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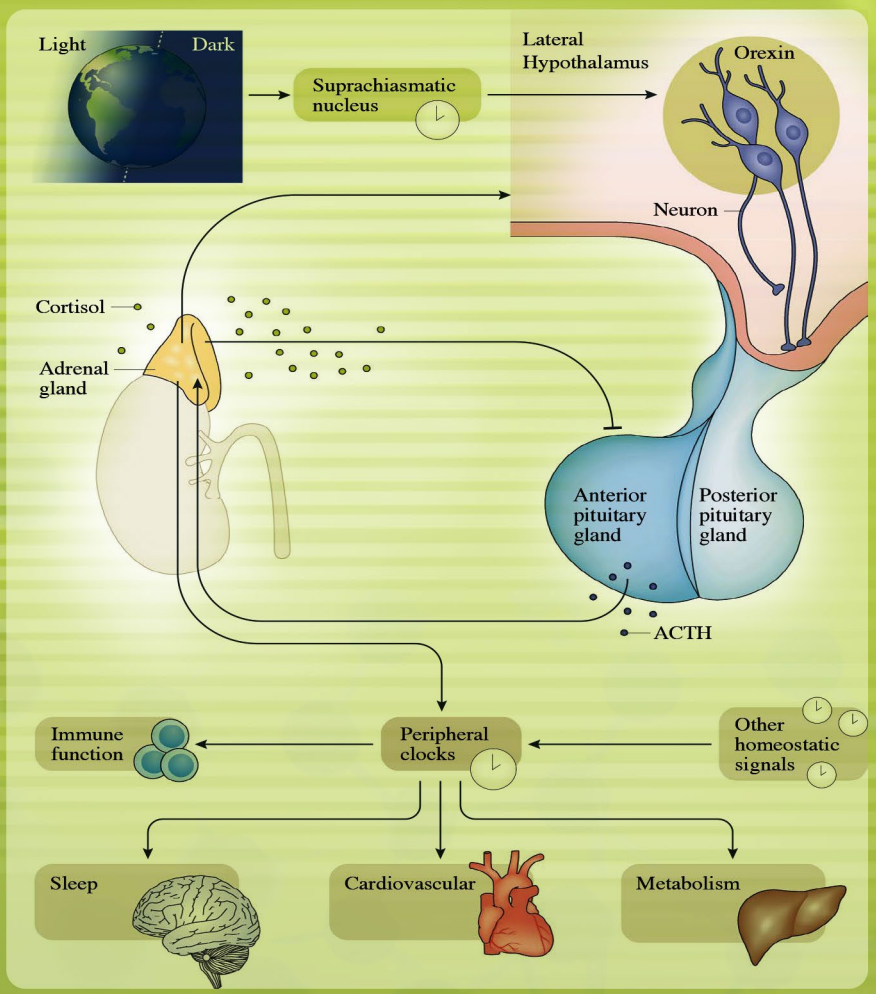

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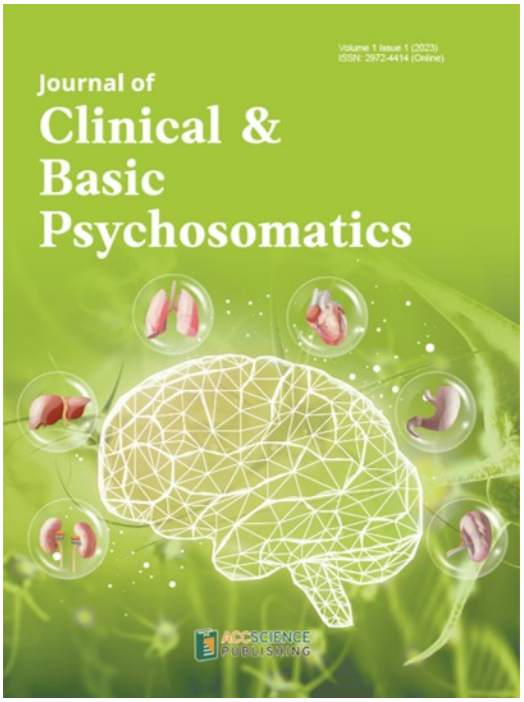

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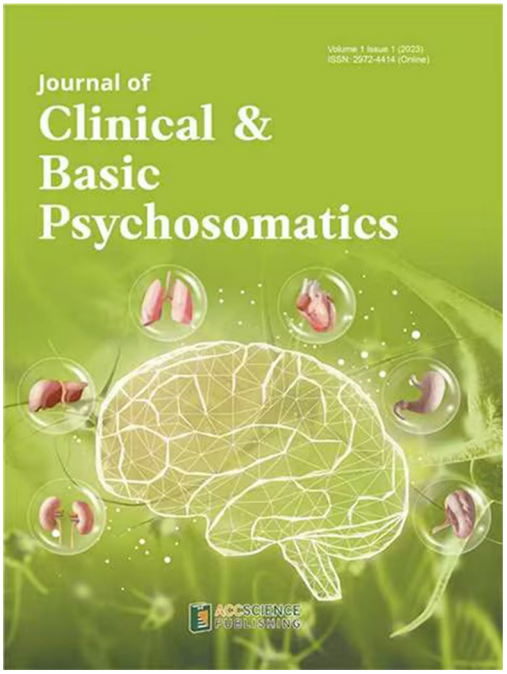

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Journal of Clinical and Basic Psychosomatics

EDITORIAL

New horizons in the *Journal of Clinical and Basic Psychosomatics*: Reflections and gratitude for our milestones

Wenhao Jiang and Yonggui Yuan*

Department of Psychiatry and Psychosomatics, Zhongda Hospital, School of Medicine, Jiangsu Provincial Key Laboratory of Brain Science and Medicine, Southeast University, Nanjing, China

As we turn the page to 2025, we would like to take this excellent opportunity to reflect on the progress that has shaped the *Journal of Clinical and Basic Psychosomatics* since its inception 2 years ago.[1] This milestone, a result of collective patience of all members involved, is not possible without the dedicated efforts of editorial board members, authors, and reviewers, whose unwavering support has laid a strong foundation for the journal.

Within just 2 years, the journal has emerged as a vibrant platform for advancing our understanding of the intricate relationships between mind and body. Our editor board has also grown tremendously in terms of the range of psychosomatic expertise, surpassing a hundred renowned experts and scholars from different parts of the world. At the same time, a youth editorial board – a booster of vitality to the journal – was also established, bringing new perspectives and foundational scholarly support that are conducive to the accelerated development of the journal. In addition, by the end of December 2024, we have published six issues with more than 60 outstanding publications, consisting of mainly original research and reviews. Notable achievements include advancing discussions on managing psychosomatic disorders,[2] brain imaging,[3] gut microbiota,[4] immune dysregulation,[5] culture-related issues,[6] and psychotherapy.[7] These contributions deepen our scientific understanding and underscore the journal's commitment to bridging basic research and clinical application.

Toward 2025, we reaffirm our commitment to publishing high-quality, impactful research that addresses both foundational and applied aspects of psychosomatic medicine. Our more specific plans this year include launching more than two special issues, expanding our editor board across borders, and holding two academic meetings. To increase the journal's recognition by renowned indexes and databases, we plan to submit applications for journal evaluation by Scopus, DOAJ, CNKI, and Clarivate's Web of Science. Thus, the coming year is critical for the journal's development, and your continuous support is crucial for enhancing the scholarly standards of our publications.

On behalf of the Editors-in-Chief and editorial board, we want to thank AccScience Publishing and the editorial office for their contributions and support. We are looking forward to witnessing 2025 as the year of transformative progress and collective achievement.

Conflict of interest

Prof. Yonggui Yuan is the Editor-in-Chief while Dr. Wenhao Jiang is the Associated Editor of this journal. The authors declared no competing interests.

***Corresponding author:**
Yonggui Yuan
(101011406@seu.edu.cn)

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References

1. Yuan Y, Linden M. Inaugural editorial: A new journal and a new opportunity. *J Clin Basic Psychosom*. 2023;1(1):0370.

   doi: 10.36922/jcbp.0370

2. Masahiro S, Fukunaga K, Kawahata I. Use of melatonin for the treatment of dementia: Addressing core symptoms and behavioral challenges. *J Clin Basic Psychosom*. 2023;1(2):1174.

   doi: 10.36922/jcbp.1174

3. Zhang L, Zhao J, Guo W. Pharmacological treatment-associated brain structural and functional alterations in major depressive disorder: A narrative review. *J Clin Basic Psychosom*. 2023;1(1):0896.

   doi: 10.36922/jcbp.0896

4. Borrego-Ruiz A, Borrego JJ. Functional neurological disorder and gut microbiome: Casual or causal relationship? J Clin Basic Psychosom. 2024;2(4):4160.

   doi: 10.36922/jcbp.4160

5. Dong G, Zhu X, Zhang Q, *et al*. Correlations between depressive disorder, obstructive sleep apnea, and hypothalamic inflammation. *J Clin Basic Psychosom*. 2023;2(1):1040.

   doi: 10.36922/jcbp.1040

6. Thompson-Assan S, Ally Y. Culturally informed coping strategies adopted in the treatment of posttraumatic stress disorder among amaXhosa in the Eastern Cape Province of South Africa. *J Clin Basic Psychosom*. 2024;2(2):2889.

   doi: 10.36922/jcbp.2889

7. Linden M. Eudaimonia as a treatment goal in psychotherapy and psychosomatic medicine. *J Clin Basic Psychosom*. 2024;2(3):2988.

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REVIEW ARTICLE

Comorbidity between somatic symptom disorder and dissociative amnesia is best explained by trauma-amnesia-pain theory

Jennifer B. Johnston*

Department of Behavioral Science, Western New Mexico University, Silver City, New Mexico, United States of America

Abstract

Dissociative amnesia is comorbid with somatic symptom disorder (SSD), yet this link is not well-understood. Clinical studies indicate that childhood trauma, especially sexual abuse and emotional abuse, are primary causal factors in the etiology of SSD. This paper provides evidence that dissociative amnesia is an explanatory variable between childhood trauma and SSD. As many or more trauma victims develop amnesia and somatic complaints as those who develop post-traumatic stress disorder (PTSD), but SSD and dissociative amnesia receive much less attention. This leaves clinicians and patients without effective intervention and sometimes causes misdiagnosis. PTSD's neuroendocrinological cascade, from peritraumatic perception to psychobehavioral endpoints is well-mapped, and it informs an opponent-process for dissociative amnesia and SSD, allowing a better conceptualization of a primary cause of SSD – trauma. The novel trauma-amnesia-pain (T-A-P) neuroendocrinological map presented here is a mirror process of the tonic immobility-PTSD pathway initiated by the hypothalamus-pituitary-adrenal (HPA) axis. Dissociative amnesia-SSD develops through the same HPA axis pathway, with PTSD essentially being a downregulated cortisol response and T-A-P an upregulated cortisol response. Copious evidence has now emerged from neurological, physiological, and clinical studies of animals and people regarding the role controllable stress/trauma plays in the etiology of both amnesia and analgesia. T-A-P also validates the decision to consolidate pain disorder, somatization disorder, and functional somatic disorder under one nosological category in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. The implications of this theory are important for both prevention and effective intervention with trauma-induced SSD.

Keywords: Traumatic amnesia; Pain disorder; Functional somatic disorders; Somatic symptom disorder; Cortisol; Peritraumatic perception

***Corresponding author:**
Jennifer B. Johnston
(johnstonj@wnmu.edu)

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1. Introduction

Three primary causes of somatic symptom disorder (SSD) are reported in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). The first is biological and the last two are environmental: increased pain sensitivity, caregiver/social-cultural conditioning and reinforcement of the sick role and somatic-only expressions of suffering, and early traumatic experiences.[1] This paper focuses on

the third, because recent research has identified childhood trauma, especially emotional abuse and sexual abuse, as explaining one-quarter of the variance in somatic symptoms and levels of daily physical discomfort in a large national sample of adults.[2] Furthermore, Eilers *et al.*[2] showed a moderate size effect (d = 0.30) of childhood trauma on later somatic symptoms, after controlling for gender, age, education level, and relationship status. Trauma specifically, not more general "early adversity," is a key variable in the etiology of SSD, but the neurodevelopmental mechanisms linking the effects of childhood trauma to long-term somatic complaints have not been well understood. Trauma-amnesia-pain (T-A-P) theory is presented as a novel conceptualization of the neuroendocrinological cascade that maps how trauma explains the comorbidity of dissociative amnesia and SSD. Clinicians need to understand the critical link for many patients between dissociative amnesia and SSD because treatment may not progress well without acknowledgment of trauma experiences, or trauma-informed intervention. It is difficult to address trauma history given the possibility of a patient's dissociative amnesia for trauma, but implications and intervention options are offered at the end of the paper.

In the DSM-5-TR under comorbidities of SSD, dissociative amnesia is not listed, but post-traumatic stress disorder (PTSD) is listed. Somewhat confusingly, in the DSM-5-TR under comorbidities of dissociative amnesia, SSD is listed.[1,p. 344] It could be an oversight to not have listed the comorbidities in both places, or it could be an indication that dissociative amnesia is presumed to be primary and casual of SSD, a secondary effect. The T-A-P model will address the primary nature of amnesia and the secondary effect of somatic symptoms, such as pain.

To diagnose SSD, at least one somatic symptom must be significantly disruptive or distressing to the sufferer, and the time, thoughts, or anxiety the sufferer spends dealing with the symptom(s) is abnormally high. Many sufferers have multiple somatic symptoms, such as neurological paralysis, numbness, tingling, and burning, but pain is most common.[3,4] Pain disorder, somatization disorder, and functional somatic disorder (FSD) are considered dimensions of SSD in the DSM-5-TR.[5,6] Sometimes the somatic symptom is medically unexplained, but excessive focus on determining whether symptoms are "psychogenic only" in earlier versions of the DSM led to the current recognition that the mind-body connection cannot and should not be dissected when diagnosing SSD.[1]

Van der Kolk[7] posited a triune trauma outcome based on his decades of case studies and experimental findings but admitted the underlying mechanisms contributing to each of the three trauma outcomes remained unknown. He argued that trauma led to either traumatic amnesia, resolution, or PTSD,[7] depending on the victim's peritraumatic perception. Importantly, he identified the connection between PTSD and analgesia. To explore whether there is also a connection between dissociative amnesia and SSD, this paper begins with the traumatic amnesia neurochemical literature, addresses the PTSD neurochemical literature, and ends with the clinical memory and somatization literature. Very quickly after sensory organs and the thalamus detect life-threatening situations, emotion, and memory systems are engaged, along with their relevant neurotransmitters.[8,9] Cortisol, acetylcholine (ACh), glutamate, adrenomedullin, and enzyme acetylcholinesterase will factor large in the model. Olff, Langeland, and Gersons' stress-coping model for PTSD informs one-half of T-A-P theory.[10]

The T-A-P pathway has five phases: Peritraumatic perception; trauma memory processing; sympathetic nervous system (SNS) response; acute somatic symptoms; and chronic somatic symptoms. After the groundwork is laid for the definition, prevalence, and clinical presentation of traumatic amnesia, each phase of the T-A-P pathway will be explained separately. Diagrams are provided that collectively distinguish and compare the triune trauma outcomes: traumatic amnesia/SSD, which is the focus of this research; PTSD/analgesia, which is the opponent process of T-A-P; and trauma integration/resolution, which is the non-clinical healthy resolution of trauma. It is important to note that although the cascade is robust in animal and human models for hours and days following trauma, the final phase of chronic psychobehavioral outcomes, such as dissociative amnesia, SSD, and PTSD can be altered by age, therapeutic intervention, social support, and cognitive reappraisal in the months following the trauma.[8,10,11]

2. Traumatic amnesia

Perhaps one reason traumatic amnesia has received little discussion in the literature in comparison to PTSD is because its behavioral consequences were generally unknown. If people cannot remember the trauma they experienced, why would they seek therapy? Large clinical populations were lacking. Furthermore, controversy swirled around how traumatic amnesia was defined and whether amnesia was an appropriate term for a condition in which trauma victims were unable to encode or consolidate key declarative memories of a trauma since the term amnesia often implies forgetting.[12] Nevertheless, most experts have settled on the term traumatic amnesia if it is defined as an absence of declarative memory, for one or more traumatic incidents, due to failure to encode or consolidate long-term memory at, or soon after, the time of

the trauma.[13-15] Given this definition, "recovering" trauma memories is impossible since they were never encoded. Importantly, this definition of traumatic amnesia does not assume that separate memory systems, such as procedural and emotional memory systems, have also failed. There is further confusion over the name dissociative amnesia because some research shows dissociation is a key determinant in PTSD etiology—PTSD's intrusive remembering being the opposite of amnesia. In the descriptions of dissociation for people with PTSD, it is an appraisal of "numbness" during and after the trauma, associated with the freeze response.[5] Yet the research below shows that dissociative amnesia is not caused by numbing/freezing, but instead by a very active response to the trauma: Fight or flight. The high cortisol generated to drive this high initial activity leads to memory blockade, and that leads to amnesia, not numbing. Dissociative amnesia falls in the DSM-5-TR category of dissociative disorders, linked by the amnesia and separation of memory systems common in dissociative identity disorder—leading to its name dissociative amnesia. However, the definition of dissociation—body separated from mind, or mind separated from present reality—is not salient in the initial creation of the disorder. The single diagnostic criteria in the DSM-5-TR for dissociative amnesia refers to amnesia for (inability to recall) autobiographical events (declarative memory) that are usually traumatic in nature. There is no symptom referring to unreality, depersonalization, or numbing of emotion or sensation. To reduce confusion, "traumatic amnesia" will be used in this review as a more general condition that encompasses dissociative amnesia.

It is helpful here also to briefly review the divergent natures and anatomy of declarative and procedural memory systems. Due to various factors, one can be impeded during encoding while the other remains intact.[16-21] Although partial impairment of recall for some aspects of trauma, and/or dissociation, and feelings of the "unreal" quality of trauma are fairly common in PTSD, PTSD sufferers are aware that they experienced a trauma, and can name it, as well as many aspects of what happened to them – when, where, and so on. In their comprehensive review, Bovin and Marx concluded that memory for trauma is stable over the course of PTSD.[8] In contrast, traumatic amnesia spares victims from intrusive, upsetting declarative memories, but preserves emotional and somatosensory memories. What at first appearance is a reprieve from the memory of a traumatic experience becomes an intrusive and painful re-living of the trauma in the form of somatic complaints.

3. Prevalence

The DSM-5-TR struggles to present a reliable prevalence rate for dissociative amnesia, listing it at 1.2%, due again, to a lack of large clinical samples.[1] We can determine prevalence rates for traumatic amnesia from population studies and unique prospective designs of documented trauma survivors, such as substantiated child sexual abuse victims or car accident victims. Six studies have been identified that share a compellingly similar prevalence rate. Three of the six reported 19% of victims, and three reported 36% of victims have no memory of the trauma event(s), immediately after a documented traumatic experience, and many of those have no memory of the trauma even months or years later.[22-28] The bimodal result seems to relate to the type of trauma; the three studies that contacted child sexual abuse victims years later found higher amnestic rates than the three studies that contacted medical/health crisis trauma victims or general population members about any kind of trauma and associated amnesia experienced. Young age and relationship to the perpetrator (betrayal trauma) affect memory.[29,30]

Traumatic amnesia is a more likely outcome of trauma exposure, yet is much less studied than PTSD. PTSD's prevalence rate is between 8% and 9%.[1,31] Has there been an assumption that what you can't remember can't hurt you? Sadly, the T-A-P theory indicates that what you can't remember does just that—it hurts you. Because of the difficulty in substantiating trauma history with many amnestic victims, if they seek any help at all, their symptoms can seem a mystery to themselves, their families, and their health providers. In the worst-case scenario, they may be labeled malingerers or hypochondriacs. In contrast, people with PTSD symptoms are more likely to be believed and treated. Van der Kolk sensitively describes how victims use fragments of recollection, external corroboration, and fuzzy intuitions to confirm that they experienced trauma.[7] They piece together the meaning behind their mental or physical dysfunction, having to trust emotional and body memory only. That delicate process has led to dead ends for some, reconstructed, potentially false memories for others, and denial for yet more (Alpert *et al.*,[29] Fredrickson,[30] Freyd,[32] and Herman[33] for discussions of how traumatic amnesia was often mischaracterized and mishandled as "repressed memory"). Traumatic amnesia complicates the detection, diagnosis, and treatment of trauma-related symptoms. However, patient progress is possible when information retained by emotional and procedural memory systems is included in clinical formulations, as somatic psychotherapists recommend.

4. Peritraumatic perception

Peritraumatic perception initiates divergent hypothalamus-pituitary-adrenal (HPA) axis responses to trauma.[34,35] Since Foa first suggested that perception of an event's potential threat might be more determinant of its impact on PTSD

than the event's manifest danger, it took over 10 years for laboratory results to prove her postulation.[9] Perception of trauma as either controllable or uncontrollable affects the HPA axis response to trauma. This review focuses on the consequences of peritraumatic perception of *control/escapability*, as opposed to peritraumatic perception of *inescapability*, or tonic immobility. For extensive coverage of the etiology of PTSD and perceived inescapability/tonic immobility (Bovin *et al*., Hagenaars and Putman, Lima *et al*., Marx *et al*., Olff *et al*., Rocha-Rego *et al*., and Volchan *et al*.[3,34-39]).

5. Defense cascade: Fight, flight, or freeze?

The defense cascade refers to a common series of physiological and behavioral events triggered by danger or perceived threat in animals and humans. Animals move through the cascade in a predictable fashion, from attentive stillness (hyperalert assessment) to fight, to flight, to freeze, depending on their species (*e.g.*, some animals are suited to fight more than flight).[38,39] Freeze, or in its extreme form, tonic immobility, is characterized by gross motor inhibition, a fixed stare, suppressed vocalization, lower body temperature, and even temporary paralysis. It is a last resort for the animal; "playing dead" is an attempt at self-preservation when no other escape seems possible.[9] In humans, as early as 1989, van der Kolk, Greenberg, Orr and Pitman hypothesized that the freeze response led to PTSD symptoms.[40] Others followed, documenting similarities between tonic immobility and symptoms observed in patients with dissociation, including some who were diagnosed with PTSD.[41] The peritraumatic dissociative experiences questionnaire was developed, with derealization and dissociation predicting PTSD symptoms.[42,43] Derealization is concerned with the perception of trauma, and dissociation is connected to a freeze response.

In humans, as dissociation increases, cortisol secretion decreases.[44] Forebrain areas engage if critical processing of the threatening situation occurs, which is a slower brain activity, whereas midbrain areas engage if immediate panic or tonic immobility occurs, which is a faster cortical reaction.[10,45] The assessment of how serious or imminent a danger or encroaching threat is, causes one cortical area to fire faster than another, determining the amount and type of neurochemicals that circulate. In the case of an inescapable threat, initial attentive stillness is followed immediately by tonic immobility, whereas when a threat is perceived as potentially escapable, an attempt to bargain, fight, or flee occurs.[9,10] The key neuroendocrinological player relevant to both these reactions is cortisol. For decades, we have known that cortisol secretion has dose-dependent, clinically relevant, differential effects on memory impairment. Newer research indicates that it also triggers nervous system effects related to pain perception and dysregulation of the parasympathetic nervous system (PNS).

6. Cortisol's central role in trauma outcomes

6.1. Memory

Perception of control is a determining factor in whether amnesia develops, or indelible memory of trauma develops, in both animal and human studies. In a seminal work by Drugan on rats exposed to trauma/stress, simply by varying 'controllability', he and his colleagues succeeded in inducing either long-term traumatic amnesia, or contrarily, tonic immobility and depression/PTSD. He defined controllable stress as "the subject is allowed to make an active behavioral response to alter the pattern, onset, duration, or intensity of stress".[46,p.246] In the escapable stress paradigm, the rats had subsequent amnesia for the experience. Postmortem, Drugan found elevated levels of corticosterone (rat cortisol) binding with nicotinic acetylcholine receptors (nAChRs) in the hippocampus, and elevated gamma-aminobutyric acid (GABA) in the amnestic rats. He concluded that a hypercorticosterone condition was created by the escapable stress paradigm, and either cortisol or GABA was responsible for the rats' traumatic amnesia.[46]

Perceiving trauma as controllable or escapable tends to have a protective amnestic effect on the mental health of people and animals, and may, in some cases, be useful for survival and species success. Moderate to high amounts of cortisol are also useful to an organism preparing for fight or flight because cortisol helps mobilize energy resources, increases cardiac activity, primes muscles for action, and potentiates the startle response.[10,47-49] However, because nearly every neurotransmitter system is affected by exposure to prolonged stress, escapable or otherwise, negative consequences are high as well.

Compelling prospective evidence in human's shows, like rats, our freeze/inescapable stress response leads to PTSD, whereas our fight/flight/escapable stress response leads to either amnesia or no PTSD[50] For example, many people who qualify for acute stress disorder in the early days following a trauma no longer meet symptom criteria after 30 days. They have resolved the trauma in some manner, and this is linked to moderate cortisol levels. Research on car accident victims is demonstrative. Delahanty found among 134 motor vehicle accident victims and 43 minor injury controls, the group who felt responsible for their vehicle crashes (peritraumatic perception of control) had significantly fewer or no PTSD symptoms, three and

6 months after trauma, compared to the accident victims who felt no control over the accident (because someone else was to blame). Delahanty's team realized they should follow up with victims of motor vehicle accidents who had amnesia for an accident (21 of 99) but had been initially excluded from the research. Those victims' urinary catecholamines (epinephrine, norepinephrine, dopamine) and cortisol levels were tested immediately after arrival to the hospital and 15 h later. Their cortisol levels were extremely high. Cortisol was the only neurochemical that significantly differentiated between motor vehicle accident victims who reported intrusive memory, and 1 month later, PTSD symptoms, and motor vehicle accident victims who had no intrusive memory or PTSD.[51]

We can now pinpoint exactly how long-term memories are consolidated or interrupted in humans. High levels of cortisol are associated with declarative memory impairment.[10,15,18,52] When there have been conflicting results about levels of cortisol and PTSD versus traumatic amnesia, it was due to comparison across studies that measured cortisol at the onset of the disorder versus cortisol levels over the duration of the disorder. T-A-P theory is concerned with cortisol levels at initiation, as opposed to maintenance during the course of traumatic amnesia or PTSD. Conflicting results are also born of measurement inconsistencies. A number of researchers have commented that salivary levels in one study have been compared to plasma or urinary levels in another study, or basal levels at different times of day have been compared, yet failed to take into account circadian rhythm effects.[51,53-56]

Below is a summary of the specific amounts of cortisol that affect memory. The lowest levels, between 9 and 120 mg, induce intrusive memory and PTSD; moderate levels, between 140 and 450 mg, stabilize the HPA axis and lead to normal memory and functioning; high levels of cortisol, between 450 and 650mg, create amnesia. The effects of cortisol can be reversed or increased within a few hours if a patient receives agonist or antagonist therapy. For example, in three human studies, administration of 25 mg of hydrocortisone (exogenous cortisol) immediately post-trauma decreased memory for trauma and prevented PTSD, but was not sufficient to induce traumatic amnesia.[56-58] In rats, plasma corticosterone levels are 400% higher after inescapable stress compared to controls (637.5 ± 99.8 ng/mL vs. 176.6 ± 50.6 ng/mL).[59] Furthermore, in accident victims with PTSD symptoms, 15 h after trauma, the average of their urinary cortisol level was 131 mg. The urinary cortisol level in accident victims without PTSD symptoms averaged 443 mg at 15 h after trauma.[51] Wahbeh and Oken [60] also found long-term lower cortisol in veterans with PTSD than in veterans without PTSD.

Although there is only one study directly controlling cortisol's role in the T-A-P pathway, Zohar *et al.*[61] successfully prevented PTSD in hospitalized trauma victims by administering a high dose of hydrocortisone immediately post-trauma. In their double-blind randomized controlled trial, they were able to facilitate a return to HPA axis homeostasis in both human and animal models and increase or facilitate normal hippocampal dendritic growth in animals. Their groundbreaking finding was that a 1-time, 100 – 140 mg weight-dependent dose of hydrocortisone administered within 6 h of trauma prevented PTSD symptoms and indelible, intrusive memory.

The inverted U-shaped relationship cortisol has with memory has been widely reported.[15,18,62-64] At very low and very high levels, cortisol is problematic in the hippocampus. At moderate levels, cortisol does not overly impede or facilitate memory. Yet, many studies have not measured cortisol in a systematic way or accounted for its nonlinear relationship. This may explain why some authors' findings conflict. Future studies of human models should report milligrams per volume unit of urine for cross-comparison. Furthermore, precise measurement of urinary cortisol levels of amnestic trauma victims needs to be included in future studies, so that exact dose ranges within which cortisol alters memory, such as the suggested guidelines above, can be confirmed.

6.2. Pain

The initiation and maintenance of pain in the body is a complex process that involves an interplay of both the SNS and PNS, simply put, tends to involve activation of the SNS first (which turns "on" the pain response), and then an activation of the PNS (which turns "off" the pain response), returning the system to allostasis. In actuality, the process involves many different neurotransmitters and the potentiation or depotentiation of both neuronal brain cells and afferent and efferent neurons in the spine and body.[47,65] Many of the neurotransmitters, receptors, and anatomical areas of the brain involved in pain perception are also involved in the body's response to trauma, particularly regarding the actions of the HPA axis and catecholamines. Catecholamines trigger cortisol production and release.[66,67]

Early PTSD researchers proposed that the freeze or tonic immobility response associated with PTSD involved sustained analgesia, an analgesia more potent and longer-lasting than stress-induced analgesia (SIA) usually seen in animals. SIA involves attentive stillness/immobility early in the defense cascade. Animal research overwhelmingly supported both a hypocortisol-analgesia connection and a hypercortisol-pain connection. In the only studies that refuted the hypercortisol-pain connection, SIA was

examined, rather than the longer-term tonic immobility-related analgesia.[67-71] Sometimes important differences in the intensity and duration of SIA, varying in response to escapability/inescapability, were not measured. For example, Pinto-Ribeiro *et al.*[69,70] reported long-term analgesia in rats exposed to chronic inescapable stress but may have mistakenly interpreted the effect as due to hypercorticosteronism. What is termed "elevated" or "high" glucocorticoid can vary depending on the study. Pinto-Ribeiro *et al.* exogenously administered 40 mg of corticosterone to rats in the 2009 study,[70] presumably to match the levels her team noted in the plasma of rats subjected to chronic inescapable stress in the 2004 study[69] (although those levels were not reported in the 2004 study). Forty milligrams would not be indicative of hypercorticosteronism but instead indicates that low corticosterone is linked both to memory for trauma and analgesia. Unfortunately, Pinto-Ribeiro overlooked Uki *et al.*'s results[72] in which plasma corticosterone levels indicating traumatic stress are 120 mg in rats.

Another critical difference is how long analgesia is measured. Drugan *et al.*[73] monitored SIA for more than 2 h. They found that SIA for rats in escapable stress paradigms rapidly declined over 2 h until there was no analgesia, whereas rats in inescapable stress paradigms experienced ongoing analgesia for over 24 h, indicating that a state of tonic immobility had also begun, although the authors did not assess that. They did note that rats in the inescapable stress condition had the benefit of endorphins, whereas the escapable stress rats did not.[73-76] By 1999, Drugan[46] determined that cortisol and GABA levels were significantly elevated in the escapable stress conditions and were linked to both amnesia and interrupted SIA.

This research begged the question: In light of the results in animal models, does traumatic amnesia interrupt analgesia and create susceptibility to chronic pain in humans as well? And, is the pain experience governed by peritraumatic perception if it is a byproduct of traumatic amnesia, neurochemically downstream from glucocorticoid (cortisol) effects? In animal models, one study[66] to date showed that cortisol differentiated pain perception along the same dose-dependent lines as it differentiated memory. Cortisol is critically tied to a fight/flight perception of trauma like it is tied to freeze/PTSD. Souza da Silva and Menescal-de-Oliveira[66] created chronic trauma-induced pain in guinea pigs using a controllable stress paradigm. Importantly, even if only exogenously administered (no stress/trauma paradigm), high levels of corticosterone caused ongoing pain.

6.3. Trauma-induced analgesia

In 2009, Janig[47] came close to mapping how peritraumatic perception dictates whether analgesia or pain is experienced in response to trauma in humans. Depending on the peritraumatic response, he said that either analgesia or pain is differentially regulated by either opioid or non-opioid mechanisms. In a fight/flight response to trauma, early rapid analgesia occurs through the prevention of SNS activation through epinephrine's action (non-opioid) at the trigeminal dorsal horn and its deactivation of ACh in the PNS. Alternately, in a freeze response, slower ongoing analgesia is maintained by ACh activation of the PNS, keeping the SNS "off" through endorphins opioid.[47] However, Janig was incorrect when he defined the initial attentive stillness phase of peritraumatic perception, which occurs in both fight/flight and freeze responses, as the complete fight/flight response. Instead, early SIA caused by attentive stillness is characterized by cholinergic-modulated analgesia, but later in the cascade, catecholamines produce hyperalgesia in the fight/flight reaction, according to many.[9,66,70,73,74] There is agreement with Janig's hypothesis that freeze/tonic immobility responses to trauma involve opioid-modulated analgesia.

For example, both Leite-Panissi *et al.*[74] and Souza da Silva and Menescal-de-Oliveira[66] substantiated that SIA is a cholinergic-modulated analgesia. However, others found that long-term analgesia caused by inescapable stress is opioid-modulated (endorphins bind with mas-related gene [$MrgX_2$] receptors) in the spinal horn.[66] Furthermore, Drugan *et al.*[73] discovered that naltrexone (an opiate antagonist) completely eliminated the analgesia in chronically inescapably shocked subjects but had no effect on the analgesic response of chronically escapably shocked subjects. In other words, in the case of inescapable stress and hypocortisol, after initial SIA in the nucleus raphe magnus, from there, projections into the spinal horn activate tonic immobility, stimulate endorphins, and thereby prevent the SNS from activating. In the case of hypercortisol and escapable stress, after initial SIA, beta-endorphins are inhibited and excessive glutamate triggers N-methyl-D-aspartic acid (NMDA) receptor activation of SNS pain while cortisol prevents ACh from calming the SNS.

From clinical studies of human beings, we know that hypercortisol also plays an important role in the onset of many types of somatization by causing misattribution and misperception of body signals.[71] Furthermore, patients with pain disorder, fibromyalgia, and chronic back pain show reduced gray matter density in cingulate-parahippocampal or fronto-limbic areas.[11,77,78] Hypercortisol has been implicated in brain matter loss in the hippocampus and surrounding areas.[55] We cannot assume that if chronic SSD patients present with ongoing hypercortisolism that it was also the cause of SSD, but there is strong evidence indicating that hypercortisolism is key to both onset and

maintenance of SSD. For example, in studies of patients with FSDs, some initially develop pain from increased SNS activity caused by hypercortisolism, yet almost all FSD patients present with a dysfunctional PNS, which disrupts allostasis and sustains pain.[71]

Methodology discrepancies explain the few examples that counter the hypercortisolism connection in pain patients. For example, women in Heim *et al.*'s study[79] revealed hypocortisol and PTSD symptomology (an expected correlation), but they also suffered with chronic pelvic pain. However, finding hypocortisolism in some of patients with pain should be cautiously evaluated because cortisol measurements were collected in vastly different ways, at different times of day, and calculated differently, so making conclusions regarding a trend toward hypocortisolism, hypercortisolism, or no effect, in maintenance of SSD is premature.[71,79] A hypercortisol condition is linked both to traumatic amnesia and initiation of SSD, through disruption of the PNS. During maintenance of the disorders, cortisol levels sometimes vary. The next section illustrates the chain of neurological events that connects amnesia and pain through the action of the HPA axis and provides a new formulation of the etiology of SSD. The model also indicates how procedural memories of trauma are cemented at the same time that declarative memories are prevented.

