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REVIEW ARTICLE

Mind and skin: Exploring the links between inflammation, sleep disturbance and neurocognitive function in patients with atopic dermatitis

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Abstract

Atopic dermatitis (AD) is a chronic, pruritic and inflammatory, dry skin condition with many known comorbidities. These include airway disease, food allergies, atopic eye disease and autoimmune conditions. Furthermore, there is often significant sleep disturbance as well as increased psychological distress and mental health problems. Severe AD therefore often has a significant impact on the quality of life of both patients and their families. In this review we discuss recent findings on the putative links between AD, its association with itch, sleep disturbance and neuropsychiatric morbidity, including the role of inflammation in these conditions. Itch was thought to predominantly drive sleep disruption in AD. We now understand changes in sleep influence immune cell distribution and the associated inflammatory cytokines, which suggests a bidirectional relationship between AD and sleep. We also increasingly recognize inflammation as a key driver in psychological symptoms and disorders. The link between cutaneous, systemic and possible brain inflammation could at least in part be driven by the sleep deprivation and itch-driven neuronal proliferation seen in AD.

KEYWORDS
atopic dermatitis, cognitive dysfunction, inflammation, quality-of-life, sleep disruption

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1 | INTRODUCTION

Atopic dermatitis (AD) is a significant health burden, with up to 20% of children and young people (CYP) and 10% of adults being diagnosed with the condition.[1,2] Around 6% of people with AD will have severe disease requiring systemic treatment. The hallmark clinical features of AD are pruritic and erythematous dry skin. Patients with AD will commonly suffer with disturbed sleep, especially if flares are not adequately controlled.

In addition to this, there are many known comorbidities associated with AD including airway disease (asthma, hay fever and obstructive sleep apnoea), food allergies, atopic eye disease and autoimmune conditions.[3] Furthermore, there is increased psychological distress and mental health problems, including anxiety, depression and attention-deficit/hyperactivity disorder (ADHD). Together, this means that severe AD and the associated comorbidities have a significant impact on the quality of life of both patients and their families.[4,5]

Atopic dermatitis is characterized by a complex interplay between genetically predetermined skin barrier dysfunction, cutaneous dysbiosis and immune dysregulation, with a T-helper 2 (Th2)-dominated cytokine profile.[6] The skin barrier has two key functions, both of which are impaired in AD, to prevent water loss and to stop the entry of external foreign substances (pathogens, antigens and allergens). Loss-of-function mutations in the filaggrin (FLG) gene, which lead to reduced skin barrier integrity, are present in up to 50% of moderate-to-severe AD patients.[7] However, not all carriers of FLG mutations will develop AD. There are also a number of other genes which have been identified as risk factors in AD, for instance linked to immunological pathways.[8] Although skin barrier dysfunction is genetically predetermined, there are significant, additional environmental contributions to the barrier dysfunction. These include water hardness, pollution, antibiotic exposure and other factors linked to a 'western' lifestyle, such as diet.[6]

The combination of skin barrier dysfunction and environmental factors triggers an inflammatory response and can also facilitate allergic sensitization to common antigens, such as house dust mite but also food proteins. Th2 cytokines: interleukin 4 (IL-4), interleukin 13 (IL-13) and the itch-inducing cytokine IL-31 have been identified as key mediators of AD inflammation.[9] This results in pruritus and the subsequent, natural response of scratching. Scratching intensifies cutaneous inflammation through mechanical stimulation, further exacerbating the itch and breakdown of the skin barrier. A vicious cycle of itching and scratching then develops. Itch is often reported to be worse at night, leading to significant sleep disturbance.[10]

In this review we will discuss recent findings on the link between AD, its association with itch, sleep disturbance and neuropsychiatric morbidity, including the role of inflammation in these conditions (Figure 1).[11,12]

2 | ATOPIC DERMATITIS AND SLEEP DISTURBANCE

The majority of children and adults with AD experience some degree of sleep disturbance. Over 60% of parents report that AD affects how well they or their child sleep.[13] Even when in clinical remission, children with AD reported worse sleep quality than healthy children.[14] A large study of 13,988 participants using parental questionnaires showed children with AD are more likely to report nightmares and early morning awakenings.[15] Other survey studies have shown children with AD between the ages of 5 and 12 have frequent night waking, less total sleep and greater difficulty awakening for school than children without AD.[16] A study using sleep-specific questionnaires revealed that children with AD also report daytime sleepiness, irritability and teacher-reported daytime sleepiness.[17] There seems to be a close relationship between increased disease activity and sleep disturbance, as demonstrated in a cohort of young children (mean age 25 months, standard deviation 16.2 months), where during AD flares, sleep was reported as disturbed during 86% of relevant nights. For the majority (59%) of these children, reported sleep disturbance was limited to when their AD was flaring.[18] Furthermore, sleep impairment has been more commonly reported among children with more severe disease and in those with comorbid asthma or allergic rhinitis.[15,19]

The above findings are consistent with the small number of studies that used objective measures of sleep, such as actigraphy and polysomnography.[17,20] A sleep study in school-aged children with AD using home-based polysomnography highlighted frequent awakenings associated with episodes of scratching and overall reduced sleep efficiency.[21] Another study showed that nocturnal scratching as measured by wrist actigraphy in the first 3 h of sleep is closely correlated with AD severity as measured by scoring atopic dermatitis (SCORAD) and plasma chemokine levels in children.[22]

3 | ITCH AND SLEEP

The main cause of sleep impairment in children with AD is thought to be nocturnal itching and scratching behaviour. Patients with AD often develop the disease in the first few months after birth when sleep-patterns and practices as well as parent-carer responses to these become established. Although children without AD commonly experience sleep disturbances during their first few years, observational studies have shown that those with AD are at particular risk due to trouble initiating sleep because of itching.[18,23] Self-reported itch intensity has a significant link with insomnia frequency and sleep quality in adults with AD.[24]

With chronicity, the itch-scratch cycle in AD can become habitual and children may continue scratching in the absence of pruritic stimuli, thus increasing itch intensity. Even with habit-reversal therapy, it is difficult for children to consciously prevent

