation or divorce, long-term financial difficulties or severe conflicts in the family, or severe illness or alcohol problems in a family member during childhood – might fundamentally alter neuroendocrine systems that regulate both the stress system and sleep/arousal system leading to chronic sleep problems [36,122]. Hypervigilance (i.e., hyperarousal) has been described to be a characteristic of subjects with adverse early-life experiences [123]; it can persist for many years and may never fully remit [124]. Changes in the nervous and endocrine system appear to render adults with adverse experience in childhood more vulnerable to stress-related disorders and more reactive when confronted with stressors. According to Barlow [125], hypervigilance in traumatized individuals may be interpreted to reflect the promptness and preparation to deal with potentially negative events. It may be considered an adaptive process of the organism and can then result in the persistence of stress-related neurophysiologic patterns, for example, chronically elevated levels of catecholamines [126] and elevation of the HPA axis, resulting in higher stress reactivity in the course of time [127]. Dysregulation of the HPA axis may provide a link between adverse childhood experiences and adult insomnia [78,113,114,116,117,120,121]. Koskenvuo et al. [116] sustained the hypothesis of the latency model [128] regarding the epidemiological life-course approach to the effect of negative early-life experiences on adult health: the dose–response association between childhood adversities and adult sleep remained after adjustments for significant adulthood confounder and modifying factors supporting the idea of the direct effect on adult health regardless of adult conditions.

4.2.2. Clinical and psychobiological hypothesis in animals

Support for a relationship between early-life stress and alterations in adult sleep regulation comes from experimental studies in laboratory rodents. One of the most commonly used animal models for early-life stress/postnatal stress is maternal separation. The preclinical literature describes some changes in sleep architecture after long maternal separation in rats, which is reported to change total sleep time and increase wakefulness compared to non-handled, handled, and brief maternal separation conditions [76,77,129,130]. To evaluate the influence of early-life environments on basal and cold stress-induced sleep patterns in rats, Tiba et al. [76] studied three groups of male rats (control, early-handling, and maternal separation) at basal and post-stress conditions. Maternally separated rats exhibited more REM sleep at baseline, compared to both control and early-handled rats. The highest corticosterone plasma concentration was observed immediately after stress. The authors concluded that maternal separation during early infancy resulted in permanent changes of the sleep architecture into adulthood reflected by augmented time spent in REM sleep. The authors confirmed these data in a later study: female rats submitted to long-term maternal separation exhibited a significant increase of REM sleep on the night following a 1-h exposure to cold stress, whereas the sleep of rats submitted to brief maternal separation was barely altered by stress. The authors concluded that stress condition during infancy may modify sleep architecture [77].

Feng et al. [129] applied daily 6 h of maternal separation from postnatal day 4 to 14 and reported that adult maternally separated rats had reduced sleep or increased total wake during the light phase/resting phase, which might be at least partly related to increased hypothalamic levels of CRH and hypocretin/orexin changes in the adult offspring. The maternally separated animals further had increased expression of orexin1 receptors in the frontal cortex and increased expression of orexin2 receptors in the hippocampus. The authors conclude that maternally separated rats in adulthood display neurobiological features and sleep patterns characteristic of hyperarousal.

Mrdal et al. [130] studied postnatal day 2–14 male rats that were exposed to either long maternal separation (180 min) or brief maternal separation (10 min). Long maternally separated offspring showed a sleep–wake nonspecific reduction in adult EEG power at the frontal EEG derivation compared to the brief maternally separated group. The quality of slow-wave sleep differed as the long maternally separated group showed lower delta power in the frontal–frontal EEG and a slower reduction of the sleep pressure. The authors concluded that early environmental conditions modulate the brain functioning in a long-lasting way.

A large body of evidence has shown that neonatal maternal deprivation leads to long-lasting alterations including elevated activation of the HPA axis. At the molecular level, maternally deprived rats show increased plasma adrenocorticotropic hormone (ACTH) and corticosterone levels at baseline as well as following stressful challenge [131]. In addition, they exhibit elevated brain CRH levels [132] and hyperexpression of CRH messenger RNA (mRNA) in the hypothalamus [133]. Further analysis of this model showed that the adult rats, which were neonatally treated with maternal deprivation, had features of insomnia, including decreased total sleep and increased total wake time during the light period [129]. In addition, hypothalamic CRH and orexin A levels are elevated in maternally deprived rats [129]. The CRH system is probably partly responsible for some of the behavioral changes and may also be highly relevant in the context of sensitivity to insomnia [129]. CRH is an important wake promoter under both baseline conditions and stress conditions [97] and it also activates other arousal systems such as the hypocretin/orexin system in the lateral hypothalamus and the noradrenergic system in the brain stem; it may be involved in the regulation of arousal and hyperarousal in the context of insomnia. A reciprocal excitatory interaction between the HPA and the orexinergic system has recently been revealed to occur, and substantial evidence suggesting a potential involvement of the hypocretin/orexin system in high-arousal conditions including stress has been described (for an overview, see Ref. [134]). Overexpression of components of the orexinergic system, for example, in the zebrafish, has been shown to induce an insomnia-like phenotype [135]. Mice that overexpress orexin display sleep abnormalities, which include fragmentation of NREM sleep, reduced REM sleep, and increased motor activity during REM sleep, suggesting an inability to maintain sleep states (for an overview, see Ref. [136]). Blocking of the orexin system at night might reduce hyperarousal, thus improving sleep continuity – an assumption supported by earlier preclinical and clinical work [137].
Thus, we hypothesize that postnatal early-life stress experiences are associated with persistent changes in both the modulation of HPA axis activity and the HPA axis-mediated response to stress with a tendency towards hyperactivity; it may be involved in the predisposition to develop hyperarousal and overreactivity in adult life leading to the development of insomnia. Other neurochemical changes that have been described to activate the arousal system may be involved as well including the hypocretin/orexin system and the noradrenergic system.