6.4. Cortisol and the HPA axis

Cortisol's role in the HPA axis as it responds to stress is mapped in Figure 1. Trauma and stress are first perceived by the sensory thalamus, which quickly sends input to the amygdala,[53] or possibly simultaneously to the amygdala and locus coeruleus, depending on the emotional content and level of arousal of the stressor.[5,67,80-83] The amygdala has been observed to release corticotropin-releasing hormone (CRH)/factor directly to the pituitary,[55] but in most HPA axis models, CRH release occurs after the amygdala is stimulated by the locus coeruleus. The action of catecholamines released directly from the locus coeruleus to the hypothalamus triggers CRH production.[67,82,83] Some hypothesize that fear-related stress would tend to trigger amygdala-mediated CRH release (and the less perceived control, the more fear, therefore the more CRH release), whereas physiological stress/trauma would tend to elicit hypothalamus-mediated CRH release.[55,81,83]

Once the catecholamines (epinephrine, norepinephrine, and dopamine) are triggered in the locus coeruleus, two relevant analog peptides in the traumatic-amnesia-pain equation are co-secreted: proadrenomedullin N terminal-20 peptide (PAMP) and mid-regional pro-adrenomedullin (MR-PAM), two of the four peptides made in the adrenal glands. PAMP downregulates further catecholamine release, likely as part of the HPA axis feedback loop, eventually returning the system to normal response.[84-87] MR-PAM has recently been shown to significantly reduce cortisol synthesis and secretion in both human infants and mice.[87] CRH then excites adrenocorticotropin hormone (ACTH) production in the pituitary gland. ACTH triggers the adrenal glands to produce cortisol.[80,88,89] Cortisol travels to numerous parts of the body. In the brain, it steroidally depotentiates ACh that has already bound with its receptors in the hippocampus, blocks further ACh from binding with ACh receptors and binds with glucocorticoid receptors.[59,89] The hippocampus contains more glucocorticoid binding sites than anywhere else in the brain, though the amygdala also contains many glucocorticoid receptors. Roozendaal *et al.*[81] discovered that high levels of cortisol binding with its receptors in the basolateral amygdala led to stronger emotional and kinesthetic memories of trauma, providing further evidence that while the hippocampus is the seat of declarative memory, the amygdala is the seat of emotional memory. It is very important to note that each is differentially affected by cortisol; the hippocampus has a curvilinear relationship with cortisol – failing to encode memory when cortisol levels are very low and very high, but indelibly or normally recording memory when levels are low to moderate. The amygdala has a linear relationship with cortisol – low levels lead to less emotional memory and high levels lead to more emotional memory.[10,52,81]

A complex algorithm dictates the normal storage of long-term declarative memories. Electrical theta and gamma oscillations that are potentiated by ACh as it binds with mAChRs and nAChRs are depotentiated by GABA and allow for continuous feedforward and feedback mechanisms between the hippocampus and other brain areas which store long-term memories, based on the strength and prior use of pathways.[82,88,90] The same neurotransmitters and receptors identified as affected during the HPA axis response to trauma – ACh and GABA, nAChRs, and muscarinic AChRs, respectively – influence how or whether any new memory is encoded.[91,92] If the delicate rhythm is interrupted, as in the case of hypercortisol, then memory is disrupted. Among nAChR inhibitors, cortisol shows moderate strength.[59] Furthermore, cortisol's blocking of nAChRs triggers GABAergic overstimulation,[72,88,93] as does cortisol's ability to bind with glutamate receptors, leaving more glutamate circulating. Excessive glutamate also overstimulates GABA's inhibitory role.[65] The hippocampus provides a feedback system for the HPA axis through the inhibition of further CRH production by both cortisol interference with hippocampus excitation, and overproduction of GABA.[80] GABA has a calming effect on

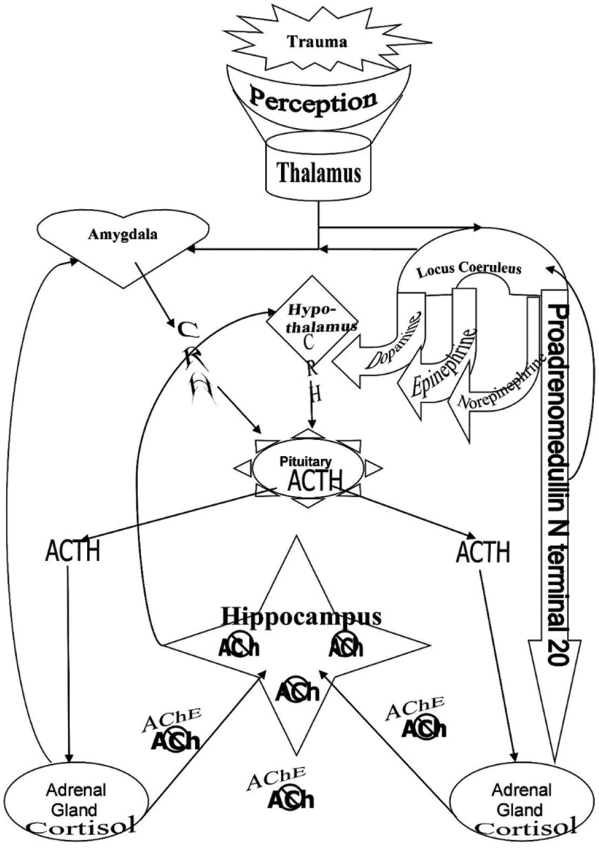

Figure 1. Hypothalamus-pituitary-adrenal axis involvement in traumatic amnesia and somatic symptom disorder
Abbreviations: ACh: Acetylcholine; ACTH: Adrenocorticotropin hormone; CRH: Corticotropin-releasing hormone/factor.

the hippocampus and other brain areas, helping the HPA axis return to normal functioning.[55,83]

It is hypothesized that PAMP (co-secreted with catecholamines) also begins working to return the HPA axis response to normal by downregulating any further catecholamine release, due to its high blocking affinity to nAChRs in the locus coeruleus (preventing catecholamine production, and downstream, further cortisol production.[87,94,95] PAMP is a high-affinity antagonist for nAChRs α9/10,[85,86] the receptors specifically implicated in amnesia,[96] so PAMP may further impair memory by blocking ACh binding, production, and secretion.[97] In rats, PAMP was observed entering the hippocampus from the locus coeruleus, but its action there was not understood.[94] The action of PAMP in humans and whether it is a co-contributor with cortisol in inducing traumatic amnesia needs validation.

6.5. Pain and the fight/flight response

As well as its primary role in memory, the hippocampus has more recently been implicated in pain perception and transmission. After testing the involvement of CA3 region hippocampal neurons in the pain perception of rats, Li *et al.* noted, "there is substantial evidence indicating that the hippocampal formation is involved in pain processing".[98,p.559] The authors suggest that hippocampal mAChR involvement in pain processing enhances organism survival because it facilitates learning and memory about how to avoid reinjury from noxious or dangerous situations. In a very recent study, Mueller *et al.*[82] identified ACh's role in allowing the PNS to remain over-activated, triggering inflammation. Along with nAChRs, mAChRs, and GABAergic receptors on neurons in the hippocampus are NMDA receptors[99] (Figure 2). Because of interactions between these four receptors, response to trauma affects not only memory but also pain perception.[46,59,82] When ACh binds with mAChRs, one result is that glutamate is released. Glutamate not only binds with its own receptors but also NMDA receptors.[100,101] NMDA receptors are the primary activators of neuropathic SNS pain activation.[59,70,82]

In the case of inescapable trauma, a hypocortisol condition allows normal ACh activation of mAChRs, preventing excessive glutamate release, so NMDA receptors and the SNS are not turned "on." Furthermore, early in any trauma response, SIA is triggered by catecholamines that stimulate both CRH production, and turn "on" mAChRs in the nucleus raphe magnus of the spine.[66] SIA in the nucleus raphe magnus benefits an organism by suppressing pain but still allows for motor movement if escape is possible. Within a couple of hours, however, peritraumatic perception of control begins to discriminate analgesic properties.[73,74] Hypercortisol in the hippocampus leads directly to the experience of pain because cortisol binds with its receptors in profusion, thereby depotentiating ACh's binding at mAChRs, both of which prevent the uptake of glutamate at the synapse. High levels of glutamate circulating causes more NMDA receptors to activate.[59,100] Cortisol travels further down in the spine as well, activating glucocorticoid receptors and NMDA receptors, turning on the SNS. Then cortisol also blocks ACh's ability to activate the PNS, which would normally shut down the SNS.[82,89,102]

The HPA axis connection to memory systems is firmly established, and the HPA axis connection to the autonomic nervous system is emerging, with the effects of ACh and cortisol on nAChRs and mAChRs figuring prominently in both memory formation and pain perception. For confirmation, there is one study of human beings regarding the pain trajectory through the HPA axis. In a large national study in Denmark, patients with chronic lower back pain had nearly 2 times higher cortisol levels within 30 min of awakening (cortisol awakening response) compared to controls with no lower back pain.[103] This is

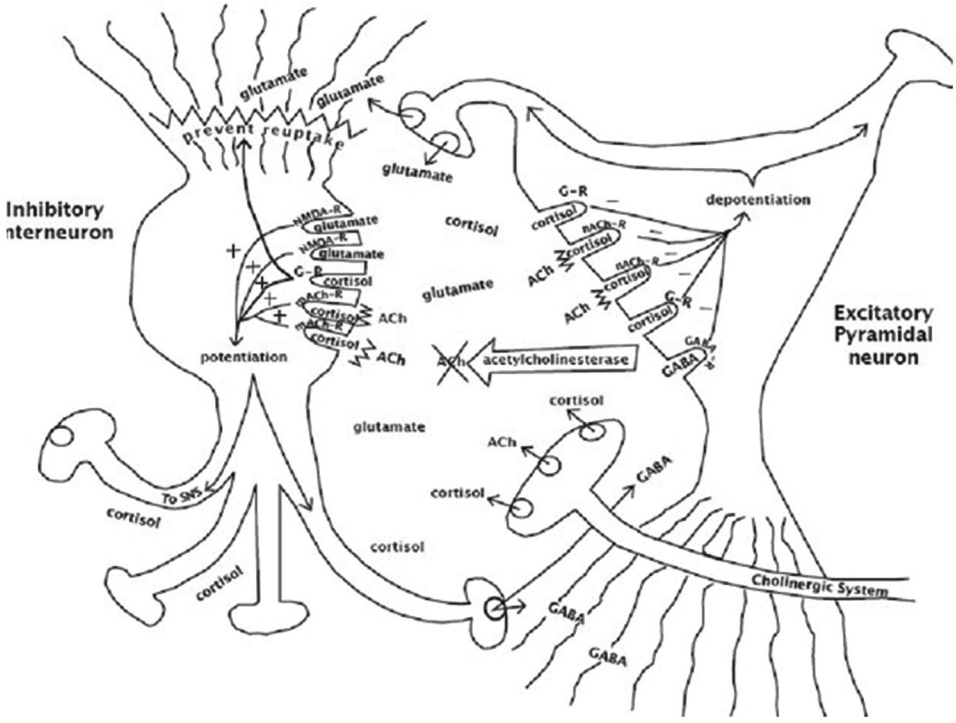

Figure 2. Hippocampal transmitters and receptors are affected by hypercortisol
Abbreviations: ACh: Acetylcholine; GABA: Gamma-aminobutyric acid; SNS: Sympathetic nervous system.

directly opposite what the researchers hypothesized, likely given the contradictory literature they found on cortisol, trauma, and pain, and the lack of this paper's map of the neurochemical cascade for trauma, memory, and pain.

7. Secondary contributors: Acetylcholinesterase and PAMP

7.1. Acetylcholinesterase

Acetylcholinesterase, the enzyme that hydrolyses or breaks down ACh at the synapse should also be considered as a possible player in the T-A-P connection. Increased activity of acetylcholinesterase is linked to memory impairment.[104,105] However, there is only one study to date that indicates acetylcholinesterase increases specifically in the wake of trauma perceived as controllable. Its results are important in that they support the cortisol findings above, as well as encourage researchers to consider interplay of HPA axis neurochemicals and receptors when it comes to understanding and treating traumatic amnesia and its consequences. In 2005, Das *et al.*[106] discovered memory impairment and higher levels of acetylcholinesterase in rats who were exposed to chronic unpredictable stress, compared to those exposed to chronic predictable stress, vs. only one episode of stress (control group). Replication of the study and confirmation of whether chronic unpredictable stress is equivalent to controllable stress is needed. It is logical that chronic unpredictable stress is perceived as controllable, unlike chronic predictable stress, which the subject comes to expect, knows the nature and length of, and therefore comes to believe there is no escaping.

As further evidence of aceytlcholinesterase's importance, there is limited literature verifying its increase in response to chronic stress when cortisol levels are high.[106-109] High levels of cortisol or exogenously administered hydrocortisone either stimulate the synthesis of acetylcholinesterase or speed up its degradation of ACh.[110] By degrading circulating ACh, high levels of acetylcholinesterase allow more glutamate release.[111] Acetylcholinesterase can also prevent ACh activation of the PNS, as discussed earlier, a key problem for chronic psychogenic pain and somatization sufferers.[82,102] Furthermore, elevated acetylcholinesterase is linked to other PNS problems, such as increased muscle fatigue and degeneration at neuromuscular junctions in mice[112] – the same complaints many fibromyalgia and chronic fatigue sufferers have. Finally, acetylcholinesterase is nearly an exact match of atropine's protein sequence (99%), and butyrylcholinesterase, a cholinesterase that also hydrolyses ACh and other choline esters, is in fact, an exact match (100%) of atropine's protein sequence according to the

National Institute of Health's open database, Genbank's B.L.A.S.T., which is a protein sequence matching tool (http://blast.ncbi.nlm.nih.gov/Blast.cgi).[113] It is hypothesized that acetylcholinesterase or butyrylcholinesterase, or both, are endogenous versions of atropine because atropine binds with high affinity to acetylcholinesterase enzymes.[114] Further, the research presented above indicates that they differentially affect memory systems in the way atropine does.[20,115] Parasympatholytics, or PNS inhibitors, such as atropine (https://pubchem.ncbi.nlm.nih.gov/compound/Atropine),[116] are a concern because PNS inhibition is a core problem for FSD sufferers. If acetylcholinesterase is endogenous atropine, then its profusion is likely causing or exacerbating FSD.

7.2. PAMP

The role PAMP has in the HPA axis as an antagonist of nAChRs and mAChRs should be considered, such as acetylcholinesterase, as also antagonizing the PNS. This paper argues that PAMP reinforces cortisol in the T-A-P pathway. High levels of PAMP (discussed above as associated with elevated catecholamines and hypercortisol in the controllable stress paradigm) could interfere with SIA and the beginning of tonic immobility in two ways. First, PAMP could prevent analgesia at the level of $MrgX_2$ receptors in the spinal dorsal horn,[67,117] because PAMP blocks $MrgX_2$ receptors with stronger affinity than six of that receptor's ligands, preventing analgesis that is normally associated with activation of $MrgX_2$ by endorphin or enkephalin.[85,117] Second, after hypercortisol activates the SNS by way of NMDA receptors,[70] the PNS' attempts to return the system to allostasis could be blocked by PAMP. If low ACh is circulating early in the controllable stress paradigm due to high catecholamines, since PAMP is an ACh receptor antagonist, it could prevent the little ACh that is circulating from activating the stabilizing effort of the PNS. If PAMP and cortisol bind with mAChRs in the PNS, then tonic immobility and analgesia are turned "off."

8. Conclusions

8.1. Chronic pain and somatic symptom sufferers

PD, FSD, and SSD patients experience a great deal of suffering and sometimes face huge costs for treatments and medications. They stand to lose functional ability at work, in relationships, and socially.[2,118-120] They are often told their symptoms have no clear explanation or origin, which is frightening or frustrating. Many patients feel their needs are not being served well by either medical doctors or mental health clinicians. In fact, only about 25% of patients with SSD ever seek psychotherapy, in part due to stigma.[121] Worse, without clear knowledge of underlying pathogenesis, their health providers may suggest inappropriate, ineffective, or even harmful treatments for the disorders. Pointedly, many treatment methods have been unsuccessful and PD/FSD patients are sometimes blamed for their lack of progress.[119] Dr. Jeffrey Staab of Minnesota's Mayo Clinic was a researcher involved in the field trials for the diagnostic criteria for SSD, and he acknowledged:

"Most psychiatrists assume that some sort of trauma, tragedy or conflict in the past is driving health-anxious fears and behaviors. Moreover, if we can't find it, and the patient can't find it, it can become a speculative wild goose chase for trauma. Trauma is more likely in these patients, but if we don't find a history of trauma, we can look at stress, and if we don't find that, we can still talk about exaggerated preoccupations with health and help patients reset and reframe that without digging around in the past."[122]

T-A-P theory posits not a completely new idea – the body keeps the score – but it is the first to delineate a neuroendocrinological sequelae between dissociative amnesia and SSD. In 2021, when looking at future directions, Mueller *et al.*[82] called for an answer to the question "does the hippocampus provide the anatomical substrate for the link between disorders of central inflammation, dysautonomia, and a dysregulated HPA axis?" T-A-P theory answers their question with a thorough map of the defense cascade that initiates and maintains SSD, locking trauma into the body for many patients. Importantly, the theory argues that somatic and emotional memory is what is persistently re-experienced in SSD, a parallel process to PTSD patients' persistent remembering of their trauma. The hippocampus' autobiographical memory is shut down by hypercortisol during traumatic amnesia, but amygdala-based memory, motor memory, and somatosensory memory systems are enhanced or unaffected by hypercortisol, encoding the trauma. When internal and external reminders or cues of the trauma occur, in the same way they frequently do with PTSD patients, SSD patients' neurochemistry is triggered into SNS activation without PNS deactivation, leading to unexplained pain and other neurological or somatic symptoms. Somatic symptoms could be considered flashbacks and treated as such in many patients. The defense cascade travels familiar neurological pathways to old injury sites or previously diagnosed medical problems (also known as "priors"), and sends signals there, or interprets signals from there, saying, "something is wrong. I still hurt!" The true message from the body may be, "something bad happened; you don't remember it; pain is our only voice to say the world is not safe; you may be under attack at any moment!" Relatedly, catastrophizing and alexithymia are primary traits associated with SSD.[123] Patients cannot voice how they feel, or it is greatly reduced

compared to normal controls, but they overvalue body messages.[3]

8.2. T-A-P model

Figure 3 displays a diagram that summarizes the T-A-P pathway. Cortisol plays the primary role in explaining how traumatic amnesia leads to PD/FSDs. Cortisol interrupts the action of ACh on nAChRs in the hippocampus, preventing declarative memory for trauma, but facilitating procedural memory for trauma in the amygdala. PAMP has fast access to hippocampal nAChRs since it is co-secreted with catecholamines before CRH and ACTH are secreted to trigger cortisol release. Elevated catecholamine secretion leads to elevated PAMP co-secretion, further preventing ACh binding with nAChRs in the hippocampus – augmenting amnesia. In the spinal dorsal root horn, PAMP competes with ACh to bind with mAChRs and competes with endorphins to bind with $MrgX_2$ receptors – augmenting and sustaining pain perception. Hypercortisol prevents tonic immobility and triggers prolonged activation of the SNS by depotentiating ACh in the spinal dorsal horn, and by increasing acetylcholinesterase which degrades ACh in the synaptic cleft there. Hypercortisol also prevents downregulation of the sympathetic response when it steroidally depotentiates ACh at nAChRs and increases acetylcholinesterase synthesis and activity in the PNS.

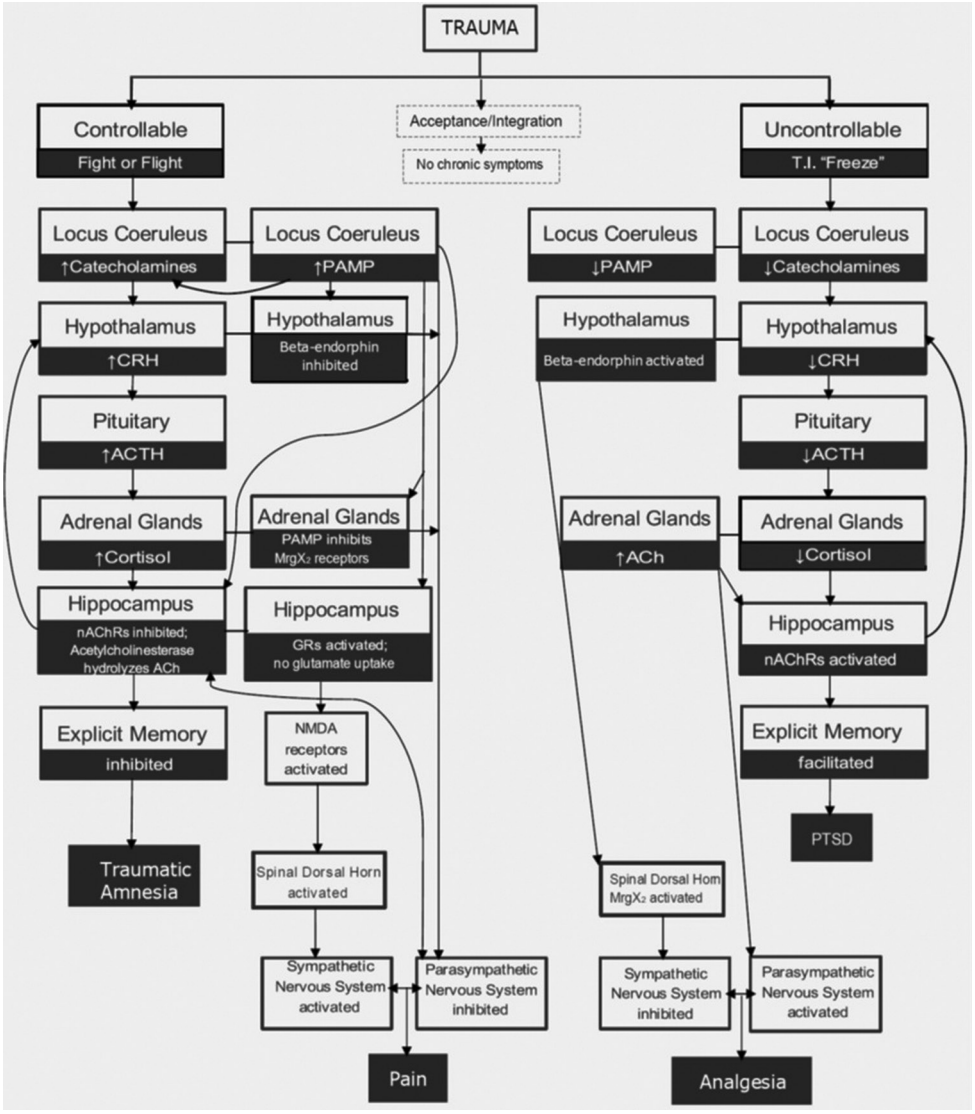

Figure 3. Trauma-amnesia-pain flow chart

Abbreviations: ACh: Acetylcholine; ACTH: Adrenocorticotropin hormone; CRH: Corticotropin-releasing hormone/factor; GRs: Glutamate receptors; nAChRs: Nicotinic acetylcholine receptors; NMDA: N-methyl-D-aspartic acid; PAMP: Proadrenomedullin N terminal-20; PTSD: Post-traumatic stress disorder; T.I.: Tonic immobility.

This novel conceptualization of the etiology of traumatic amnesia and SSD also explains why SSD is comorbid with dissociative amnesia. The findings are based on a large body of neurological, physiological, and clinical research, which converges to conclude that hypercortisol and peritraumatic perception of control are key factors in both disorders. The shared etiology of PD, somatization disorder, and FSD also legitimizes the DSM-5-TR move to unify the disorders under one umbrella, SSD. Considered as a whole for the 1st time, this comprehensive review provides definitive evidence that how trauma is perceived is the linchpin that explains the dose-dependent effects of cortisol (and its co-contributors, acetylcholinesterase, and PAMP) on both memory and somatic symptoms. It appears that traumatic amnesia affords individuals protection from excessive fear, anxiety, and intrusive explicit memories. However, the by-product of this escape route is either pain, extra sensitivity to pain, or unpleasant somatic symptoms.[3] Sufferers of dissociative amnesia and patients with SSD deserve a better understanding of their symptoms and challenges. T-A-P theory predicted what Vinkers' research found with the NESDA cohort: Remembered childhood trauma does not lead directly to dysregulations of the HPA axis and autonomic nervous system.[124] The people not captured in Vinkers' study were those who do not remember childhood trauma, yet are much more likely to experience HPA and PNS dysregulation. By taking into account the perception of trauma and its underlying neuroendocrinological processes, we will drive more effective clinical treatment methods and appropriate pharmacological interventions.

9. Recommendations

When screening for SSD, clinicians need to also screen for dissociative amnesia. If a history of cumulative traumatic effects, especially emotional abuse or sexual abuse can be informed by family or other sources, clinicians must treat underlying trauma alongside somatic symptoms. Cognitive-behavioral treatment strategies have shown some effectiveness with PD, SSD, and FSDs, such as fibromyalgia, chronic back pain, and irritable bowel syndrome.[1,11] As an adjunct to the core cognitive-behavioral strategies, clinicians can monitor whether patient pain experience is maintained by regular internal "procedural memory" triggers and intervene with each trigger either through avoidance, system-calming techniques, or experience validation and normalization.[1,125] We know memory is retrieved and influenced by pre-existing beliefs, expectations, and knowledge, but it is also influenced by the context of retrieval.[49,52] Recognition that SSD patients may have procedural memory fragments (well-preserved in the amygdala) that trigger elevated HPA axis responses, may assist clinicians in helping patients manage or prevent ongoing pain.[29,32,33,102,125] This type of experience has been termed a "body-loop feedback" for pain, or "top-down" pain signals by some authors,[1,11,47] and may be likened to a type of repetitive re-experiencing of the trauma, as in PTSD, but through the procedural memory systems. For the T-A-P theory to be fully substantiated, not only replication of some of the animal studies is needed, but human studies that control for peritraumatic perception are also required. The inclusion of amnestic trauma victims in clinical samples is a must.

Future studies should validate the T-A-P pathway using consistent glucocorticoid (cortisol) measurement, especially reporting and standardization of "high" versus "low" glucocorticoid amounts. Future research should also focus on determining how much predictive influence acetylcholinesterase and PAMP have relative to cortisol in the T-A-P pathway in both animal and human trials. Furthermore, future studies need to address the other two primary causes of SSD, reinforcement learning of the sick role due to social acceptability, and biological sensitivity to pain. Both of these conceivably strengthen T-A-P connections, but how so remains to be discovered. Furthermore, prevention and intervention with these factors were beyond the scope of this paper.

Treatment should explore the use of new pharmacotherapy options in SSD intervention, in light of research presented here regarding the neurochemicals and receptors involved in SSD. The effectiveness of nAChR agonists in the treatment of both neuropathic and psychogenic pain is emerging. In the same way that ACh—nAChR agonist – is the mind's natural way to enhance memory and provide analgesia, other nAChR agonists have shown initial effectiveness in treating pain. The effectiveness and lack of side effects of nAChR and mAChR agonists, such as acetyl-L-carnitine (ALCAR) and ABT-594, an epibatidine analog, has been established in the treatment of pain in animal models.[126,127] Future research with humans is needed and will contribute to further validation of the T-A-P connection. nAChR antagonists such as MK-801, atropine – and its isomers scopolamine and hyoscyamine – have also been used as pain relievers under the suspicion that an endogenous nAChR antagonist (like PAMP) was the primary culprit in displacing ACh and triggering pain.[128] Interestingly, the newest nAChR α9/10-specific antagonists RgIA and Vc1.1, are showing potential as analgesics,[102,129,130] and PAMP shares an exact protein match with nACh α9/10 receptor subtypes.

Acetylcholinesterase inhibitors like neostigmine have also been tested as possible analgesics (assuming acetylcholinesterase is the primary culprit in degrading

and preventing ACh from providing pain relief), but to be effective, it must be a high dose. Unfortunately, high doses come with dangerous side effects, such as respiratory failure.[102] Finally, research indicates that when combined with opioid drugs, nAChR agonists increase pain relief,[100,131] which is useful for patients who use opioids to manage pain, but must carefully avoid addiction and overdose. In contrast, nAChR agonists are not known to be addictive, so they should be explored more thoroughly.[130]

Finally, as mentioned earlier in this review, Zohar *et al.*'s study[61] provides hope that traumatic amnesia and SSD could be prevented altogether. In the same way that high doses of glucocorticoids have successfully prevented PTSD; traumatic amnesia and some SSD should be preventable by reducing glucocorticoids within 72 h post-trauma. It is concerning that little discussion of Zohar *et al.*'s study, or widespread implementation of their results, has occurred in the past 10 years. Another candidate for trauma intervention is neuropeptide Y, which calms the SNS and prevents PTSD, providing yet more validation of the link between memory and somatization. Neuropeptide Y has three benefits: (i) it can be taken nasally; (ii) it is safe at fairly high doses; and (iii) it prevents PTSD even if administered 1 week after trauma exposure.[132] We must take advantage of this current knowledge to offer victims of trauma to measure and regulate their cortisol output, up- or down-regulate glucocorticoids, or possibly take neuropeptide Y, and thereby prevent either amnesia and pain or PTSD. It is recommended that human trials continue until FDA approval is granted. In cases where prevention is not possible, pharmacological interventions with SSD and FSD need to consider nAChR agonists, acetylcholinesterase antagonists, and anti-adrenergic beta blockers.

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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: American Psychiatric Publishing; 2022.

   doi: 10.1176/appi.books.9780890425787

2. Eilers H, Aan Het Rot M, Jeronimus BF. Childhood trauma and adult somatic symptoms. *Psychosom Med.* 2023;85:408-416.

   doi: 10.1097/PSY.0000000000001208

3. Löwe B, Toussaint A, Rosmalen JG, *et al*. Persistent physical symptoms: Definition, genesis, and management. *Lancet*. 2024;403(10444):2649-2662.

   doi: 10.1016/S0140-6736(24)00623-8

4. Fink P, Schröder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. J *Psychosom Res.* 2011;68(5):415-426.

   doi: 10.1016/j.jpsychores.2010.02.004

5. Hiller W, Heuser J, Fichter MM. The DSM-IV nosology of chronic pain: A comparison of pain disorder and multiple somatization syndrome. *Eur J Pain.* 2000;4:45-55.

   doi: 10.1053/eujp.1999.0155

6. Kanaan RAA, Lepine JP, Wessely SC. The association or otherwise of the functional somatic syndromes. *Psychosom Med*. 2007;69:855-859.

   doi: 10.1097/PSY.0b013e31815b001a

7. van der Kolk BA. *The Body Keeps the Score: Brain, Mind, and Body in the Healing of Trauma.* New York: Penguin Books; 2014.

8. Bovin MJ, Marx B. The importance of the peritraumatic experience in defining traumatic stress. *Psychol Bull*. 2011;137(1):47-67.

   doi: 10.1037/a0021353

9. Foa EB, Zinbarg R, Rothbaum BO. Uncontrollability and unpredictability in post-traumatic stress disorder: An animal model. *Psychol Bull.* 1992;112:218-238.

   doi: 10.1037/0033-2909.112.2.218

10. Olff M, Langeland W, Gersons BPR. Effects of appraisal and coping on the neuroendocrine response to extreme stress. *Neurosci Biobehav Rev.* 2005;29:457-467.

    doi: 10.1016/j.neubiorev.2004.12.006

11. Mayer EA, Bushnell MC. Synthesis. In: Mayer EA, Bushnell MC, editors. *Functional Pain Syndromes:*

Presentation and Pathophysiology. Washington DC: IASP Press; 2009. p. 531-565.

12. McNally RJ. The science and folklore of traumatic amnesia. *Clin Psychol Sci Pract*. 2004;11(1):29-33.

    doi: 10.1093/clipsy.bph056

13. Bremner JD, Marmar CR, editors. *Trauma, Memory, and Dissociation*. Washington, DC: American Psychiatric Press; 1998.

14. Brewin CR. Autobiographical memory for trauma: Update on four controversies. *Memory*. 2007;15(3):227-248.

    doi: 10.1080/09658210701256423

15. Joseph R. Traumatic amnesia, repression, and hippocampus injury due to emotional stress, corticosteroids and enkephalins. *Child Psychiatry Hum Dev*. 1998;29(2):169-185.

    doi: 10.1023/A:1025092117657

16. Gaensbauer TJ. Representations of trauma in infancy: Clinical and theoretical implications for the understanding of early memory. *Infant Ment Health J*. 2002;23(3):259-277.

    doi: 10.1002/imhj.10020

17. Gazzaniga MS, Ivry RB, Mangun GR. *Cognitive Neuroscience: The Biology of the Mind*. New York: Norton; 2002.

18. Jacobs WJ, Nadel L. Neurobiology of reconstructed memory. *Psychol Public Policy Law*. 1998;4(4):1110-1134.

    doi: 10.1037/1076-8971.4.4.1110

19. Mancia M. Implicit memory and unrepressed unconscious. In: Mancia M, editor. *Psychoanalysis and Neuroscience*. Milan, Italy: Springer; 2006. p. 97-123.

20. Nissen MJ, Knopman DS, Schacter DL. Neurochemical dissociation of memory systems. *Neurology*. 1987;37:789-794.

    doi: 10.1212/WNL.37.5.789

21. Tulving E. Multiple memory systems and consciousness. *Hum Neurobiol*. 1987;5:57-80.

22. Alexander KW, Quas JA, Goodman GS, *et al*. Traumatic impact predicts long-term memory for documented child sexual abuse. *Psychol Sci*. 2005;16:33-40.

    doi: 10.1111/j.0956-7976.2005.00777.x

23. Bremner JD. The neurobiology of trauma and memory in children. In: Howe ML, Goodman GS, Cichetti D, editors. *Stress, Trauma, and Children's Memory Development: Neurobiological, Cognitive, Clinical, and Legal Perspectives*. New York: Oxford University Press; 2008. p. 11-49.

24. Brewerton TD, Dansky BS, Kilpatrick DG, O'Neil PM. Bulimia nervosa, PTSD, and forgetting: Results from the national women's study. In: Williams LM, Banyard VL, editors. *Trauma and Memory*. Thousand Oaks, CA: Sage Publications; 1999. p. 127-138.

25. Delahanty DL, Glover D, Golier J. Neurobiology of memory and dissociation in trauma survivors. *Ann N Y Acad Sci*. 2004;1032:183-185.

    doi: 10.1196/annals.1314.016

26. Goodman GS, Ghetti S, Quas JA, *et al*. A prospective study of memory for child sexual abuse: New findings relevant to the repressed-memory controversy. *Psychol Sci*. 2003;14:113-118.

    doi: 10.1111/1467-9280.01428

27. Widom CS, Morris S. Accuracy of adult recollections of childhood victimization, Part 2: Childhood sexual abuse. *Psychol Assess*. 1997;9:34-46.

    doi: 10.1037/1040-3590.9.1.34

28. Williams LM. Recall of childhood trauma: A prospective study of women's memories of child sexual abuse. *J Consult Clin Psychol*. 1994;62:1167-1176.

    doi: 10.1037/0022-006X.62.6.1167

29. Alpert JL, Brown LS, Courtois CA. Symptomatic clients and memories of childhood abuse: What the trauma and child sexual abuse literature tells us. *Psychol Public Policy Law*. 1998;4(4):941-995.

    doi: 10.1037/1076-8971.4.4.941

30. Fredrickson R. *Repressed Memories: A Journey of Recovery from Sexual Abuse*. New York: Simon and Schuster; 1992.

31. Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P. Trauma and posttraumatic stress disorder in the community: The 1996 Detroit area survey of trauma. *Arch Gen Psychiatry*. 1998;55(7):626-632.

    doi: 10.1001/archpsyc.55.7.626

32. Freyd JJ. *Betrayal Trauma: The Logic of Forgetting Childhood Abuse*. Cambridge, MA: Harvard University Press; 1997.

33. Herman JL. *Trauma and Recovery*. New York: Basic Books; 1992.

34. Lima AA, Fiszman A, Marques-Portella C, *et al*. The impact of tonic immobility reaction on the prognosis of posttraumatic stress disorder. *J Psychiatr Res*. 2010;44(4):224-228.

    doi: 10.1016/j.jpsychires.2009.08.005

35. Rocha-Rego V, Fiszman A, Portugal LC, *et al*. Is tonic immobility the core sign among conventional peritraumatic signs and symptoms listed for PTSD? *J Affect Disord*. 2009;115:269-273.

    doi: 10.1016/j.jad.2008.09.005

36. Bovin MJ, Jager-Hyman S, Gold SD, Marx BP, Sloan DM. Tonic immobility mediates the influence of peritraumatic fear and perceived inescapability on posttraumatic stress symptom severity among sexual assault survivors. *J Trauma Stress*. 2008;21:402-409.

    doi: 10.1002/jts.20354

37. Hagenaars MA, Putman P. Attentional control affects the relationship between tonic immobility and intrusive memories. *J Behav Ther Exp Psychiatry*. 2011;42:379-383.

    doi: 10.1016/j.jbtep.2011.02.013

38. Marx BP, Forsyth JP, Gallup GG, Fuse T, Lexington JM. Tonic immobility as an evolved predator defense: Implications for sexual assault survivors. *Clin Psychol Sci Pract*. 2008;15:74-90.

doi: 10.1111/j.1468-2850.2008.00112

39. Volchan E, Souza GG, Franklin CM, *et al*. Is there tonic immobility in humans? Biological evidence from victims of traumatic stress. *Biol Psychol*. 2011;88:13-19.

doi: 10.1016/j.biopsycho.2011.06.002

40. Van der Kolk BA, Greenberg MS, Orr SE, Pitman RK. Endogenous opioids, stress induced analgesia, and posttraumatic stress disorder. *Psychopharmacol Bull*. 1989;25:417-422.

41. Nijenhuis ER, Spinhoven P, van Dyck R, van der Hart O, Vanderlinden J. Degree of somatoform and psychological dissociation in dissociative disorder is correlated with reported trauma. *J Trauma Stress*. 1998;11:711-730.

doi: 10.1023/A:1024493332751

42. Sijbrandij M, Engelhard IM, Opmeer BC, *et al*. The structure of peritraumatic dissociation: A cross validation in clinical and nonclinical samples. *J Trauma Stress*. 2012;25(4):475-479.

doi: 10.1002/jts.21716

43. Werner KB, Griffin MG. Peritraumatic and persistent dissociation as predictors of PTSD symptoms in a female cohort. *J Trauma Stress*. 2012;25:401-407.

doi: 10.1002/jts.21725

44. Delahanty DL, Royer DK, Raimonde AJ, Spoonster E. Peritraumatic dissociation is inversely related to catecholamine levels in initial urine samples of motor vehicle accident victims. *J Trauma Dissociation*. 2003;4(1):65-80.

doi: 10.1300/J229v04n01_05

45. Mobbs D, Marchant JL, Hassabis D, *et al*. From threat to fear: The neural organization of defensive fear systems in humans. *J Neurosci*. 2009;29(39):12236-12243.

doi: 10.1523/jneurosci.2378-09.2009

46. Drugan RC. Coping with traumatic stress interferes with memory for the event. In: Williams LM, Banyard VL, editors. *Trauma and Memory*. Thousand Oaks, CA: Sage Publications; 1999. p. 245-256.

47. Janig W. Autonomic nervous system dysfunction. In: Mayer EA, Bushnell MC, editorss. *Functional Pain Syndromes: Presentation and Pathophysiology*. Seattle, WA: IASP Press; 2009. p. 265-300.

48. Navalta CP, Tomoda A, Teicher MH. Trajectories of neurobehavioral development: The clinical neuroscience of child abuse. In: Howe MLG, Cichetti D, editors. *Stress, Trauma, and Children's Memory Development: Neurobiological, Cognitive, Clinical, and Legal Perspectives*. Oxford: Oxford University Press; 2008. p. 50-82.

49. Schacter DL, Koutstaal W, Norman KA. Can cognitive neuroscience illuminate the nature of traumatic childhood memories? In: Williams LM, Banyard VL, editors. *Trauma and Memory*. United States: Sage Publications; 1999. p. 257-269.

50. Delahanty DL, Herberman HB, Craig KJ, *et al*. Acute and chronic distress and posstraumatic stress disorder as a function of responsibility for serious motor vehicle accidents. *J Consult Clin Psychol*. 1997;65(4):560-567.

doi: 10.1037/0022-006x.65.4.560

51. Delahanty DL, Raimonde AJ, Spoonster E. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. *Biol Psychiatry*. 2000;48:940-947.

doi: 10.1016/S0006-3223(00)00896-9

52. Payne JD, Jackson ED, Hoscheidt S, Ryan L, Jacobs WJ, Nadel L. Stress administered prior to encoding impairs neutral but enhances emotional long-term episodic memories. *Learn Mem*. 2007;14:861-868.

doi: 10.1101/lm.743507

53. Cianciulli C. *Declarative Memory, Cortisol Reactivity, and Psychological Symptoms in Chronically Abused Girls*. Dissertation. United States: University of Massachusetts-Amherst; 2000.