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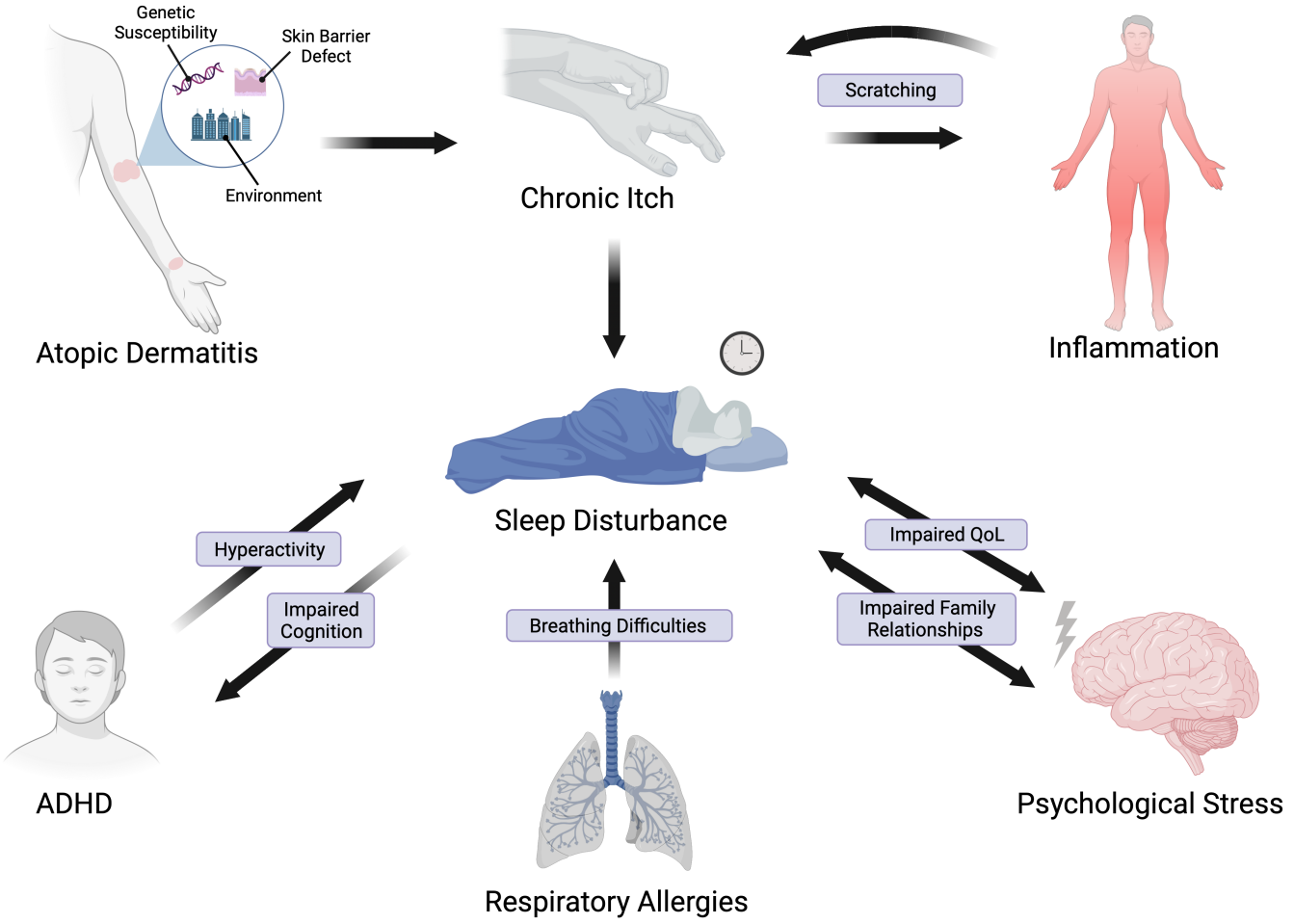

FIGURE 1 The interplay of atopic dermatitis, sleep disturbance, inflammation and psychological disorders. AD manifests itself as a profoundly itchy skin condition, influenced by the environment, skin barrier dysfunction and genetic factors. A vicious cycle of itching and scratching potentiates cutaneous and systemic inflammation. Nocturnal itching significantly disturbs sleep, which in children is vital for normal neurocognitive processing and memory formation. There is a strong association between AD and psychiatric disorders such as ADHD, depression and anxiety. These conditions are also significantly associated with disturbed sleep. AD has a significant impact on quality of life and often causes a huge burden on patients and their families. Often disturbed sleep causes stress on the parents of children leading to impaired family relationships. Respiratory allergies, such as asthma, also contribute to sleep disturbance. ADHD, attention-deficit/hyperactivity disorder; QoL, quality of life.

scratching at night-time, which then contributes to the increased itching. However, scratching episodes have been documented to only account for 15% of arousals and awakenings, suggesting that scratching alone does not fully explain sleep fragmentation in these patients.[25]

Itching in AD is often reported to be worse at night. Theories to explain the night-time itching phenomenon have implicated nocturnal variation in skin barrier function. Transepidermal water loss (TEWL) is one measure of skin barrier integrity and is associated with itch intensity in AD.[26] As peripheral skin temperature increases at night (as part of the mechanism to decrease core temperature), TEWL may increase nocturnally therefore increasing itch.[27] Circadian fluctuations in hormone secretion, including cortisol and subsequent variations in immunological activity, may also increase nocturnal itching,[11,28] for instance due to fluctuating expression of pruritogenic cytokines, such as IL-2 and IL-31.[29] Other than itch, causes of sleep disturbance include skin-related pain and skin-related fearful thoughts.[30]

4 | CHRONIC PRURITIS IN AD

Chronic pruritis (CP) is defined as itch lasting more than 6 weeks. The current understanding of the pathophysiology of CP in AD is growing. Yosipovitch et al. outlined the contribution of the nervous system and its interaction with immune pathways in AD-associated pruritis in a recent review.[31] CP is mediated by pruritogen binding to pruritogen receptors located on a subset of primary afferent c-fibres, or pruriceptors, that synapses at the spinal cord with secondary afferents (Figure 2). The secondary afferents ascend to the

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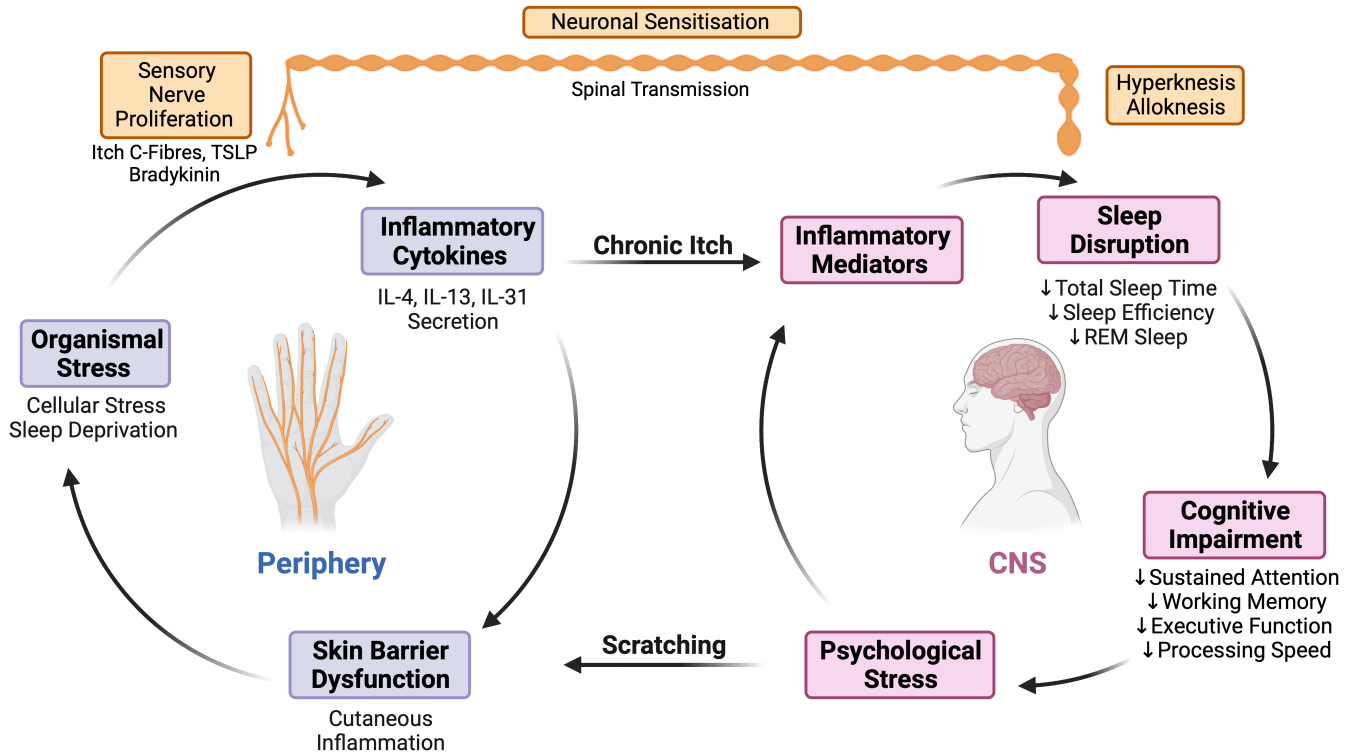