Postnatal stress, similar to prenatal stress, has lasting effects on neurogenesis, markers of neural plasticity, synaptic pruning, brain glia, and development of monoaminergic fiber systems and hippocampus, in both rodents and nonhuman primates [53,138]. Hippocampal plasticity, structure, and function are affected in animal models of maternal neglect. Reduced neurogenesis, altered cell dendritic morphology, reduced numbers of hippocampal neurons and glia, and reduced fiber density have been reported (for an overview, see Refs. [54,101,139]).

Similar to prenatal stress, we may hypothesize postnatal stress to alter hippocampal neurogenesis in the offspring, which may persist into adulthood and may be related to insomnia development.

4.2.3. Postnatal early-life epigenetic programming of the stress system: implications for insomnia development

Epigenetic mechanisms in childhood have also been hypothesized to shape the adult HPA response to stress and they may be implicated in mediating the persistent effects of early-life experience on gene expression in the brain (for an overview, see Refs. [82,101,105,140–142]). Animal models of perinatal stress have documented sustained alterations in the expression of genes regulating HPA function, such as the GR. As adults, offspring of animals exposed to prenatal stress display life-long epigenetic alterations of the GR promoter in the hippocampus and in the prefrontal cortex [101,140]. It has been proposed that these DNA methylation adaptations early in life are involved in the shaping of the HPA axis, which persist into adult life [141,143]. The GR/NR3C1 gene encoding the GR and involved in the stress response by regulating the GR expression exhibits differences in DNA methylation and histone acetylation in the hippocampus of the offspring of high- and low-licking-and-grooming mothers. Differences in DNA methylation in response to variations in maternal licking and grooming emerged early in life and remained stable into adulthood illustrating that epigenetic effect [144,145]. Furthermore, early-life stress in mice caused sustained DNA hypomethylation of an important regulatory region of the arginine vasopressin (AVP) gene. Maternal separation in mice persistently upregulates AVP gene expression associated with reduced DNA methylation of a region in the AVP enhancer. Early-life stress can dynamically control DNA methylation in postmitotic neurons to generate stable changes in AVP expression that trigger neuroendocrine and behavioral alterations [140]. Similar patterns have been observed among humans in recent years. Methylation in the GR NR3C1 has also been examined, and three independent research groups reported that a history of childhood abuse was associated with altered methylation of NR3C1 in hippocampal-derived DNA [141,142,146].

These epigenetic mechanisms that alter the HPA and its response to stress into adulthood are also hypothesized to increase the vulnerability to stress-related disorders including depression and post-traumatic stress disorder [140,142,146].

Postnatal epigenetic, especially DNA methylation may, in turn, regulate the responsiveness of the HPA axis to subsequent stressors, toward a hyperresponsivity, thus substantially contributing to the vulnerability to develop insomnia.

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**Fig. 2.** Prenatal stress and childhood adversity may interact with the genome to produce epigenetic modification in the regulation of stress and arousal systems. Prenatal stress may alter the expression of genes that regulate permeability of the placenta and both prenatal and early life stress can affect the expression of glucocorticoid receptors in the brain of the developing child. This may ultimately result in neurobiological changes that persist into adulthood, including an increased activity and reactivity of the hypothalamic-pituitary-adrenal (HPA) axis, an increased activity of specific wake promoting systems such as the noradrenergic system and the hypocretin-orexin system, and reduced neurogenesis and brain plasticity. These changes may then promote increased reactivity and hyperarousal responses to negative life events predisposing the individual to the development of insomnia.
development of stable individual differences in HPA responsiveness to stressful stimuli. It may produce long-lasting modifications of the developing brain and long-term effects on the behavioral and neuroendocrine response to stressors increasing the vulnerability to stress-related disorders including insomnia.

5. Conclusions

Models of adult insomnia suggest a predisposition to develop the disorders in response to stressors. Hyperarousal has been hypothesized to be a characteristic of individuals with elevated stress–sleep reactivity; it may also constitute a premorbid characteristic of people with insomnia. Stress is considered to be an important cause of disrupted sleep and insomnia, although the effects of stress on sleep–wake regulation have been described to be complex depending on several factors [147]. From a life-course perspective on health and disease on the basis of the reviewed evidence, we may hypothesize prenatal–early-life stress to be related to the development of insomnia in newborns and later in adult life. Both prenatal and early-life stresses may result in an alteration of the HPA axis, which may produce long-lasting amplifications in stress reactivity. It may include an effect on the arousal regulating system, such as the orexin and noradrenergic systems, and hippocampal neurogenesis that may persist into adulthood. This effect might play an important role in predisposing to a vulnerability to hyperarousal reactions to negative life events contributing to the development of sleep disturbance and evolution to chronic insomnia. It might predispose to stress-related hyperarousal and insomnia into adulthood. We might hypothesize epigenetic mechanisms in shaping the response to stress and HPA dysregulation into adulthood secondary to prenatal–early-life stress. This may be in line with the recently proposed epigenetic hypothesis of insomnia [86] (Fig. 2).

Conflict of interest

The authors have no conflict of interest to declare. The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.10.013.

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