54. McEwen BS. Plasticity of the hippocampus: Adaptation to chronic stress and allostatic load. *Ann N Y Acad Sci*. 2001;933:265-277.

doi: 10.1111/j.1749-6632.2001.tb05830

55. O'Donnell TM. *CRH and AVP in Depressed Women with and Without Histories of Interpersonal Trauma*. Dissertation. Canada: University of Alberta-Edmonton; 2009.

56. Schelling G. Effects of stress hormones on traumatic memory formation and the development of posttraumatic stress disorder in critically ill patients. *Neurobiol Learn Mem*. 2002;78(3):596-609.

doi: 10.1006/nlme.2002.4083

57. Schelling G, Roozendaal B, de Quervain DJF. Can posttraumatic stress disorder be prevented with glucocorticoids? *Ann N Y Acad Sci*. 2004;1032:158-166.

doi: 10.1196/annals.1314.013

58. Soravia LM, de Quervain DJ, Heinrichs M. Glucocorticoids do not reduce subjective fear in healthy subjects exposed to social stress. *Biol Psychol*. 2009;81(3):184-188.

doi: 10.1016/j.biopsycho.2009.04.001

59. Alexander JK, DeVries AC, Kigerl KA, Dahlman JM, Popovich PG. Stress exacerbates neuropathic pain via glucocorticoid and NMDA receptor activation. *Brain Behav Immun*. 2009;23(6):851-860.

doi: 10.1016/j.bbi.2009.04.001

60. Wahbeh H, Oken BS. Salivary cortisol lower in posttraumatic

stress disorder. *J Trauma Stress*. 2013;26(2):241-248.

doi: 10.1002/jts.21798

61. Zohar J, Yahalom H, Kozlovsky N, *et al*. High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: Interplay between clinical and animal studies. *Eur Neuropsychopharmacol*. 2011;21(11):796-809.

doi: 10.1016/j.euroneuro.2011.06.001

62. Andreano JM, Cahill L. Glucocorticoid release and memory consolidation in men and women. *Psychol Sci*. 2006;17(6):466-470.

doi: 10.1111/j.1467-9280.2006.01729.x

63. Korel DL, Gold PE. Modulation of learning and memory by adrenal and ovarian hormones. In: Kesner RP, Martinez JL Jr., editors. *Neurobiol Learn Mem*. 2nd ed. Burlington, MA: Academic Press; 2007. p. 621.

64. McCleery JM, Harvey AG. Integration of psychological and biological approaches to trauma memory: Implications for pharmacological prevention of PTSD. *J Trauma Stress*. 2004;17(6):485-496.

doi: 10.1007/s10960-004-5797-5

65. Qiu GL, Peng LJ, Wang P, *et al*. *In vivo* imaging reveals a synchronized correlation among neurotransmitter dynamics during propofol and sevoflurane anesthesia. *Zool Res*. 2024;45(3):679-690.

doi: 10.24272/j.issn.2095-8137.2023.302

66. Souza da Silva LF, Menescal-de-Oliveira L. Cholinergic modulation of tonic immobility and nociception in the NRM of guinea pig. *Physiol Behav*. 2006;87:821-827.

doi: 10.1016/j.physbeh.2006.01.019

67. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res*. 2002;53(4):865-871.

doi: 10.1016/S0022-3999(02)00429-4

68. Girdler SS, Maixner W, Naftel HA, Stewart PW, Moretz RL, Light KC. Cigarette smoking, stress-induced analgesia and pain perception in men and women. *Pain*. 2005;114(3):372-385.

doi: 10.1016/j.pain.2004.12.035

69. Pinto-Ribeiro F, Almeida A, Pego JM, Cerqueira J, Sousa N. Chronic unpredictable stress inhibits nociception in male rats. *Neurosci Lett*. 2004;359:73-76.

doi: 10.1016/j.neulet.2004.02.016

70. Pinto-Ribeiro F, Moreira V, Pego JM, Leão P, Almeida A, Sousa N. Antinociception induced by chronic glucocorticoid treatment is correlated to local modulation of spinal neurotransmitter content. *Mol Pain*. 2009;5(24):41.

doi: 10.1186/1744-8069-5-41

71. Tak LM, Rosmalen JGM. Psychoneuroendocrinology of functional somatic disorders. In: Czerbska MT, editor. *Psychoneuroendocrinology Research Trends*. Waltham, MA: Nova Biomedical Books; 2007. p. 463-495.

72. Uki M, Nabekura J, Akaike N. Suppression of the nicotinic acetylcholine response in rat superior cervical ganglionic neurons by steroids. *J Neurochem*. 1999;72(2):808-814.

doi: 10.1046/j.1471-4159.1999.0720808

73. Drugan RC, Ader DN, Maier SF. Shock controllability and the nature of stress-induced analgesia. *Behav Neurosci*. 1985;99(5):791-801.

doi: 10.1037/0735-7044.99.5.791

74. Leite-Panissi CRA, Rodrigues CL, Brentegani MR, Menescal-de-Oliveira L. Endogenous opiate analgesia induced by tonic immobility in guinea pigs. *Braz J Med Biol Res*. 2001;34:245-250.

doi: 10.1590/S0100-879X2001000200013

75. Drugan RC, Basile AS, Ha JH, Ferland R. The protective effects of stress control may be mediated by increased brain levels of benzodiazepine receptor agonists. *Brain Res*. 1994;661:127-136.

doi: 10.1016/0006-8993(94)91189-4

76. Drugan RC, Basile AS, Ha JH, Healy D, Ferland RJ. Analysis of the importance of controllable versus uncontrollable stress on subsequent behavioral and physiological functioning. *Brain Res Brain Res Protoc*. 1997;2:69-74.

doi: 10.1016/S1385-299X(97)00031-7

77. Bhatnagar S, Shanks N, Meaney MJ. Plaque-forming cell responses and antibody titers following injection of sheep red blood cells in nonstressed, acute, and/or chronically stressed handled and nonhandled animals. *Dev Psychobiol*. 1996;29:171-181.

doi: 10.1002/(SICI)1098-2302(199603)29:2<171:AID-DEV6>3.0.CO;2-P

78. Valet M, Gundel H, Sprenger T, *et al*. Patients with pain disorder show gray-matter loss in pain-processing structures: A voxel-based morphometric study. *Psychosom Med*. 2009;71:49-56.

doi: 10.1097/PSY.0b013e31818d1e02

79. Heim C, Ehlert U, Hanker JP, Hellhammer DH. Psychological and endocrine correlates of chronic pelvic pain associated with adhesions. *J Psychosom Obstet Gynecol*. 1999;20(1):11-20.

doi: 10.3109/01674829909075572

80. Herman JP, McKlveen JM, Ghosal S, *et al*. Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr Physiol*. 2016;6(2):603-621.

doi: 10.1002/cphy.c150015

81. Roozendaal B, Schelling G, McGaugh JL. Corticotropin-releasing factor in the basolateral amygdala enhances memory consolidation via an interaction with the Beta-adrenoceptor-

cAMP pathway: Dependence on glucocorticoid receptor activation. *J Neurosci*. 2008;28(26):6642-6651.

doi: 10.1523/jneurosci.1336-08.2008

82. Mueller B, Figueroa A, Robinson-Papp J. Structural and functional connections between the autonomic nervous system, hypothalamic-pituitary-adrenal axis, and the immune system: A context and time dependent stress response network. *Neurol Sci*. 2022;43(2):951-960.

doi: 10.1007/s10072-021-05810-1

83. Nemeroff CB, Vale WW. The neurobiology of depression: Inroads to treatment and new drug discovery. *J Clin Psychiatry*. 2005;66(Suppl 7):5-13.

84. Kamohara M, Matsuo A, Takasaki J, *et al*. Identification of MrgX2 as a human G-protein-coupled receptor for proadrenomedullin N-terminal peptides. *Biochem Biophys Res Commun*. 2005;330:1146-1152.

doi: 10.1016/j.bbrc.2005.03.0888

85. Katoh F, Kitamura K, Niina H, *et al*. Proadrenomedullin N-terminal 20 peptide (PAMP), an endogenous anticholinergic peptide: Its exocytotic secretion and inhibition of catecholamine secretion in adrenal medulla. *J Neurochem*. 1995;64:459-461.

doi: 10.1046/j.1471-4159.1995.64010459.x

86. Masada K, Nagayama T, Hosokawa A, *et al*. Effects of adrenomedullin and PAMP on adrenal catecholamine release in dogs. *Am J Physiol Regul*. 1999;276(4):R1118-R1124.

doi: 10.1152/ajpregu.1999.276.4.R1118

87. Travers S, Martinerie L, Xue QY, *et al*. Adrenomedullin: New inhibitory regulator for cortisol synthesis and secretion. *J Endocrinol*. 2021;251(1):97-109.

doi: 10.1530/JOE-20-0564

88. Strohle A, Holsboer F. Stress responsive neurohormones in depression and anxiety. In: Kasper S, den Loer JA, Sitsen JAM, editors. *Handbook of Depression and Anxiety: A Biological Approach*. United States: CRC Press; 2003. p. 207-228.

89. Vinkers CH, Kuzminskaite E, Lamers F, Giltay EJ, Penninx B. An integrated approach to understand biological stress system dysregulation across depressive and anxiety disorders. *J Affect Disord*. 2021;283:139-146.

doi: 10.1016/j.jad.2021.01.051

90. Hasselmo ME, Wyble BP. Free recall and recognition in a network model of the hippocampus: Simulating effects of scopolamine on human memory function. *Behav Brain Res*. 1997;89:1-34.

doi: 10.1016/S0166-4328(97)00048-x

91. Sabban EL, Serova L, Nahvi RJ, Liu X. Potential benefits of intranasal neuropeptide Y include sustained extinction of fear memory. *J Neuroendocrinol*. 2023;35(11):e13279.

doi: 10.1111/jne.13279

92. Hasselmo ME, Wyble BP, Wallenstein GV. Encoding and retrieval of episodic memories: Role of cholinergic and GABAergic modulation in the hippocampus. *Hippocampus*. 1996;6:693-708.

doi: 10.1002/(SICI)1098-1063(1996)6:6<693:AID-HIPO12>3.0.CO;2-W

93. Buhlman LM. *Heterologous Expression of Alpha6*Nicotinic Acetylcholine Receptors and the Natural Distribution of Alpha6 Subunits*. Dissertation. United States: University of Arizona; 2007.

94. Nabekura J, Murata O, Ishibashi H, Akaike N. Use-dependent suppression of the nicotinic acetylcholine receptor response by the proadrenomedullin N-terminal 20-amino acid peptide in rat locus coeruleus neurons. *J Neurochem*. 1998;70:865-870.

doi: 10.1046/j.1471-4159.1998.70020865.x

95. Takano K, Yamashita N, Fujita T. Proadrenomedullin NH2-terminal 20 peptide inhibits the voltage-gated $Ca2^{+}$ channel current through a pertussis toxin-sensitive G protein in rat pheochromocytoma-derived PC 12 cells. *J Clin Invest*. 1996;98(1):14-17.

doi: 10.1172/JCI118758

96. Hardman JG, Limbird PB, Gilman AG, editors. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill; 2001.

97. Iwasaki H, Hirata Y, Iwashina M, Sato K, Marumo F. Specific binding sites for proadrenomedullin N-terminal 20 peptide (PAMP) in the rat. *Endocrinology*. 1996;137(7):3045-3050.

doi: 10.1210/en.137.7.3045

98. Li GZ, Liang QC, Jin YH, *et al*. The effect of acetylcholine on pain-related electric activities in the hippocampal CA3 of rats. *J Neural Transm* (*Vienna*). 2011;118(4):555-561.

doi: 10.1007/s00702-010-0545

99. Wenk GL. Neurodegenerative diseases and memory: A treatment approach. In: Kesner RP, Martinez JL Jr., editors. *Neurobiology of Learning and Memory*. 2nd ed. Burlington, MA: Academic Press; 2007. p. 621.

100. Meldrum BS. Glutamate as a neurotransmitter in the brain: Review of physiology and pathology. *J Nutr*. 2000;130:1007S-1015S.

doi: 10.1093/jn/130.4.1007S

101. Rousseaux CG. A review of glutamate receptors II: Pathophysiology and pathology. *J Toxicol Pathol*. 2008;21(3):133-173.

doi: 10.1293/tox.21.133

102. Jones PG, Dunlop J. Targeting the cholinergic system as a therapeutic strategy for the treatment of pain. *Neuropharmacology*. 2007;53:197-206.

doi: 10.1016/j.neuropharm.2007.04.002

103. Sveinsdottir V, Eriksen HR, Ursin H, Hansen ÅM, Harris A. Cortisol, health, and coping in patients with nonspecific low back pain. *Appl Psychophysiol Biofeedback*. 2016;41:9-16.

doi: 10.1007/s10484-015-9300-2

104. Ofek K, Krabbe KS, Evron T, *et al*. Cholinergic status modulations in human volunteers under acute inflammation. *J Mol Med* (*Berl*). 2007;85(11):1239-1251.

doi: 10.1007/s00109-007-0226

105. Zimmerman G, Soreq H. Termination and beyond: Acetylcholinesterase as a modulator of synaptic transmission. *Cell Tissue Res*. 2006;326:655-669.

doi: 10.1007/s00441-006-0239-8

106. Das A, Rai D, Dikshit M, Palit G, Nath C. Nature of stress: Differential effects on brain acetylcholinesterase activity and memory in rats. *Life Sci*. 2005;77(18):2299-2311.

doi: 10.1006/phrs.2000.0678

107. Gabriel NN, Soliman KFA. Effect of stress on the acetylcholinesterase activity of the hypothalamus-pituitary-adrenal axis in the rat. *Horm Res*. 1983;17:43-48.

doi: 10.1159/000179673

108. Sailaja BS, Cohen-Carmona D, Zimmerman G, Soreq H, Meshorer E. Stress-induced epigenetic transcriptional memory of acetylcholinesterase by HDAC4. *Proc Natl Acad Sci U S A*. 2012;109(52):E3687-E3695.

doi: 10.1073/pnas.1209990110

109. Tagliari B, Tagliari AP, Schmitz F, da Cunha AA, Dalmaz C, Wyse AT. Chronic variable stress alters inflammatory and cholinergic parameters in hippocampus of rats. *Neurochem Res*. 2011;36(3):487-493.

doi: 10.1007/s11064-010-0367-0

110. Grisaru D, Pick M, Perry C, *et al*. Hydrolytic and nonenzymatic functions of acetylcholinesterase comodulate hemopoietic stress responses. *J Immunol*. 2006;176:27-35.

doi: 10.4049/jimmunol.176.1.27

111. Marchi M, Bocchieri P, Garbarino L, Raiteri M. Muscarinic inhibition of endogenous glutamate release from rat hippocampus synaptosomes. *Neurosci Lett*. 1989;96(2):229-234.

doi: 10.1016/0304-3940(89)90063-3

112. Soreq H, Yirmiya R, Cohen O, Glick D. Acetylcholinesterase as a window onto stress responses. *Tech Behav Neural Sci*. 2005;15:585-608.

doi: 10.1016/s0921-0709(05)80032-x

113. National Institutes of Health. *Genbank Basic Local Alignment Search Tool*. Washington, DC: National Institutes of Health; 2013. Available from: https://blast.ncbi.nlm.nih.gov/blast.cgi [Last accessed on 2013 Jun 10].

114. Mir SA, Razzokov J, Mukherjee V, Baitharu I, Nayak, B. An exploration of the binding prediction of anatoxin-a and atropine to acetylcholinesterase enzyme using multi-level computer simulations. *Phys Biol*. 2023;21(1):016002.

doi: 10.1088/1478-3975/ad0caa

115. Dhume RA, Noronha A, Nagwekar MD, Mascarenhas JF. Effect of dorsal hippocampal lesion compared to dorsal hippocampal blockade by atropine on reference memory in vision deprived rats. *Indian J Med Res*. 1989;90:379-385.

116. National Institutes of Health. *Pubchem Acetylcholinesterase*. Washington, DC: National Institutes of Health; 2024. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/atropine [Last accessed on 2024 Sep 24].

117. Akuzawa N, Obinata H, Izumi T, Shigeki T. Morphine is an exogenous ligand for MrgX2, a G protein-coupled receptor for cortistatin. *J Cell Anim Biol*. 2007;2(1):4-9.

118. Arnold BS, Alpers GW, Sub H, *et al*. Affective pain modulation in fibromyalgia, somatoform pain disorder, back pain, and healthy controls. *Eur J Pain*. 2008;12:329-338.

doi: 10.1016/j.ejpain.2007.06.007

119. Mayer EA, Bushnell MC. Preface. In: Mayer EA, Bushnell MC, editors. *Functional Pain Syndromes: Presentation and Pathophysiology*. Washington, DC: IASP Press; 2009. p. xv-xviii.

120. Sarason IG, Sarason BR. *Abnormal Psychology: The Problem of Maladaptive Behavior*. 11th ed. Hoboken: Pearson Prentice Hall; 2005.

121. von dem Knesebeck O, Lehmann M, Löwe B, Lüdecke D. Causal attributions for somatic symptom disorder. *J Psychosom Res*. 2020;129:109910.

doi: 10.1016/j.jpsychores.2019.109910

122. National Institutes of Health. *DSM-5 Redefines Hypochondriasis*. Rochester, MN: Mayo Clinic; 2013. Available from: https://www.mayoclinic.org/documents/mc7900-0213-pdf/doc-20079285 [Last accessed on 2024 Sep 24].

123. Burba B, Oswald R, Grigaliunien V, Neverauskiene S, Jankuviene O, Chue P. A controlled study of alexithymia in adolescent patients with persistent somatoform pain disorder. *Can J Psychiatry*. 2006;51:468-471.

doi: 10.1177/070674370605100709

124. Kuzminskaite E, Vinkers CH, Elzinga BM, Wardenaar KJ, Giltay EJ, Penninx B. Childhood trauma and dysregulation of multiple biological stress systems in adulthood: Results from the Netherlands study of depression and anxiety (NESDA). *Psychoneuroendocrinology*. 2020;121:104835.

doi: 10.1016/j.psyneuen.2020.104835

125. Van der Kolk BA, van der Hart O. The intrusive past: The flexibility of memory and the engraving of trauma. *Am Imago*. 1991;48(4):425-454.

126. Bannon AW, Decker MW, Holladay MW, *et al*. Broad-spectrum, non-opioid analgesic activity by selective modulation of neuronal nicotinic acetylcholine receptors. *Science*. 1998;279:77-81.

doi: 10.1126/science.279.5347.77

127. Di Cesare Mannelli L, Ghelardini C, Calvani M, *et al*. Neuroprotective effects of acetyl-L-carnitine on neuropathic pain and apoptosis: A role for the nicotinic receptor. *J Neurosci Res*. 2009;87:200-207.

doi: 10.1002/jnr.21815

128. Coutinho MR, Menescal-de-Oliveira L. Role of homocysteic acid in the guinea pig (*Cavia porcellus*) anterior cingulate cortex in tonic immobility and the influence of NMDA receptors on the dorsal PAG. *Behav Brain Res*. 2010;208:237-242.

doi: 10.1016/j.bbr.2009.11.047

129. Vincler M, McIntosh JM. Targeting the alpha9alpha10 nicotinic acetylcholine receptor to treat severe pain. *Expert Opin Ther Targets*. 2007;11:891-897.

doi: 10.1517/14728222.11.7.891

130. Vincler M, Wittenaur S, Parker R, Ellison M, Olivera BM, McIntosh JM. Molecular mechanism for analgesia involving specific antagonism of alpha9alpha10 nicotinic acetylcholine receptors. *Proc Natl Acad Sci U S A*. 2006;103(47):17880-17884.

doi: 10.1073/pnas.0608715103

131. Amat J, Dolzani SD, Tilden S, *et al*. Previous ketamine produces an enduring blockade of neurochemical and behavioral effects of uncontrollable stress. *J Neurosci* 2016;36:153-161.

doi: 10.1523/JNEUROSCI.3114-15.2016

132. Nwokafor C, Serova LI, Sabban EL. Preclinical findings on the potential of intranasal neuropeptide Y for treating hyperarousal features of PTSD. *Ann N Y Acad Sci*. 2019;1455(1):149-159.

doi: 10.1111/nyas.14172

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REVIEW ARTICLE

The molecular basis of psychotherapy: Focus on BDNF in talking therapies

Zhi Xu[1], Yihan Yao[1], and Gavin P. Reynolds[2,3]*

[1]Department of Psychosomatics and Psychiatry, Zhongda Hospital, School of Medicine, Jiangsu Provincial Key Laboratory of Brain Science and Medicine, Southeast University, Nanjing, China

[2]Biomolecular Sciences Research Centre, Sheffield Hallam University, Sheffield, United Kingdom

[3]Rotherham, Doncaster and South Humber NHS Foundation Trust, Doncaster, United Kingdom

Abstract

Psychotherapy is effective in treating various types of mental disorders. However, the biological processes underlying its therapeutic efficacy in the relief of depression and anxiety remain unclear. An approach to investigating these therapeutic mechanisms derives from an understanding of disease pathogenesis, in which the dysfunction of brain-derived neurotrophic factor (BDNF) is strongly implicated. This study provides a review of various studies investigating the link between the efficacy of talking therapies in anxiety and depression and the measures of BDNF variability, the latter determined by plasma and serum BDNF concentrations, BDNF gene polymorphisms, and DNA methylation. Despite the few intriguing findings supporting the underlying hypothesis that reduced BDNF function results in poor response, many studies are limited by inadequate methodology and poor control of confounding factors. Thus, opportunities remain for further well-designed investigations, particularly utilizing the little-studied epigenetic factor of BDNF gene methylation.

Keywords: Psychotherapy; Brain-derived neurotrophic factor; Molecular mechanism; Depression; Anxiety

***Corresponding author:**
Gavin P. Reynolds
(Gavin.reynolds@shu.ac.uk)

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1. Introduction

Strong evidence shows that various psychotherapeutic approaches are effective in treating psychiatric disorders. Efficacy has been demonstrated in people with various anxiety states[1] as well as affective disorders[2] and psychoses.[3] A psychotherapeutic response is often seen in people not responding well to pharmacological interventions,[4] although the extent of symptom relief measured as percentage response is comparable between psychotherapeutic and pharmacotherapeutic responders.[5]

The mechanisms underlying the psychotherapeutic response remain unclear. Previous research has focused on interpreting responses in terms of psychological concepts rather than exploring the underlying molecular mechanisms. These non-biological, or at least non-molecular, processes invoked an understanding of psychotherapy outcomes often related to the therapeutic relationship in therapy.[6] In terms of psychosocial aspects, the factors addressed may include resilience, coping strategies, social support, and quality of life.[7] Yet the current biological interpretation of psychiatric disorders as brain dysfunction

implies that changes in neural processes with correlates, ultimately, in brain chemistry underlie the effects of any successful therapeutic intervention.

The increasing arsenal of molecular biological techniques developed over the past 60 years has only recently been applied to understanding the neuronal mechanisms of psychotherapy. These techniques have progressed from the assessing of neurotransmitters and other small molecules, through the determination of proteins both structural and functional, to the measurement of mRNA as an indicator of gene expression, as well as the identification of genetic and, most recently, epigenetic factors that might influence neuronal function. However, in the past few years, there has been an increasing recognition that these molecular approaches may be of value in understanding the processes underlying psychotherapies, often with the particular aim of identifying those individuals likely, or likely not, to respond to a particular treatment.

The targets for investigation of therapeutic mechanisms have often derived from current understanding of the molecular pathology of the relevant disease, in this context the most pertinent of which are anxiety and depression. The neurotransmitter dysfunction thought to be involved in some of the symptoms of these disorders, notably but not exclusively serotonin, provides a source for the development of hypotheses to study. Although important in pharmacotherapy, such neurotransmitter systems may not represent the primary pathology of mood disorders or explain the pathogenic mechanisms. Other substances fundamental to maintaining the structure and function of the healthy brain have attracted interest. One such molecule is the brain-derived neurotrophic factor (BDNF).

BDNF is a protein expressed in many organs of the body, including the brain, where it appears to play an essential role in the growth, maintenance, and survival of neurons through actions at its specific receptor TrkB.[8] Through these mechanisms, it is implicated in learning and memory processes and their associated dysfunction.[9] As such, it has been studied in various neurological and psychiatric diseases, ranging from Alzheimer's disease to schizophrenia, with numerous studies investigating its potential involvement in major depressive disorder (MDD)[10] and anxiety.[11]

Among the various ways of assessing BDNF function, two features have been particularly valuable in supporting research: a common functional polymorphism (rs6265; val66met) in *BDNF*[12] and the fact that BDNF is measurable in blood samples, both in low levels in the plasma and higher concentrations in the serum because it is released from platelet stores.[13] Other study targets related to BDNF activity include DNA methylation sites in *BDNF*, which may influence transcriptional activity,[14] as well as the downstream effectors of BDNF, specifically the TrkB receptor, which responds to BDNF activity and is considered a critical mediator of antidepressant and antianxiety effects.[15]

Each of these factors has been implicated in the brain dysfunction associated with both MDD[16,17] and anxiety disorders.[18,19] Furthermore, they have been investigated in relation to the response to antidepressant pharmacotherapy. This can increase BDNF in the blood (serum, plasma, and platelets) in patients with depression after treatment; however, differences in the response to antidepressant treatment are also associated with BDNF genotypes.[20]

This review and commentary aimed to assess the current status of research investigating the role of BDNF in the responses of people with anxiety and depression to psychotherapy. Both anxiety- and depression-like behaviors can be induced by chronic stress, which can also reduce BDNF levels.[21] Therefore, effective psychotherapy may also influence BDNF in conjunction with stress reduction, ameliorating the symptoms of depression and anxiety. Psychotherapeutic treatment covers a broad range of interventions; in this review, we will focus on talking therapies, of which cognitive behavioral therapy (CBT) is the most commonly studied. Other therapeutic interventions included are interpersonal, psychodynamic, and family therapies as well as meditation and mindfulness-based (MBCT) approaches. All relevant studies were indexed in PubMed and Web of Science before April 30, 2024. In total, 135 articles were retrieved with the search terms "BDNF CBT; BDNF psychotherapy; BDNF mindfulness therapy or meditation therapy; BDNF interpersonal therapy; BDNF methylation psychotherapy." We also reviewed the search terms "BDNF mindfulness meditation therapy, BDNF MBCT, BDNF psychodynamic psychotherapy" and found that they were all included in the previous search. Thereafter, the 135 papers were reviewed individually to determine whether they contained original data on the association of BDNF protein, genotype, or gene methylation with psychotherapeutic outcome, resulting in the identification of 14 relevant papers (Tables 1 and 2).

2. BDNF and psychotherapy

2.1. Plasma and serum BDNF

Peripheral BDNF is a readily available measure obtained from blood plasma or serum. These two sources yield very different concentrations of BDNF protein: typically, two orders of magnitude higher in serum due to the release of stored platelet BDNF on coagulation. Unfortunately, many studies and reviews of blood BDNF have not considered or discussed this difference, often including plasma and

Table 1. Serum BDNF/plasma BDNF after psychotherapy

Study	Diagnosis	Subjects (N)	Comparison group (N)	Type of therapy	Length of therapy	Material analyzed	Main findings
Koch *et al.*[35] (2009)	Depression	30	N/A	IPT	6 weeks	Plasma BDNF	No significant effect
Sadhasivam *et al.*[36] (2020)	Depression and anxiety disorders	142	N/A	Meditation therapy	4 days	Plasma BDNF	Increased by over 70%
Bruijniks *et al.*[28] (2020)	Depression	170	N/A	CBT or IPT	6 months	Serum BDNF, polymorphism of BDNF (rs6265)	No significant effect
Kobayashi *et al.*[33] (2005)	Panic disorder	42	31 (healthy people)	CBT	10 weeks	Serum BDNF	Significantly lower in the adverse response group
Da Silva *et al.*[34] (2018)	Depression	158	N/A	CBT	16 sessions	Serum BDNF	No significant correlation
Xu *et al.*[32] (2023)	Depression	30	30 patients	MBCT or GC	8 weeks	Serum BDNF	Increased in the MBCT group
Guo *et al.*[29] (2022)	Depression	80	80 patients	MBCT	8 weeks	Serum BDNF	Increased in the MBCT group
Orosz *et al.*[31] (2020)	Depression	71	N/A	ICBT	6 weeks	Serum BDNF	Increased after treatment

Abbreviations: CBT: Cognitive behavioral therapy; ICBT: Individual cognitive behavioral therapy; IPT: Interpersonal psychotherapy; MBCT: Mindfulness-based cognitive therapy.

Table 2. Polymorphism of BDNF and psychotherapy

Study	Diagnosis	Subjects (N)	Comparison group (N)	Type of Therapy	Length of therapy	Material analyzed	Main findings
Bruijniks *et al.*[28] (2020)	Depression	170	N/A	CBT or IPT	6 months	Serum BDNF, polymorphism of BDNF (rs6265)	No significant correlation
Schosser *et al.*[38] (2022)	Depression	277	N/A	CBT	6 weeks	Polymorphism of BDNF (rs10501087, rs11030104, and rs6265)	Associated with the treatment response
Peters *et al.*[39] (2021)	Depression	106	N/A	CBT or CNT	7 sessions	Polymorphism of BDNF (rs6265)	Associated with depression scores before and after CBT
Santacana *et al.*[42] (2016)	Panic disorder	97	N/A	GCBT	9 weeks	Polymorphism of BDNF (rs6265)	No significant correlation
Hedman *et al.*[43] (2012)	Social anxiety disorder	126	N/A	ICBT and GCBT	15 weeks	Polymorphism of BDNF (rs6265)	No significant effect
Lester *et al.*[41] (2012)	Anxiety disorders	374	459 (healthy people)	CBT	Unknown	Polymorphism of BDNF (rs6265)	No significant correlation
Bakker *et al.*[40] (2014)	Depression	63	63 patients	MBCT	8 weeks	Polymorphism of BDNF (rs6265, rs11030101, and rs11030102)	No significant correlation

Abbreviations: CBT: Cognitive behavioral therapy; CNT: Cognitive narrative therapy; GCBT: Group cognitive behavioral therapy; ICBT: Individual cognitive behavioral therapy; IPT: Interpersonal psychotherapy; MBCT: Mindfulness-based cognitive therapy.

serum findings together or even, erroneously, using the two terms interchangeably.[22] The fact that platelets may also release BDNF in response to pharmacological stimulation provides a potential confound, particularly in plasma studies,[23] since even small amounts of platelet cell lysis may affect plasma concentrations. However, serum should contain all blood BDNF following its release from platelets during clot formation. In contrast, plasma BDNF levels may serve as a useful state marker related to inflammation measures.[24] Given that several disorders, including depression, may reflect a chronic inflammatory state in some individuals,[25] this interpretation of plasma BDNF changes warrants further investigation.

Studies on circulating blood BDNF implicitly test one or more of three related working hypotheses of the association between the psychotherapeutic response and BDNF,

namely, baseline BDNF predicts good outcomes, the change in BDNF correlates with symptom improvement, or BDNF at outcome relates to measures of the psychotherapeutic response. The reports are summarized in Table 1.

Several studies investigating the effect of psychotherapeutic techniques (such as CBT and MBCT) in individuals with depression have shown relatively greater increases in serum BDNF compared to controls, along with greater symptom relief.[26-30] Bruijniks *et al.* reported that baseline measures of serum BDNF, while not significantly higher ($P = 0.07$) in responders to CBT and interpersonal psychotherapy (IPT) and not significantly correlated with depression score after 6 months, demonstrated a significant effect on individuals with high working memory. However, a proportion of the study participants were also receiving antidepressant pharmacotherapy, which may have confounded the findings. A study on panic disorder indicated that those responding well to CBT had significantly higher serum BDNF than poor responders.[31] These studies were generally small, with sample sizes of 30 – 80. A larger study of CBT[32] examined 170 people with depression and found no significant correlations between depression scores and serum BDNF before or after treatment.

In contrast, a study of plasma BDNF found no significant association with the treatment response to IPT in individuals with depression.[33] However, another uncontrolled investigation of changes in plasma BDNF following a 4-day yoga-based meditation reported substantial increases in BDNF accompanied by improvements in anxiety and depression scale scores.[34] These authors report concentrations of BDNF in the range more associated with serum studies, and it seems likely that clotted blood or plasma contaminated with platelets was studied here.

2.2. BDNF genetic polymorphisms

The functionality of the single-nucleotide polymorphism (SNP) rs6265 in *BDNF* is well established. This SNP codes for a val66met change in the pro-BDNF protein, of which the met allelic form exhibits impaired intracellular trafficking and secretion, affecting memory and hippocampal neurochemistry.[35] Occasionally, other SNPs have been investigated, many of which are in very close linkage disequilibrium with rs6265[36] and thus may have effects resulting from this val66met change in the protein structure of pro-BDNF.

Of the studies identified (Table 2), Bruijniks *et al.*[26] did not find any effect of the rs6265 genotype on outcome measures over 6 months after IPT and CBT in 138 people with depression or a relationship between the genotype and serum BDNF levels. However, a larger study with a 6-week intervention showed significant effects. Schosser *et al.*[36] found a strong association between three closely related SNPs, including rs6265, and treatment response to CBT in 277 individuals with depression. This study identified the heterozygous genotype of each SNP to be associated with a better response, a consistent result reflecting their close linkage disequilibrium.

Peters *et al.*[37] ($n = 106$) did not find an association between rs6265 genotype and depression scores before or after CBT but observed an interesting association of the genotype with resilience. In a controlled investigation of MBCT in depression, Bakker *et al.*[38] found no association of several BDNF SNPs, including rs6265, with the effects of the intervention.

Studies on anxiety disorders have not provided strong support for the role of the rs6265 SNP in affecting the outcomes of cognitive therapies. Lester *et al.*[39] conducted a large controlled study and found no effect of genotype on treatment response, whereas two smaller studies focusing on panic disorder[40] and social anxiety disorder[41] also failed to identify significant associations with treatment response.

2.3. BDNF DNA methylation

DNA methylation is an epigenetic factor that can influence gene expression, primarily through the enzymatic methylation of cytosine residues in CpG sequences on DNA, potentially affecting transcription factor binding. There has been much interest in the possible environmental influences on DNA methylation, with risk factors for psychiatric diseases, such as childhood trauma, affecting DNA methylation.[42] BDNF has been extensively investigated in this respect across several sequences within the gene. One of these is at a binding site for the transcription factor cAMP-response element binding protein (CREB), which is an essential component of the intracellular processes regulating BDNF transcription.[43]

DNA methylation of *BDNF* is altered in affective disorders and schizophrenia, potentially affecting CREB binding to its recognition site and consequent BDNF expression. Several studies have identified the relationship of BDNF methylation to antidepressant treatment response;[44] however, DNA methylation research is limited in terms of psychotherapeutic response. Two studies investigated its relationship with psychotherapy for borderline personality disorder[13] but did not identify a significant effect. However, we found no studies relating BDNF methylation to talking therapies for depression or anxiety disorders. This represents a major gap that needs to be addressed in future studies.

3. Discussion

Given the limited information obtained, we lack a clear set of findings that support the main hypothesis: increased BDNF function is associated with an effective psychotherapeutic response in anxiety and depression. Where significant effects are identified, they may associate treatment efficacy with an increase in BDNF concentrations or function, although this is not always the case. The single positive genetic finding, showing an association of the heterozygous genotype with response, does not clearly support this interpretation, indicating very little consistency between studies. Many reasons may underlie the variability between the findings.

Methodological factors are a likely major concern. While it is considered that over 99% of blood BDNF resides in platelet stores, most investigations of plasma concentrations report findings that are typically 5% of concentrations in serum. This is likely to reflect the release of platelet stores into the plasma in some participants, which in turn will contribute to higher variances, as demonstrated in the methodological study of Gejl *et al.*[45] These authors also highlighted the importance of other variables such as storage time and centrifugation protocol in both plasma and serum preparation. In many of the reviewed articles, such technical information, along with temperatures, delays before centrifugation, and so on, are incompletely reported, making replication difficult.

The origins of circulating BDNF are unclear. Although many of the studies have implied that it derives from the brain, evidence is very limited and open to criticism.[46] Other organs contain and rely on BDNF, which is likely to contribute to circulating concentrations and confound the interpretation of any changes, as indicated below.

In contrast, BDNF genotypes, particularly those of rs6265, have known effects on the cellular disposition and function of the resultant protein. This has established consequences on the brain, with both anatomical and functional correlates.[47] Furthermore, it is a genetic factor and therefore unmodifiable; any association found is likely to be causal, in contrast to blood-derived BDNF measures.

How might psychotherapy influence or be influenced by these various measures of BDNF? One hypothetical mechanism can be simply described as stress reduction. The stress response, involving an increase in cortisol secretion mediated by the hypothalamic–pituitary–adrenal (HPA) axis, is often chronically dysfunctional in affective and anxiety disorders.[48] Stress can lead to various physiological changes in addition to the activation of the HPA axis; this includes increases in cortisol and proinflammatory cytokines and reductions in BDNF,[49] of which the latter two may be causally related.[50] Although it is reasonable to assume that the reverse process may be true, that is, a reduction in the consequences of stressful events through psychotherapy may normalize BDNF function, this assumption also implies a deficit in BDNF activity in patients undergoing treatment. A review of meta-analyses indicates that in terms of blood BDNF levels in individuals with MDD, this may be true.[51]

Associations or correlations between BDNF markers and outcomes do not indicate a causal or mechanistic role of BDNF in psychotherapy. Although that is a possible interpretation, alternative theories suggest reverse causality, in which the neurobiological effects of effective psychotherapy – potentially through the normalization of HPA axis function and/or a reduction in inflammatory activation – result in disinhibition of BDNF production. Such theoretical processes are consistent with our understanding of the relationship between stress and BDNF;[50] however, they do not explain the mechanism behind the initial effects of psychotherapy on symptoms.

A further possibility is that observed BDNF changes are epiphenomena associated with one or more of the various behavioral, social, and physiological consequences of a successful psychotherapeutic intervention. Two such secondary consequences might be increases in physical activity and improved dietary intake. Notably, poor activity and diet contribute to the somatic symptoms of depression.[52] The effects of physical activity and exercise on peripheral BDNF levels have been studied extensively, particularly because BDNF, in addition to its effects on maintaining normal neuronal function, also plays an important role in the maintenance of cardiovascular health.[53] Furthermore, interest in the role of diet and the gut microbiota in depression and its treatment outcomes has been increasing,[54] with some evidence showing that this can affect peripheral BDNF.