FIGURE 2 Bidirectional pathways for the putative mechanisms between the periphery and central nervous system driving sleep disturbance in atopic dermatitis. Skin barrier dysfunction, including cutaneous inflammation, results in organismal stress, including cellular stress and sleep deprivation. This acute stress results in the expression of inflammatory cytokines such as IL-4, IL-13 and IL-31. These peripheral signals mediate pruritis and are communicated to the central nervous system (CNS) to induce cytokine activity in the brain, exacerbating sleep disturbances, leading to reduced total sleep time and sleep efficiency as well as reduced duration of rapid eye movement (REM) sleep. Reductions in sleep continuity and REM sleep are associated with cognitive impairment such as reduced sustained attention, working memory, executive function and processing speed. Both reduced sleep and cognitive impairment lead to psychological stress which can lower the central itch threshold,[1] including nocturnal scratching, which further damages the skin barrier. Sensory nerve proliferation in the periphery results in neuronal sensitization whereby a lower itch threshold of nociceptors on neurons, is induced by inflammatory mediators, and results in increased itch C-fibre responsiveness and release of neurotransmitters such as glutamate and brain-derived neurotrophic factor. This results in the phenomenon of the intense itch experienced by patients with relatively mild AD. ('Sleep efficiency' refers to the proportion of time in bed that is spent sleeping, TSLP, thymic stromal lymphopoietin.)

thalamus where the signals convey to different regions of the brain that translate them into the sensation of itch and coordinate the motoric response of scratching.[32–35]

Immune cells and keratinocytes release pruritogens (IL-4, IL-13, IL-31, TSLP, IL-33 and substance P) and other factors that increase sensitivity to itch in AD.[33,36,37] Receptors (IL-31, IL-13, IL-33, TSLPR, NK-1R, MRGPRX+ and IL-4) expressed on histamine-independent C fibres interact with these factors amplifying pruritus further.[34] TSLP and substance P can also indirectly promote itch and atopic skin inflammation by activating Th2 immune cells. These immune cells, including eosinophils and mast cells, release pruritogenic type 2 T helper cell cytokines and neurogenic peptides, which activate these neuroinflammatory pathways in AD and stimulate release of pro-inflammatory mediators.[38] Interactions between the C fibres, keratinocytes and immune cells all drive the development of CP in AD. When a patient with AD scratches, epidermal keratinocytes are injured, which causes the release of pruritogens and indirectly activates Th2 immune cells. When these pruritogens bind to pruriceptive nerves, the patient will be inclined to continue scratching, leading to the 'itch-scratch' cycle.

In patients with AD, itch can be triggered by a lower threshold stimulus or may persist even when the stimulus is removed. This phenomenon has been demonstrated in several studies where the threshold for electrically evoked itch is lower in patients with AD than healthy controls.[39] The increased amount of inflammatory molecules in AD may increase the frequency of action potentials from the primary afferents increasing the amount of released neurotransmitters at the spinal level. This may give rise to neuropathic changes and abnormal sensory functions such as hyperknesis, where increased perception of itch is evoked from pruritogens, and alloknesis where itch is evoked from normally non-pruritic stimuli like increased temperature or mechanical stimuli from wearing certain fabrics like wool.[32,33,40]

The increased inflammatory molecules and the abnormal sensory states in AD may increase the intensity of itch further. The perception of itch intensity seems to depend on increased activation of the primary and secondary somatosensory cortices and the anterior part of the insular cortex.[35,41] There appears to be both inflammatory, peripheral and central nervous system contribution to CP.

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This is why intense itching may persist after cutaneous inflammation has subsided as experienced in some patients with mild AD and might influence nocturnal arousals (the shift from deep sleep to lighter sleep) and disrupted sleep. For example, studies by Feld et al. have demonstrated nerve proliferation associated with IL-31, both in in vitro and in vivo models.[42] Primary sensory neuron culture systems were stimulated with IL-31. Transcriptional profiling showed enrichment in genes promoting nervous system development, neuronal outgrowth and negatively regulating cell death. In addition, nerve fibre extension was seen in small-diameter neurons. In mice studies, subcutaneously delivered IL-31 induced an increase in the cutaneous nerve fibre density in lesional skin. These findings might explain the clinical observation seen in patients with AD, who experience severe itch associated with minimal stimulation.

5 | ITCH, ATTENTION, AFFECT AND EXPECTANCIES

In addition to the complex neurobiology of itch, there is a close relationship between itch and psychological factors such as attention, affect and expectancies.[43] Research in experimental and clinical settings has shown that cognitive–affective factors play a role in both the maintenance and exacerbation of (chronic) itch. Indeed, itch is a bodily signal that is evolutionarily primed to capture attention. The attention-capturing nature of itch evolved to signal the presence of potentially harmful environmental agents such as ectoparasites, and thus to promote the protective behaviour of scratch.[44] Yet when itch is chronic, as is often the case in AD, this means that patients will be recurrently disturbed by the itch and potentially also by social reactions of others (e.g. stigma), which can negatively impact their quality of life.[41] In line with this, the experience of chronic itch can also be accompanied by stress, anxiety and depressive symptoms These affective consequences of itch may also exacerbate the scratching behaviour within a vicious cycle of increased negative affect and itch.[45] Lastly, studies largely in experimental settings have shown the self-fulfilling nature of itch expectancies. In healthy volunteers, itch can be induced by expectancies alone, sometimes termed the 'nocebo effect'.[46] In patients with AD, nocebo-induced itch has been observed from administration of an inert saline solution, with similar brain regions underlying the experience of real and nocebo-induced itch.[47] On the flip side, positive expectancies can reduce the experience of itch. In healthy volunteers, expecting itch relief from a topical lotion can reduce itch.[48] In the placebo arm of randomized controlled trials, patients often report improvements in itch.[49] These findings hold promise for enhancing the effectiveness of current treatments for AD. Enhancing expectancies that topical or immunomodulatory treatments will reduce itch may improve overall treatment outcomes. Such a promising effect was shown in a recent study of children receiving immunotherapy treatment for peanut allergy, wherein positive expectancies were cleverly induced by helping children to understand that allergy-related symptoms were a positive sign that the treatment was active and working in their body.[50] Taken together, findings suggest that cognitive–affective factors are important to target in holistic treatment of chronic itch in AD. Cognitive–affective factors also likely interact closely with sleep and neurocognitive functioning in ways yet to be explored and defining these interactions will further help to harness the beneficial impact of these psychological factors on AD treatment.

6 | SLEEP AND NEUROCOGNITIVE DEVELOPMENT

Early life is a critical period for neurocognitive development. Circadian rhythms are established in babies around 6 months old.[51] Naturally occurring sleep is a central nervous system (CNS)-mediated psychophysiological process. There is evidence that sleep has several neural functions, including supporting brain connectivity.[52,53] During early life development, major increases in white matter structural and cortical functional connectivity are seen in association with cognitive and behavioural maturation.[54,55] Brain maturation is reflected in the sleep EEG, which suggests that brain development and sleep are bidirectional.[56] Poor neonatal sleep has been linked to impaired neurological outcomes,[57] and sleep state–specific differences in connectivity are seen in preterm infants in comparison to those born at full term, which also correlate with later neurodevelopmental outcomes.[58,59] Transition from quiet to active sleep in newborn infants is marked by a substantial reorganization of large-scale cortical activity and functional brain networks[59] with reduced reorganization seen in preterm infants, which correlates with reduced visual performance at 2 years of age.

Sufficient duration and quality of sleep have been shown to be important for the development of memory, language, sustained attention, processing speed and executive functions.[60–62] Shorter sleep duration in the first 3 years in healthy children is also associated with hyperactivity and lower cognitive performance on neurodevelopmental tests at age 6, demonstrating that inadequate sleep in early life can produce long-standing effects on neurocognitive function.[63] A study in preterm babies, evaluating whether sleep–wake state organization was related to developmental milestones in the first year after birth revealed that the stability and duration of sleep may be predictive of mental performance at 24 and 52 weeks of age.[64] Both shortened sleep duration and disrupted sleep in children have been associated with reduced cognitive and academic/school performance as well as dimensional (externalising and internalising) psychopathology problems.[53,61] Cognitively, the most consistent effect of compromised sleep in school children seems to be on multiple domain cognitive functions and school performance,[61] but others have observed effects in (working) memory, sustained attention, executive function and processing speed.[63,65]

Recent reviews by Cheng et al. and Astill et al. suggested that sleep deprivation in healthy adolescents has an effect on cognition, including impaired sustained attention, working memory, encoding and consolidation of long-term memories, slower processing speed,

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as well as behaviours such as decreased positive mood states, increased anxiety and emotional dysregulation.[53,61] Interestingly, sleep efficiency, but not sleep duration, of healthy children has been linked to enhanced learning performance and improved educational outcomes.[66]

When AD starts in early childhood sleep disruption begins during these formative years of childhood development. Longitudinal follow-up of over 1600 infants from birth demonstrated that parent-reported sleep disturbance due to AD in infancy was associated with subsequent emotional and behavioural problems at 10 years of age.[67,68] AD persists throughout childhood and adolescence in up to 30% of cases; meanwhile, sleep requirements and sleep patterns change dramatically during this period. Children and teenagers with moderate-to-severe AD were shown to have significantly higher wake after sleep onset (WASO) and poorer sleep efficiency compared to age-matched healthy controls, but similar overall sleep duration, measured using actigraphy (a wristwatch device that contains an accelerometer from which an approximation of sleep wake cycles is derived).[13]

7 | SLEEP AND INFLAMMATION

Sleep and its relationship with the immune system has long been described in medicine, as it was observed that sleep is induced in states of fever and illness. Therefore, it was believed to help in the recovery from such disease. Researchers have since discovered antimicrobial peptides and cytokines that have somnogenic properties and induce sleep, potentially providing a survival advantage.[69] Patients suffering with insomnia have been shown to have an increased risk of depression, infections and inflammatory disorders.[12] Therefore it is believed that sleep is imperative to support host defence and cognitive resilience.

It is also now understood that sleep supports the neurally integrated immune system. This means changes in sleep, influence immune cell distribution and the associated inflammatory cytokines.[69] Inflammatory signals are transmitted indirectly to the CNS via neural pathways. The function of mast cells, dendritic cells, eosinophils and T cells may be shaped or regulated by various neuropeptides released from the sensory neurons.[70] Thus it is likely that both activation of the immune system and activation of itch fibres may shape one another.[71]

Further, it is hypothesized that disturbed sleep leads to dysregulation of the immune system and inflammatory pathways in the CNS.[69] In normal sleep, sympathetic nervous system (SNS) activity is reduced. In sleep deprivation, increases in SNS activity results in higher levels of noradrenaline and adrenaline.[72] In turn, further production of inflammatory biomarkers is triggered. An additional factor driving inflammation in chronic sleep deprivation is the innate upregulation of the hypothalamic–pituitary–adrenal axis,[73] which can lead to a degree of glucocorticoid resistance.[74] This link between cortisol production and the establishment of sleep patterns via clock gene upregulation first emerges in the postnatal period.[51]

Experimental work which has studied systemic and cellular inflammatory markers in humans during the course of normal sleep–wake cycles versus continuous wakefulness over 24 h have shown that IL-6, which usually has a circadian profile, is switched to increased daytime production in acute sleep deprivation.[75] Toll-like receptor 4 (TLR4) stimulated monocytes nocturnally increase IL-6 alongside tumour necrosis factor. This suggests that sleep influences different inflammatory cytokines, and it is plausible that the usual inflammatory homeostasis is further disturbed by sleep disruption in those with AD.

In another human study, sleep loss was shown to activate cellular inflammation and signal transducer and activator of transcription (STAT) family proteins. Spontaneous monocytic expression of IL-6 and TNF-α was significantly increased in partial sleep deprivation.[76] A similar increase in nuclear factor kappa B (Nf-kB) has been measured during experimental sleep deprivation in humans.[77] Interestingly, this pathway is also activated during sleep deprivation in neural tissue,[78] supporting the hypothesis that sleep disruption not only has an effect on neurocognition and development but also acts as a proinflammatory driver, which may contribute to a neurally mediated exacerbation of pruritus and skin inflammation in AD.