Studies in healthy subjects have shown that increases in physical activity, particularly aerobic exercise, result in increases in peripheral BDNF levels,[55,56] which occur without any neurological correlation.[57] These effects are greater in the plasma than in the serum BDNF, and the limited evidence suggests sex differences, with stronger changes in men.[55] Similarly, food intake can affect blood BDNF, with elevations associated with various dietary supplements, notably polyphenol-containing foods.[58] Physical activity and diet are examples of potentially important confounders that may be difficult, if not impossible, to control in studies of therapeutic responses in psychiatric illness. The possibility that changes in BDNF might correlate with improvements in somatic symptoms rather than those directly associated with brain function

does not invalidate its value as an indicator of disease or treatment response.[51] However, it implies that blood BDNF measures do not necessarily reflect mechanisms related to central nervous system effects and therefore cannot be interpreted as such.

Although genetic investigation avoids these concerns, no consistent association of the BDNF genotype with the treatment response has been identified. The discrepancy between studies is notable; the highly significant findings of Schosser *et al.*[36] contrast strongly with the negative findings of other smaller studies of depression. No evidence on the role of a BDNF genotype in studies of psychotherapy for anxiety disorders was apparent, despite one report of a particularly large controlled investigation.[39]

How these findings compare with those from studies of antidepressant or anxiolytic drug response may be relevant to understanding the therapeutic mechanisms.

The BDNF polymorphism rs6265 (Val66Met), the most studied variant, shows some consistency in findings indicating a significant effect on antidepressant efficacy, with the Met allele associated with a better treatment response.[59] Most studies of peripheral blood BDNF levels report lower levels before antidepressant treatment than after. Different antidepressant drugs elevate serum/plasma BDNF, which are reportedly reduced in patients with depression.[60] Furthermore, animal studies have shown that antidepressant medication increases BDNF mRNA and BDNF protein levels in the cerebral cortex and hippocampus.[61] Therefore, BDNF may mediate the effect of antidepressants in reversing depression-related neuronal dysfunction by promoting neurogenesis and plasticity.[62] An association between BDNF Val66Met and BDNF peripheral levels was also suggested, in which the Met allele was associated with higher BDNF serum levels.[63]

4. Conclusion

In this review, we did not conduct meta-analyses of the findings but critically assessed individual reports, occasionally identifying major methodological concerns that question research validity. In addition, we did not summarize and analyze all types of psychotherapies but focused on talking therapies such as CBT, interpersonal therapy, psychodynamic therapy, family therapy, and MBCT. Further limitations are shared with many of the reviewed reports. Consideration is not always given to why the participants undergo psychotherapy rather than pharmacotherapy. An important question is whether the subjects are drug-naïve and at an early stage of their illness or have previously received drug treatment to which they have not responded adequately. This would differentiate the two highly dissimilar cohorts. Many other variable factors could influence the findings, including those relating to disease pathogenesis, such as the role of childhood trauma and other environmental or genetic risk factors.[64] The few positive reports of associations with psychotherapy may still present a view distorted by publication bias. Nevertheless, strong circumstantial evidence supports the role of BDNF in depressive and anxiety disorders as well as their treatment, warranting further studies to enhance the understanding of the mechanisms underlying their response to psychotherapeutic interventions. However, it would be premature to draw any clinical implications from this work.

Studies of blood BDNF do not, and perhaps cannot, yield consistent results concerning psychotherapeutic response for at least two reasons. First, serious methodological issues, particularly in studies of plasma, have rarely been adequately considered. Second, peripheral blood BDNF is likely to have a strong contribution from peripheral organs, including the cardiovascular system and gut, which confounds the interpretation that changes in BDNF levels might reflect its activity in the brain. Any attempts to further investigate the peripheral measurement of BDNF need to be performed in well-designed studies that pay more attention to these and other confounding factors.

Genetic association studies have the advantage of the known relationships with some aspects of brain function and dysfunction, and their inherent nature indicates that any association is likely causal rather than consequential. However, the evidence for the influence of BDNF SNPs on the psychotherapeutic response is inconsistent and very limited. Future work needs to consider interactions with other known or likely influences, such as underlying cognitive function and pathogenic risk factors.

The lack of DNA methylation studies on *BDNF* in response to talking therapies in the contexts of depression or anxiety is disappointing, especially given the rapid expansion of findings supporting the role of this epigenetic factor in the control of BDNF expression and its influence on various aspects of psychiatric disease and treatment. This area presents a significant opportunity for future research to determine the importance of BDNF changes in psychotherapy, despite the challenges in differentiating the somatic and psychiatric correlates of such changes.

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Conflict of interest

Zhi Xu and Gavin P. Reynolds are Editorial Board Members of this journal but were not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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References

1. Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JAJ, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: A meta-analysis of randomized placebo-controlled trials. *Depress Anxiety*. 2018;35(6):502-514.

   doi: 10.1002/da.22728

2. Negt P, Brakemeier EL, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: A systematic review and meta-analysis of randomized-controlled clinical trials. *Brain Behav*. 2016;6(8):e00486.

   doi: 10.1002/brb3.486

3. Haram A, Fosse R, Jonsbu E, Hole T. Impact of psychotherapy in psychosis: A retrospective case control study. *Front Psychiatry*. 2019;10:204.

   doi: 10.3389/fpsyt.2019.00204

4. Kappelmann N, Rein M, Fietz J, *et al*. Psychotherapy or medication for depression? Using individual symptom meta-analyses to derive a Symptom-Oriented Therapy (SOrT) metric for a personalised psychiatry. *BMC Med*. 2020;18(1):170.

   doi: 10.1186/s12916-020-01623-9

5. Dunlop BW, LoParo D, Kinkead B, *et al*. Benefits of sequentially adding cognitive-behavioral therapy or antidepressant medication for adults with nonremitting depression. *Am J Psychiatry*. 2019;176(4):275-286.

   doi: 10.1176/appi.ajp.2018.18091075

6. Luong HK, Drummond SPA, Norton PJ. Elements of the therapeutic relationship in CBT for anxiety disorders: A systematic review. *J Anxiety Disord*. 2020;76:102322.

   doi: 10.1016/j.janxdis.2020.102322

7. Goncalves L, Barbisan GK, Reboucas C, Da Rocha NS. Longitudinal investigation of psychotherapy outcomes (LIPO): Description of the study protocol. *Front Psychiatry*. 2019;10:212.

   doi: 10.3389/fpsyt.2019.00212

8. Wang Y, Liang J, Xu B, Yang J, Wu Z, Cheng L. TrkB/BDNF signaling pathway and its small molecular agonists in CNS injury. *Life Sci*. 2024;336:122282.

   doi: 10.1016/j.lfs.2023.122282

9. Xu L, Zhu L, Zhu L, *et al*. Moderate exercise combined with enriched environment enhances learning and memory through BDNF/TrkB signaling pathway in rats. *Int J Environ Res Public Health*. 2021;18(16):8283.

   doi: 10.3390/ijerph18168283

10. Sharma V, Singh TG, Kaur A, Mannan A, Dhiman S. Brain-derived neurotrophic factor: A novel dynamically regulated therapeutic modulator in neurological disorders. *Neurochem Res*. Feb 2023;48(2):317-339.

    doi: 10.1007/s11064-022-03755-1

11. Wang Y, Zhang H, Li Y, *et al*. BDNF Val66Met polymorphism and plasma levels in Chinese Han population with obsessive-compulsive disorder and generalized anxiety disorder. *J Affect Disord*. 2015;186:7-12.

    doi: 10.1016/j.jad.2015.07.023

12. Lonsdorf TB, Kalisch R. A review on experimental and clinical genetic associations studies on fear conditioning, extinction and cognitive-behavioral treatment. *Transl Psychiatry*. 2011;1(9):e41.

    doi: 10.1038/tp.2011.36

13. Piotrkowicz M, Janoska-Jazdzik M, Koweszko T, Szulc A. The influence of psychotherapy on peripheral brain-derived neurotrophic factor concentration levels and gene methylation status: A systematic review. *J Clin Med*. 2021;10(19):4424.

    doi: 10.3390/jcm10194424

14. Wade PA. Dynamic regulation of DNA methylation coupled transcriptional repression: BDNF regulation by MeCP2. *Bioessays*. 2004;26(3):217-220.

    doi: 10.1002/bies.20018

15. Casarotto P, Umemori J, Castren E. BDNF receptor TrkB as the mediator of the antidepressant drug action. *Front Mol Neurosci*. 2022;15:1032224.

doi: 10.3389/fnmol.2022.1032224

16. Zelada MI, Garrido V, Liberona A, *et al*. Brain-derived neurotrophic factor (BDNF) as a predictor of treatment response in major depressive disorder (MDD): A Systematic review. *Int J Mol Sci*. 2023;24(19):14810.

doi: 10.3390/ijms241914810

17. Zou Y, Zhang Y, Tu M, *et al*. Brain-derived neurotrophic factor levels across psychiatric disorders: A systemic review and network meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2024;131:110954.

doi: 10.1016/j.pnpbp.2024.110954

18. Dou SH, Cui Y, Huang SM, Zhang B. The role of brain-derived neurotrophic factor signaling in central nervous system disease pathogenesis. *Front Hum Neurosci*. 2022;16:924155.

doi: 10.3389/fnhum.2022.924155

19. Sha Z, Xu J, Li N, Li O. Regulatory molecules of synaptic plasticity in anxiety disorder. *Int J Gen Med*. 2023;16:2877-2886.

doi: 10.2147/IJGM.S413176

20. Nikolac Perkovic M, Gredicak M, Sagud M, Nedic Erjavec G, Uzun S, Pivac N. The association of brain-derived neurotrophic factor with the diagnosis and treatment response in depression. *Expert Rev Mol Diagn*. 2023;23(4):283-296.

doi: 10.1080/14737159.2023.2200937

21. Berry A, Bellisario V, Capoccia S, *et al*. Social deprivation stress is a triggering factor for the emergence of anxiety- and depression-like behaviours and leads to reduced brain BDNF levels in C57BL/6J mice. *Psychoneuroendocrinology*. 2012;37(6):762-772.

doi: 10.1016/j.psyneuen.2011.09.007

22. Gomutbutra P, Srikhamjak T, Sapinun L, *et al*. Corrigendum to "Effect of intensive weekend mindfulness-based intervention on BDNF, mitochondria function, and anxiety. A randomized, crossover clinical trial" [Compr. Psychoneuroendocrinol. (2022) 100137]. *Compr Psychoneuroendocrinol*. 2022;11:100141.

doi: 10.1016/j.cpnec.2022.100141

23. Fujimura H, Altar CA, Chen R, *et al*. Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thromb Haemost*. 2002;87(4):728-734.

24. Chimienti G, Mezzapesa A, Rotelli MT, Lupo L, Pepe G. Plasma concentrations but not serum concentrations of brain-derived neurotrophic factor are related to pro-inflammatory cytokines in patients undergoing major abdominal surgery. *Clin Biochem*. 2012;45(9):631-636.

doi: 10.1016/j.clinbiochem.2012.02.025

25. Sochal M, Ditmer M, Gabryelska A, Bialasiewicz P. The role of brain-derived neurotrophic factor in immune-related diseases: A narrative review. *J Clin Med*. 2022;11(20):6023.

doi: 10.3390/jcm11206023

26. Bruijniks SJE, Van Grootheest G, Cuijpers P, *et al*. Working memory moderates the relation between the brain-derived neurotropic factor (BDNF) and psychotherapy outcome for depression. *J Psychiatr Res*. 2020;130:424-432.

doi: 10.1016/j.jpsychires.2020.07.045

27. Guo H, Ren Y, Huang B, Wang J, Yang X, Wang Y. Psychological status, compliance, serum brain-derived neurotrophic factor, and nerve growth factor levels of patients with depression after augmented mindfulness-based cognitive therapy. *Genet Res (Camb)*. 2022;2022:1097982.

doi: 10.1155/2022/1097982

28. Liu W, Yuan J, Wu Y, *et al*. A randomized controlled trial of mindfulness-based cognitive therapy for major depressive disorder in undergraduate students: Dose- response effect, inflammatory markers and BDNF. *Psychiatry Res*. 2024;331:115671.

doi: 10.1016/j.psychres.2023.115671

29. Orosz A, Federspiel A, Eckert A, *et al*. Exploring the effectiveness of a specialized therapy programme for burnout using subjective report and biomarkers of stress. *Clin Psychol Psychother*. 2021;28(4):852-861.

doi: 10.1002/cpp.2539

30. Xu L, Wang F, Yuan J, *et al*. A randomized controlled trial of mindfulness-based cognitive therapy (MBCT) for major depressive disorder in undergraduate students in China: The efficacy, serum proinflammatory cytokines and brain-derived neurotrophic factor. *Asian J Psychiatr*. 2023;88:103718.

doi: 10.1016/j.ajp.2023.103718

31. Kobayashi K, Shimizu E, Hashimoto K, *et al*. Serum brain-derived neurotrophic factor (BDNF) levels in patients with panic disorder: As a biological predictor of response to group cognitive behavioral therapy. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(5):658-663.

doi: 10.1016/j.pnpbp.2005.04.010

32. Da Silva SK, Wiener C, Ghisleni G, *et al*. Effects of cognitive-behavioral therapy on neurotrophic factors in patients with major depressive disorder. *Braz J Psychiatry*. 2018;40(4):361-366.

doi: 10.1590/1516-4446-2017-2357

33. Koch JM, Hinze-Selch D, Stingele K, *et al*. Changes in CREB phosphorylation and BDNF plasma levels during psychotherapy of depression. *Psychother Psychosom*. 2009;78(3):187-192.

doi: 10.1159/000209350

34. Sadhasivam S, Alankar S, Maturi R, *et al*. Inner engineering practices and advanced 4-day isha yoga retreat are associated with cannabimimetic effects with increased endocannabinoids and short-term and sustained improvement in mental health: A prospective observational study of meditators. *Evid Based Complement Alternat Med*. 2020;2020:8438272.

doi: 10.1155/2020/8438272

35. Egan MF, Kojima M, Callicott JH, *et al*. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003;112(2):257-269.

doi: 10.1016/s0092-8674(03)00035-7

36. Schosser A, Fischer-Hansal D, Swoboda MM, *et al*. BDNF gene polymorphisms predicting treatment response to CBT-based rehabilitation of depression: To be submitted to: European Neuropsychopharmacology. *Eur Neuropsychopharmacol*. 2022;58:103-108.

doi: 10.1016/j.euroneuro.2022.03.005

37. Peters RB, Xavier J, Mondin TC, *et al*. BDNF Val66Met polymorphism and resilience in major depressive disorder: The impact of cognitive psychotherapy. *Braz J Psychiatry*. 2020;43(1):22-28.

doi: 10.1590/1516-4446-2019-0726

38. Bakker JM, Lieverse R, Menne-Lothmann C, *et al*. Therapygenetics in mindfulness-based cognitive therapy: Do genes have an impact on therapy-induced change in real-life positive affective experiences? *Transl Psychiatry*. 2014;4(4):e384.

doi: 10.1038/tp.2014.23

39. Lester KJ, Hudson JL, Tropeano M, *et al*. Neurotrophic gene polymorphisms and response to psychological therapy. *Transl Psychiatry*. 2012;2(5):e108.

doi: 10.1038/tp.2012.33

40. Santacana M, Arias B, Mitjans M, *et al*. Predicting response trajectories during cognitive-behavioural therapy for panic disorder: No association with the BDNF gene or childhood maltreatment. *PLoS One*. 2016;11(6):e0158224.

doi: 10.1371/journal.pone.0158224

41. Hedman E, Andersson E, Ljotsson B, *et al*. Clinical and genetic outcome determinants of Internet- and group-based cognitive behavior therapy for social anxiety disorder. *Acta Psychiatr Scand*. 2012;126(2):126-136.

doi: 10.1111/j.1600-0447.2012.01834.x

42. Reynolds GP. Early life trauma, DNA methylation and mental illness. *Epigenomics*. 2021;13(11):825-827.

doi: 10.2217/epi-2021-0128

43. Tao X, Finkbeiner S, Arnold DB, Shaywitz AJ, Greenberg ME. Ca2+ influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. *Neuron*. 1998;20(4):709-726.

doi: 10.1016/s0896-6273(00)81010-7

44. Li L, Wang T, Chen S, Yue Y, Xu Z, Yuan Y. DNA methylations of brain-derived neurotrophic factor exon VI are associated with major depressive disorder and antidepressant-induced remission in females. *J Affect Disord*. 2021;295:101-107.

doi: 10.1016/j.jad.2021.08.016

45. Gejl AK, Enevold C, Bugge A, Andersen MS, Nielsen CH, Andersen LB. Associations between serum and plasma brain-derived neurotrophic factor and influence of storage time and centrifugation strategy. *Sci Rep*. 2019;9(1):9655.

doi: 10.1038/s41598-019-45976-5

46. Brand SJ, Moller M, Harvey BH. A review of biomarkers in mood and psychotic disorders: A dissection of clinical vs. preclinical correlates. *Curr Neuropharmacol*. 2015;13(3):324-368.

doi: 10.2174/1570159x13666150307004545

47. Du D, Tang Q, Han Q, *et al*. Association between genetic polymorphism and antidepressants in major depression: A network meta-analysis. *Pharmacogenomics*. 2020;21(13):963-974.

doi: 10.2217/pgs-2020-0037

48. Bandelow B, Baldwin D, Abelli M, *et al*. Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part II: Neurochemistry, neurophysiology and neurocognition. *World J Biol Psychiatry*. 2017;18(3):162-214.

doi: 10.1080/15622975.2016.1190867

49. Cattane N, Vernon AC, Borsini A, *et al*. Preclinical animal models of mental illnesses to translate findings from the bench to the bedside: Molecular brain mechanisms and peripheral biomarkers associated to early life stress or immune challenges. *Eur Neuropsychopharmacol*. 2022;58:55-79.

doi: 10.1016/j.euroneuro.2022.02.002

50. Jin Y, Sun LH, Yang W, Cui RJ, Xu SB. The role of BDNF in the neuroimmune axis regulation of mood disorders. *Front Neurol*. 2019;10:515.

doi: 10.3389/fneur.2019.00515

51. Kishi T, Yoshimura R, Ikuta T, Iwata N. Brain-derived neurotrophic factor and major depressive disorder: Evidence from meta-analyses. *Front Psychiatry*. 2017;8:308.

doi: 10.3389/fpsyt.2017.00308

52. Kapfhammer HP. Somatic symptoms in depression. *Dialogues Clin Neurosci*. 2006;8(2):227-239.

doi: 10.31887/DCNS.2006.8.2/hpkapfhammer

53. Pius-Sadowska E, Machalinski B. BDNF-a key player in

cardiovascular system. *J Mol Cell Cardiol*. 2017;110:54-60.

doi: 10.1016/j.yjmcc.2017.07.007

54. Matin S, Dadkhah M. BDNF/CREB signaling pathway contribution in depression pathogenesis: A survey on the non-pharmacological therapeutic opportunities for gut microbiota dysbiosis. *Brain Res Bull*. 2024;207:110882.

doi: 10.1016/j.brainresbull.2024.110882

55. Dinoff A, Herrmann N, Swardfager W, Lanctot KL. The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: A meta-analysis. *Eur J Neurosci*. 2017;46(1):1635-1646.

doi: 10.1111/ejn.13603

56. Huang T, Larsen KT, Ried-Larsen M, Moller NC, Andersen LB. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. *Scand J Med Sci Sports*. 2014;24(1):1-10.

doi: 10.1111/sms.12069

57. Tsai CL, Pan CY, Chen FC, Wang CH, Chou FY. Effects of acute aerobic exercise on a task-switching protocol and brain-derived neurotrophic factor concentrations in young adults with different levels of cardiorespiratory fitness. *Exp Physiol*. 2016;101(7):836-850.

doi: 10.1113/EP085682

58. Gravesteijn E, Mensink RP, Plat J. Effects of nutritional interventions on BDNF concentrations in humans: A systematic review. *Nutr Neurosci*. 2022;25(7):1425-1436.

doi: 10.1080/1028415X.2020.1865758

59. Yan T, Wang L, Kuang W, *et al*. Brain-derived neurotrophic factor Val66Met polymorphism association with antidepressant efficacy: A systematic review and meta-analysis. *Asia Pac Psychiatry*. 2014;6(3):241-251.

doi: 10.1111/appy.12148

60. Shi Y, Luan D, Song R, Zhang Z. Value of peripheral neurotrophin levels for the diagnosis of depression and response to treatment: A systematic review and meta-analysis. *Eur Neuropsychopharmacol*. 2020;41:40-51.

doi: 10.1016/j.euroneuro.2020.09.633

61. Cubillos S, Engmann O, Brancato A. BDNF as a mediator of antidepressant response: Recent advances and lifestyle interactions. *Int J Mol Sci*. 2022;23(22):14445.

doi: 10.3390/ijms232214445

62. Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. *Int J Mol Sci*. 2020;21(20):7777.

doi: 10.3390/ijms21207777

63. Caldieraro MA, McKee M, Leistner-Segal S, *et al.* Val66Met polymorphism association with serum BDNF and inflammatory biomarkers in major depression. *World J Biol Psychiatry*. Aug 2018;19(5):402-409.

doi: 10.1080/15622975.2017.1347713

64. Fachim HA, Corsi-Zuelli F, Loureiro CM, *et al*. Early-life stress effects on BDNF DNA methylation in first-episode psychosis and in rats reared in isolation. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;108:110188.

doi: 10.1016/j.pnpbp.2020.110188

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REVIEW ARTICLE

Psychosomatic influences on insomnia: Mechanisms, diagnosis, and treatment strategies

Alejandro Camacho-Zamora[1], Josué Camberos-Barraza[1,2], Ángel R. Rábago-Monzón[1,2], Hugo J. Sosa-Arámbula[1,3], and Alberto K. De la Herrán-Arita[1]*

[1]Facultad de Medicina, Universidad Autónoma de Sinaloa, Culiacán, México

[2]Doctorado en Ciencias en Biomedicina Molecular, Universidad Autónoma de Sinaloa, Culiacán, Sinaloa, México

[3]Maestría en Ciencias en Biomedicina Molecular, Universidad Autónoma de Sinaloa, Culiacán, Sinaloa, México

Abstract

Insomnia is the most prevalent sleep disorder with significant implications for mental and physical health. While traditionally understood through a biomedical lens, increasing evidence highlights the role of psychosomatic factors in its onset and perpetuation. This narrative review explores the relationship between psychological and somatic influences on insomnia, examining the underlying mechanisms, diagnostic challenges, and treatment strategies. We discuss neurobiological pathways, including the hypothalamic–pituitary–adrenal axis and neurotransmitter imbalances, alongside psychological factors such as anxiety, hyperarousal, and cognitive distortions. Somatic symptoms, particularly chronic pain, and other physical conditions are also regarded as integral contributors to insomnia. Diagnosis of psychosomatic insomnia requires a comprehensive approach that incorporates both psychological and physical assessments, utilizing a combination of clinical interviews, standardized questionnaires, and differential diagnostic techniques. Treatment strategies are discussed in this paper with an emphasis on cognitive-behavioral therapy for insomnia, pharmacological interventions, and integrative approaches that address the multifaceted nature of the disorder. The review also highlights the importance of lifestyle modifications and the potential role of alternative therapies in managing insomnia. A rounded understanding of psychosomatic influences is crucial for effective diagnosis and treatment of insomnia. Future research should focus on personalized therapeutic approaches and further interpreting the complex interconnections between mind and body in the pathophysiology of insomnia. This perspective has the potential to enhance clinical practice and improve outcomes for individuals suffering from this challenging disorder.

Keywords: Insomnia; Sleep–wake cycle; Somatization; Stress

***Corresponding author:**
Alberto K. De la Herrán-Arita
(alberto.kousuke@uas.edu.mx)

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1. Introduction

Insomnia is a common yet complex sleep disorder, characterized by difficulties in initiating or maintaining sleep or experiencing non-restorative sleep. These difficulties

often arise from various external factors such as financial, personal, or psychological ones that can prevent individuals from having adequate sleep. Insomnia affects an estimated 10 – 30% of the global population, depending on the diagnostic criteria used, with chronic insomnia (lasting 3 months or more) affecting about 10% of adults. Short-term insomnia impacts up to 30 – 40% of people at some point in their lives, making it a widespread issue. Notably, women are 1.5 – 2 times more likely than men to experience insomnia, largely due to hormonal fluctuations related to menstruation, pregnancy, and menopause, as well as higher rates of anxiety and depression. In contrast, men are more prone to sleep disorders such as obstructive sleep apnea. Insomnia has profound effects on both the mental and physical health of the affected individuals, increasing the risk of depression, anxiety, cardiovascular disease, and impaired daytime functioning. Research indicates that insomnia is more common among the elderly, with estimates suggesting that approximately 30 – 50% of older adults experience sleep disturbances, compared to around 10 – 15% of younger adults. This disparity can be attributed to a combination of physiological, psychological, and environmental factors. Aging promotes the occurrence of physiological changes within sleep architecture, such as reduced slow-wave sleep and alterations in circadian rhythms, which can lead to increased nighttime awakenings and difficulties in initiating sleep. In addition, the prevalence of comorbid conditions, including chronic pain, depression, and anxiety, is higher in older adults, further contributing to insomnia. Conversely, younger populations, while not immune to sleep disturbances, tend to experience insomnia primarily due to lifestyle factors such as stress, irregular sleep schedules, and the pervasive use of electronic devices.

Historically, insomnia has been treated from a biomedical perspective, focusing on sleep physiology and pharmacological interventions. However, emerging research highlights the significant role psychosomatic factors play in both the onset and perpetuation of insomnia, underscoring the need for a more integrative approach.[1-3]

The diagnosis of insomnia is based on specific criteria established in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and is characterized by the following key features:

(i) *Difficulties in sleep initiation*, *maintenance*, *or early awakening*. Individuals must experience persistent difficulties in falling asleep, staying asleep, or waking up too early and being unable to return to sleep
(ii) *Sleep disturbances occur at least 3 times per week*. These sleep difficulties must occur at least 3 times per week to meet diagnostic criteria
(iii) *Duration of sleep problems*. The sleep disturbances should be present for at least 3 months to be classified as chronic insomnia
(iv) *Significant distress or impairment*. The insomnia must cause significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
(v) *Not attributable to other sleep disorders*. The sleep disturbance cannot be better explained by other sleep disorders, such as sleep apnea or restless legs syndrome, or be solely attributed to the physiological effects of a substance (e.g., drug abuse and medication)
(vi) *Exclusion of coexisting conditions*. The sleep difficulties cannot be better explained by other mental disorders, such as major depressive disorder or anxiety disorders, although insomnia can coexist with these conditions.

Psychosomatic influences refer to the interplay between psychological processes and physical symptoms, where mental states such as stress, anxiety, and depression manifest as somatic complaints, including sleep disturbances.[4,5] In insomnia, these psychosomatic influences involve a complex interaction between psychological stressors, emotional dysregulation, and physiological responses such as hyperarousal and neuroendocrine dysfunction.[6,7] These factors often set up a cycle that creates and perpetuates insomnia, complicating the treatment process.

Insomnia also results from disruptions in the sleep–wake cycle (SWC) regulated by molecular mechanisms that integrate circadian rhythms, homeostatic processes, and neurotransmitter systems. Circadian rhythms, governed by the molecular clock, are central to regulating sleep and wakefulness. This internal clock coordinates physiological processes, and its disruptions can lead to insomnia and other sleep disorders.[8,9] The molecular clock functions through a network of clock genes, including *Clock*, *Bmal1*, *Per1*, *Per2*, *Cry1*, and *Cry2*, whose protein products form feedback loops to maintain circadian rhythms. Regulators such as REV-ERBα, RORα, and DBP help fine-tune these rhythms, aligning sleep with environmental cues such as light exposure.[10-13]

Light serves as a crucial cue that helps synchronize the circadian rhythm with the environment. Signals from retinal cells reach the suprachiasmatic nucleus of the hypothalamus, the brain's circadian pacemaker, which adjusts the timing of the molecular clock to align with the day–night cycle, ensuring proper sleep timing and quality.[14,15] Another key player in sleep regulation is orexin (also known as hypocretin), a neurotransmitter that stabilizes wakefulness and appetite. Produced in the lateral hypothalamus, orexin interacts with brain regions involved in arousal and alertness, such as the ventrolateral preoptic

nucleus and brainstem arousal systems.[16-22] Disruptions in orexin signaling are linked to insomnia, where heightened arousal and vigilance hinder the ability to transition into and maintain sleep.[22-26]

In addition to circadian rhythms, the homeostatic sleep drive, which builds up during wakefulness, plays a critical role in sleep regulation. Adenosine, a neuromodulator, accumulates during wakefulness and promotes sleep as its levels rise. Disruptions in adenosine signaling can contribute to difficulties falling asleep and maintaining restful sleep, which are hallmarks of insomnia.[27,28,33] Molecular disruptions affecting circadian rhythms, homeostatic drive, and neurotransmitter systems, such as orexin, exacerbate insomnia by increasing arousal and reducing sleep efficiency.[29-35]

The aim of this review is to provide a comprehensive analysis of psychosomatic influences on insomnia, examining the neurobiological, psychological, and somatic mechanisms involved. The review also explores diagnostic challenges and proposes integrative treatment strategies to address both the physical and mental aspects of insomnia, contributing to a holistic understanding and management of the disorder. This review uniquely focuses on the interaction between neurobiological mechanisms (e.g., hypothalamic–pituitary–adrenal [HPA] axis dysregulation) and psychological factors (e.g., emotional dysregulation), a topic less explored in earlier research. In addition, it emphasizes integrative treatment approaches such as mindfulness and lifestyle modifications alongside traditional methods, while highlighting the importance of personalized treatment strategies tailored to individual patient profiles. Finally, it delves into the underexplored bidirectional relationship between chronic medical conditions and insomnia, offering new insights into the complexity of this disorder.

2. Mechanisms of psychosomatic influences on insomnia

2.1. Neurobiological mechanisms

The neurobiological mechanisms underlying psychosomatic influences on insomnia involve a complex interaction between the central nervous system, neuroendocrine pathways, and the body's physiological responses to stress. These mechanisms not only contribute to the onset of insomnia but also play a crucial role in its persistence, especially in the presence of psychological stressors and emotional dysregulation.

2.1.1. Dysregulation of HPA axis

The HPA axis is a central component of the body's stress response system, which is responsible for regulating the release of cortisol, a hormone that plays a critical role in the SWC. In response to stress, the hypothalamus releases corticotropin-releasing hormone, which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH then triggers the adrenal glands to produce cortisol (Figure 1). Under normal conditions, cortisol levels follow a diurnal rhythm, peaking in the early morning and gradually declining throughout the day.[36-38] However, chronic stress and emotional disturbances can lead to HPA axis dysregulation, characterized by elevated cortisol levels, particularly in the evening, when they should be at their lowest.[39-41] This abnormal cortisol secretion disrupts the SWC, contributing to difficulties in falling asleep and maintaining sleep. Elevated cortisol levels are also associated with increased nighttime awakenings and lighter, less restorative sleep. The persistent activation of the HPA axis in response to stress not only perpetuates insomnia but also exacerbates the psychological factors, such as anxiety and hyperarousal, that contribute to the disorder.[42]

2.1.2. Neurotransmitter imbalances

Neurotransmitters play a crucial role in regulating mood, arousal, and sleep. Imbalances in these chemical messengers are closely linked to both psychological states and sleep disturbances. Serotonin, gamma-aminobutyric acid (GABA), norepinephrine, histamine, and glutamate are particularly important in the context of insomnia.

Serotonin is involved in mood regulation, and its deficiency is associated with depression and anxiety, both of which are common in individuals with insomnia.[43] Serotonin is also a precursor to melatonin, a hormone that regulates the SWC. Reduced serotonin levels can lead to impaired melatonin production, disrupting sleep onset and quality. GABA is the primary inhibitory neurotransmitter in the brain, promoting relaxation and reducing neuronal excitability. In individuals with insomnia, GABAergic activity is often diminished, leading to increased arousal and difficulty in initiating sleep. This reduction in GABA activity is thought to be linked to stress and anxiety, further contributing to insomnia.[44] Norepinephrine is associated with the body's fight-or-flight response and is typically elevated during periods of stress. Increased norepinephrine levels can lead to heightened arousal and vigilance, making it difficult to relax and fall asleep.[45] Chronic elevation of norepinephrine due to stress can also disrupt rapid eye movement (REM) sleep, leading to fragmented and less restorative sleep (Figure 2).[46,47] Histamine plays a dual role in sleep regulation; whereas it is involved in promoting wakefulness through its action in the hypothalamus, elevated levels of histamine can lead to insomnia and sleep disturbances. Histamine release is often increased during stress responses, contributing

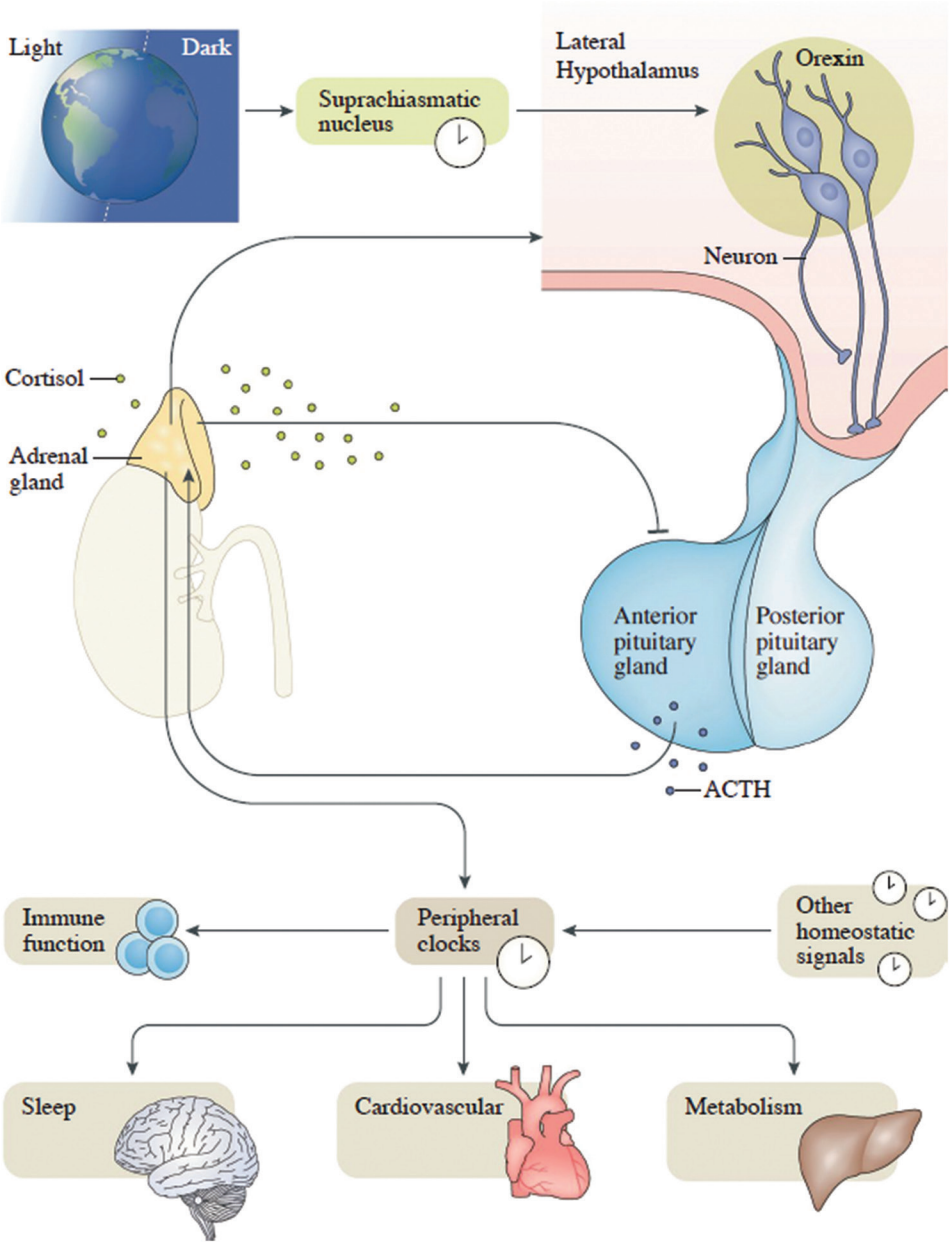

Figure 1. Hypothalamic–pituitary–adrenal (HPA) axis dysregulation and its role in insomnia. In response to stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH), which then triggers the adrenal glands to produce cortisol, a stress hormone that follows a natural diurnal rhythm. Normally, cortisol levels peak in the morning and decrease in the evening. However, chronic stress or emotional disturbances lead to an abnormal increase in evening cortisol levels, disrupting the sleep–wake cycle and contributing to insomnia. Elevated cortisol levels are linked to increased nighttime awakenings and lighter, non-restorative sleep. This figure also shows how sustained hyperarousal, triggered by the HPA axis dysregulation, perpetuates insomnia and interacts with psychological factors such as anxiety and hyperarousal. The anterior, lateral, and posterior regions of the hypothalamus are shown to emphasize the different areas affected by stress-related neuroendocrine changes. CRH, ACTH, and cortisol are highlighted to depict the core elements of HPA axis involvement in insomnia. Image created by authors using BioRender.

to heightened alertness and difficulty in transitioning to sleep.[48] Glutamate is the primary excitatory neurotransmitter in the brain. Elevated glutamate levels can lead to increased neuronal excitability and arousal, further complicating sleep initiation and maintenance. Dysregulation of glutamate signaling has been implicated in various stress-related disorders, including insomnia, by promoting a state of hyperarousal.[49]

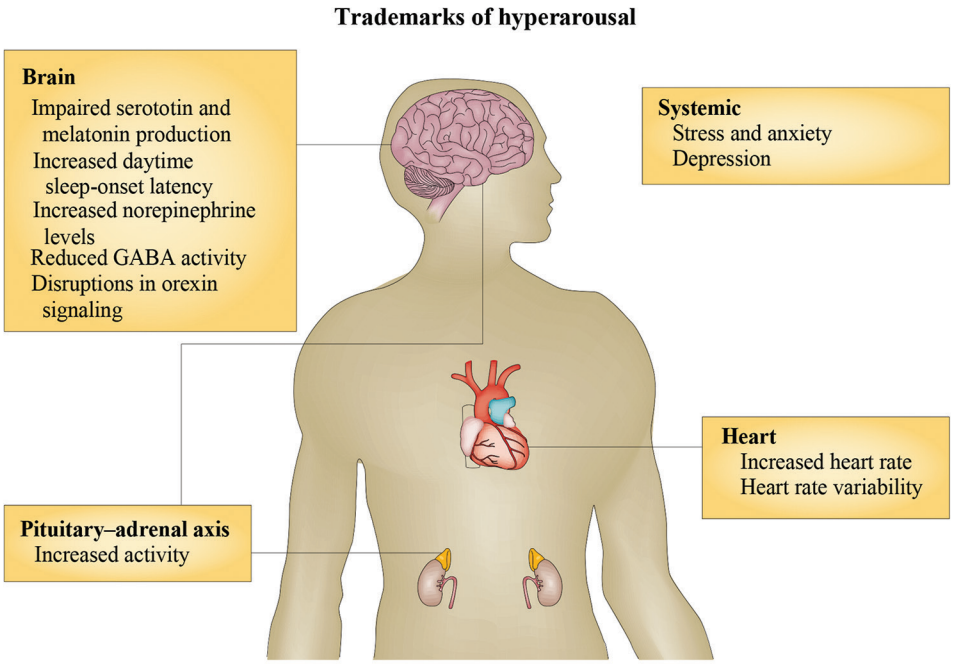

Figure 2. The role of neurotransmitter imbalances and autonomic nervous system dysregulation in the pathophysiology of insomnia. Key neurotransmitters involved in sleep regulation include serotonin, gamma-aminobutyric acid (GABA), norepinephrine, and orexin (hypocretin). Serotonin, which regulates mood and sleep, may be deficient in individuals with insomnia, affecting both sleep onset and quality. Reduced activity of GABA, which is the brain's primary inhibitory neurotransmitter, leads to increased arousal and difficulty in initiating sleep. Elevated norepinephrine levels, associated with the fight-or-flight response, contribute to hyperarousal and disrupt rapid eye movement sleep. The figure also depicts autonomic dysregulation, showing increased sympathetic nervous system activity (e.g., elevated heart rate and decreased heart rate variability), which interferes with restorative sleep. Hyperactivity in arousal centers of the brain, such as the amygdala and prefrontal cortex, even during sleep, is present in insomnia, highlighting the role of central nervous system hyperarousal in sustaining insomnia symptoms. Image created by authors using BioRender.