Studies on humans have tested whether pharmacologically blocking cytokines, in disorders of chronic states of inflammation, can result in improved sleep. For example, in patients with rheumatoid arthritis, infliximab (anti-TNF) increased slow wave sleep (SWS).[79] There remains limited experimental and observational data on this topic, however. As our understanding of the links between sleep and inflammation grows so would therapeutic strategies. Dupilumab (Il-4 and Il-13 antagonist) has been shown to significantly improve sleep in adult patients with AD.[80] These studies used visual analogue scales (VAS) to assess the degree of sleep loss over the preceding 3 days. This is a crude subjective measure of sleep disturbance and further work to understand the effect on the brain would provide an important insight to better understand how these drugs improve sleep.

8 | INFLAMMATION, SLEEP, PSYCHOPATHOLOGY AND ATOPIC DERMATITIS

It was long believed that the CNS was protected from immunological disease by specialized barriers. This understanding has significantly altered in recent times, as more and more pathways between the CNS and the immune system are being discovered. In healthy brains interactions between neurons, glial cells and the immune system have been associated with functional properties such as cognition and learning performance.[81] This is partially demonstrated by the relationship between sleep and inflammation as described above, and we are only starting to understand the potential links between sleep disruption and neuropsychiatric disorders.

There is epidemiological evidence for an association between AD and ADHD, depression and anxiety in childhood as well as

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schizophrenia and suicidality in adults.[82,83] Interestingly, only those children with AD that experience disrupted sleep appear at increased risk of developing ADHD.[84] Anxiety and depression occur more frequently in patients with AD than in controls, affecting up to 30% of patients.[82,85] Both of these mental health conditions can also affect sleep and neuroinflammatory processes. Moreover, sleep disturbance is associated with a wide spectrum of psychiatric diseases, including schizophrenia, autism spectrum disorder, bipolar disorder and depression. Implicated pathways involved include microglial activation, pro-inflammatory cytokines, molecular mimicry, anti-neuronal autoantibodies, self-reactive T cells and disturbance of the blood–brain barrier.[81]

As we increasingly recognize inflammation as a key driver in psychiatric disorders, inflammation caused by AD could also be linked to an increased risk to develop psychiatric conditions. We know that in AD, Th2 (IL-4, IL-13 and IL-31) and various other inflammatory cytokines (e.g. TSLP and IL-22) are not only upregulated in the skin but also systemically.[86] The link between cutaneous, systemic and possible brain inflammation could at least in part be driven by sleep deprivation and itch-driven neuronal proliferation.

Central nervous system homeostasis is dependent on an equilibrium between innate and adaptive immune cells, neurones and glial cells. Inflammation anywhere in the body can impact cognitive function and behaviour. This is demonstrated by 'sickness behaviour' seen in acute infections and inflammation which is thought to have been evolutionary protective. However, chronic infection and inflammation can cause neurotoxicity and neurodegeneration. One such example is obesity, where low grade inflammation results in damage to neuronal circuits and the blood–brain barrier, resulting in cognitive dysfunction. Although similar studies have not been performed in AD this would support the previous hypothesis.

In addition, chronic threats to the CNS, such as interpersonal loss or conflict, have been shown to increase pro-inflammatory cytokines tested in the saliva of adolescents, which likely indicates increased systemic inflammation.[87,88] Self-reported stress is a well-recognized risk factor for exacerbation of many psychiatric as well as non-psychiatric disorders, such as multiple sclerosis and also AD. There is evidence that stress exacerbations in psychiatric disorders are mediated in part by inflammatory processes. Interestingly, there are mounting data from studies in adults, summarized in a meta-analysis by Baumeister et al., that suggests childhood trauma results in higher CRP, IL-6 and TNF levels in adulthood.[89] Children with AD often have difficult childhoods due to poor symptom control and severe impairment of quality of life. We propose the psychological impact of the disease could in fact be causing more severe disease throughout the patients' lives.

9 | CURRENT TREATMENTS FOR SLEEP DISTURBANCE IN AD

There are currently limited guidelines on how to manage sleep disturbance in patients with AD. Interventions mainly focus on reducing itch.[90] The most common approach of itch management is controlling AD using a multistep approach starting with emollients, topical corticosteroids, topical calcineurin inhibitors and progressing to systemic immunomodulating agents. Additionally, clinicians may trial short-term use of sedating antihistamines at night-time.[91]

Behavioural modifications such as sleep hygiene advice are also considered an important first-line treatment.[92,93] Patients are advised to have a regular bedtime, eat a balanced diet, avoid caffeine and 'screen-time' just before bed. It is also advised to keep the bedroom cool and wear light bedclothes.[94] Patient education around scratch management through individual nurse consultations led to improved sleep alongside lower severity of pruritis.[95]

Mindfulness and meditation have been shown to be effective for sleep disruption and improve the quality of life of patients with AD.[96] Habit reversal therapy, aiming to reduce the itch-scratch cycle, can improve sleep and AD symptoms.[97] Similarly educational programmes, delivered face-to-face, have been shown to improve clinician-assessed and patient-reported severity scores in CYP.[98] Itch perception and parent quality of life also improved in this study. Another randomized control trial introduced an education programme in adults with AD and showed improvement in SCORAD and psychosocial measurements.[99] However, such interventions are yet to be studied using objective sleep measurements, such as polysomnography, in patients with AD.

Melatonin can be given to aid sleep, when clinically indicated.[100,101] This has been more extensively tested in other conditions. There is a suggestion, albeit from small studies, that it can improve sleep and reduce disease severity in AD. Studies have shown melatonin to improve both disease severity and to reduce sleep-onset latency in both children and adolescents with AD.[102,103] As a result, increasing numbers of AD patients are being prescribed melatonin instead of sedating antihistamines, but there is a need for an adequately powered randomized controlled trial using polysomnography to show its efficacy and safety. A study showed that lower melatonin secretion was significantly associated with sleep disturbance in patients with AD,[20] which would support its therapeutic use.

10 | THE EPITHELIAL BARRIER HYPOTHESIS—LOOKING BEYOND ATOPIC DERMATITIS

Patients with AD commonly have allergic comorbidities. The 'epithelial barrier hypothesis'[104,105] links the cutaneous inflammatory processes in AD with those seen in asthma and allergic rhinoconjunctivitis as well as the gastrointestinal tract (food allergies). With this paradigm, the rise in allergic conditions is proportionate to the extent of industrialization of a country,[106] due to the environmental factor-induced damage of the barriers of the skin, respiratory and gastrointestinal tracts and reshaping of the microbiota, in part caused by exposomal factors, such as air pollution.[104] These, in turn, can drive epigenetic changes, disruption of the immune balance and chronic Th2 inflammation of the epithelial

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barriers, making patients more vulnerable to exogenous allergens and microbes.[104,107] Significant concomitant respiratory allergies will also directly contribute to the sleep disturbance seen in association with AD.[108] Allergy-driven inflammation in the respiratory and gastrointestinal tracts could also cause higher systemic inflammation levels.

11 | CONCLUSIONS

New immunological insights point toward inflammation playing an important role in psychiatric disease. We hypothesize that similar links exist between the activation of cutaneous and systemic inflammatory and neuronal pathways in AD. The sleep disruption associated with the intense pruritus in AD is likely to amplify these pathways, as lack of sleep and increased psychological stress have equally been linked to inflammatory biomarkers. There is more to be learned about the bidirectional relationship between AD, psychological stress and sleep disruption and how these may lead to psychological and psychiatric comorbidities, often seen in those with significant AD. Such research requires a collaborative, multidisciplinary approach bringing together expertise from dermatology, sleep medicine, imaging science, immunology, psychiatry and cognitive neuroscience to enhance our understanding of the underpinning mechanisms with the quest to develop novel pharmaceutical or behavioural treatments such as patient education programmes, to therefore reduce the long-term impact on health and well-being of those with AD. Our team is now pursuing such a study https://beta.clinicaltrials.gov/study/NCT05790330.

AUTHOR CONTRIBUTIONS

Shona Cameron and Carsten Flohr formulated the overarching goals and aims of the manuscript. They designed the methodology and performed the project management and coordination of the manuscript. Shona Cameron and Ali Donnelly performed the initial data curation and evidence collection. Shona Cameron and Ali Donnelly were responsible for the visualization of the manuscript. Carsten Flohr provided supervision, leadership and oversight of producing the manuscript. Shona Cameron, Ali Donnelly and Carsten Flohr wrote the original draft. Shona Cameron, Ali Donnelly, Conor Broderick, Tomoki Arichi, Ullrich Bartsch, Paola Dazzan, Jesper Elbeling, Emma Godfrey, Paul Gringras, Lauren C. Heathcote, Desaline Joseph, Tobias C. Wood, Carmine Pariante, Katya Rubia and Carsten Flohr provided validation of the manuscript. They provided extensive critical review and comments for revision of the manuscript prior and post submission.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. Larsen FS, Hanifin JM. Epidemiology of atopic dermatitis. *Immunol Allergy Clin*. 2002;22(1):1-24.
2. de Lusignan S, Alexander H, Broderick C, et al. The epidemiology of eczema in children and adults in England: a population-based study using primary care data. *Clin Exp Allergy*. 2021;51(3):471-482.
3. de Lusignan S, Alexander H, Broderick C, et al. Atopic dermatitis and risk of autoimmune conditions: population-based cohort study. *J Allergy Clin Immunol*. 2022;150:709-713.
4. Yang EJ, Beck KM, Sekhon S, Bhutani T, Koo J. The impact of pediatric atopic dermatitis on families: a review. *Pediatr Dermatol*. 2019;36(1):66-71.
5. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol*. 2017;137(1):26-30.
6. Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. *Allergy*. 2020;75(1):63-74.
7. Baurecht H, Irvine AD, Novak N, et al. Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data. *J Allergy Clin Immunol*. 2007;120(6):1406-1412.
8. Drislane C, Irvine AD. The role of filaggrin in atopic dermatitis and allergic disease. *Ann Allergy Asthma Immunol*. 2020;124(1):36-43.
9. Klonowska J, Gleń J, Nowicki R, Trzeciak M. New cytokines in the pathogenesis of atopic dermatitis—new therapeutic targets. *Int J Mol Sci*. 2018;19(10):3086.
10. Fishbein AB, Vitaterna O, Haugh IM, et al. Nocturnal eczema: review of sleep and circadian rhythms in children with atopic dermatitis and future research directions. *J Allergy Clin Immunol*. 2015;136(5):1170-1177.
11. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nat Rev Immunol*. 2011;11(9):625-632.
12. Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. *Annu Rev Psychol*. 2015;66:143.
13. Chamlin SL, Mattson CL, Frieden IJ, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med*. 2005;159(8):745-750.
14. Camfferman D, Kennedy JD, Gold M, Martin AJ, Lushington K. Eczema and sleep and its relationship to daytime functioning in children. *Sleep Med Rev*. 2010;14(6):359-369.
15. Ramirez FD, Chen S, Langan SM, et al. Association of atopic dermatitis with sleep quality in children. *JAMA Pediatr*. 2019;173(5):e190025.
16. Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S, Sampson HA, Lupo M. Sleep disturbances in children with atopic dermatitis. *Arch Pediatr Adolesc Med*. 1995;149(8):856-860.
17. Fishbein AB, Mueller K, Kruse L, et al. Sleep disturbance in children with moderate/severe atopic dermatitis: a case-control study. *J Am Acad Dermatol*. 2018;78(2):336-341.
18. Reid P, Lewis-Jones MS. Sleep difficulties and their management in preschoolers with atopic eczema. *Clin Exp Dermatol*. 1995;20(1):38-41.
19. Kong TS, Han TY, Lee JH, Son SJ. Correlation between severity of atopic dermatitis and sleep quality in children and adults. *Ann Dermatol*. 2016;28(3):321-326.
20. Chang Y-S, Chou YT, Lee JH, et al. Atopic dermatitis, melatonin, and sleep disturbance. *Pediatrics*. 2014;134(2):e397-e405.
21. Stores G, Burrows A, Crawford C. Physiological sleep disturbance in children with atopic dermatitis: a case control study. *Pediatr Dermatol*. 1998;15(4):264-268.
22. Hon KL, Lam MC, Leung TF, et al. Nocturnal wrist movements are correlated with objective clinical scores and plasma chemokine levels in children with atopic dermatitis. *Br J Dermatol*. 2006;154(4):629-635.
23. Johnson CM. Infant and toddler sleep: a telephone survey of parents in one community. *J Dev Behav Pediatr*. 1991;12(2):108-114.
24. Kaaz K, Szepietowski JC, Matusiak Ł. Influence of itch and pain on sleep quality in atopic dermatitis and psoriasis. *Acta Derm Venereol*. 2019;99(2):175-180.
25. Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med*. 1999;153(3):249-253.
26. Lee CH, Chuang HY, Shih CC, Jong SB, Chang CH, Yu HS. Transepidermal water loss, serum IgE and beta-endorphin as important and independent biological markers for development of itch intensity in atopic dermatitis. *Br J Dermatol*. 2006;154(6):1100-1107.
27. Yosipovitch G, Xiong GL, Haus E, Sackett-Lundeen L, Ashkenazi I, Maibach HI. Time-dependent variations of the skin barrier function in humans: transepidermal water loss, stratum corneum hydration, skin surface pH, and skin temperature. *J Invest Dermatol*. 1998;110(1):20-23.
28. Thorburn PT, Riha RL. Skin disorders and sleep in adults: where is the evidence? *Sleep Med Rev*. 2010;14(6):351-358.
29. Bollinger T, Bollinger A, Skrum L, Dimitrov S, Lange T, Solbach W. Sleep-dependent activity of T cells and regulatory T cells. *Clin Exp Immunol*. 2009;155(2):231-238.
30. Tamschick R, Navarini A, Strobel W, Müller S. Insomnia and other sleep disorders in dermatology patients: a questionnaire-based study with 634 patients. *Clin Dermatol*. 2021;39(6):996-1004.
31. Yosipovitch G, Rosen JD, Hashimoto T. Itch: from mechanism to (novel) therapeutic approaches. *J Allergy Clin Immunol*. 2018;142(5):1375-1390.
32. Andersen HH, Elberling J, Sølvsten H, Yosipovitch G, Arendt-Nielsen L. Nonhistaminergic and mechanical itch sensitization in atopic dermatitis. *Pain*. 2017;158(9):1780-1791.
33. Legat FJ. Itch in atopic dermatitis–what is new? *Front Med*. 2021;8:644760.
34. Cevikbas F, Lerner EA. Physiology and pathophysiology of itch. *Physiol Rev*. 2020;100(3):945-982.
35. Najafi P, Misery L, Carré JL, Ben Salem D, Dufor O. Itch matrixes. *Front Med*. 2021;8:636904.
36. Schwendinger-Schreck J, Wilson SR, Bautista DM. Interactions between keratinocytes and somatosensory neurons in itch. *Handb Exp Pharmacol*. 2015;226:177-190.
37. Das P, Mounika P, Yellurkar ML, et al. Keratinocytes: an enigmatic factor in atopic dermatitis. *Cell*. 2022;11(10):1683.
38. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? *Clin Rev Allergy Immunol*. 2016;51(3):263-292.
39. Ikoma A, Handwerker H, Miyachi Y, Schmelz M. Electrically evoked itch in humans. *Pain*. 2005;113(1–2):148-154.
40. Andersen HH, Akiyama T, Nattkemper LA, et al. Alloknesis and hyperknesis—mechanisms, assessment methodology, and clinical implications of itch sensitization. *Pain*. 2018;159(7):1185-1197.
41. Mochizuki H, Kakigi R. Central mechanisms of itch. *Clin Neurophysiol*. 2015;126(9):1650-1660.
42. Feld M, Garcia R, Buddenkotte J, et al. The pruritus-and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J Allergy Clin Immunol*. 2016;138(2):500-508.e24.
43. Evers AW, Peerdeman KJ, van Laarhoven AI. What is new in the psychology of chronic itch? *Exp Dermatol*. 2019;28(12):1442-1447.
44. Eccleston C. *Embodied: the Psychology of Physical Sensation*. Oxford University Press; 2016.
45. Sanders KM, Akiyama T. The vicious cycle of itch and anxiety. *Neurosci Biobehav Rev*. 2018;87:17-26.