2.1.3. Hyperarousal and the central nervous system

Hyperarousal, defined as a heightened state of physiological and cognitive arousal, is a hallmark of insomnia, influencing both its onset and perpetuation. This state is characterized by increased activity in critical brain regions associated with arousal and emotional regulation, including the reticular activating system (RAS) and the limbic system. The RAS plays a pivotal role in maintaining wakefulness, whereas the limbic system is essential for emotional responses, underscoring the intertwined nature of physiological arousal and emotional regulation in sleep disturbances.[49,50] The relationship between hyperarousal and insomnia is reciprocal, creating a vicious cycle where difficulty sleeping heightens stress and anxiety, which subsequently exacerbates hyperarousal. Individuals struggling with insomnia often report racing thoughts and worries about their inability to sleep, leading to increased sympathetic nervous system activity, which in turn elevates cortisol levels and intensifies the stress response.[48] This cycle can be particularly pronounced in individuals with coexisting psychological conditions, such as anxiety and depression, further complicating the neurobiological underpinnings of insomnia.

Recent functional neuroimaging studies have provided valuable insights into the neurobiological correlates of hyperarousal in insomnia. Research has demonstrated that individuals with insomnia exhibit increased metabolic activity in brain regions associated with arousal, including the amygdala and prefrontal cortex, even during sleep (Figure 2). This heightened activity suggests a failure to effectively downregulate arousal systems during the transition from wakefulness to sleep, contributing to sustained wakefulness and fragmented sleep patterns.[49,50] The amygdala, in particular, is involved in processing emotional stimuli and stress responses; increased amygdala activity during sleep may reflect heightened emotional reactivity, leading to disturbed sleep continuity.[48] In addition to central nervous system factors, hyperarousal is closely linked to dysregulation of the autonomic nervous system. Individuals with insomnia often display increased sympathetic nervous system activity, characterized by elevated heart rates and reduced heart rate variability during sleep. Heart rate variability, a measure of the autonomic nervous system's flexibility in responding to stressors, is typically reduced in those with insomnia,

indicating a persistent state of physiological arousal.[48] This heightened autonomic arousal further impairs the ability to achieve restorative sleep, perpetuating the insomnia cycle.[51] The interplay between hyperarousal and the autonomic nervous system underscores the importance of considering both central and peripheral factors in understanding insomnia.

This heightened brain activity reflects a failure to adequately downregulate arousal systems during the transition from wakefulness to sleep, contributing to the sustained wakefulness and sleep fragmentation characteristic of insomnia. In addition to these central mechanisms, hyperarousal is also linked to autonomic nervous system dysregulation. This heightened autonomic arousal further interferes with the ability to achieve restorative sleep, perpetuating the cycle of insomnia (Figure 1).[51,52]

2.2. Psychological mechanisms

Psychological mechanisms also play a pivotal role in the development and maintenance of insomnia, particularly in the context of psychosomatic influences. These mechanisms encompass a range of cognitive and emotional factors that interact with neurobiological processes, contributing to the persistence of sleep disturbances.

2.2.1. Cognitive factors

Cognitive factors are central to the psychosomatic model of insomnia, with dysfunctional thought patterns often exacerbating or even initiating sleep difficulties. Individuals with insomnia frequently engage in excessive rumination and worry, particularly about their inability to sleep and the potential consequences of poor sleep. This cognitive activity typically occurs during the pre-sleep period, when the individual is lying in bed, leading to increased arousal and difficulty in falling asleep.[53] The repetitive nature of these thoughts creates a cycle of anxiety and hyperarousal, which further impairs sleep. Another critical factor is catastrophizing, which is described as the tendency to anticipate the worst possible outcomes, often related to the effects of sleep loss. For instance, individuals with insomnia might believe that a poor night's sleep will severely impair their ability to function the next day, leading to heightened anxiety and stress[54] (Figure 2). This negative thinking not only exacerbates insomnia but also reinforces the perception that sleep is beyond their control, further compounding sleep difficulties. In addition, patients with insomnia often hold unrealistic expectations about how much sleep they need or how quickly they should fall asleep.[55-58] These expectations can lead to frustration and increased effort to sleep, which paradoxically makes sleep more elusive. The discrepancy between their expectations and actual sleep experience creates cognitive dissonance, fueling anxiety and perpetuating insomnia.

2.2.2. Emotional regulation and affective states

Emotional regulation refers to the ability to manage and respond to emotional experiences in a flexible and adaptive way. Impairments in emotional regulation are closely linked to insomnia, particularly when negative emotions such as anxiety, depression, and stress are involved.[59,60]

Anxiety is one of the most common psychological factors associated with insomnia. It can manifest as generalized anxiety disorder, specific phobias, or situational anxiety related to stressors such as work, relationships, or health concerns. Anxiety enhances cognitive arousal, making it difficult to relax and fall asleep (Figure 2). Furthermore, anxiety can trigger hypervigilance during the night, causing frequent awakenings and poor sleep quality. The chronic nature of anxiety can lead to sustained insomnia, with each reinforcing the other.[57,61]

Depression is another major contributor to insomnia, causing many individuals to experience difficulty in both falling asleep and maintaining sleep.[62,63] Depression is often associated with negative rumination and a pervasive sense of hopelessness, which can disrupt sleep. In addition, changes in sleep architecture, such as reduced slow-wave sleep and shortened REM latency, are common in depression, further impairing sleep quality. The bidirectional relationship between insomnia and depression means that sleep disturbances can exacerbate depressive symptoms, creating a vicious cycle.[56,57,64]

Furthermore, individuals with insomnia often struggle with emotional dysregulation, characterized by difficulty in managing intense emotions and stress. This dysregulation can lead to heightened emotional responses to everyday stressors, increasing cognitive and physiological arousal at bedtime. Over time, this chronic state of emotional dysregulation can condition the mind and body to associate bedtime with stress and negative emotions, making sleep increasingly difficult to achieve.[65]

2.2.3. Stress and the role of hyperarousal

Stress is a well-established trigger for insomnia, particularly when it leads to hyperarousal, a state of heightened physiological and cognitive alertness that interferes with the ability to fall and stay asleep. Stress-related insomnia often arises in response to life events such as work pressures, relationship difficulties, or health concerns. When stress becomes chronic, it can lead to sustained hyperarousal, which is characterized by increased heart rate, elevated cortisol levels, and intrusive thoughts (Figure 2). Over time, the bed and sleep environment can become

conditioned stimuli that trigger hyperarousal. For example, after repeated nights of poor sleep, individuals may begin to associate their bed with wakefulness, frustration, and anxiety. This conditioned arousal perpetuates insomnia, as the very act of getting into bed triggers the body's stress response, making sleep even more difficult to achieve. The way individuals appraise and cope with stress also plays a significant role in insomnia. Those who perceive stress as overwhelming or unmanageable are more likely to experience sleep disturbances. Ineffective coping strategies, such as avoidance, denial, or maladaptive behaviors (e.g., substance use), can further exacerbate stress and contribute to the persistence of insomnia.[66]

2.3. Somatic mechanisms

Somatic mechanisms play a critical role in the manifestation and perpetuation of insomnia, particularly when physical symptoms and chronic health conditions contribute to sleep disturbances. These mechanisms involve the interaction between the body's physiological state and its impact on sleep quality, often exacerbated by underlying psychological factors.

2.3.1. Chronic pain and insomnia

Chronic pain is one of the most common somatic contributors to insomnia. Pain can interfere with sleep in several ways, including difficulty in finding a comfortable sleeping position, frequent awakenings due to pain flare-ups, and increased arousal due to discomfort. The relationship between chronic pain and insomnia is bidirectional, with each condition exacerbating the other. The presence of chronic pain increases physiological arousal, making it difficult for individuals to relax and fall asleep.[67,68] Pain triggers the body's stress response, leading to the release of stress hormones such as cortisol and adrenaline, which further disrupt sleep. This heightened state of arousal can persist throughout the night, leading to fragmented and non-restorative sleep. Sleep deprivation, in turn, increases sensitivity to pain, creating a vicious cycle. When sleep is disrupted, the body's ability to modulate pain is impaired, leading to an increase in pain perception. This heightened pain sensitivity can exacerbate chronic pain conditions, further interfering with sleep and perpetuating insomnia.[69,70]

2.3.2. Medical conditions and sleep disturbances

A variety of medical conditions are associated with insomnia, either directly through symptoms that interfere with sleep or indirectly through the psychological distress they cause. Gastroesophageal reflux disease can cause discomfort and pain, particularly when lying down, leading to frequent awakenings and difficulty falling back asleep. The nocturnal symptoms of gastroesophageal reflux disease, such as heartburn and regurgitation, can be particularly disruptive, resulting in poor sleep quality.[71,72] Conditions such as asthma and chronic obstructive pulmonary disease can lead to breathing difficulties during the night, causing awakenings and disrupted sleep. The need to manage symptoms, such as coughing or shortness of breath, can make it difficult to maintain continuous sleep.[73,74] Cardiovascular conditions, such as hypertension and heart disease, are often accompanied by nocturnal symptoms, including palpitations, chest pain, and difficulty breathing. These symptoms can interfere with the ability to achieve and maintain sleep, leading to insomnia.[75,76] Conditions such as Parkinson's disease, restless legs syndrome, and multiple sclerosis are associated with a range of symptoms that can disrupt sleep, including muscle rigidity, involuntary movements, and sensory disturbances. These symptoms often worsen at night, contributing to sleep fragmentation and insomnia.[77-80]

2.3.3. Somatic hypervigilance and perception of bodily symptoms

Somatic hypervigilance refers to an increased awareness and monitoring of bodily sensations, often accompanied by an exaggerated response to these sensations. Individuals with insomnia, particularly those with psychosomatic influences, may exhibit heightened sensitivity to normal bodily sensations, such as heart rate, breathing, or muscle tension. This heightened awareness can lead to amplification of symptoms such as somatic hypervigilance, which can cause individuals to perceive normal bodily sensations as more intense or distressing than they are, leading to increased anxiety and arousal.[81] For example, a person might become overly focused on their heart rate or breathing pattern while trying to fall asleep, which can increase stress and interfere with the sleep process. The preoccupation with bodily sensations can also lead to sleep-related anxiety, where individuals become fearful of the sensations they experience at night, such as palpitations or shortness of breath. This anxiety further disrupts sleep by increasing arousal and making it difficult to relax.

Somatic conditions often have a significant impact on psychological well-being, contributing to the development of insomnia. Chronic pain, for example, is associated with increased rates of depression and anxiety, both of which are common comorbidities in individuals with insomnia.[71] The presence of a chronic medical condition can lead to feelings of helplessness, frustration, and fear about the future, all of which contribute to sleep disturbances. In addition, the interaction between cognitive processes (such as worry about health) and affective states (such as anxiety and depression) can exacerbate somatic symptoms

and contribute to the perpetuation of insomnia. Somatic conditions can also lead to maladaptive behaviors that perpetuate insomnia, such as avoiding physical activity due to pain or discomfort, which can disrupt sleep patterns and reduce sleep quality.[64,65,82,83] In some cases, individuals may engage in behaviors that they believe will improve sleep but that actually worsen it, such as spending excessive time in bed or using sleep medications inappropriately.

3. Diagnosis of psychosomatic insomnia

Diagnosing psychosomatic insomnia requires a nuanced approach that considers the intricate interplay between psychological, somatic, and neurobiological factors. The diagnostic process involves identifying the underlying psychosomatic influences that contribute to sleep disturbances, distinguishing psychosomatic insomnia from other sleep disorders, and utilizing appropriate assessment tools to accurately evaluate the condition.

3.1. Diagnostic criteria

The diagnosis of psychosomatic insomnia typically relies on a combination of clinical criteria that reflect the psychological and somatic components of the disorder:

(i) Difficulty initiating sleep, maintaining sleep, or experiencing non-restorative sleep, occurring at least 3 nights per week for a minimum of 3 months[84,85]
(ii) The presence of sleep disturbance that is significant enough to cause distress or impairment in daytime functioning
(iii) The presence of psychological factors that contribute to the onset or maintenance of insomnia, such as stress, anxiety, or depression, which manifest as excessive worry about sleep, cognitive hyperarousal, or emotional dysregulation[86]
(iv) Manifestation of somatic symptoms or chronic medical conditions, including chronic pain, gastrointestinal issues, respiratory problems, or other sleep-interfering physical conditions, that may contribute to sleep disturbances
(v) The presence of significant daytime impairment due to sleep disturbances, such as fatigue, mood disturbances, cognitive impairment, or decreased quality of life
(vi) The presence of sleep disturbance is not accounted for by another sleep disorder (e.g., sleep apnea and restless legs syndrome) or causally related to the effects of substance use or medication.[85-87]

3.2. Assessment tools

Accurate diagnosis of psychosomatic insomnia requires the use of various assessment tools that help identify the contributing factors and severity of the disorder. Structured or semi-structured clinical interviews are essential for gathering detailed information about a patient's sleep history, psychological state, and somatic symptoms. Interviews should explore the onset, duration, and nature of sleep disturbances, as well as any associated psychological or physical factors. Patients may be asked to maintain a sleep diary over a period of 1 – 2 weeks. The diary typically includes entries on sleep onset, wake times, nighttime awakenings, sleep quality, and daytime functioning. This tool helps to identify patterns in sleep behavior and the impact of psychosomatic factors on sleep. Several validated questionnaires and self-report scales can be used to assess insomnia severity, psychological distress, and somatic symptoms. Commonly used tools include: the Insomnia Severity Index, a widely used questionnaire that assesses the severity of insomnia and its impact on daily life;[88] the Pittsburgh Sleep Quality Index, a comprehensive tool for assessing sleep quality and disturbances over the past month;[89] the Beck Depression Inventory and Beck Anxiety Inventory, tools that assess the presence and severity of depressive and anxiety symptoms, which are often associated with insomnia;[90] the Brief Pain Inventory, a tool for assessing the severity of pain and its impact on daily functioning, useful in cases where chronic pain contributes to insomnia;[91] polysomnography, employed in cases where there is a suspicion of coexisting sleep disorders such as sleep apnea, or when the diagnosis is unclear; and actigraphy, a non-invasive method involving wearing a wristwatch-like device that monitors movement to estimate sleep patterns over several days or weeks.[92]

4. Treatment strategies

Effective treatment of psychosomatic insomnia requires a multidisciplinary approach that addresses the psychological, somatic, and behavioral aspects of the disorder. Treatment strategies typically involve a combination of psychological interventions, pharmacological approaches, integrative and holistic therapies, and lifestyle modifications.

4.1. Psychological interventions

Psychological interventions are central to the treatment of psychosomatic insomnia, particularly given the significant role of cognitive and emotional factors in the disorder.

As the gold-standard psychological treatment for insomnia, cognitive-behavioral therapy for insomnia (CBT-I) can effectively address both cognitive and behavioral aspects of the disorder.[93-95] The core components of CBT-I include cognitive restructuring, which focuses on identifying and challenging dysfunctional beliefs and attitudes about sleep, such as catastrophic thinking about the consequences of poor sleep or unrealistic sleep expectations.[96] Sleep restriction therapy is a well-known

strategy that focuses on limiting the time spent in bed to match the actual amount of sleep obtained, thereby increasing sleep efficiency and reducing the time spent awake in bed.[97-100] Another strategy known as stimulus control therapy centers on reinforcing the association between the bed and sleep by establishing a regular sleep–wake schedule and avoiding activities such as reading or watching TV in bed.[101]

Other approaches such as relaxation techniques, such as progressive muscle relaxation, deep breathing, or mindfulness meditation, reduce pre-sleep arousal and facilitate the sleep onset process. Mindfulness-based stress reduction (MBSR) is a therapeutic approach that incorporates mindfulness meditation and awareness practices to reduce stress and enhance emotional regulation. For individuals with psychosomatic insomnia, MBSR can help break the cycle of stress and hyperarousal that disrupts sleep. By fostering a non-judgmental awareness of thoughts and sensations, MBSR allows patients to disengage from unhelpful cognitive patterns that contribute to insomnia.[102-104] Also, acceptance and commitment therapy focuses on helping individuals accept their insomnia-related thoughts and feelings without trying to control or avoid them. The therapy emphasizes the importance of living a meaningful life despite sleep difficulties, which can reduce the anxiety and frustration associated with insomnia.[105-107] Lastly, biofeedback, which involves using electronic devices to monitor physiological processes such as heart rate, muscle tension, and skin temperature, enables patients to learn to control these processes through relaxation techniques, which can help reduce physiological arousal and improve sleep quality.[108]

4.2. Pharmacological approaches

Pharmacological treatment may be considered for individuals with psychosomatic insomnia, particularly when psychological interventions alone are insufficient. However, medications should be used with caution and typically as part of a broader treatment plan.[109]

Short-term use of hypnotic medications, such as benzodiazepines (e.g., temazepam) or non-benzodiazepine sleep aids (e.g., zolpidem, eszopiclone), can help alleviate acute sleep disturbances. These medications are effective in reducing sleep latency and improving sleep duration but should be prescribed cautiously due to the risk of dependence, tolerance, and withdrawal symptoms.[110,111] Certain antidepressants, particularly those with sedative properties such as trazodone or mirtazapine, are often prescribed to treat insomnia, especially when the patient is comorbid with depression or anxiety. These medications can help regulate sleep architecture and reduce the psychological symptoms that contribute to insomnia.[112-114]

Other compounds such as melatonin, a hormone that regulates the SWC, and melatonin receptor agonists such as ramelteon, can be used to address circadian rhythm disturbances and improve sleep onset. Melatonin is particularly useful in cases of delayed sleep phase syndrome or jet lag.[115,116] Orexin receptor antagonists, such as suvorexant, are a newer class of sleep medications that target the orexin system, which regulates wakefulness. These medications help to reduce wakefulness and promote sleep without the sedative side effects associated with other hypnotics.[117-119] Finally, antihistamines (e.g., diphenhydramine) are sometimes used as sleep aids due to their sedative effects.[120] However, they are generally not recommended for long-term use due to the potential side effects, including next-day drowsiness and cognitive impairment.

Cannabinoids are therapeutic agents that are gaining a lot of interest in this field. Cannabinoids are the active compounds found in the cannabis plant. The most prominent cannabinoids, namely tetrahydrocannabinol (THC) and cannabidiol (CBD) interact with the body's endocannabinoid system (ECS), which is integral to regulating sleep, mood, pain, and other physiological processes. The ECS is a complex network that includes cannabinoid receptors, primarily CB1 and CB2, along with endogenous cannabinoids such as anandamide and 2-arachidonoylglycerol.[121,122] These receptors are widely distributed throughout the central nervous system and peripheral tissues. The ECS helps regulate various physiological functions, including the SWC, by modulating neurotransmitter release and influencing neural activity in brain regions involved in sleep regulation.[123,124] THC, the psychoactive component of cannabis, is known for its ability to induce sedation and alter sleep patterns. THC primarily acts on CB1 receptors, which are abundant in brain regions associated with sleep regulation, such as the hypothalamus and brainstem. By binding to these receptors, THC can reduce sleep latency (i.e., the time it takes to fall asleep) and increase overall sleep duration, making it a potential remedy for individuals with insomnia. However, THC's effects on sleep architecture are complex. While it may increase slow-wave sleep (deep sleep), it can also reduce REM sleep, which is essential for cognitive functions such as memory consolidation.[125,126] The reduction in REM sleep could be a potential drawback, especially for long-term use. CBD, on the other hand, has gained popularity for its non-psychoactive properties and its ability to promote relaxation and reduce anxiety. CBD interacts with the ECS differently than THC. It has a low affinity for CB1 and CB2 receptors but exerts its effects by influencing other receptors and pathways, such as serotonin receptors (specifically 5-HT1A) and GABAergic transmission. CBD

has been shown to have anxiolytic (anxiety-reducing) effects, which can be particularly beneficial for individuals whose insomnia is driven by anxiety or stress.[127,128] Unlike THC, CBD does not have sedative effects at typical doses, but it can help improve sleep by reducing the cognitive arousal and anxiety that often interfere with sleep onset. Moreover, CBD has been found to modulate the SWC through its effects on the hypothalamus, which plays a crucial role in maintaining circadian rhythms.[129,130] By interacting with these pathways, CBD may help stabilize sleep patterns, particularly in individuals with disrupted circadian rhythms or those suffering from sleep disorders related to anxiety. When THC and CBD are used together, they may produce synergistic effects that enhance their potential benefits for treating insomnia.[131] THC's sedative properties can help reduce sleep latency, whereas CBD's anxiolytic effects can improve sleep quality by alleviating the anxiety that often accompanies insomnia. This combination might be particularly effective for patients who have difficulty falling asleep due to stress or chronic pain, as CBD can also reduce inflammation and pain perception.[132,133]

4.3. Integrative approaches

Integrative and holistic approaches to managing psychosomatic insomnia emphasize treating the whole person, addressing both mind and body. These strategies complement conventional psychological and pharmacological treatments, offering a multifaceted approach to sleep disturbances. By focusing on the interplay between physical health, emotional well-being, and lifestyle choices, these integrative therapies aim to create a more balanced and supportive environment for restful sleep.

Herbal remedies have been utilized for centuries to promote relaxation and enhance sleep quality. Commonly used herbs include valerian root, chamomile, and passionflower. Valerian root, known for its sedative properties, has been shown to shorten the time for falling asleep and improve overall sleep quality. Specifically, valerian is thought to increase GABA levels in the brain, helping calm nervous activity and promote sleep.[134] Chamomile, often consumed as tea, possesses mild sedative effects and has been linked to improved sleep quality and reduced insomnia symptoms; research indicates that its antioxidant properties may contribute to its relaxing effects.[135] Passionflower is another herb traditionally used to alleviate anxiety and promote sleep; some studies suggest that it may increase GABA levels, thereby enhancing its calming effects.[134,135] Despite the varying evidence regarding their efficacy, these herbs are generally considered safe when used appropriately. However, it is crucial for individuals to consult with a healthcare provider before incorporating herbal supplements into their routine, especially if they are already taking medications, to avoid potential interactions and ensure that the chosen remedy aligns with their health profile.

Mind-body practices play a significant role in integrative approaches to insomnia by combining physical movement, breathing exercises, and meditation to promote relaxation and reduce stress. Regular practice of yoga has been associated with improvements in sleep quality and reductions in insomnia symptoms by reducing cortisol levels, enhancing emotional regulation, and improving overall well-being, contributing to better sleep.[136] A systematic review found that yoga interventions significantly improved sleep quality in individuals with chronic insomnia, suggesting that the combination of physical activity, controlled breathing, and mindfulness inherent in yoga may create a conducive environment for restful sleep.[136] Similarly, Tai Chi, a form of gentle martial arts emphasizing slow, deliberate movements and deep breathing, has been shown to improve sleep quality and reduce insomnia symptoms, particularly in older adults. A study has indicated that Tai Chi can promote relaxation and reduce anxiety, which are crucial factors in managing insomnia.[137] These practices foster relaxation and encourage mindfulness, helping individuals better manage stress and anxiety, which are common contributors to insomnia.

Dietary factors are also essential in the integrative management of insomnia, as certain nutrients can significantly influence sleep quality. For instance, magnesium, a mineral required in sleep regulation, is critical for maintaining healthy sleep patterns. It has been shown that magnesium supplementation can improve sleep quality, especially in individuals with deficiencies, and its role in regulating neurotransmitters, such as GABA, further highlights its importance in sleep health.[138] In addition to supplementation, focusing on a balanced diet that supports stable blood sugar levels is crucial for sleep health. Consuming whole foods rich in vitamins, minerals, and antioxidants can enhance overall health and well-being, thereby promoting better sleep. Avoiding stimulants, such as caffeine and nicotine, particularly in the hours leading up to bedtime, is also important, as these substances can interfere with the body's natural SWC.[142]

Furthermore, the timing of meals can affect sleep quality; late-night eating or consuming heavy meals close to bedtime can lead to discomfort and disrupt the sleep cycle. Adopting a diet that emphasizes sleep-promoting nutrients, such as tryptophan (found in turkey and dairy), can also support better sleep.[139-141] Overall, these integrative

strategies provide a holistic framework for addressing psychosomatic insomnia, fostering both immediate relief and long-term resilience against sleep disturbances.

4.4. Lifestyle modifications

Lifestyle modifications are an essential component of treating psychosomatic insomnia. These changes aim to promote healthy sleep habits, reduce stress, and support overall well-being. Good sleep hygiene practices are foundational to managing insomnia. Going to bed and waking up at the same time each day helps regulate the body's internal clock. The bedroom should be quiet, dark, and cool, with a comfortable mattress and pillows. Removing electronic devices from the bedroom can also reduce exposure to blue light, which interferes with melatonin production.[143]

Other modifications include avoiding caffeine, nicotine, and alcohol, particularly in the hours leading up to bedtime, which can help prevent sleep disturbances. Regular physical activity has been shown to improve sleep quality and reduce symptoms of insomnia. Moderate aerobic exercise, such as walking, swimming, or cycling, can be particularly effective.[144-146] However, it is important to avoid vigorous exercise close to bedtime, as it may increase arousal and make it difficult to fall asleep. Limiting activities that require intense cognitive engagement close to bedtime, such as working, studying, or engaging in stimulating conversations, can help reduce cognitive arousal and facilitate sleep onset.

5. Discussion

The examination of psychosomatic factors establishes insomnia as a complex and multifaceted disorder, characterized by the intricate interplay of neurobiological, psychological, and somatic mechanisms. Understanding these interconnections is crucial for accurate diagnosis and effective treatment, as each mechanism contributes to the persistence and severity of insomnia.

At the core of psychosomatic insomnia are neurobiological mechanisms that play a pivotal role in both the onset and perpetuation of this disorder. Dysregulation of the HPA axis, coupled with hyperactivity of the autonomic nervous system, emerges as a particularly significant factor. Chronic stress, a prevalent precursor to insomnia, elevates levels of cortisol and other stress hormones, thereby intensifying arousal and disrupting the natural SWC.[147] This heightened physiological arousal perpetuates a state of hypervigilance, making it increasingly challenging to fall asleep and maintain restorative sleep. Moreover, disruptions in circadian rhythms often exacerbated by stress and psychological distress further complicate the regulation of sleep, leading to chronic sleep disturbances.[148]

Equally critical in understanding psychosomatic insomnia are the psychological mechanisms that influence sleep quality. Cognitive factors, including heightened arousal, persistent worry about sleep, and maladaptive beliefs, contribute significantly to the disorder.[149] These psychological processes create a vicious cycle where concerns about sleep exacerbate anxiety, leading to further disturbances in sleep. Emotional dysregulation, frequently observed in conditions such as anxiety and depression, plays a pivotal role in perpetuating insomnia. The bidirectional relationship between insomnia and these psychological disorders underscores the necessity for interventions that address both cognitive and emotional dimensions. CBT-I, in particular, has proven effective in disrupting this cycle by targeting maladaptive thought patterns and behaviors.[150]

Compounding the challenge of insomnia are somatic mechanisms, as physical symptoms and chronic medical conditions often contribute to sleep disturbances. Conditions such as chronic pain, gastrointestinal issues, and respiratory problems can lead to fragmented sleep and increased nighttime awakenings.[150] The interplay between somatic complaints and psychological factors establishes a feedback loop where physical discomfort exacerbates psychological distress and *vice versa*. This interconnectedness highlights the importance of a comprehensive treatment approach that addresses both the physical and psychological dimensions of insomnia.

To effectively diagnose insomnia, comprehensive and integrative diagnostic approaches are required to recognize the complex interactions among these mechanisms. Utilizing diagnostic criteria that encompass both psychological and somatic factors is paramount. Assessment tools, including clinical interviews, sleep diaries, standardized questionnaires, and objective measures such as polysomnography, play a vital role in accurately diagnosing psychosomatic insomnia. In addition, differential diagnosis is crucial in distinguishing this condition from other sleep disorders, such as sleep apnea or restless legs syndrome, which may present with similar symptoms but necessitate different treatment strategies.

Treatment strategies for psychosomatic insomnia must be personalized and multifaceted, addressing the neurobiological, psychological, and somatic components of the disorder. Psychological interventions, particularly CBT-I, stand as the cornerstone of treatment, effectively targeting maladaptive thoughts and behaviors contributing to insomnia. Pharmacological approaches, including

hypnotics and antidepressants, may be necessary in some cases, especially when insomnia is severe or when psychological interventions alone are insufficient. Furthermore, integrative and holistic approaches such as acupuncture, herbal remedies, and mind-body practices such as yoga offer additional avenues for treatment, particularly for patients who prefer non-pharmacological options.[151] Lifestyle modifications, such as good sleep hygiene, regular physical activity, and stress management techniques, are also essential components of a comprehensive treatment plan.

Despite significant advances in understanding and treating psychosomatic insomnia, several challenges and controversies persist. One major hurdle is the heterogeneity of the disorder, with patients presenting a wide array of symptoms and contributing factors. This variability complicates the development of standardized diagnostic criteria and treatment protocols. In addition, ongoing debates regarding the optimal approaches to treatment, particularly the relative merits of pharmacotherapy versus psychological interventions, continue to evolve. While CBT-I has demonstrated high efficacy for many patients, others may not respond favorably, and the long-term use of hypnotic medications raises concerns about dependency and potential side effects. Moreover, gaps in the literature persist regarding the long-term outcomes of various treatment strategies. For example, while integrative and holistic approaches are gaining popularity, more research is needed to establish their efficacy and safety in treating psychosomatic insomnia. The relationship between somatic conditions and insomnia remains poorly understood, particularly regarding the mechanisms through which physical symptoms interact with psychological factors to perpetuate sleep disturbances. Future research should aim to address these challenges, emphasizing personalized treatment approaches that consider the unique combination of neurobiological, psychological, and somatic factors each individual presents. Longitudinal studies are particularly warranted to explore the long-term efficacy and safety of diverse treatment strategies, especially integrative and holistic methods. Furthermore, understanding the mechanisms underlying the interactions between somatic conditions and insomnia could lead to more targeted interventions.

Within this framework, the interactions among CBD, THC, and the ECS merit attention, as they present a promising avenue for addressing insomnia. The ECS plays a crucial role in maintaining homeostasis within the body, influencing various physiological processes, including sleep regulation, stress response, and mood. Both CBD and THC interact with the ECS, albeit in different ways, contributing to their respective therapeutic effects. CBD is primarily known for its anxiolytic and anti-inflammatory properties. It does not produce the psychoactive effects associated with THC, making it an appealing option for individuals seeking relief from insomnia, without causing cognitive impairment that THC may induce.[152] CBD's influence on the ECS appears to enhance the body's natural ability to regulate sleep, potentially by modulating anxiety levels and promoting relaxation. This can be particularly beneficial for those whose insomnia is rooted in psychological distress or stress-related conditions. THC, on the other hand, is the psychoactive component of cannabis, known for its sedative properties. THC may facilitate sleep onset by reducing sleep latency; however, its use can also lead to alterations in sleep architecture, such as reduced REM sleep, which could have implications for overall sleep quality. The effects of THC can vary widely among individuals, depending on factors such as dosage, tolerance, and the presence of other cannabinoids and terpenes within the cannabis plant.

The interplay between CBD, THC, and the ECS suggests that a balanced approach, utilizing both compounds, may offer the most effective treatment for insomnia. Some studies indicate that a combination of CBD and THC may enhance the sedative effects of THC while mitigating potential side effects, such as anxiety or cognitive impairment, associated with higher doses of THC alone. This synergy highlights the potential of cannabis-based therapies in addressing the multifaceted nature of insomnia, particularly when tailored to individual needs and responses.

A deeper understanding of the complex interplay between neurobiological, psychological, and somatic factors in psychosomatic insomnia will pave the way for more effective and personalized treatment strategies. Integrating advancements in technology, such as wearable devices for monitoring sleep patterns and physiological responses, alongside genetic and biomarker research, could lead to the precise identification of individuals at risk for psychosomatic insomnia and the development of targeted interventions that address specific biological pathways. Ultimately, these comprehensive approaches hold the promise of improving outcomes for individuals grappling with this challenging disorder.

6. Conclusion

Psychosomatic insomnia is a multifaceted disorder characterized by the interaction between neurobiological, psychological, and somatic mechanisms, each contributing to the persistence and complexity of sleep disturbances. The synthesis of current research emphasizes the importance of understanding these interactions to develop effective

diagnostic and treatment strategies. Neurobiological dysregulation, particularly involving the HPA axis and circadian rhythms, plays a crucial role in the disorder, whereas psychological factors such as cognitive arousal and emotional dysregulation further complicate the SWC. In addition, somatic conditions such as chronic pain and other physical health issues significantly contribute to insomnia, creating a feedback loop that exacerbates both psychological and physical symptoms.

Accurate diagnosis of psychosomatic insomnia requires a comprehensive approach, integrating diagnostic criteria that consider psychological, somatic, and neurobiological factors. Assessment tools, including clinical interviews, sleep diaries, and objective measures such as polysomnography, are essential for understanding the scope of the disorder and differentiating it from other sleep disorders. Effective treatment strategies, combining psychological interventions such as CBT-I with pharmacological approaches, integrative therapies, and lifestyle modifications, should be deployed to address the disorder's multifaceted nature.

Despite advances in treatment, challenges and uncertainties remain, including variability in patient responses, the debate over pharmacotherapy versus psychological interventions, and the gaps in understanding the long-term outcomes of various treatments. Future research should focus on personalized approaches, exploring the long-term efficacy of different treatment strategies, and leveraging technological advancements to improve diagnosis and treatment. Understanding the complex interactions between neurobiological, psychological, and somatic factors will be key to developing more effective, bespoke interventions and improving outcomes for individuals affected by psychosomatic insomnia.

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Author contributions

Conceptualization: Alejandro Camacho-Zamora, Alberto K. De la Herrán-Arita

Visualization: Josué Camberos-Barraza, Alberto K. De la Herrán-Arita

Writing–original draft: Alejandro Camacho-Zamora, Josué Camberos-Barraza, Ángel R. Rábago-Monzón, Alberto K. De la Herrán-Arita

Writing–review & editing: Ángel R. Rábago-Monzón, Hugo J. Sosa-Arámbula, Alberto K. De la Herrán-Arita

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References

1. Sutton EL. Insomnia. *Ann Intern Med*. 2021;174(3):ITC33-ITC48.

   doi: 10.7326/aitc202103160

2. Perlis ML, Posner D, Riemann D, Bastien CH, Teel J, Thase M. Insomnia. *Lancet*. 2022;400(10357):1047-1060.

   doi: 10.1016/s0140-6736(22)00879-0

3. Buysse DJ. Insomnia. *JAMA*. 2013;309(7):706-716.

   doi: 10.1001/jama.2013.193

4. Tatayeva R, Ossadchaya E, Sarculova S, Sembayeva Z, Koigeldinova S. Psychosomatic aspects of the development of comorbid pathology: A review. *Med J Islam Repub Iran*. 2022;36:152.

   doi: 10.47176/mjiri.36.152

5. Koliadenko NV, Bachurina NO, Zhyvaho KS, Shopsha MM, Shopsha OL. Psychosomatic manifestations of military psychotrauma. *Clin Prev Med*. 2023;8:30-38.

   doi: 10.31612/2616-4868.8.2023.03

6. Taylor GJ. Psychoanalysis and psychosomatics: A new synthesis. *Psychodyn Psychiatry*. 2022;50(2):306-325.

   doi: 10.1521/pdps.2022.50.2.306

7. Khazaei H, Zakiei A, Rezaei M, Hoseini SM, Alikhani M. Emotional dysregulation leads to reduced sleep quality when the level of repetitive negative thoughts is high: Findings of a structural equation model. *Iran J Psychiatry Behav Sci*. 2019;13:e64661.

   doi: 10.5812/ijpbs.64661

8. Van Someren EJW. Brain mechanisms of insomnia: New perspectives on causes and consequences. *Physiol Rev*. 2020;101(3):995-1046.

   doi: 10.1152/physrev.00046.2019

9. Riemann D, Benz F, Dressle R, *et al*. Insomnia disorder:

State of the science and challenges for the future. *J Sleep Res*. 2022;31(4):e13604.

doi: 10.1111/jsr.13604

10. Stanton D, Justin HS, Reitzel AM. Step in time: Conservation of circadian clock genes in animal evolution. *Integr Comp Biol*. 2022;62:1503-1518.

doi: 10.1093/icb/icac140

11. Ke P, Zheng C, Liu F, *et al*. Relationship between circadian genes and memory impairment caused by sleep deprivation. *PeerJ*. 2022;10:e13165.

doi: 10.7717/peerj.13165

12. Xiao Y, Yuan Y, Jimenez M, Soni N, Yadlapalli S. Clock proteins regulate spatiotemporal organization of clock genes to control circadian rhythms. *Proc Natl Acad Sci*. 2021;118:e2019756118.

doi: 10.1073/pnas.2019756118

13. Yang Y, Wu G, Sancar A, Hogenesch JB. Mutations of the circadian clock genes Cry, Per, or Bmal1 have different effects on the transcribed and nontranscribed strands of cycling genes. *Proc Natl Acad Sci U S A*. 2024;121(8):e2316731121.

doi: 10.1073/pnas.2316731121

14. Zhuang Y, Li Z, Xiong S, *et al*. Circadian clocks are modulated by compartmentalized oscillating translation. *Cell*. 2023;186(15):3245-3260.e23.

doi: 10.1016/j.cell.2023.05.045

15. Lu Q, Kim JY. Mammalian circadian networks mediated by the suprachiasmatic nucleus. *FEBS J*. 2021;289:6589-6604.

doi: 10.1111/febs.16233

16. Sakurai T, Amemiya A, Ishii M, *et al*. Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*. 1998;92(4):573-585.

doi: 10.1016/s0092-8674(00)80949-6

17. Sharma R, Sahota P, Thakkar MM. Melatonin promotes sleep in mice by inhibiting orexin neurons in the perifornical lateral hypothalamus. *J Pineal Res*. 2018;65(2):e12498.

doi: 10.1111/jpi.12498

18. Chemelli RM, Willie JT, Sinton CM, *et al*. Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation. *Cell*. 1999;98(4):437-451.

doi: 10.1016/s0092-8674(00)81973-x

19. Toor B, Ray LB, Pozzobon A, Fogel SM. Sleep, orexin and cognition. *Front Neurol Neurosci*. 2021;45:38-51.

doi: 10.1159/000514960

20. Sun Y, Tisdale RK, Kilduff TS. Hypocretin/orexin receptor pharmacology and sleep phases. *Front Neurol Neurosci*. 2021;45:22-37.

doi: 10.1159/000514963

21. Pizza F, Barateau L, Dauvilliers Y, Plazzi G. The orexin story, sleep and sleep disturbances. *J Sleep Res*. 2022;31(4):e13665.

doi: 10.1111/jsr.13665

22. De Luca R, Nardone S, Grace KP, *et al*. Orexin neurons inhibit sleep to promote arousal. *Nat Commun*. 2022;13(1):4163.

doi: 10.1038/s41467-022-31591-y

23. De la Herrán-Arita AK, Guerra-Crespo M, Drucker-Colín, R. Narcolepsy and orexins: An example of progress in sleep research. *Front Neurol*. 2011;2:26.

doi: 10.3389/fneur.2011.00026

24. Li SB, Damonte VM, Chen C, *et al*. Hyperexcitable arousal circuits drive sleep instability during aging. *Science*. 2022;375(6583):eabh3021.

doi: 10.1126/science.abh3021

25. De la Herrán-Arita AK, García-García F. Narcolepsy as an immune-mediated disease. *Sleep Disord*. 2014;2014:792687.

doi: 10.1155/2014/792687

26. De la Herrán-Arita AK, Zomosa-Signoret VC, Millán-Aldaco DA, *et al*. Aspects of the narcolepsy-cataplexy syndrome in O/E3-null mutant mice. *Neuroscience*. 2011;183:134-143.

doi: 10.1016/j.neuroscience.2011.03.029

27. Borbély A. The two-process model of sleep regulation: Beginnings and outlook. *J Sleep Res*. 2022;31(4):e13598.

doi: 10.1111/jsr.13598

28. Ho MCW, Tabuchi M, Xie X, *et al*. Sleep need-dependent changes in functional connectivity facilitate transmission of homeostatic sleep drive. *Curr Biol*. 2022;32(22):4957-4966.e5.

doi: 10.1016/j.cub.2022.09.048

29. Piltz SH, Diniz Behn CG, Booth V. Habitual sleep duration affects recovery from acute sleep deprivation: A modeling study. *J Theor Biol*. 2020;504:110401.

doi: 10.1016/j.jtbi.2020.110401

30. Khodasevich D, Tsui S, Keung D, Skene DJ, Revell V, Martinez ME. Characterizing the modern light environment and its influence on circadian rhythms. *Proc Biol Sci*. 2021;288(1955):20210721.

doi: 10.1098/rspb.2021.0721

31. Faragó A, Zsindely N, Bodai L. Mutant huntingtin disturbs circadian clock gene expression and sleep patterns in *Drosophila*. *Sci Rep*. 2019;9(1):7174.

doi: 10.1038/s41598-019-43612-w

32. Hor CN, Yeung J, Jan M, *et al*. Sleep-wake-driven and circadian contributions to daily rhythms in gene expression and chromatin accessibility in the murine cortex. *Proc Natl Acad Sci*. 2019;116(51):25773-25783.

doi: 10.1073/pnas.1910590116

33. Rijo-Ferreira F, Bjorness TE, Cox KH, Sonneborn A, Greene RW, Takahashi JS. Sleeping sickness disrupts the sleep-regulating adenosine system. *J Neurosci*. 2020;40(48):9306-9316.

doi: 10.1523/JNEUROSCI.1046-20.2020

34. Hirano A, Hsu PK, Zhang L, *et al*. DEC_2 modulates orexin expression and regulates sleep. *Proc Natl Acad Sci*. 2018;115(13):3434-3439.

doi: 10.1073/pnas.1801693115

35. Leistner C, Menke A. Hypothalamic-pituitary-adrenal axis and stress. *Handb Clin Neurol*. 2020;175:55-64.

doi: 10.1016/B978-0-444-64123-6.00004-7

36. Goncharova ND. The HPA axis under stress and aging: Individual vulnerability is associated with behavioral patterns and exposure time. *BioEssays*. 2020;42(9):e2000007.

doi: 10.1002/bies.202000007

37. Raise-Abdullahi P, Meamar M, Vafaei A, *et al*. Hypothalamus and post-traumatic stress disorder: A review. *Brain Sci*. 2023;13(7):1010.

doi: 10.3390/brainsci13071010

38. Juruena MF, Eror F, Cleare AJ, Young AH. The role of early life stress in HPA axis and anxiety. *Adv Exp Med Biol*. 2020;1191(1191):141-153.

doi: 10.1007/978-981-32-9705-0_9

39. Chan JF, Andersen JP. Physiological stress responses associated with high-risk occupational duties. In: *Occupational Wellbeing*. London: IntechOpen; 2021.

doi: 10.5772/intechopen.93943

40. Hayes B, Brent J, Zhong Y, *et al*. Early cortisol and inflammatory responses to parental cancer and their impact on functional impairment in youth. *J Clin Med*. 2021;10(4):576.

doi: 10.3390/jcm10040576

41. Okajima I, Kadotani H, On behalf of the NinJa Sleep Study Group. Association of sleep reactivity and anxiety sensitivity with insomnia-related depression and anxiety among City government employees in Japan. *Clocks Sleep*. 2023;5(2):167-176.

doi: 10.3390/clockssleep5020015

42. Vanini G, Torterolo P. Sleep-wake neurobiology. *Adv Exp Med Biol*. 2021;1297:65-82.

doi: 10.1007/978-3-030-61663-2_5

43. Li YI, Starr LR, Wray-Lake L. Insomnia mediates the longitudinal relationship between anxiety and depressive symptoms in a nationally representative sample of adolescents. *Depress Anxiety*. 2018;35(6):583-591.

doi: 10.1002/da.22764

44. Xiang T, Liao J, Cai Y, *et al*. Impairment of GABA inhibition in insomnia disorders: Evidence from the peripheral blood system. *Front Psychiatry*. 2023;14:1134434.

doi: 10.3389/fpsyt.2023.1134434

45. Holst SC, Landolt HP. Sleep-wake neurochemistry. *Sleep Med Clin*. 2018;13(2):137-146.

doi: 10.1016/j.jsmc.2018.03.002

46. Kiehn JT, Faltraco F, Palm D, Thome J, Oster H. Circadian clocks in the regulation of neurotransmitter systems. *Pharmacopsychiatry*. 2019;56:108-117.

doi: 10.1055/a-1027-7055

47. Dressle RJ, Riemann D. Hyperarousal in insomnia disorder: Current evidence and potential mechanisms. *J Sleep Res*. 2023;32(6):e13928.

doi: 10.1111/jsr.13928

48. Jang G, Jung HW, Kim J, *et al*. Hyperarousal-state of insomnia disorder in wake-resting state quantitative electroencephalography. *Clin Psychopharmacol Neurosci*. 2023;22(1):95-104.

doi: 10.9758/cpn.23.1063

49. Dressle RJ, Riemann D, Spiegelhalder K, Frase L, Perlis ML, Feige B. On the relationship between EEG spectral analysis and pre-sleep cognitive arousal in insomnia disorder: Towards an integrated model of cognitive and cortical arousal. *J Sleep Res*. 2023;32:e13861.

doi: 10.1111/jsr.13861

50. Taran S, Gros P, Gofton T, *et al*. The reticular activating system: A narrative review of discovery, evolving understanding, and relevance to current formulations of brain death. *J Can Anesth*. 2023;70(4):788-795.

doi: 10.1007/s12630-023-02421-6

51. Camberos-Barraza J, Camacho-Zamora A, Bátiz-Beltrán JC, *et al*. Sleep, glial function, and the endocannabinoid system: Implications for neuroinflammation and sleep disorders. *Int J Mol Sci*. 2024;25(6):3160-3160.

doi: 10.3390/ijms25063160

52. Tang NKY, Saconi B, Jansson-Fröjmark M, Ong JC, Carney CE. Cognitive factors and processes in models of insomnia: A systematic review. *J Sleep Res*. 2023;32(6):e13923.

doi: 10.1111/jsr.13923

53. Brown LA, Hamlett GE, Zhu Y, *et al*. Worry about COVID-19 as a predictor of future insomnia. *J Sleep Res*. 2022;31:e13564.

doi: 10.1111/jsr.13564

54. Manzar MD, Salahuddin M, Pandi-Perumal SR, Bahammam AS. Insomnia may mediate the relationship between stress and anxiety: A cross-sectional study in

university students. *Nat Sci Sleep.* 2021;13:31-38.

doi: 10.2147/nss.s278988

55. Brewster GS, Riegel B, Gehrman PR. Insomnia in the older adult. *Sleep Med Clin*. 2022;17(2):233-239.

doi: 10.1016/j.jsmc.2022.03.004

56. Chellappa SL, Aeschbach D. Sleep and anxiety: From mechanisms to interventions. *Sleep Med Rev*. 2022;61(61):101583.

doi: 10.1016/j.smrv.2021.101583

57. Riemann D, Krone LB, Wulff K, Nissen C. Sleep, insomnia, and depression. *Neuropsychopharmacology*. 2019;45(1):74-89.

doi: 10.1038/s41386-019-0411-y

58. Benham G. Bedtime repetitive negative thinking moderates the relationship between psychological stress and insomnia. *Stress Health*. 2021;37(5):949-961.

doi: 10.1002/smi.3055

59. Palagini L, Moretto U, Novi M, *et al*. Lack of resilience is related to stress-related sleep reactivity, hyperarousal, and emotion dysregulation in insomnia disorder. *J Clin Sleep Med*. 2018;14(5):759-766.

doi: 10.5664/jcsm.7100

60. Zakiei A, Khazaie H, Reshadat S, Rezaei M, Komasi S. The comparison of emotional dysregulation and experiential avoidance in patients with insomnia and non-clinical population. *J Caring Sci*. 2020;9(2):87-92.

doi: 10.34172/jcs.2020.013

61. Norell-Clarke A, Hagström M, Jansson-Fröjmark M. Sleep-related cognitive processes and the incidence of insomnia over time: Does anxiety and depression impact the relationship? *Front Psychol*. 2021;12:677538.

doi: 10.3389/fpsyg.2021.677538

62. Bjorvatn B, Jernelöv S, Pallesen S. Insomnia - A heterogenic disorder often comorbid with psychological and somatic disorders and diseases: A narrative review with focus on diagnostic and treatment challenges. *Front Psychol*. 2021;12:639198.

doi: 10.3389/fpsyg.2021.639198

63. Chen J, Chen X, Mao R, *et al*. Hypertension, sleep quality, depression, and cognitive function in elderly: A cross-sectional study. *Front Aging Neurosci*. 2023;15:1051298.

doi: 10.3389/fnagi.2023.1051298

64. Riemann D, Dressle RJ, Benz F, *et al*. Chronic insomnia, REM sleep instability and emotional dysregulation: A pathway to anxiety and depression? *J Sleep Res*. 2024:e14252.

doi: 10.1111/jsr.14252

65. Birch JN, Vanderheyden WM. The molecular relationship between stress and insomnia. *Adv Biol*. 2022;6(11):e2101203.

doi: 10.1002/adbi.202101203

66. Todd J, Austin H, Clarke P, Notebaert L. Chronic pain, insomnia and their mutual maintenance: A call for cognitive bias research. *J Pain*. 2022;23:1530-1542.

doi: 10.1016/j.jpain.2022.03.241

67. Arnison T, Schrooten MGS, Hesser H, Jansson-Fröjmark M, Persson J. Longitudinal, bidirectional relationships of insomnia symptoms and musculoskeletal pain across adolescence: The mediating role of mood. *Pain*. 2021;163:287-298.

doi: 10.1097/j.pain.0000000000002334

68. Bean DJ, Horne J, Lee AC, Johnson MH. Pre-sleep cognitive arousal exacerbates sleep disturbance in chronic pain: An exploratory daily diary and actigraphy study. *Scand J Pain*. 2021;21(4):724-731.

doi: 10.1515/sjpain-2020-0185

69. Ostovar-Kermani T, Arnaud D, Almaguer A, *et al*. Painful sleep: Insomnia in patients with chronic pain syndrome and its consequences. *Folia Med* (*Plovdiv*). 2020;62(4):645-654.

doi: 10.3897/folmed.62.e50705

70. Daguet I, Raverot V, Bouhassira D, Gronfier C. Circadian rhythmicity of pain sensitivity in humans. *Brain*. 2022;145(9):3225-3235.

doi: 10.1093/brain/awac147

71. Huang GJ, Li SH, Long CQ, Fan ZJ. Laryngopharyngeal reflux and insomnia. *Eur Arch Otorhinolaryngol*. 2022;279(7):3749-3750.

doi: 10.1007/s00405-022-07337-3

72. Kim JS, Seo SI, Kang SH, *et al*. Effects of tegoprazan versus esomeprazole on nighttime heartburn and sleep quality in gastroesophageal reflux disease: A multicenter double-blind randomized controlled trial. *J Neurogastroenterol Motil*. 2023;29(1):58-64.

doi: 10.5056/jnm22104

73. Li SQ, Sun XW, Zhang L, *et al*. Impact of insomnia and obstructive sleep apnea on the risk of acute exacerbation of chronic obstructive pulmonary disease. *Sleep Med Rev*. 2021;58:101444.

doi: 10.1016/j.smrv.2021.101444

74. Aldabayan YS. Mental health and sleep quality among patients with asthma and COPD. *Front Med.* 2023;10:1181742.

doi: 10.3389/fmed.2023.1181742

75. Bhatt P, Patel V, Motwani J, *et al*. Insomnia and cardiovascular health: Exploring the link between sleep disorders and cardiac arrhythmias. *Curr Cardiol Rep.* 2023;25:1211-1221.

doi: 10.1007/s11886-023-01939-x

76. Li C, Shang S. Relationship between sleep and hypertension: Findings from the NHANES (2007-2014). *Int J Environ Res Public Health*. 2021;18(15):7867.

doi: 10.3390/ijerph18157867

77. Malhotra RK. Neurodegenerative disorders and sleep. *Sleep Med Clin*. 2022;17:307-314.

doi: 10.1016/j.jsmc.2022.02.009

78. Xu Z, Anderson KN, Saffari SE, *et al*. Progression of sleep disturbances in Parkinson's disease: A 5-year longitudinal study. *J Neurol*. 2021;268(1):312-320.

doi: 10.1007/s00415-020-10140-x

79. Song ML, Park KM, Motamedi GK, Cho YW. Cognitive behavioral therapy for insomnia in restless legs syndrome patients. *Sleep Med*. 2020;74:227-234.

doi: 10.1016/j.sleep.2020.07.011

80. Zeng X, Dorstyn DS, Edwards G, Kneebone I. The prevalence of insomnia in multiple sclerosis: A meta-analysis. *Sleep Med Rev*. 2023;72:101842.

doi: 10.1016/j.smrv.2023.101842

81. Köteles F, Witthöft M. Somatosensory amplification - An old construct from a new perspective. *J Psychosom Res*. 2017;101:1-9.

doi: 10.1016/j.jpsychores.2017.07.011

82. Lerman SF, Campbell CM, Buenaver LF, *et al*. Exploring the role of negative cognitions in the relationship between ethnicity, sleep, and pain in women with temporomandibular joint disorder. *J Pain*. 2018;19(11):1342-1351.

doi: 10.1016/j.jpain.2018.05.009

83. Sivertsen B, Hysing M, Harvey AG, Petrie KJ. The epidemiology of insomnia and sleep duration across mental and physical Health: The SHoT study. *Front Psychol*. 2021;12:662572.

doi: 10.3389/fpsyg.2021.662572

84. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4(5):487-504.

doi: 10.5664/jcsm.27286

85. Dopheide JA. Insomnia overview: Epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. *Am J Manag Care*. 2020;26(4):S76-S84.

doi: 10.37765/ajmc.2020.42769

86. Porosnicu Rodriguez KA, Salas RME, Schneider L. Insomnia. *Neurol Clin*. 2023;41(1):1-19.

doi: 10.1016/j.ncl.2022.07.004

87. Cerri L, Justo MC, Clemente V, Gomes AA, Pereira AA, Marques DR. Insomnia severity index: A reliability generalisation meta-analysis. *J Sleep Res*. 2023;32(4):e13835.

doi: 10.1111/jsr.13835

88. Zitser J, Allen IE, Falgàs N, *et al*. Pittsburgh Sleep Quality Index (PSQI) responses are modulated by total sleep time and wake after sleep onset in healthy older adults. *PLoS One*. 2022;17(6):e0270095.

doi: 10.1371/journal.pone.0270095

89. Asghari A, Mohammadi F, Kamrava SK, Tavakoli S, Farhadi M. Severity of depression and anxiety in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2012;269(12):2549-2553.

doi: 10.1007/s00405-012-1942-6

90. Walton DM, Putos J, Beattie T, MacDermid JC. Confirmatory factor analysis of 2 versions of the brief pain inventory in an ambulatory population indicates that sleep interference should be interpreted separately. *Scand J Pain*. 2016;12(1):110-116.

doi: 10.1016/j.sjpain.2016.05.002

91. Correll DJ. The measurement of pain. In: *Pain Management*. Philadelphia, PA: Elsevier; 2011. p. 191-201.

doi: 10.1016/b978-1-4377-0721-2.00022-2

92. Chinoy ED, Cuellar JA, Huwa KE, *et al*. Performance of seven consumer sleep-tracking devices compared with polysomnography. *Sleep*. 2020;44(5):zsaa291.

doi: 10.1093/sleep/zsaa291

93. Dewald-Kaufmann J, de Bruin E, Michael G. Cognitive behavioral therapy for insomnia in school-aged children and adolescents. *Sleep Med Clin*. 2022;17(3):355-365.

doi: 10.1016/j.jsmc.2022.06.003

94. Feng G, Han M, Li X, Geng L, Miao Y. The clinical effectiveness of cognitive behavioral therapy for patients with insomnia and depression: A systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2020;2020(1):8071821.

doi: 10.1155/2020/8071821

95. Van Straten A, van der Zweerde T, Kleiboer A, Cuijpers P, Morin CM, Lancee J. Cognitive and behavioral therapies in the treatment of insomnia: A meta-analysis. *Sleep Med Rev*. 2018;38:3-16.

doi: 10.1016/j.smrv.2017.02.001

96. Alimoradi Z, Jafari E, Broström A, *et al*. Effects of cognitive behavioral therapy for insomnia (CBT-I) on quality of life: A systematic review and meta-analysis. *Sleep Med Rev*. 2022;64(1):101646.

doi: 10.1016/j.smrv.2022.101646

97. Kyle SD, Siriwardena AN, Espie CA, *et al*. Clinical and cost-effectiveness of nurse-delivered sleep restriction therapy

for insomnia in primary care (HABIT): A pragmatic, superiority, open-label, randomised controlled trial. *Lancet*. 2023;402(10406):975-987.

doi: 10.1016/S0140-6736(23)00683-9

98. Maurer LF, Schneider J, Miller CB, Espie CA, Kyle SD. The clinical effects of sleep restriction therapy for insomnia: A meta-analysis of randomised controlled trials. *Sleep Med Rev*. 2021;58:101493.

doi: 10.1016/j.smrv.2021.101493

99. Maurer LF, Espie CA, Omlin X, *et al*. Isolating the role of time in bed restriction in the treatment of insomnia: A randomized, controlled, dismantling trial comparing sleep restriction therapy with time in bed regularization. *Sleep*. 2020;43(11):zsaa096.

doi: 10.1093/sleep/zsaa096

100. Maurer LF, Espie CA, Omlin X, Emsley R, Kyle SD. The effect of sleep restriction therapy for insomnia on sleep pressure and arousal: A randomized controlled mechanistic trial. *Sleep*. 2022;45(1):zsab223.

doi: 10.1093/sleep/zsab223

101. Verreault MD, Granger É, Neveu X, Delage JP, Bastien CH, Vallières A. The effectiveness of stimulus control in cognitive behavioural therapy for insomnia in adults: A systematic review and network meta-analysis. *J Sleep Res*. 2023;33:e14008.

doi: 10.1111/jsr.14008

102. Guo W, Nazari N, Sadeghi M. Cognitive-behavioral treatment for insomnia and mindfulness-based stress reduction in nurses with insomnia: A non-inferiority internet delivered randomized controlled trial. *PeerJ*. 2024;12:e17491.

doi: 10.7717/peerj.17491

103. Kim SM, Park JM, Seo HJ, Kim J, Noh JW, Kim HL. Effects of mindfulness-based stress reduction on adults with sleep disturbance: An updated systematic review and meta-analysis. *BMJ Open*. 2022;12(11):e058032.

doi: 10.1136/bmjopen-2021-058032

104. Chen TL, Chang SC, Hsieh HF, Huang CY, Chuang JH, Wang HH. Effects of mindfulness-based stress reduction on sleep quality and mental health for insomnia patients: A meta-analysis. *J Psychosom Res*. 2020;135(1):110144.

doi: 10.1016/j.jpsychores.2020.110144

105. Saldaña KS, McGowan SK, Martin JL. Acceptance and commitment therapy as an adjunct or alternative treatment to cognitive behavioral therapy for insomnia. *Sleep Med Clin*. 2023;18(1):73-83.

doi: 10.1016/j.jsmc.2022.09.003

106. Shin JW, Kim S, Shin YJ, Park B, Park S. Comparison of acceptance and Commitment Therapy (ACT) and Cognitive Behavior Therapy (CBT) for chronic insomnia: A pilot randomized controlled trial. *Nat Sci Sleep*. 2023;15:523-531.

doi: 10.2147/NSS.S409981

107. Martin JL, Carlson GC, Kelly MR, *et al*. Novel treatment based on acceptance and commitment therapy versus cognitive behavioral therapy for insomnia: A randomized comparative effectiveness trial in women veterans. *J Consult Clin Psychol*. 2023;91(11):626-639.

doi: 10.1037/ccp0000836

108. Kremer S, Blue T. Biofeedback as an adjunct or alternative intervention to cognitive behavioral therapy for insomnia. *Sleep Med Clin*. 2023;18(1):85-93.

doi: 10.1016/j.jsmc.2022.10.003

109. Cicolin A, Giordano A. Cognitive-behavioral and pharmacological treatments for insomnia: A combined approach. *Clin Manag Issues*. 2020;14(1):27-38.

doi: 10.7175/cmi.v14i1.1474

110. Riemann D, Baglioni C, Bassetti C, *et al*. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*. 2017;26(6):675-700.

doi: 10.1111/jsr.12594

111. Kunz D. Rethinking the use of hypnotics for treatment of insomnia in the elderly. *Expert Opin Pharmacother*. 2021;22:953-957.

doi: 10.1080/14656566.2021.1900116

112. Wichniak A, Wierzbicka A, Jarema M. Treatment of insomnia - effect of trazodone and hypnotics on sleep. *Psychiatr Pol*. 2021;55(4):743-755.

doi: 10.12740/pp/125650

113. Riaz A, Shahid Q, Yousaf HM, *et al*. Mirtazapine in primary insomnia: Case report and literature review. *World J Adv Res Rev*. 2024;23(1):2576-2581.

doi: 10.30574/wjarr.2024.23.1.2213

114. Pelayo R, Bertisch SM, Morin CM, Winkelman JW, Zee PC, Krystal AD. Should trazodone be first-line therapy for insomnia? A clinical suitability appraisal. *J Clin Med*. 2023;12(8):2933.

doi: 10.3390/jcm12082933

115. Choi K, Lee YJ, Park S, Je NK, Suh HS. Efficacy of melatonin for chronic insomnia: Systematic reviews and meta-analyses. *Sleep Med Rev*. 2022;66:101692.

doi: 10.1016/j.smrv.2022.101692

116. Maruani J, Reynaud È, Chambe J, Palagini L, Bourgin P, Geoffroy PA. Efficacy of melatonin and ramelteon for the acute and long-term management of insomnia disorder in adults: A systematic review and meta-analysis. *J Sleep Res*. 2023;32:e13939.

doi: 10.1111/jsr.13939

117. De la Herrán-Arita AK, Equihua-Benítez AC, Drucker-Colín R. Treatment of cataplexy. *Expert Opin Orphan Drugs*. 2013;1(3):199-210.

doi: 10.1517/21678707.2013.765359

118. Equihua AC, De La Herrán-Arita AK, Drucker-Colin R. Orexin receptor antagonists as therapeutic agents for insomnia. *Front Pharmacol*. 2013;4:163.

doi: 10.3389/fphar.2013.00163

119. De la Herrán-Arita AK, Equihua-Benítez AC, Drucker-Colín R. Orexin/hypocretin antagonists in insomnia: From bench to clinic. In: *Milestones in Drug Therapy*. Cham: Springer; 2014. p. 191-207.

doi: 10.1007/978-3-319-11514-6_9

120. De la Herrán-Arita AK, García-García F. Current and emerging options for the drug treatment of narcolepsy. *Drugs*. 2013;73(16):1771-1781.

doi: 10.1007/s40265-013-0127-y

121. Osuna-Ramos JF, Camberos-Barraza J, Torres-Mondragón LE, *et al*. Interplay between the glymphatic system and the endocannabinoid system: Implications for brain health and disease. *Int J Mol Sci*. 2023;24(24):17458-17458.

doi: 10.3390/ijms242417458

122. Pérez-Morales M, De La Herrán-Arita AK, Méndez-Díaz M, Ruiz-Contreras AE, Drucker-Colín R, Prospéro-García O. 2-AG into the lateral hypothalamus increases REM sleep and cFos expression in melanin concentrating hormone neurons in rats. *Pharmacol Biochem Behav*. 2013;108:1-7.

doi: 10.1016/j.pbb.2013.04.006

123. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. *Int J Mol Sci*. 2018;19(3):833.

doi: 10.3390/ijms19030833

124. Low ZXB, Lee XR, Soga T, Goh BH, Alex D, Kumari Y. Cannabinoids: Emerging sleep modulator. *Biomed Pharmacother*. 2023;165:115102.

doi: 10.1016/j.biopha.2023.115102

125. Mechoulam R, Gaoni Y. A total synthesis of dl-delta-1-tetrahydrocannabinol, the active constituent of hashish. *J Am Chem Soc*. 1965;87:3273-3275.

doi: 10.1021/ja01092a065

126. Glodosky NC, Cuttler C, McLaughlin RJ. A review of the effects of acute and chronic cannabinoid exposure on the stress response. *Front Neuroendocrinol*. 2021;63:100945.

doi: 10.1016/j.yfrne.2021.100945

127. Masataka N. Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. *Front Psychol*. 2019;10:2466.

doi: 10.3389/fpsyg.2019.02466

128. Rodrigues da Silva N, Gomes FV, Sonego AB, da Silva NR, Guimarães FS. Cannabidiol attenuates behavioral changes in a rodent model of schizophrenia through 5-HT1A, but not CB_1 and CB_2 receptors. *Pharmacol Res*. 2020;156:104749.

doi: 10.1016/j.phrs.2020.104749

129. Hablitz LM, Gunesch AN, Cravetchi O, Moldavan M, Allen CN. Cannabinoid Signaling recruits astrocytes to modulate presynaptic function in the suprachiasmatic nucleus. *eNeuro*. 2020;7(1).

doi: 10.1523/eneuro.0081-19.2020

130. Torres-Mondragón LE, León-Pimentel LC, Pérez-Tamayo DE, De la Herrán-Arita AK. The endocannabinoid system: A new frontier in addressing psychosomatic challenges. *J Clin Basic Psychosom*. 2024;2(1):2288.

doi: 10.36922/jcbp.2288

131. Ried K, Tamanna T, Matthews S, Sali A. Medicinal cannabis improves sleep in adults with insomnia: A randomised double-blind placebo-controlled crossover study. *J Sleep Res*. 2023;32(3):e13793.

doi: 10.1111/jsr.13793

132. Xantus G, Zavori L, Matheson C, Gyarmathy VA, Fazekas LM, Kanizsai P. Cannabidiol in low back pain: Scientific rationale for clinical trials in low back pain. *Expert Rev Clin Pharmacol*. 2021;14(6):671-675.

doi: 10.1080/17512433.2021.1917379

133. Namdar D, Koltai H. Medical cannabis for the treatment of inflammation. *Nat Prod Commun*. 2018;13(3):249-254.

doi: 10.1177/1934578x1801300304

134. Bruni O, Ferini-Strambi L, Giacomoni E, Pellegrino P. Herbal remedies and their possible effect on the GABAergic system and sleep. *Nutrients*. 2021;13(2):530.

doi: 10.3390/nu13020530

135. Zeng H, Xu J, Zheng L, *et al*. Traditional Chinese herbal formulas modulate gut microbiome and improve insomnia in patients with distinct syndrome types: Insights from an interventional clinical study. *Front Cell Infect Microbiol*. 2024;14:1395267.

doi: 10.3389/fcimb.2024.1395267

136. Deuel LM, Seeberger LC. Complementary therapies in parkinson disease: A review of acupuncture, Tai Chi, Qi Gong, Yoga, and *Cannabis*. *Neurotherapeutics*. 2020;17(4):1434-1455.

doi: 10.1007/s13311-020-00900-y

137. Li H, Chen J, Xu G, *et al*. The effect of Tai Chi for improving sleep quality: A systematic review and meta-analysis. *J Affect Disord*. 2020;274:1102-1112.

doi: 10.1016/j.jad.2020.05.076

138. Binks H. Vincent GE, Gupta C, Irwin C, Khalesi S. Effects of diet on sleep: A narrative review. *Nutrients*. 2020;12(4):936.

doi: 10.3390/nu12040936

139. Godos J, Grosso G, Castellano S, Galvano F, Caraci F, Ferri R. Association between diet and sleep quality: A systematic review. *Sleep Med Rev*. 2021;57:101430.

doi: 10.1016/j.smrv.2021.101430

140. Mah J, Pitre T. Oral magnesium supplementation for insomnia in older adults: A systematic review and meta-analysis. *BMC Complement Med Ther*. 2021;21(1):125.

doi: 10.1186/s12906-021-03297-z

141. Zhang Y, Chen C, Lu L, *et al*. Association of magnesium intake with sleep duration and sleep quality: Findings from the CARDIA study. *Sleep*. 2022;45(4):zsab276.

doi: 10.1093/sleep/zsab276

142. Pei H, Li S, Su X, Lu Y, Wang Z, Wu S. Association between triglyceride glucose index and sleep disorders: Results from the NHANES 2005-2008. *BMC Psychiatry*. 2023;23(1):156.

doi: 10.1186/s12888-022-04434-9

143. Baranwal N, Yu PK, Siegel NS. Sleep physiology, pathophysiology, and sleep hygiene. *Prog Cardiovasc Dis*. 2023;77:59-69.

doi: 10.1016/j.pcad.2023.02.005

144. Baldassarri SR, Chu J, Deng A, *et al*. Nicotine, alcohol, and caffeine use among individuals with untreated obstructive sleep apnea. *Sleep Breath*. 2023;27:2479-2490.

doi: 10.1007/s11325-023-02830-3

145. Spadola CE, Guo N, Johnson DA, *et al*. Evening intake of alcohol, caffeine, and nicotine: Night-to-night associations with sleep duration and continuity among African Americans in the Jackson Heart Sleep Study. *Sleep*. 2019;42(11):zsz136.

doi: 10.1093/sleep/zsz136

146. Aragón-Arreola JF, Moreno-Villegas CA, Armienta-Rojas DA, De la Herrán-Arita AK. An insight of sleep disorders in Africa. *eNeurologicalSci*. 2016;3:37-40.

doi: 10.1016/j.ensci.2016.02.006

147. O'Byrne NA, Yuen F, Butt WZ, Liu PY. Sleep and circadian regulation of cortisol: A short review. *Curr Opin Endocr Metab Res*. 2021;18:178-186.

doi: 10.1016/j.coemr.2021.03.011

148. Arrigoni E, Fuller PM. The sleep-promoting ventrolateral preoptic nucleus: What have we learned over the past 25 years? *Int J Mol Sci*. 2022;23(6):2905.

doi: 10.3390/ijms23062905

149. Hertenstein E, Trinca E, Wunderlin M, *et al*. Cognitive behavioral therapy for insomnia in patients with mental disorders and comorbid insomnia: A systematic review and meta-analysis. *Sleep Med Rev*. 2022;62(1):101597.

doi: 10.1016/j.smrv.2022.101597

150. Hasan F, Tu YK, Yang CM, *et al*. Comparative efficacy of digital cognitive behavioral therapy for insomnia: A systematic review and network meta-analysis. *Sleep Med Rev*. 2022;61:101567.

doi: 10.1016/j.smrv.2021.101567

151. Kim SA, Lee SH, Kim JH, *et al*. Efficacy of acupuncture for insomnia: A systematic review and meta-analysis. *Am J Chin Med*. 2021;49(5):1135-1150.

doi: 10.1142/s0192415x21500543

152. Kaul M, Zee PC, Sahni AS. Effects of cannabinoids on sleep and their therapeutic potential for sleep disorders. *Neurotherapeutics*. 2021;18(1):217-227.

doi: 10.1007/s13311-021-01013-w

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PERSPECTIVE ARTICLE

Bridging the gap: Policy recommendations to address suicides committed by Indigenous youth in Victoria

Sheikh Shoib[1,2,3], Soumitra Das[4], Fahimeh Saeed[5], Miyuru Chandradasa[6], and Ilham Zaidi[7]*

[1]Department of Psychiatry, DH Pulwama, Kashmir, India

[2]Sharda University, Greater Noida, Uttar Pradesh, India

[3]Mind Wellness Center, Nawab Bazar Srinagar, India

[4]Department of Emergency, Sunshine Hospital, Melbourne, Australia

[5]Psychosis Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

[6]Department of Psychiatry, University of Kelaniya, Ragama, Sri Lanka

[7]Department of Public Health, International Society for Chronic Illnesses, New Delhi, India

Abstract

The Aboriginal population comprises 3.3% of the total Australian population, and youth represent 19% of this segment. In general, the Aboriginal inhabitants of Australia experience discrimination, limited access to education, and low socioeconomic conditions, and exhibit high mental disorder rates. The rate of suicide attempts by the Indigenous people of Victoria increased by 75% in 2021. This study examined the possible risk factors associated with suicides committed by Indigenous youth in Victoria. It focused on the health profiles of Victorian Aboriginal individuals, identified stakeholders who could help improve their mental well-being, addressed the needs and issues related to Aboriginal mental health, and examined substance abuse in this population segment. Finally, recommendations are offered to mitigate the studied problem. Rising suicide rates represent an urgent concern because they reflect the diminished mental health conditions of a society, particularly among its marginalized populations. It is crucial to develop an integrated suicide prevention act that takes into account the biological, psychological, social, cultural, and spiritual determinants of this population.

Keywords: Suicide; Mental health; Youth; Aborigine; Victoria; Australia

***Corresponding author:**
Ilham Zaidi
(ilhamasgher@gmail.com)

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1. Introduction

As per the 2016 census, 0.9% of the Victorian population identifies as Aboriginal in origin. The Aboriginal people represent 3.3% of the total Australian population, and youth aged between 15 and 24 years form approximately 19% of this segment.[1] The education levels of Indigenous Victorians are improving, but their incomes and quality of life remain low compared to the non-Indigenous population and require further enhancement.[1]

The perception of discrimination and inequity is high among Indigenous Australians.[2] According to "The Youth Survey 2019," half of the surveyed Aboriginal youth were

optimistic about life, approximately one-third suffered from psychological distress, and almost 30% experienced bullying that impacted their sense of well-being.[3] In addition, Aboriginal youth were thrice more likely to experience homelessness than their non-Aboriginal peers.[3]

Suicides are also 3 times higher among Aboriginal youth under 18 than among other young Australians. This rate becomes 12 times higher than other Australians[4] if we only consider young people aged below 15 years. This section of Aboriginal youth exhibits poor educational attainment and employment, experiences forced cultural and housing-related displacements, perceives discrimination, and lives in poverty from youth to adulthood. The traumas and cycle of poor attachment continue from adolescence to adulthood for the First Nations people because they lack stability in early life. Transgenerational trauma stemming from historical abuse and forced displacement is often an underlying factor in youth suicides.[5]

In 2021, Victoria registered a 75% increase in suicide among the First Nations people compared to previous years.[6] Places in regional Victoria such as Mildura and Shepperton reported the highest suicide frequencies. Coroner's reports reveal that Aboriginal and Torres Strait Islander people in Victoria died by suicide at a rate three and a half times higher than non-Indigenous people between 2018 and 2021. Some themes related to deaths by suicide have emerged in recent years: anxieties resulting from suicide committed by a member of a close-knit community, the absence of support for people struggling with substance abuse, and increasing incidents of incarceration, domestic violence, loneliness, or failed relationships. The coronavirus disease 19 (COVID-19) pandemic and multiple lockdowns negatively affected the mental health of Aboriginal youth.[6] Several suicide prevention strategies are being implemented but suicides among Aboriginal youth continue to rise. As the Ottawa Charter suggests, integrating social, cultural, family, community, and personal factors will result in a better understanding of the prevailing problem.[7]

Thus, this study aims to deliver a snapshot of the present circumstances related to suicides by Aboriginal youth. It also attempts to outline the engagement of potential stakeholders to prevent suicides.