13989995, 2024, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.15818 by South African Medical Research, Wiley Online Library on [03/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

46. Meeuwis SH, van Middendorp H, van Laarhoven AIM, et al. Placebo and nocebo effects for itch and itch-related immune outcomes: a systematic review of animal and human studies. *Neurosci Biobehav Rev*. 2020;113:325-337.
47. Napadow V, Li A, Loggia ML, et al. The imagined itch: brain circuitry supporting nocebo-induced itch in atopic dermatitis patients. *Allergy*. 2015;70(11):1485-1492.
48. Darragh M, Chang JWH, Booth RJ, Consedine NS. The placebo effect in inflammatory skin reactions: the influence of verbal suggestion on itch and weal size. *J Psychosom Res*. 2015;78(5):489-494.
49. Van Laarhoven AI, van der Sman-Mauriks IM, Donders ART, Pronk MC, van de Kerkhof PCM, Evers AWM. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. *J Invest Dermatol*. 2015;135(5):1234-1243.
50. Howe LC, Leibowitz KA, Perry MA, et al. Changing patient mindsets about non–life-threatening symptoms during oral immunotherapy: a randomized clinical trial. *J Allergy Clin Immunol Pract*. 2019;7(5):1550-1559.
51. Joseph D, Chong NW, Shanks ME, et al. Getting rhythm: how do babies do it? *Arch Dis Child Fetal Neonatal Ed*. 2015;100(1):F50-F54.
52. Dutil C, Walsh JJ, Featherstone RB, et al. Influence of sleep on developing brain functions and structures in children and adolescents: a systematic review. *Sleep Med Rev*. 2018;42:184-201.
53. Cheng W, Rolls E, Gong W, et al. Sleep duration, brain structure, and psychiatric and cognitive problems in children. *Mol Psychiatry*. 2021;26(8):3992-4003.
54. Mills KL, Tamnes CK. Methods and considerations for longitudinal structural brain imaging analysis across development. *Dev Cogn Neurosci*. 2014;9:172-190.
55. Rubia K. Functional brain imaging across development. *Eur Child Adolesc Psychiatry*. 2013;22(12):719-731.
56. Tarokh L, Saletin JM, Carskadon MA. Sleep in adolescence: physiology, cognition and mental health. *Neurosci Biobehav Rev*. 2016;70:182.
57. Tham EK, Schneider N, Broekman BF. Infant sleep and its relation with cognition and growth: a narrative review. *Nat Sci Sleep*. 2017;9:135.
58. Tokariev A, Stjerna S, Lano A, Metsäranta M, Palva JM, Vanhatalo S. Preterm birth changes networks of newborn cortical activity. *Cereb Cortex*. 2019;29(2):814-826.
59. Tokariev A, Roberts JA, Zalesky A, et al. Large-scale brain modes reorganize between infant sleep states and carry prognostic information for preterms. *Nat Commun*. 2019;10(1):1-9.
60. Svingos A, Greif S, Bailey B, Heaton S. The relationship between sleep and cognition in children referred for neuropsychological evaluation: a latent modeling approach. *Children*. 2018;5(3):33.
61. Astill RG, van der Heijden KB, van IJzendoorn MH, van Someren EJW. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. *Psychol Bull*. 2012;138(6):1109.
62. Prehn-Kristensen A, Göder R. Sleep and cognition in children and adolescents. *Z Kinder Jugendpsychiatr Psychother*. 2018;46(5):405-422.
63. Touchette E, Petit D, Séguin JR, Boivin M, Tremblay RE, Montplaisir JY. Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. *Sleep*. 2007;30(9):1213-1219.
64. Anders TF, Keener MA, Kraemer H. Sleep-wake state organization, neonatal assessment and development in premature infants during the first year of life. II. *Sleep*. 1985;8(3):193-206.
65. Short MA, Chee MWL. Adolescent sleep restriction effects on cognition and mood. In: Whitney P, Hinson JM, Honn KA, Chee MWL, eds. *Progress in Brain Research*. Elsevier; 2019:55-71.
66. Gruber R, Somerville G, Enros P, Paquin S, Kestler M, Gillies-Poitras E. Sleep efficiency (but not sleep duration) of healthy school-age children is associated with grades in math and languages. *Sleep Med*. 2014;15(12):1517-1525.
67. Schmitt J, Chen CM, Apfelbacher C, et al. Infant eczema, infant sleeping problems, and mental health at 10 years of age: the prospective birth cohort study LISAplus. *Allergy*. 2011;66(3):404-411.
68. Sadeh A, Gruber R, Raviv A. Sleep, neurobehavioral functioning, and behavior problems in school-age children. *Child Dev*. 2002;73(2):405-417.
69. Irwin MR. Sleep and inflammation: partners in sickness and in health. *Nat Rev Immunol*. 2019;19(11):702-715.
70. Ruppenstein A, Limberg MM, Loser K, Kremer AE, Homey B, Raap U. Involvement of neuro-immune interactions in pruritus with special focus on receptor expressions. *Front Med*. 2021;8:627985.
71. Wang F, Kim BS. Itch: a paradigm of neuroimmune crosstalk. *Immunity*. 2020;52(5):753-766.
72. Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev*. 2013;17(4):241-254.
73. Abell JG, Shipley MJ, Ferrie JE, Kivimäki M, Kumari M. Recurrent short sleep, chronic insomnia symptoms and salivary cortisol: a 10-year follow-up in the Whitehall II study. *Psychoneuroendocrinology*. 2016;68:91-99.
74. Webster JC, Oakley RH, Jewell CM, Cidlowski JA. Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative β isoform: a mechanism for the generation of glucocorticoid resistance. *Proc Natl Acad Sci USA*. 2001;98(12):6865-6870.
75. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metabol*. 1999;84(8):2603-2607.
76. Irwin MR, Witarama T, Caudill M, Olmstead R, Breen EC. Sleep loss activates cellular inflammation and signal transducer and activator of transcription (STAT) family proteins in humans. *Brain Behav Immun*. 2015;47:86-92.
77. Irwin MR, Wang M, Ribeiro D, et al. Sleep loss activates cellular inflammatory signaling. *Biol Psychiatry*. 2008;64(6):538-540.
78. Krueger JM. The role of cytokines in sleep regulation. *Curr Pharm Des*. 2008;14(32):3408-3416.
79. Zamarron C, Maceiras F, Mera A, Gómez-Reino JJ. Effect of the first infliximab infusion on sleep and alertness in patients with active rheumatoid arthritis. *Ann Rheum Dis*. 2004;63(1):88-90.
80. Beck L, Silverberg JI, Simpson EL, et al. Dupilumab significantly improves sleep outcomes in adult patients with atopic dermatitis: results from five randomized clinical trials. *J Eur Acad Dermatol Venereol*. 2021;35(2):e130.
81. Pape K, Tamouza R, Leboyer M, Zipp F. Immunoneuropsychiatry—novel perspectives on brain disorders. *Nat Rev Neurol*. 2019;15(6):317-328.
82. Rønnstad ATM, Halling-Overgaard AS, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;79(3):448-456.e30.
83. Strom MA, Fishbein AB, Paller AS, Silverberg JI. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. *Br J Dermatol*. 2016;175(5):920-929.
84. Romanos M, Gerlach M, Warnke A, Schmitt J. Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health*. 2010;64(3):269-273.
85. Eckert L, Gupta S, Gadkari A, Mahajan P, Gelfand JM. Burden of illness in adults with atopic dermatitis: analysis of National Health and Wellness Survey data from France, Germany, Italy, Spain, and the United Kingdom. *J Am Acad Dermatol*. 2019;81(1):187-195.
86. Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM, et al. Serum biomarker profiles suggest that atopic dermatitis is a systemic disease. *J Allergy Clin Immunol*. 2018;141(4):1523-1526.