2. Health profile of the Victorian Aboriginal and Torres Strait Islander people

Children born to Victorian Aboriginal mothers are twice as likely to register low birth weights as babies born to non-Aboriginal mothers.[8] A Victorian Aboriginal woman is 45 times more likely to experience domestic violence than a non-Aboriginal woman.[9] An Aboriginal child in Victoria is 8 times more likely to qualify for child protection services than a non-Aboriginal child. Aboriginal Victorians are 4 times more likely to be homeless than non-Aboriginal people. Moreover, Aboriginal people aged above 18 years use tobacco 3 times more than non-Aboriginal people. Furthermore, Aboriginal Victorians are more than 4 times more likely than other Victorians to visit medical emergency facilities for alcohol-related reasons. Further, Aboriginal Victorians are approximately 3 times more likely to suffer from severe or extreme emotional distress than members of other communities.[8]

3. Needs and issues related to Aboriginal mental health

Dickson's systematic review revealed elevated rates of suicide, self-harm, and suicidal ideation in Indigenous youth vis-à-vis the non-Indigenous population. Common risk factors for suicides by Indigenous youth include a history of incarceration, substance use, and more significant social and emotional distress.[10] Heard's qualitative study explored discrete themes underlying perceived barriers to implementing suicide prevention strategies and reported perceived powerlessness, skill deficiencies, lack of resilience apropos factual discussions, perceived absence of professional support, and other systemic issues as commonplace themes.[11]

Cox conducted a focus group discussion and reported that mentoring, cultural values, and community cohesion were vital for the health and well-being of Indigenous communities.[12] Nasir and Kiseley's community consultation study highlighted factors that were counterproductive for suicide prevention programs in remote communities: inconsistencies in the content and delivery of gatekeeper training, time-consuming and unsustainable programs, and irrelevant materials. Societies must focus on the social, emotional, cultural, and spiritual underpinnings of community well-being in developing suicide prevention strategies.[13] Existing cross-cultural studies have identified some common themes associated with youth suicides, for instance, poor mental health literacy, cultural issues, lack of access, high stigma, unstable finances, and housing.[14]

Varied difficulties have been pinpointed to underpin the high suicide rates among Aboriginal youth in Victoria. The extant research suggests that 90% of Aboriginal people with mental health issues have expressed suicidal ideas in the last 12 months. Furthermore, mental health issues, including depression, have been detected in 90% of the population of individuals who have attempted suicide.[6,15] Females are more likely to attempt suicide but males have a higher rate of suicide deaths. Young people who do not conform to conventional gender roles are at greater

risk of committing suicide because of discrimination, rejection, and harassment: For instance, youth identifying as LGBTQIA+. In addition, individuals in remote communities are at greater risk of death by suicide because of limited support systems and restricted access to mental health resources.[6,15]

The risk of suicide is further escalated by the negative mental health effects of substance use and impulsive behaviors associated with it. Substance abuse is also intricately linked with domestic violence, unstable family dynamics, and myriad physical health issues.[6,15] In addition, the COVID-19 pandemic and multiple lockdowns imposed in Victoria impacted the mental health of the Aboriginal population.

Moreover, transgenerational trauma causes epigenetic changes and results in neurodevelopmental deficits.[16] Family violence and systematic discrimination also often retrigger trauma.[6,15] Transgenerational trauma must be addressed to prevent suicides, especially in communities affected by systemic oppression and historical trauma. The impact of trauma that remains unresolved across generations can manifest in community violence, substance misuse, and suicidal behaviors. Effective strategies focus on establishing trauma-informed services that respect cultural practices, build community resilience, and support cross-generational healing. The existing research emphasizes community-driven programs such as culturally embedded counseling and education, which help individuals connect with their identity and heritage, buffer against the adverse effects of trauma, and promote psychological well-being.[17] Out-of-home care is 10 times higher among Aboriginal children, and child protection notification rates are 7 times higher than the frequencies for non-Aboriginal children. In addition, a sizable proportion of the Aboriginal population lives in poverty with limited satisfaction of basic needs. It is known that poverty, inadequate access to health care, lack of trust, and overcrowded living conditions impact the mental health status of First Australians and increase their suicide risks.[15]

Specific cultural, historical, and political considerations contribute to the excessive prevalence of mental health problems in Aboriginal and Torres Strait Islander people and mandate a rethinking of traditional models and assumptions. In 2018 – 2019, 31% of Aboriginal Australians and 23% of Torres Strait Islanders aged 18 years and above reported experiencing severe or very severe emotional distress.[18]

4. Substance abuse and suicides by Indigenous youth

Substance abuse among Indigenous youth is regarded as a triggering factor for suicide and self-harm attempts.[19] The need to address the issues of substance abuse among Aboriginal youth is significantly unmet and requires immediate attention to prevent further damage.[20] Aboriginal youth reported less sociocultural control and exposure to modern adversities after colonization. Per the data obtained from the Australian Institute of Health and Welfare, alcohol abuse has doubled in the last decade in Aboriginal youth compared to non-Aboriginal populations. However, a steep decline in alcohol consumption has been observed in the community since 2022. The 2018 – 2019 National Aboriginal and Torres Strait Islander Health Survey compiled data on illicit substance use among First Nations people aged 15 years and above. The findings revealed that 25.2% of this population had used illicit substances in the past 12 months, and males reported significantly higher usage (36.7%) than females (21.1%). Age was also found to influence substance use, with younger people (15 – 29 years) reporting higher rates (32.9%) than individuals aged 45 years and above (21.2%). Marijuana, hashish, and cannabis resin were the most commonly used substances, and 24% of the respondents (31.4% of the males and 17.7% of the females) had used these items. Other substances such as heroin, cocaine, non-medical analgesics, sedatives, amphetamines, and ecstasy were reported in lower proportions, and the use of each category ranged between 3.3% and 5.9% of respondents.[18] Many remote communities are concerned about substance abuse among their youth and are worried about the ineffectiveness of prevention strategies.[20]

Psychological distress and low self-esteem increase the risks of substance abuse. Conversely, higher self-esteem, resilience, confidence, and a sense of ownership reduce the consumption of substance abuse in a population.[21] Chances of substance abuse are also diminished when health is prioritized, literacy is emphasized, and youngsters engage in sports. Low educational attainment, school dropout, and unemployment increase the risk of cannabis and other drug abuse among First Australians.[21] Moreover, young people who have been incarcerated are at higher risk of abusing cannabis, tobacco, and methamphetamine.[21] According to Snijder, younger people aged between 15 and 24 years are more prone to substance abuse and drinking and driving offenses. Males are more likely than females to abuse alcohol, smoke tobacco, and commit driving offenses. Peer pressure, social isolation, broken families, domestic violence, and partners with substance abuse issues increase the chances of substance abuse and relapse.[21] Indigenous populations in urban areas encompass high-risk factors for alcohol abuse and illicit drug use, whereas Indigenous people living in rural areas display higher likelihoods of tobacco use and drinking offenses.[22] Cannabis, crystal methamphetamine, and tobacco are increasingly available

among young populations because their access is unregulated.[21] A study conducted with Aboriginal women revealed that hopelessness, depression, and despair can result in alcohol abuse and suicide.[23]

A person struggling with substance abuse is 10 times more likely to commit suicide than the general population.[24] A meta-analysis pertaining to youth populations disclosed that substance abuse significantly increased suicide risk.[25] Substance abuse often causes impulsivity, reduces inhibition, or triggers ongoing stressors. Thus, people struggling with substance abuse feel incapable of coping with their circumstances; in general, alcohol abuse can increase suicide risk by 65%.[26,27]

5. Recommendations to help reduce suicides among Aboriginal youth in Victoria

The *National Aboriginal and Torres Strait Islander Peoples' Drug Strategy 2014 – 2019* was developed to guide governments, communities, service providers, and individuals to identify key issues and prioritize action areas. This policy document acknowledges the need to implement culturally safe, evidence-based procedures to lessen damage from drug- and alcohol-related difficulties. The perspective is focused on reducing demand, supply, and harm through procedures that reflect the ownership of the Aboriginal community.[28] Thus, approaches to mitigate such damages must consider the biological, psychological, social, cultural, and spiritual determinants of substance abuse.[29]

Considerable stigma is attached to Aboriginal communities accessing healthcare, which is implemented using Western concepts and principles.[29] Perceived discrimination and absence of trust in culturally unsafe hospital environments often create a vicious cycle. Thus, Aboriginal youth do not seek appropriate care because they fear stigmatization.[30] Culturally safe community and school-based education programs must be instituted to improve resilience in Aboriginal communities.[31] Care-related policies and activities should be developed after consultation with Aboriginal leaders and persons with lived experience.[32] Currently, strategies focus primarily on hospital-based treatment. A home-based design should be optimized, which will require funding and workforce development.[29]

Evaluation strategies should measure the impact, acceptability, and appropriateness of programs designed to reduce suicides among Aboriginal youth. Such evaluations may be accomplished through community surveys or focused group discussions between healthcare workers in specific communities. The impact of programs can be measured through outcomes such as per capita alcohol and drug consumption, the number of presentations to emergency care facilities in each period, and data related to incidences of self-harm and suicide. The ratio of per capita substance consumption and healthcare access can provide awareness of the community's trust in the system. Follow-up consumer and carer surveys conducted after the completion of each home-based drug rehabilitation program can serve as excellent indicators of the effectiveness of newer strategies. Measures of specific outcomes such as the Health of the Nation Outcome Scales represent effective assessment tools for such rehabilitation programs.[33]

The benefits of culturally safe community-based programs include wider accessibility, trustworthiness, fewer restrictions, community acceptability, and family-focused and evidence-informed care provided in less intense environments. However, such programs can be resource intensive, require experienced and confident clinicians, be challenging to implement in remote settings and require robust risk mitigation processes in cases of worsening health.

A compelling need exists for widely available and accessible screening tools to assess and manage healthcare and rehabilitation programs. Targeting subpopulations mandates experienced, youth-friendly clinicians who are confident about providing evidence-informed treatment. The treatment approach should be culturally safe and should be developed after consultation with young people with lived experience. Appropriate referral pathways should be stipulated if the young person receiving treatment requires more intensive hospital-based care, which would boost the confidence of ground workers as well as family members. Young care receivers often value confidentiality regarding their treatments; thus, clinicians should be trained in the nuances concerning individual and family rights.

6. Identifying stakeholders to improve mental well-being

Indigenous suicide prevention stakeholders should be able to inform, support, or contribute to the implementation of integrated approaches to suicide prevention in community settings. At least one stakeholder should participate from each of the various groups such as community governance bodies, elders, health professionals, educational services, and recognized local leaders. The stakeholder composition can vary depending on the regional or metropolitan status of communities. The availability of the workforce and services can also influence the participation of different stakeholders.[34] Stakeholders function essentially in systems-based suicide prevention programs adopting structured governance and community-centered approaches. For example, the Tasmanian Suicide Prevention Trial Advisory

Group and the Primary Health Network (PHN) were instrumental in establishing guidelines, identifying priority groups, selecting focus areas, and providing foundational support for regional implementation. Their key responsibilities entailed ensuring that local working groups composed of community members, volunteers, and local organizations could operate effectively and tailor their suicide prevention activities to specific community needs. Working groups supported by host organizations such as local councils were responsible for the direct implementation of activities and endeavored to adapt the lifespan framework to the regional context. The PHN acted as a connector, facilitating essential partnerships with local organizations (e.g., the Coroner's office) to support data access and resource sharing. Host organizations helped bridge the gaps between the national model and local needs, leveraging community insights and fostering engagement to ensure that the undertaken activities were relevant and sustainable in their communities.[35] Multisectoral team members can introduce discrete strategies such as peer-to-peer suicide prevention training in the youth, understanding the distinctive needs of communities, and pushing local authorities to release funds. Further, stakeholders must advocate for the implementation of newer services, research, analyses, and evaluations of existing programs. Stakeholders need to codesign high-quality, culturally appropriate suicide prevention services for high-risk youth, create awareness, and motivate their specific communities to engage in the concerned programs.[36]

7. Youth-focused programs: A critical analysis

Varied programs focusing on culturally informed approaches that resonate with Indigenous identities and values have been designed to specifically address youth suicides in Australian Aboriginal communities. The "Yiriman Project" is a prominent example of such a program that involves at-risk youth in the Kimberley region. Young participants connect deeply with their heritage through bush trips and activities such as land care and cultural storytelling. These processes foster a sense of belonging, resilience, and community identity in the participants. Evaluations of the Yiriman Project have reported its positive effects on the mental well-being and reduced suicidal ideation of participants. Nevertheless, the program confronts pitfalls such as its excessive reliance on intermittent funding, which makes sustained efforts challenging.

Another initiative titled "Alive and Kicking Goals!" targets Aboriginal youth aged between 15 and 24 years. This program integrates suicide prevention messaging within peer education and sports settings. It leverages community sports events and deploys peer mentors to destigmatize mental health discussions and encourage help-seeking behaviors. Reports indicate that participants gain confidence and acquire knowledge about mental health resources. However, the program's reach is sometimes limited because of insufficient resources and geographic constraints in remote areas.

"Tough in It Out" is another notable program that aims to enhance resilience in Indigenous youth by building mental health awareness and inculcating practical crisis management strategies. This program is delivered through workshops, tackles common mental health issues, inculcates emotional regulation skills, and promotes peer support. The program effectively builds youth confidence in handling mental health challenges. However, its limited scale and inconsistent funding hinder it from wielding a broader community impact.

The *National Aboriginal and Torres Strait Islander Suicide Prevention Strategy* emphasizes culturally specific interventions targeting social, emotional, and mental well-being across multiple age groups and includes specific components for youth. It encourages community involvement and ownership and aims to empower Indigenous communities to drive customized suicide prevention efforts. The program is promising but its impact is often hampered by challenges in measuring long-term outcomes because of the absence of consistent evaluative frameworks.

Each of the mentioned programs highlights the critical role of culturally tailored approaches to prevent suicides by youth in Aboriginal populations. However, common pitfalls across initiatives include funding instabilities, limited scalability, and gaps in long-term outcome evaluations. These difficulties underscore the need for more sustained investment and systematic evaluation processes to comprehensively understand the effectiveness of programs and ascertain their potential for wider applications.[37]

8. Limitations

Our study is descriptive and based on a mix of peer-reviewed and gray literature. The studied topic is relatively under-researched; therefore, we were compelled to include information obtained from discrete well-recognized government websites. Furthermore, some information could have been updated during or after the publication of this paper because of continuing developments.

9. Conclusion

Understanding the conceptual framework underlying suicides by the Indigenous people in Victoria enables a

more wide-ranging grasp of suicide-related behaviors displayed among First Nation people in other countries. Numerous cultural differences exist between them, but a few similarities may be found in their cultural explanations. We believe this study could offer researchers in other nations some ideas about working on suicide prevention in Indigenous populations in their countries.

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Conceptualization: Sheikh Shoib
Writing–original draft: Soumitra Das
Writing–review & editing: Sheikh Shoib, Fahimeh Saeed, Miyuru Chandradasa, Ilham Zaidi

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Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Australian Bureau of Statistics (ABS). *Aboriginal and Torres Strait Islander Population - Victoria*. Canberra: Australian Bureau of Statistics; 2022.
2. Department of Health in Victoria. *Demographic Data 2018*; 2022b.
3. Australia M. *Mission Australia's National Aboriginal and Torres Strait Islander Youth Report: Youth Survey*; 2019.
4. Australian Bureau of Statistics. *VICTORIA - 2021 Census All Persons QuickStats*. Canberra: Australian Bureau of Statistics; 2021.
5. Gibson M, Stuart J, Leske S, Ward R, Tanton R. Suicide rates for young Aboriginal and Torres Strait Islander people: The influence of community level cultural connectedness. *Med J Aust*. 2021;214(11):514-518.

   doi: 10.5694/mja2.51084
6. Coroners Court. *Suicides of Aboriginal and Torres Strait Islander People*. Queensland: Coroners Court; 2021.
7. WHO. *The 1st International Conference on Health Promotion*. Ottawa: WHO; 1986.
8. Department of Health in Victoria. *Aboriginal and Torres Strait Islander Victorians*; 2022a. Available from: https://www.health.vic.gov.au/chief-health-officer/aboriginal-and-torres-strait-islander-victorians [Last accessed on 2024 May 15].
9. Buxton-Namisnyk E. Domestic violence policing of First Nations women in Australia: 'Settler' frameworks, consequential harms and the promise of meaningful self-determination. *Br J Criminol*. 2022;62(6):1323-1340.

   doi: 10.1093/bjc/azab103
10. Dickson JM, Cruise K, McCall CA, Taylor PJ. A systematic review of the antecedents and prevalence of suicide, self-harm and suicide ideation in Australian aboriginal and Torres strait Islander youth. *Int J Environ Res Public Health*. 2019;16(17):3154.

    doi: 10.3390/ijerph16173154
11. Heard TR, McGill K, Skehan J, Rose B. The ripple effect, silence and powerlessness: Hidden barriers to discussing suicide in Australian Aboriginal communities. *BMC Psychol*. 2022;10(1):23.

    doi: 10.1186/s40359-022-00724-9
12. Cox T, Hoang H, Mond J, Cross M. 'It all comes back to community!': A qualitative study of Aboriginal Elders promoting cultural well-being. *Aust J Rural Health*. 2021;29(6):909-917.

    doi: 10.1111/ajr.12791
13. Nasir B, Kisely S, Hides L, *et al*. An Australian Indigenous community-led suicide intervention skills training program: Community consultation findings. *BMC Psychiatry*. 2017;17(1):219.

    doi: 10.1186/s12888-017-13805
14. Isaacs AN. Strategies to facilitate mental healthcare access in marginalised local communities: Case studies from India and Australia. *J Ment Health Policy Econ*. 2022;25(1):11-19.
15. Silburn S, Robinson G, Leckning B, Henry D, Cox A, Kickett D. *Preventing Suicide among Aboriginal Australians*. Ch. 9. Australian Government Department of the Prime Minister and Cabinet: Australia; 2014. p. 147-164.
16. Bale TL. Lifetime stress experience: Transgenerational epigenetics and germ cell programming. *Dialogues Clin Neurosci*. 2014;16:297-305.

    doi: 10.31887/DCNS.2014.16.3/tbale
17. Atkinson J, Nelson J, Brooks R, Atkinson C, Ryan K. Addressing Individual and Community Transgenerational Trauma. In: *Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practice*.

Ch. 17. 2014. p. 289-306.

18. Australian Institute of Health and Welfare. *National Drug Strategy Household Survey 2019: Summary*; 2019. Available from: https://www.aihw.gov.au/reports/illicit-use-of-drugs/national-drug-strategy-household-survey-2019/contents/summary [Last accessed on 2024 May 15].

19. Steele ML, Meurk C, Schess J, *et al*. Substance use and help-seeking among justice-involved young people in Queensland and Western Australia: A cross-sectional survey of 14-17-year-olds. *Drug Alcohol Rev.* 2021;40(4):617-626.

doi: 10.1111/dar.13238

20. Geia L, Broadfield K, Grainger D, Day A, Watkin-Lui F. Adolescent and young adult substance use in Australian Indigenous communities: A systematic review of demand control program outcomes. *Aust N Zeal J Public Health*. 2018;42(3):254-261.

doi: 10.1111/1753-6405.12789

21. Snijder M, Lees B, Stearne A, *et al*. An ecological model of drug and alcohol use and related harms among Aboriginal and Torres Strait Islander Australians: A systematic review of the literature. *Prev Med Rep.* 2021;21:101277.

doi: 10.1016/j.pmedr.2020.101277

22. Ramamoorthi R, Jayaraj R. Epidemiology, aetiology, and motivation of alcohol misuse among Australian Aboriginal and Torres Strait Islanders of the Northern Territory: A descriptive review. *J Ethn Subst Abuse*. 2015;14(1):1-11.

doi: 10.1080/15332640.2014.958642

23. Lee KS, Harrison K, Mills K, Conigrave KM. Needs of Aboriginal Australian women with comorbid mental and alcohol and other drug use disorders. *Drug alcohol Rev.* 2014;33(5):473-481.

doi: 10.1111/dar.12127

24. Rontziokos H, Deane F. Systematic review of suicidal behaviour in individuals who have attended substance abuse treatment. *Int J Ment Health Addict.* 2019;17(6):1580-1598.

doi: 10.1007/s11469-018-9994-5

25. Miranda-Mendizabal A, Castellví P, Parés-Badell O, *et al*. Gender differences in suicidal behaviour in adolescents and young adults: Systematic review and meta-analysis of longitudinal studies. *Int J Public Health*. 2019;64(2):265-283.

doi: 10.1007/s00038-018-1196-1

26. Fisher A, Marel C, Morley K, Teesson M, Mills K. *The Role of Alcohol and Other Drugs in Suicidal Behaviour and Effective Interventions to Reduce Suicidal Thoughts and Behaviours: Evidence Check Prepared for the National Suicide Prevention Task Force and Commissioned through the Suicide Prevention Research Fund, Managed by Suicide Prevention Australia*; 2020.

27. Amiri S, Behnezhad S. Alcohol use and risk of suicide: A systematic review and Meta-analysis. *J Addict Dis*. 2020;38(2):200-213.

doi: 10.1080/10550887.2020.1736757

28. Inter-Governmental Committee on Drugs. *National Aboriginal and Torres Strait Islander Peoples' Drug Strategy, 2014-2019*. Intergovernmental Committee on Drugs; 2015.

29. Boffa J, Tilton E, Ah Chee D. Preventing alcohol-related harm in Aboriginal and Torres Strait Islander communities: The experience of an Aboriginal Community Controlled Health Service in Central Australia. *Aust J Gen Pract*. 2018;47:851-854.

doi: 10.31128/AJGP-08-18-4661

30. Healthinfonet AI. *Overview of Aboriginal and Torres Strait Islander Health Status 2021*; 2021.

31. Australian Institute of Health and Welfare (AIHW). *Reducing Alcohol and Other Drug-related Harm*. Australia: AIHW; 2017.

32. Australian Government Department of Health and Aged Care. *National Aboriginal and Torres Strait Islander Peoples' Drug Strategy*; 2019.

33. James M, Painter J, Buckingham B, Stewart MW. A review and update of the Health of the Nation Outcome Scales (HoNOS). *BJPsych Bull*. 2018;42(2):63-68.

doi: 10.1192/bjb.2017.17

34. Dudgeon P, Darwin L, McPhee R, *et al*. *Implementing Integrated Suicide Prevention in Aboriginal and Torres Strait Islander Communities [Guide]*. Australia: Centre of Best Practice in Aboriginal and Torres Strait Islander Suicide Prevention; 2018. Available from: https://apo.org.au/node/254751 [Last accessed on 2024 May 15].

35. Grattidge L, Purton T, Auckland S, Lees D, Mond J. Stakeholder insights into implementing a systems-based suicide prevention program in regional and rural Tasmanian communities. *BMC Public Health.* 2022;22:2323.

doi: 10.1186/s12889-022-14721-5

36. WAPHA. *The Kimberley Aboriginal Suicide Prevention Trial*. Australia: WAPHA; 2019.

37. Ridani R, Shand FL, Christensen H, *et al*. Suicide prevention in Australian Aboriginal communities: A review of past and present programs. *Suicide Life Threat Behav.* 2015;45(1):111-140.

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ORIGINAL RESEARCH ARTICLE

Impact of protein consumption on sleep problems: Insights from NHANES data

Chenxi Zhang[1]*, Yan Xu[1], Weimin Li[1], Qianyun Wu[1], Bingnan Hou[2], Qiguang Li[3], and Bin Zhang[1]*

[1]Department of Psychiatry, Nanfang Hospital, Southern Medical University; Center of Sleep Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

[2]College of Computer, National University of Defense Technology, Changsha, Hunan, China

[3]Department of Psychiatry, Xi'an Mental Health Center, Xi' an, Shaanxi, China

Abstract

Sleep problems are common and significantly impact health and well-being. Diet, particularly protein intake, may affect sleep, yet the precise relationship remains unclear. This study investigates the association between protein consumption and sleep problems while considering potential confounders and gender differences, using data from the National Health and Nutrition Examination Survey. Our cross-sectional analysis included 18,077 women (51.3%) and 17,175 men (48.7%), averaging 45.9 years (standard deviation = 17.7). Protein consumption was assessed through 24-h dietary recall interviews and sleep problems were assessed through the question: "Have you ever told a doctor or other health professional that you have trouble sleeping?" Using binary logistic regression models, we found that 24.6% of individuals reported sleep problems. A statistically significant association emerged between protein consumption and the likelihood of experiencing sleep problems across quartiles of protein intake. Specifically, individuals in the highest quartile of protein consumption had the lowest odds of sleep problems compared to those in the lowest quartile, even after adjusting for various demographic and lifestyle factors ($P < 0.001$). Gender-stratified analysis revealed a persistent association between protein intake and sleep problems, with a stronger effect observed in females ($P < 0.002$) compared to males ($P = 0.337$). Overall, our findings suggest that higher protein consumption is independently associated with reduced odds of sleep problems. This underscores the importance of adequate protein intake for promoting better sleep outcomes and highlights potential implications for public health interventions and clinical practice.

Keywords: Protein; Sleep; Sleep problem; Diet; High protein diet

***Corresponding authors:**
Chenxi Zhang
(zhangchx@smu.edu.cn)
Bin Zhang
(zhang73bin@hotmail.com)

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1. Introduction

Sleep problems, including difficulties with sleep initiation, maintenance, or overall sleep quality, are prevalent issues affecting individuals worldwide.[1] In addition to negatively impacting daily functioning and quality of life, sleep problems have been related to various adverse health consequences, such as cardiovascular diseases, metabolic disorders, and mental health disorders.[2,3] Given the substantial burden of sleep problems on public

health, understanding factors that influence sleep quality is of paramount importance.[4]

Recent studies have revealed mechanisms by which a high-protein diet may enhance sleep quality. For instance, a study published in *Cell* indicates that a protein-rich diet can induce the secretion of a peptide that reduces sensory arousal, thereby promoting deep and restorative sleep.[5] Dietary habits have emerged as a key factor influencing sleep.[6-8] Research suggests that high protein intake boosts post-meal alertness and modulates rapid eye movement (REM) – non-REM sleep balance, impacting overall sleep quality.[6,9,10] One possible mechanism is that protein-rich foods contain tryptophan, an amino acid that promotes the production of sleep-regulating neurotransmitters such as serotonin and melatonin. A systematic review and meta-regression found that better sleep is linked to higher protein energy intake, based on 15 cross-sectional studies and four randomized controlled trials (RCTs).[11] Furthermore, subjective sleep quality showed a positive association with protein consumption in several studies.[12] Further investigations, encompassing eight studies with diverse designs, yielded conflicting results regarding the influence of protein consumption on subjective sleep quality.[12] While some studies reported significantly better sleep scores with high protein intake, others found no significant differences. Moreover, prospective cohort studies have failed to establish a clear association between total protein intake and sleep quality.[7,13] Despite these findings, the overall evidence linking protein consumption to sleep outcomes remains inconclusive, with conflicting results across studies. Moreover, most research has focused on general dietary patterns rather than specifically examining the role of protein intake in sleep health.[9,14]

To address these gaps in the literature, the present study aims to investigate the association between protein consumption and sleep problems using data from the National Health and Nutrition Examination Survey (NHANES). By leveraging a large, nationally representative dataset, this study seeks to provide a comprehensive understanding of the relationship between protein intakes and sleep outcomes. The findings could inform public health initiatives designed to promote healthy dietary patterns for improved sleep health. Moreover, elucidating the role of protein consumption in sleep outcomes may guide health-care providers in offering dietary recommendations to individuals experiencing sleep disturbances. Given the growing recognition of sleep's importance for overall health and well-being, investigating the dietary determinants of sleep quality is a critical step toward developing effective interventions to improve sleep health and mitigate associated health risks.

2. Methods

2.1. Study population resources

This study utilized data from the NHANES conducted between 2005 and 2018, focusing on cycles where participants were assessed for sleep problems. Sleep problems were evaluated with a single question: "Have you ever told a doctor or other health professional that you have trouble sleeping?" Of the 70,076 participants, we excluded those under 18 years old (n = 31,748), as well as individuals with incomplete data on sleep problems (n = 17), protein consumption data (n = 2,738), or weight (n = 321). Ultimately, 35,252 subjects were included in our analysis (Figure 1). The NHANES was approved by the National Center for Health Statistics Ethics Review Board, and all participants provided written informed consent before participating in the study.

2.2. Covariate assessment

The study collected sociodemographic data, including information on participants' age, gender, body mass index (BMI), race, marital status, education level, smoking status (categorized as every day, some days, or not at all), alcohol use (defined as having consumed at least 12 alcoholic drinks), and physical activity (measured in minutes of sedentary activity). Protein consumption was assessed using 24-h dietary recall interviews.

2.3. Statistics

All statistical analyses were performed using R version 4.2.1. Initially, univariate analyses, including analysis of variance for continuous variables and the Chi-square test for categorical variables, were used to characterize the study population. Logistic regression models were then applied to explore the relationship between protein consumption (predictor variable) and sleep problems (dependent variable), with the continuous protein consumption variable categorized into quartiles to examine potential non-linear relationships. Four models were utilized: (i) the crude model without adjustments; (ii) model 1, adjusted for age and gender; (iii) model 2, further adjusted for race, education, BMI, marital status, and total energy intake; and (iv) model 3 additionally adjusted for smoking status, alcohol use, and sedentary activity. In addition, sensitivity analyses were conducted using restricted cubic spline (RCS) regression to visualize potential non-linear patterns between protein consumption and sleep problems. These analyses were adjusted for covariates, including age, gender, race, marital status, education, total energy intake, smoking status, alcohol use, and sedentary activity. Statistical significance was determined by a two-sided $P < 0.05$.

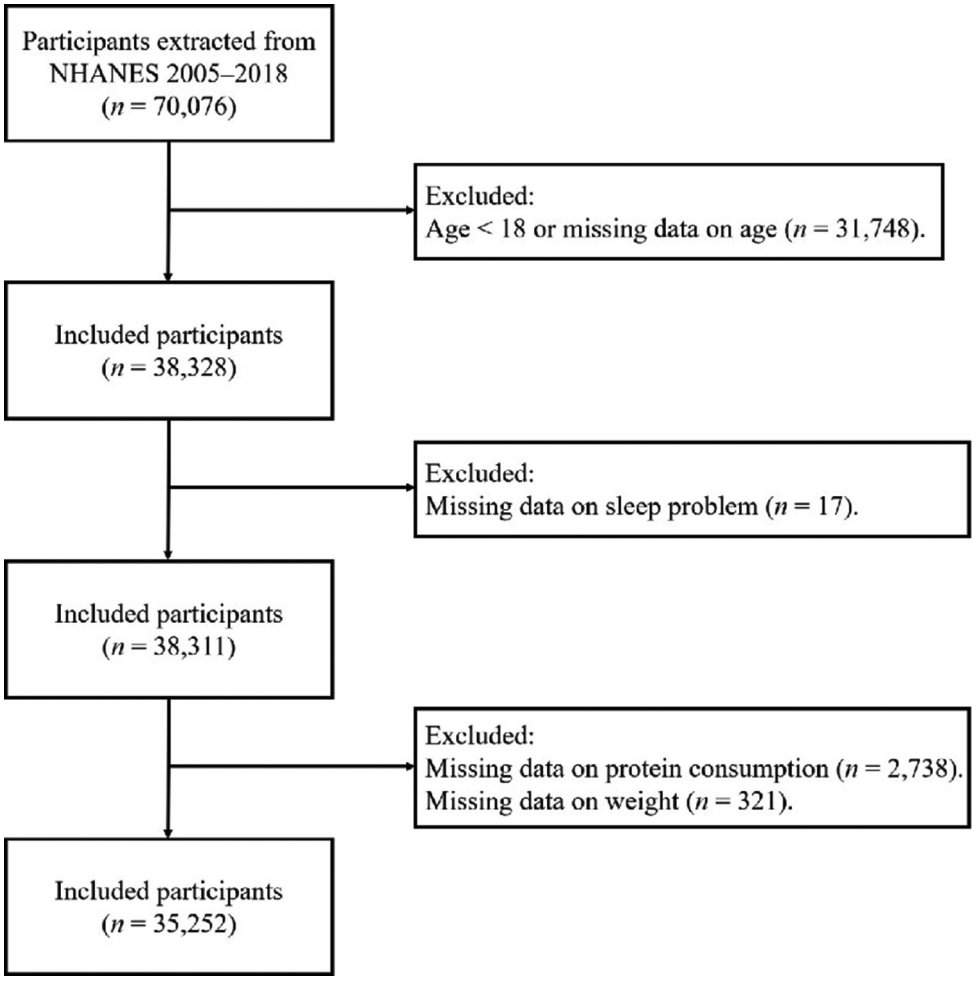

Figure 1. Flowchart of study population selection
Abbreviation: NHANES: National health and nutrition examination survey.

3. Results

3.1. Baseline demographic characteristics by quartiles of protein consumption

Table 1 presents baseline demographic characteristics categorized by quartiles of protein consumption from the NHANES. The mean age of participants varies across quartiles, with Quartile 4 (Q4) having the lowest mean age (41.4 years) and Quartile 2 (Q2) having the highest mean age (48.5 years). The distribution of gender varies across quartiles. Quartile 2 has the highest proportion of females (61.7%), whereas Q4 has the highest proportion of males (60.0%). Mean BMI decreases as protein consumption quartiles increase. Quartile 4 has the lowest mean BMI (25.4), whereas Q2 has the highest mean BMI (33.0). Total energy intake increases with higher quartiles of protein consumption. The prevalence of sleep problems decreases as quartiles of protein consumption increase. The distribution of race also varies across quartiles. Quartile 4 has the highest proportion of non-Hispanic white participants (42.3%), whereas Q2 has the highest proportion of non-Hispanic black participants (30.0%). There is variation in education level across quartiles, with Q2 having the highest proportion of participants with less than a 9th-grade education (11.3%). Quartile 3 (Q3) has the highest proportion of married participants (54.7%), whereas Q4 has the lowest (50.4%). The prevalence of smoking differs across quartiles, with Q4 having the highest proportion of participants who smoke every day (42.5%). The prevalence of alcohol use increases as quartiles of protein consumption increase. Mean sedentary physical activity time slightly decreases as quartiles advance.

3.2. Association between protein consumption and sleep problems

Table 2 presents the results of binary logistic regression analysis models examining the association between protein

Table 1. Baseline characteristics by quartiles of protein consumption from the National Health and Nutrition Examination Survey

Variable	Total (*n*=35,252)	Quartile 1, (0, 0.6485) (*n*=8,811)	Quartile 2, (0.6485, 0.9329) (*n*=8,817)	Quartile 3, (0.9329, 1.3154) (*n*=8,812)	Quartile 4, (1.3154, 8.1053) (*n*=8,812)	*P*
Age, mean (standard deviation [*SD*])	45.9 (17.7)	48.5 (17.9)	48.1 (17.6)	45.8 (17.4)	41.4 (16.8)	<0.001
BMI, mean (*SD*)	29.1 (7.1)	33.0 (8.3)	30.1 (6.6)	28.0 (5.7)	25.4 (4.9)	<0.001
Protein consumption (g/kg per d), mean (*SD*)	1.1 (0.6)	0.5 (0.1)	0.8 (0.1)	1.1 (0.1)	1.9 (0.6)	<0.001
Total energy intake, mean (*SD*)	2,032.4 (1003.1)	1,364.7 (568.4)	1,888.8 (645.2)	2,267.3 (745.9)	3,012.2 (1137.2)	<0.001
Sleep problems (Yes), *n* (%)	8,688 (24.6)	2,673 (30.3)	2,255 (25.6)	2,015 (22.9)	1,745 (19.8)	<0.001
Gender, *n* (%)						<0.001
Female	18,077 (51.3)	5,436 (61.7)	4,823 (54.7)	4,295 (48.7)	3,523 (40.0)	
Male	17,175 (48.7)	3,375 (38.3)	3,994 (45.3)	4,517 (51.3)	5,289 (60.0)	
Race, *n* (%)						<0.001
Mexican American	5,926 (16.8)	1,228 (13.9)	1,422 (16.1)	1,560 (17.7)	1,716 (19.5)	
Non-Hispanic Black	7,930 (22.5)	2,642 (30.0)	2,002 (22.7)	1,679 (19.1)	1,607 (18.2)	
Non-Hispanic White	14,148 (40.1)	3,434 (39.0)	3,670 (41.6)	3,731 (42.3)	3,313 (37.6)	
Other Hispanic	3,427 (9.7)	798 (9.1)	866 (9.8)	853 (9.7)	910 (10.3)	
Other race	3,821 (10.8)	709 (8.0)	857 (9.7)	989 (11.2)	1,266 (14.4)	
Education level, *n* (%)						<0.001
< 9th grade	3,332 (10.1)	938 (11.3)	855 (10.2)	802 (9.7)	737 (9.1)	
9–11th grade	4,698 (14.2)	1,281 (15.4)	1,143 (13.6)	1,088 (13.1)	1,186 (14.7)	
High School grade	7,610 (23.0)	2,123 (25.5)	1,937 (23.0)	1,749 (21.1)	1,801 (22.4)	
College	9,861 (29.8)	2,597 (31.2)	2,598 (30.8)	2,432 (29.3)	2,234 (27.7)	
> College	7,605 (23.0)	1,381 (16.6)	1,889 (22.4)	2,237 (26.9)	2,098 (26.0)	
Marital status, *n* (%)						<0.001
Married	17,216 (51.2)	3,977 (47.2)	4,461 (52.3)	4,622 (54.7)	4,156 (50.4)	
Widowed	1,919 (5.7)	675 (8.0)	557 (6.5)	445 (5.3)	242 (2.9)	
Divorced	3,677 (10.9)	1,125 (13.3)	946 (11.1)	848 (10.0)	758 (9.2)	
Separated	1,180 (3.5)	332 (3.9)	318 (3.7)	265 (3.1)	265 (3.2)	
Never married	6,735 (20.0)	1,664 (19.7)	1,538 (18.0)	1,550 (18.4)	1,983 (24.1)	
Living with a partner	2,921 (8.7)	656 (7.8)	715 (8.4)	714 (8.5)	836 (10.1)	
Smoking status, *n* (%)						<0.001
Every day	5,825 (39.1)	1,564 (40.6)	1,363 (36.8)	1,337 (36.8)	1,561 (42.5)	
Some days	1,360 (9.1)	321 (8.3)	305 (8.2)	329 (9.1)	405 (11.0)	
Not at all	7,708 (51.8)	1,968 (51.1)	2,071 (55.4)	1,964 (54.1)	1,705 (46.4)	
Alcohol use (had at least 12 cups of alcoholic drinks)	19,823 (71.4)	4,429 (64.5)	4,941 (70.4)	5,188 (73.9)	5,265 (76.8)	<0.001
Physical activity (sedentary) (min), mean (*SD*)	348.6 (201.5)	354.4 (204.7)	353.6 (205.1)	347.9 (199.1)	338.4 (196.8)	<0.001

Note: $P<0.05$ is considered significant.

consumption and sleep problems. As the quartiles of protein consumption increase (from Q1 to Q4), there is a decreasing trend in the odds of having sleep problems. Taking into account various factors such as age, gender, race, marital status, education, total energy intake, smoking status, alcohol use, and sedentary activity offers valuable insights into the standalone relationship between protein consumption and sleep problems. These adjustments reveal that higher protein intake remains associated with reduced odds of experiencing sleep problems, underscoring the potential beneficial effect of increased protein consumption on sleep quality, independent of these confounding variables.