13989995, 2024, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.15818 by South African Medical Research, Wiley Online Library on [03/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

87. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull*. 2014;140(3):774.
88. Slavich GM, Giletta M, Helms SW, et al. Interpersonal life stress, inflammation, and depression in adolescence: testing social signal transduction theory of depression. *Depress Anxiety*. 2020;37(2):179-193.
89. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol Psychiatry*. 2016;21(5):642-649.
90. NICE. Atopic eczema in under 12s: diagnosis and management. 2007. Accessed July 16, 2023. https://www.nice.org.uk/guidance/CG57/chapter/Recommendations#assessment-of-severity-psychological-and-psychosocial-wellbeing-and-quality-of-life-2
91. He A, Feldman SR, Fleischer AB Jr. An assessment of the use of antihistamines in the management of atopic dermatitis. *J Am Acad Dermatol*. 2018;79(1):92-96.
92. Findling RL, Gringras P, Nir T, Zisapel N. Short-and long-term prolonged release melatonin treatment for sleep disorders in children with autism Spectrum disorders–results of a phase III randomized clinical trial in 64th annual meeting. *AACAP*. 2017;56:S167.
93. Appleton RE, Jones AP, Gamble C, et al. The use of MElatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). *Health Technol Assess*. 2012;16(40):i-239.
94. Bawany F, Northcott CA, Beck LA, Pigeon WR. Sleep disturbances and atopic dermatitis: relationships, methods for assessment, and therapies. *J Allergy Clin Immunol Pract*. 2021;9(4):1488-1500.
95. Rolinck-Werninghaus C, Trentmann M, Reich A, Lehmann C, Staab D. Improved management of childhood atopic dermatitis after individually tailored nurse consultations: a pilot study. *Pediatr Allergy Immunol*. 2015;26(8):805-810.
96. Accessed July 16, 2023. https://nationaleczema.org/wp-content/uploads/2013/08/SID_meditation-and-pruritus_-MJ.pdf?x73548
97. Bridgett C. Habit reversal therapy: a behavioural approach to atopic eczema and other skin conditions. *Practical Psychodermatology*. Wiley-Blackwell; 2014:66-71.
98. Staab D, Diepgen TL, Fartasch M, et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ*. 2006;332(7547):933-938.
99. Heratizadeh A, Werfel T, Wollenberg A, et al. Effects of structured patient education in adults with atopic dermatitis: multicenter randomized controlled trial. *J Allergy Clin Immunol*. 2017;140(3):845-853.e3.
100. Gringras P, Nir T, Breddy J, Frydman-Marom A, Findling RL. Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2017;56(11):948-957.e4.
101. Gringras P, Gamble C, Jones AP, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ*. 2012;345:e6664.
102. Chang YS, Lin MH, Lee JH, et al. Melatonin supplementation for children with atopic dermatitis and sleep disturbance: a randomized clinical trial. *JAMA Pediatr*. 2016;170(1):35-42.
103. Taghavi Ardakani A, Farrehi M, Sharif MR, et al. The effects of melatonin administration on disease severity and sleep quality in children with atopic dermatitis: a randomized, double-blinded, placebo-controlled trial. *Pediatr Allergy Immunol*. 2018;29(8):834-840.
104. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21(11):739-751.
105. Sozener ZC, Özbey Yücel Ü, Altiner S, et al. The external exposome and allergies: from the perspective of the epithelial barrier hypothesis. *Front Allergy*. 2022;3:887672.
106. Leung AS, Wong GW, Tang ML. Food allergy in the developing world. *J Allergy Clin Immunol*. 2018;141(1):76-78.e1.
107. Sugita K, Soyka MB, Wawrzyniak P, et al. Outside-in hypothesis revisited: the role of microbial, epithelial, and immune interactions. *Ann Allergy Asthma Immunol*. 2020;125(5):517-527.
108. Brockmann PE, Bertrand P, Castro-Rodriguez JA. Influence of asthma on sleep disordered breathing in children: a systematic review. *Sleep Med Rev*. 2014;18(5):393-397.

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