3.3. Association between protein consumption and sleep problems stratified by gender

Table 3 presents odds ratio estimates for the association between protein consumption and sleep problems stratified by gender. In the unadjusted analysis, among females, higher quartiles of protein consumption (Q2, Q3, and Q4) are associated with statistically significantly lower odds of sleep problems compared to the reference group (Q1). Similarly, among males, Q3 and Q4 show statistically significantly lower odds of sleep problems compared to Q1. After adjusting for various factors, the association between protein consumption and sleep problems remains statistically significant among females, with Q2 and Q3 showing lower odds, although Q4 does not reach statistical significance. Among males, only Q4 maintains a statistically significant association with lower odds of sleep problems. These results suggest that the relationship between protein consumption and sleep problems may differ by gender, with a more consistent association observed among females even after adjusting for potential confounding factors.

3.4. Non-linear relationships using RCS regression

In our examination employing RCS regression, we identified a prominent positive non-linear correlation between protein consumption and the probability of experiencing sleep problems (Figure 2A). Moreover, we discovered a noteworthy non-linear relationship between sleep problems and protein consumption among females (Figure 2B), whereas no statistically significant non-linear association was evident in males (Figure 2B) in the subgroup analysis by gender.

4. Discussion

Our study reveals a consistent trend, indicating that higher protein consumption is associated with lower odds of experiencing sleep problems. The significance of the association persists even after adjusting for various demographic and lifestyle factors, suggesting that the relationship between protein consumption and sleep problems is independent of potential confounders. While higher protein intake is consistently associated with lower odds of sleep problems among females, the association is less consistent among males. These highlights emphasize the importance of adequate protein intake for promoting better sleep outcomes.

The significance of the association persists even after adjusting for various demographic and lifestyle factors, including age, gender, race, education, marital status, total energy intake, smoking status, alcohol consumption, and sedentary activity. This robustness indicates that the relationship between protein consumption and sleep problems is independent of these potential confounders.

Table 2. The association between protein consumption and sleep problems in binary logistic regression analysis models

EPA	Unadjusted model (OR [95% CI])	P	Model 1 (OR [95% CI])	P	Model 2 (OR [95% CI])	P	Model 3 (OR [95% CI])	P
Quartile 1	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Quartile 2	0.789 (0.739, 0.843)	<0.001	0.811 (0.758, 0.867)	<0.001	0.862 (0.801, 0.928)	0.003	0.826 (0.729, 0.935)	0.061
Quartile 3	0.681 (0.636, 0.728)	<0.001	0.744 (0.694, 0.796)	<0.001	0.842 (0.775, 0.914)	0.028	0.855 (0.744, 0.983)	<0.001
Quartile 4	0.567 (0.529, 0.608)	<0.001	0.693 (0.645, 0.745)	<0.001	0.806 (0.727, 0.893)	0.002	0.757 (0.636, 0.901)	<0.001

Notes: Model 1: Adjusted for age and gender. Model 2: In addition, adjusted for race, marital status, education, and total energy intake. Model 3: In addition, adjusted for smoking status, alcohol use, and sedentary activity. P<0.05 is considered significant.
Abbreviations: CI: Confidence interval; EPA: Eicosapentaenoic acid; OR: Odds ratio.

Table 3. Odds ratio estimates for the association between protein consumption and sleep problems by gender

Protein	*n*	Quartile 1	Quartile 2 (OR 95% CI)	P	Quartile 3 (OR 95% CI)	P	Quartile 4 (OR 95% CI)	P
Unadjusted								
Female	18077	1.000	0.774 (0.712, 0.842)	<0.001	0.662 (0.606, 0.724)	<0.001	0.613 (0.557, 0.675	<0.001
Male	17175	1.000	0.860 (0.708, 1.045)	0.129	0.762 (0.624, 0.930)	0.008	0.736 (0.606, 0.895)	0.002
Adjusted*								
Female	18077	1.000	0.734 (0.616, 0.873)	<0.001	0.719 (0.584, 0.886)	0.002	0.790 (0.607, 1.029)	0.080
Male	17175	1.000	0.926 (0.771, 1.111)	0.407	0.981 (0.809, 1.190)	0.847	0.769 (0.606, 0.975)	0.030

Notes: *Adjusted model: Adjusted for age, gender, race, marital status, education, total energy intake, smoking status, alcohol use, and sedentary activity. *P*<0.05 is considered significant.
Abbreviations: CI: Confidence interval; OR: Odds ratio.

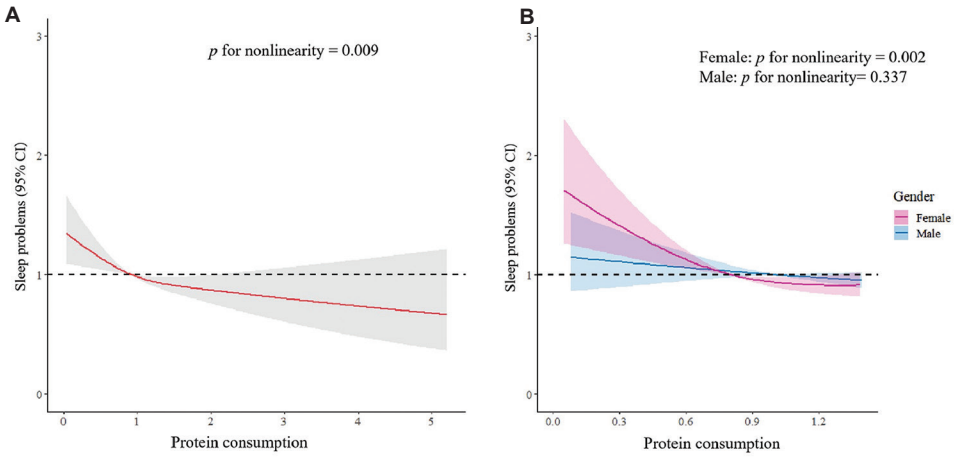

Figure 2. Analysis of restricted cubic spline regression, adjusted for age, gender, race, marital status, education, total energy intake, smoking status, alcohol use, and sedentary activity
Abbreviation: CI: Confidence interval.

Several studies consistently indicate that higher protein intake is linked to better sleep quality. For example, during energy restriction, high protein intake was linked to statistically significantly improve global sleep scores compared to low protein intake.[15,16] Similarly, a study found tendencies toward better-perceived sleep quality following a week of protein-rich breakfast compared to skipping breakfast.[17] Furthermore, a systematic review and meta-analysis of RCTs demonstrated a correlation between higher protein intake and better sleep quality.[12] These findings collectively support the notion that increasing protein consumption may contribute to improved sleep outcomes.

Our findings reveal gender differences in the association between protein consumption and sleep problems. Higher protein intake consistently correlates with lower odds of sleep problems among females, while the association is less consistent among males. This finding aligns with previous studies,[13,18] highlighting a gender disparity that warrants further investigation into underlying mechanisms and dietary patterns. Incorporating protein-rich foods into the diet could potentially alleviate hyperarousal and enhance sleep quality, particularly for individuals experiencing prolonged sleep onset, especially women.[5,19] Women may exhibit a greater tendency to adopt unhealthy habits due to a combination of psychological and sociocultural influences.[17,20] Studies exploring mental health and eating behaviors suggest gender discrepancies, with women being more prone to dieting, experiencing heightened levels of body dissatisfaction, and engaging in behaviors associated with eating disorders.[21] Therefore, understanding these gender-specific influences on dietary choices and their impact on sleep health is crucial for developing targeted interventions and promoting better sleep outcomes, particularly among women.

The relationship between protein consumption and sleep quality involves complex physiological mechanisms. First, proteins are composed of amino acids, some of which serve as precursors for neurotransmitters involved in sleep regulation.[22] For example, the amino acid tryptophan is a precursor for serotonin, which is subsequently converted into melatonin, a hormone that regulates the sleep–wake cycle.[23] Adequate levels of serotonin and melatonin are essential for promoting sleep onset and maintenance.[24] Second, protein intake can influence the balance of neurotransmitters in the brain, including dopamine, serotonin, and gamma-aminobutyric acid, which are crucial for regulating sleep. For instance, higher protein consumption may promote the synthesis of serotonin, enhancing feelings of relaxation and facilitating sleep.[25] Third, protein consumption, particularly when consumed in combination with carbohydrates, can affect blood sugar levels and insulin secretion. Maintaining stable blood sugar levels throughout the night is crucial for preventing disruptions in sleep, as fluctuations in blood sugar can trigger awakenings.[26] Consuming protein-rich snacks before bedtime may help stabilize blood sugar levels and promote uninterrupted sleep. Furthermore, protein consumption influences the secretion of hormones involved in hunger and satiety regulation, such as ghrelin and leptin.[27] Consuming protein-rich meals may promote feelings of fullness and reduce hunger, thereby preventing nighttime awakenings due to hunger and promoting more restful sleep. Overall, while the mechanisms underlying the relationship between protein consumption and sleep quality are multifaceted and interconnected, ensuring

adequate protein intake as part of a balanced diet may contribute to better sleep outcomes. However, further research is needed to elucidate the specific pathways through which protein influences sleep and to determine optimal protein intake recommendations for promoting sleep health.

5. Implications

These findings have implications for public health interventions aimed at promoting healthy dietary patterns for improved sleep health. Encouraging adequate protein intake, particularly among populations with lower consumption levels, may be beneficial in reducing the prevalence of sleep problems. Health-care providers should consider assessing dietary habits, including protein consumption, as part of routine clinical evaluations, especially among individuals reporting sleep disturbances. Counseling on dietary modifications to optimize protein intake could be integrated into sleep management strategies. Future research should focus on elucidating the underlying mechanisms linking protein consumption to sleep outcomes, including prospective studies to establish causality and intervention trials to evaluate the effectiveness of dietary interventions targeting protein intake in improving sleep quality. In addition, further investigation into gender-specific differences in the association between protein consumption and sleep problems is warranted, considering potential physiological and behavioral factors that may contribute to these disparities.

6. Limitations

While the analysis provides valuable insights into the association between protein consumption and sleep problems, several limitations may be considered. First, the cross-sectional study design employed in this research restricts the ability to establish causality between variables. It is challenging to determine the direction of the observed association, and reverse causation cannot be ruled out. Longitudinal studies are necessary to validate the temporal relationship between protein consumption and sleep problems. Second, the data on protein consumption, sleep problems, and other variables are self-reported, which introduces the potential for recall bias and measurement error. Individuals may not accurately recall their dietary intake or sleep patterns, leading to misclassification and potentially biased results. Third, despite adjusting for various demographic and lifestyle factors, residual confounding may still exist. Other unmeasured or inadequately controlled variables, such as physical activity level, stress, or underlying medical conditions, could influence both protein consumption and sleep problems, confounding the observed association. Fourth, the measure of sleep may miss individuals with sleep issues who have not sought medical help, thereby underestimating the true prevalence of sleep issues. Fifth, the analysis conducted in our study did not differentiate between plant-based and animal-based protein sources, which could indeed affect the results. The relationship between different protein sources and sleep quality may vary due to differences in amino acid composition, fat content, and other factors.

7. Conclusion

The analysis provided valuable insights into the association between protein consumption and sleep problems, highlighting the potential benefits of adequate protein intake for promoting better sleep outcomes. These findings enhanced our comprehension of the connection between diet and sleep health, emphasizing the significance of integrating dietary considerations into sleep management strategies and public health initiatives.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Chenxi Zhang, Bin Zhang
Data curation: Chenxi Zhang, Yan Xu, Bingnan Hou
Formal analysis: All authors
Writing – original draft: Bin Zhang, Chenxi Zhang, Yan Xu, Weimin Li, Qianyun Wu, Qiguang Li
Writing – review & editing: Bin Zhang, Chenxi Zhang, Yan Xu, Weimin Li, Qianyun Wu, Qiguang Li

Ethics approval and consent to participate

The NHANES was approved by the National Center for Health Statistics' Ethics Review Board, and all participants provided written informed consent.

Consent for publication

Participants have given their consent to publish their data.

Availability of data

The data used in this study are publicly available and can be accessed through the NHANES official website.

References

1. McArdle N, Ward SV, Bucks RS, *et al*. The prevalence of common sleep disorders in young adults: A descriptive population-based study. *Sleep*. 2020;43(10):zsaa072.

   doi: 10.1093/sleep/zsaa072

2. Baglioni C, Nanovska S, Regen W, *et al*. Sleep and mental disorders: A meta-analysis of polysomnographic research. *Psychol Bull*. 2016;142(9):969-990.

   doi: 10.1037/bul0000053

3. Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: A systematic review, meta-analysis, and meta-regression. *Sleep Med*. 2017;32:246-256.

   doi: 10.1016/j.sleep.2016.08.006

4. Chattu VK, Manzar MD, Kumary S, Burman D, Spence DW, Pandi-Perumal SR. The global problem of insufficient sleep and its serious public health implications. *Healthcare* (*Basel*). 2018;7(1):1.

   doi: 10.3390/healthcare7010001

5. Titos I, Juginović A, Vaccaro A, *et al*. A gut-secreted peptide suppresses arousability from sleep. *Cell*. 2023;186(7):1382-1397.e1321.

   doi: 10.1016/j.cell.2023.02.022

6. Peuhkuri K, Sihvola N, Korpela R. Diet promotes sleep duration and quality. *Nutr Res*. 2012;32(5):309-319.

   doi: 10.1016/j.nutres.2012.03.009

7. Sutanto CN, Loh WW, Toh DWK, Lee DPS, Kim JE. Association between dietary protein intake and sleep quality in middle-aged and older adults in Singapore. *Front Nutr*. 2022;9:832341.

   doi: 10.3389/fnut.2022.832341

8. Zhao M, Tuo H, Wang S, Zhao L. The effects of dietary nutrition on sleep and sleep disorders. *Mediators Inflam*. 2020;2020:3142874.

   doi: 10.1155/2020/3142874

9. Dashti HS, Scheer FA, Jacques PF, Lamon-Fava S, Ordovás JM. Short sleep duration and dietary intake: Epidemiologic evidence, mechanisms, and health implications. *Adv Nutr*. 2015;6(6):648-659.

   doi: 10.3945/an.115.008623

10. Binks H, Gupta EV Gupta C, Irwin C, Khalesi S. Effects of diet on sleep: A narrative review. *Nutrients*. 2020;12(4):936.

    doi: 10.3390/nu12040936

11. Sutanto CN, Wang MX, Tan D, Kim JE. Association of sleep quality and macronutrient distribution: A systematic review and meta-regression. *Nutrients*. 2020;12(1):126.

    doi: 10.3390/nu12010126

12. Wirth J, Hillesheim E, Brennan L. Protein intake and its effect on sleep outcomes: A systematic review and meta-analysis of randomized controlled trials. *Nutr Rev*. 2023;81(3):333-345.

    doi: 10.1093/nutrit/nuac061

13. Wirth J, Lin K, Brennan L, Wu K, Giovannucci E. Protein intake and its association with sleep quality: Results from 3 prospective cohort studies. *Eur J Clin Nutr*. 2024;78:413-419.

    doi: 10.1038/s41430-024-01414-y

14. Halson SL. Sleep in elite athletes and nutritional interventions to enhance sleep. *Sports Med*. 2014;44(Suppl 1):S13-S23.

    doi: 10.1007/s40279-014-0147-0

15. Zhou J, Kim JE, Armstrong CL, Chen N, Campbell WW. Higher-protein diets improve indexes of sleep in energy-restricted overweight and obese adults: Results from 2 randomized controlled trials. *Am J Clin Nutr*. 2016;103(3):766-774.

    doi: 10.3945/ajcn.115.124669

16. Suzuki F, Morita E, Miyagi S, *et al*. Protein intake in inhabitants with regular exercise is associated with sleep quality: Results of the Shika study. *PLoS One*. 2021;16(2):e0247926.

    doi: 10.1371/journal.pone.0247926

17. Gwin JA, Leidy HJ. Breakfast consumption augments appetite, eating behavior, and exploratory markers of sleep quality compared with skipping breakfast in healthy young adults. *Curr Dev Nutr*. 2018;2(11):nzy074.

    doi: 10.1093/cdn/nzy074

18. Martínez-Rodríguez A, Rubio-Arias JÁ, Ramos-Campo DJ, Reche-García C, Leyva-Vela B, Nadal-Nicolás Y. Psychological and sleep effects of tryptophan and magnesium-enriched mediterranean diet in women with fibromyalgia. *Int J Environ Res Public Health*. 2020;17(7):2227.

    doi: 10.3390/ijerph17072227

19. Ohayon MM, Reynolds CF 3rd, Dauvilliers Y. Excessive sleep duration and quality of life. *Ann Neurol*. 2013;73(6):785-794.

    doi: 10.1002/ana.23818

20. Larsen AE, Bibby BM, Hansen M. Effect of a whey protein supplement on preservation of fat free mass in overweight and obese individuals on an energy restricted very low caloric diet. *Nutrients*. 2018;10(12):1918.

    doi: 10.3390/nu10121918

21. Legget KT, Cornier MA, Sarabia L, *et al*. Sex differences in effects of mood, eating-related behaviors, and bmi on food appeal and desire to eat: A cross-sectional survey study. *Nutrients*. 2023;15(3):762.

doi: 10.3390/nu15030762

22. Friedman M, Analysis, nutrition, and health benefits of tryptophan. *Int J Tryptophan Res*. 2018;11:1178646918802282.

    doi: 10.1177/1178646918802282

23. Lai ML, Li AQ, Senior AM, Neely GG, Simpson SJ, Wang QP. Nutritional geometry framework of sleep. *Life Sci*. 2023;316:121381.

    doi: 10.1016/j.lfs.2023.121381

24. Yousef P, Rosen J, Shapiro C. Tryptophan and its role in sleep and mood. In: Rahman A, editor. *Studies in Natural Products Chemistry*. Ch. 1. Netherlands: Elsevier; 2024. p. 1-14.

25. Siegel JM. The neurotransmitters of sleep. *J Clin Psychiatry*. 2004;65(Suppl 16):4-7.

26. Spaeth AM. Additional sleep duration associates with improved blood sugar regulation. *Sleep*. 2015;38(5):663-664.

    doi: 10.5665/sleep.4648

27. Shukla C, Basheer R. Metabolic signals in sleep regulation: Recent insights. *Nat Sci Sleep*. 2016;8:9-20.

    doi: 10.2147/NSS.S62365

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ORIGINAL RESEARCH ARTICLE

Development and validation of a neuroticism scale: Assessment of reliability and validity

Qingfei Liu[1†], Linlin You[2†], Yonggui Yuan[2], and Wenhao Jiang[2*]

[1]Department of Psychology, Medical Humanities, School of Southeast University, Nanjing, Jiangsu, China

[2]Department of Psychosomatics and Psychiatry, ZhongDa Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, China

Abstract

Neuroticism, a personality trait linked to emotional instability and negative emotions, is associated with increased anxiety, depression, and poor mental health outcomes, particularly in individuals with psychiatric disorders. However, existing neuroticism scales often have too many items, are not tailored for psychiatric populations, and lack cultural adaptation for Chinese contexts. We aimed to develop a brief neuroticism scale with adequate reliability and validity for the Chinese population, including individuals with psychiatric disorders. The 14-item scale was developed based on the five-factor model and Eysenck's personality theory. The scale, in the form of a questionnaire, was distributed to college students from Southeast University and patients from the Affiliated Zhongda Hospital of Southeast University. A total of 554 participants were recruited, and demographic information, the neurotic subscale of the Neuroticism Extraversion Openness Five-Factor Inventory (NEO-FFI), Patient Health Questionnaire (PHQ-9), and generalized anxiety disorder (GAD-7) were collected along with the neuroticism scale. Correlation analysis, Cronbach's alpha, exploratory factor analysis (EFA), and confirmatory factor analysis (CFA) were conducted to test and revise the scale. EFA indicated that the neuroticism scale consisted of four factors: Low self-esteem, excessive emotional sensitivity, unstable mood, and excessive worry. The Cronbach's alpha was 0.926. CFA suggested a good fit of the scale structure (χ^2/df =2.506, root mean square error of approximation =0.039, Tucker–Lewis index =0.947, comparative fit index =0.959, and standardized root mean square residual =0.032). The total scores of the neuroticism scale were positively related to those of PHQ-9, GAD-7, and NEO-FFI. The results indicate that the neuroticism scale exhibited a stable four-dimensional structure with good reliability and validity in the Chinese population. It is useful and time-saving for assessing neuroticism in individuals with psychiatric disorders.

Keywords: Neuroticism; Factor analysis; Reliability; Validity

[†]These authors contributed equally to this work.

***Corresponding author:**
Wenhao Jiang
(wjiang@seu.edu.cn)

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1. Introduction

Neuroticism, a personality trait, reflects individuals' emotional stability and is closely related to negative emotions.[1] Historically, the concept of neuroticism originated from Freud's theory, which supported that repression leads to the subconscious mind causing neurosis.[2] Subsequently, Karen Horney argued that neuroticism arises from fundamental anxiety in individuals.[3] Eysenck was one of the first to operationalize the definition of "neuroticism,"

a term that had been widely used before his work.[4] His studies revealed that emotionality and anxiety share similar emotional experiences and noted that individuals with high levels of neuroticism exhibit rapid emotional arousal. Eysenck further identified a link between neuroticism and the function of the autonomous nervous system, especially the sympathetic nervous system. Neuroticism is often seen as a reflection of maladaptive and negative emotionality, contrasting with emotional stability. Contemporary views suggest that neuroticism reflects an individual's capacity for emotional stability and adjustment.[5]

It is commonly understood that positive mental health functioning is negatively correlated with neuroticism.[6] At the same time, neuroticism can predict the severity of depressive symptoms.[7-9] Individuals with high neuroticism tend to exhibit neurological susceptibility, characterized by anxiety manifested through somatic symptoms, depression, and difficulties in emotion regulation. These individuals often struggle to respond to stress appropriately, leading to a gradual decline in mental health.[10] Some researchers believe that higher levels of neuroticism may also increase the risk of suicidal ideation.[9]

High levels of neuroticism, often present in psychiatric patients, can significantly impact their clinical outcomes and overall quality of life. Consequently, developing a shorter, culturally relevant neuroticism scale is crucial for providing rapid and accurate assessments, enabling timely interventions that can vastly improve patient care. Furthermore, it is essential to ensure the reliability and validity of such scales using a homogeneous sample with specific psychiatric diagnoses. By developing a brief neuroticism scale with robust reliability and validity tailored to the Chinese population suffering from psychiatric disorders, we aim to address existing limitations of current scales, such as their length, lack of specificity for psychiatric populations, and cultural inadaptability.

To date, the standard tools used to measure neuroticism are mainly the Eysenck Personality Questionnaire (EPQ) and Neuroticism Extraversion Openness (NEO) Personality Inventory Scale. The EPQ, first proposed in the 1940s, has undergone several revisions and includes subscales for neuroticism, extraversion, psychoticism, and a lie scale.[11] However, the EPQ has several limitations: (i) inconsistencies exist between different versions of the scale; (ii) there is an overlap between the neuroticism scale and scales measuring related emotional disorders[12]; and (iii) its binary response format restricts the accuracy of assessments. Costa and McCrae[13] formulated the NEO-Five-Factor Inventory (NEO-FFI), which consists of 60 items, including a neuroticism subscale with 12 items.[14] The NEO-FFI has demonstrated excellent reliability and validity.[15] However, it shares similarities with scales assessing mood disorders and is highly susceptible to individual differences.

In summary, existing scales present the following problems: (i) they contain too many items; (ii) they were not specifically developed for populations with psychiatric disorders; and (iii) they were not developed within the context of Chinese culture. Therefore, our goal is to develop a brief neuroticism scale with adequate reliability and validity, specifically tailored for the Chinese population suffering from psychiatric disorders.

2. Methods

2.1. Development of the neuroticism scale

To develop the neuroticism scale, we initially conducted interviews with a diverse group of participants,[16] including 20 patients diagnosed with psychiatric disorders, 12 clinical psychologists, and 20 laypersons without any psychiatric diagnoses. The aim was to gather characteristics associated with neuroticism. Each interview lasted approximately 30 min and followed a semi-structured format to ensure consistency while allowing for in-depth exploration of individual experiences. The responses were categorized into three main themes: difficulty in adjusting negative emotions, excessive worry about potential future events, and insomnia due to worry. An expert working group was recruited to draft the neuroticism scale. From the analysis of the items, an initial version of the scale containing 30 items was developed.

Subsequently, a homogeneity test was carried out to assess the internal consistency of the original 30-item scale, using Cronbach's alpha to evaluate reliability. The test results indicated that Items 16, 20, 21, 23, and 29 were not highly correlated with the total score, suggesting that these items should be removed to improve the scale's coherence.

To further refine the scale, an exploratory factor analysis (EFA) was performed to identify the underlying factor structure. The Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy was 0.88, indicating that the data were suitable for factor analysis. Bartlett's test of sphericity was significant ($P < 0.001$), suggesting that the correlations between items were sufficiently strong for EFA. We used the principal component method with varimax orthogonal rotation to identify the factor loadings. Items with factor loadings below 0.45 were considered for deletion.[17] After this process, four factors comprising 14 items were retained, cumulatively explaining 57.9% of the variance. The four factors were identified and labeled as low self-esteem, excessive emotional sensitivity, unstable mood, and excessive worry. Finally, the cumulative interpretation

rate reached 57.9%. A confirmatory factor analysis (CFA) was then performed to finalize the item selection.

2.2. Participants

Before participant recruitment, the study received ethical approval from the Medical Ethics Committee for Clinical Research at Zhongda Hospital, affiliated with Southeast University. The study involved a total of 554 participants, comprising college students from Southeast University and patients diagnosed with various psychiatric conditions at Zhongda Hospital of Southeast University in Nanjing. The recruitment aimed to create a homogeneous sample for the study. Informed consent was obtained from all participants, ensuring they were aware of the study's purpose and their rights. Questionnaires were distributed in both paper form and electronic formats. All participants were of Han Chinese ethnicity.

The study population was divided into two distinct samples to assess differences between college students without psychiatric conditions and individuals with varying psychiatric diagnoses. Detailed descriptions of the samples are as follows:

i. Sample 1 (n = 168, age: 20.18 ± 1.78 years): A total of 200 questionnaires were distributed among college students without psychiatric diagnoses, resulting in 168 valid responses (98 men and 70 women).
ii. Sample 2 (n = 386, age: 39.23 ± 11.49 years): In this group, 430 questionnaires were distributed. Participants completed a self-designed neurotic questionnaire with 14 questions, along with the NEO-FFI, the Patient Health Questionnaire (PHQ-9), and the generalized anxiety disorder questionnaire (GAD-7). A total of 386 valid responses were collected, consisting of 173 men and 213 women. Among these, 163 were outpatients with psychiatric diagnoses, while 223 were normal subjects without psychiatric conditions.

2.3. Assessments

2.3.1. *Neurotic subscale of the NEO-FFI*

The NEO Personality Inventory (NEO-PI) was originally developed by Costa and McCrae[13] in 1985. To enhance its practical application, the NEO-FFI was developed, consisting of 60 items. The neuroticism subscale of the NEO-FFI includes 12 items rated on a 5-point scale. Xi *et al.*[18] verified the reliability of this subscale, with a Cronbach's alpha coefficient of 0.84.

2.3.2. *PHQ-9*

The PHQ-9 is a widely used depression screening instrument in psychiatric settings. The PHQ-9 can be scored using different methods, including an algorithm based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, or a cutoff based on summed item scores.[19] It consists of 9 items scored from 0 to 3, reflecting the severity of depressive symptoms over the past 2 weeks. Higher scores indicate more severe depressive symptoms.[20]

2.3.3. *GAD-7*

The GAD-7 scale is used to assess anxiety symptoms. It comprises seven items scored from 0 to 3, with higher scores indicating more severe anxiety symptoms.[21] The GAD-7 has been validated for use in primary care settings.[22]

2.4. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 16.0 for descriptive statistics, correlation analysis, and EFA.[23] Mplus7 was used for CFA.[24]

Data from both normal participants and outpatients were analyzed to verify the item characteristics, internal consistency, and construct validity of the neuroticism scale. Internal consistency for the neuroticism scale and its subscales was estimated using Cronbach's alpha coefficient. Criterion validity was investigated using Spearman's correlation between the neuroticism scale and other measures, including GAD-7, PHQ-9, and the neuroticism subscale of the NEO-FFI (NEO-FFI-N). Construct validity of the neuroticism scale was assessed using CFA.

3. Results

3.1. Overall item characteristics

Descriptive analysis and independent sample t-tests were primarily used to analyze the validity of each item. Participants were divided into high-score and low-score groups for further analysis, and a homogeneity test was carried out. The homogeneity test results indicated that Items 16, 20, 21, 23, and 29 were not highly correlated with the total score, leading to the decision to remove these items (Table 1).

3.2. EFA

EFA was performed on Sample 1 (n = 168). The results showed a KMO value of 0.88 and a significance level of $P < 0.001$. Principal component analysis with variance maximal orthogonal rotation was used to determine factor loadings. Items with factor loadings below 0.45 were removed.[25] Finally, four factors comprising 14 items were retained, which were named: low self-esteem, excessive emotional sensitivity, unstable mood, and excessive worry. The cumulative interpretation rate reached 57.9% (Table 2).

3.3. Content validity

Content validity was evaluated by experts who determined the conformity of the neuroticism scale items with the intended constructs. The evaluation concluded that the questionnaire demonstrated good content validity.

3.4. Criterion validity

Three criteria were selected for assessing criterion validity: the NEO-FFI-N, the GAD-7, and the PHQ-9. Correlation analysis results showed that the total score of the neuroticism scale, along with scores for low self-esteem, excessive emotional sensitivity, unstable mood, and excessive worry, were positively correlated ($r \geq 0.50$) with the total scores of the NEO-FFI-N neuroticism subscale, PHQ-9, and GAD-7. These results indicate that the neuroticism scale has good criterion validity (Table 3).

Table 1. Initial test of neuroticism scale

Item	Determination	Item	Determination	Item	Determination
V1	7.637***	V11	7.582***	V21	4.421***
V2	7.262***	V12	5.070***	V22	6.990***
V3	6.943***	V13	6.131***	V23	4.592***
V4	5.377***	V14	0.842	V24	7.120***
V5	5.474***	V15	1.512	V25	5.829***
V6	6.308***	V16	2.158**	V26	7.673***
V7	6.731***	V17	4.430***	V27	8.118***
V8	6.232***	V18	6.764***	V28	8.060***
V9	7.773***	V19	9.331***	V29	4.724***
V10	9.128***	V20	4.598***	V30	10.07***

Note: *** indicates $P<0.001$; ** indicates $P<0.01$.

3.5. Construct validity

CFA was conducted using Mplus 7 to validate the factor structure identified in the EFA. The analysis was performed on Sample 2, which included 386 participants. The fit indices indicated a good model fit: Chi-square value (χ^2) =177.960 and degrees of freedom (df) =71, resulting in a chi-square to degrees of freedom ratio (χ^2/df) of 2.506, which is below the recommended threshold of 3.0. The root-mean-square error of approximation was 0.039, indicating a good fit as it is below the 0.05 threshold. The comparative fit index was 0.959, and the Tucker-Lewis index was 0.947, both exceeding the acceptable fit threshold of 0.90. The standardized root mean square residual was 0.032, indicating an excellent fit as it is below the 0.08 threshold (Table 4).

3.6. Reliability test

The Cronbach's alpha coefficient for the overall neuroticism scale was 0.926, indicating high internal consistency. The Cronbach's alpha coefficient of each factor ranged from 0.70 to 0.83, with an average of 0.762. The mean inter-item correlation coefficients ranged from 0.70 to 0.926, demonstrating good reliability across the scale (Table 5).

4. Discussion

Our data demonstrated good item characteristics, internal reliability, and constructed validity of the neuroticism subscale in the sample population ($n = 554$). The neuroticism scale comprised four dimensions: low self-esteem, excessive emotional sensitivity, unstable mood, and excessive worry. A detailed discussion of each dimension is as follows:

Table 2. Exploratory factor analysis results

Item	Factor 1	Factor 2	Factor 3	Factor 4	Communalities
I am sensitive to the expression in others' eyes		0.763			0.633
I feel everyone is hostile to me		0.706			0.606
I'm a little nervous		0.672			0.622
It's hard for me to regulate my mood			0.455		0.396
I get angry easily			0.709		0.590
I will suddenly cry			0.706		0.512
My mood is up and down			0.650		0.564
Stress can break me	0.538				0.479
I feel completely worthless	0.745				0.624
Setbacks tend to make me give up	0.660				0.562
I want to hide from anyone	0.757				0.702
I'm afraid of making mistakes				0.769	0.628
I'm afraid of failure				0.761	0.662
I'm always worried about my health				0.647	0.527

Table 3. Criterion validity

	Low self-esteem	Excessive emotional sensitivity	Moodiness	Worry	Total
NEO-FFI-N	0.651**	0.620**	0.623**	0.576**	0.688**
PHQ-9	0.657**	0.670**	0.737**	0.655**	0.779**
GAD-7	0.617**	0.669**	0.578**	0.639**	0.711**

Note: ** indicates $P<0.01$.
Abbreviation: NEO-FFI: NEO five-factor inventory; PHQ-9: Patient health questionnaire-9; GAD-7: Generalized anxiety disorder-7.

Table 4. Fitting coefficients

Coefficient	χ^2/df	TLI	CFI	SRMR	RMSEA
Value	2.506	0.947	0.959	0.032	0.039

Note: χ^2/df: Chi-square to degrees of freedom ratio; CFI: Comparative fit index; RMSEA: Root mean square error of approximation; SRMR: Standardized root mean square residual; TLI: Tucker-Lewis index.

Table 5. Internal consistency coefficient

	Low self-esteem	Excessive emotional sensitivity	Unstable mood	Excessive worry	Total
Cronbach's α	0.823	0.734	0.785	0.706	0.926

- Low self-esteem (Items 8, 9, 10, and 11): Individuals with low self-esteem often deny their worth and feel ashamed.
- Excessive emotional sensitivity (Items 1, 2, and 3): People with high emotional sensitivity tend to be overly attentive to others, perceiving every external feedback as highly personal. They often experience prolonged discomfort after receiving negative feedback.
- Unstable mood (Items 4, 5, and 6): These individuals exhibit noticeable negative emotions that are difficult to control, struggling with emotional regulation.
- Excessive worry (Items 11, 12, 13, and 14): This dimension captures a tendency to frequently worry about events that have not happened, highlighting the multidimensional nature of neuroticism.

These four dimensions effectively summarize the characteristics of neurotic individuals from distinct perspectives.

The Cronbach's alpha coefficient for the total score was 0.926, indicating good internal consistency. CFA confirmed that the model fitted the data well, supporting the theoretical structure of the neuroticism scale. The overall model fit was acceptable, validating the utility of both the total scale score and the individual subscale score. This brief scale can be completed by patients and the general population in a short period, making it an acceptable screening instrument in general hospitals and large-scale studies. Overall, the neuroticism questionnaire demonstrated good reliability and validity.

The neuroticism scale showed a strong correlation with GAD-7 (r = 0.657 – 0.779), in line with previous results.[26] This suggests that anxiety, which commonly arises in response to threats or stress, is closely related to the neurotic characteristics of individuals.[27] Similarly, the correlation coefficients between the PHQ-9 and the neuroticism scale were high across each subscale (0.578 – 0.711), aligning with previous studies indicating a strong association between neuroticism and depression.[28] Smith *et al.*[29] also supported the view that neuroticism is a heritable risk factor for depression. Anxiety and depression are prevalent emotional symptoms that positively correlate with neuroticism and negative affectivity.[30]

4.1. Advantages of the scale

The advantages of the neuroticism scale are reflected in several aspects. First, it is a dedicated neuroticism scale rather than a single dimension of a broader personality scale. This focused approach allows for a more precise assessment of neurotic traits.

Second, the scale was specifically developed and validated within a specific cultural context, addressing the unique characteristics and expressions of neuroticism in the Chinese population. While widely used scales, such as the NEO-PI, were primarily developed in Western contexts, they may not fully capture culturally specific manifestations of neurotic traits.

Third, the scale's development involved a rigorous methodological approach, including both exploratory and confirmatory factor analyses. These steps ensured a robust factor structure, high reliability, and validity. Although the EPQ and NEO-PI are well-validated tools, they do not necessarily reflect the same level of cultural and contextual relevance as our scale.

Fourth, the scale includes items particularly relevant to individuals with psychiatric disorders, focusing on specific symptoms such as difficulty in adjusting negative emotions, excessive worry about potential future events, and insomnia due to worry. These aspects are critical for effective clinical assessment and intervention, providing healthcare providers with a targeted tool.

In addition, the scale is designed to assess the level of neuroticism in both general and clinical populations. Clinically, many psychosomatic patients exhibit high neuroticism, which often affects their clinical outcomes. Therefore, accurately evaluating patients' neurotic

tendencies is essential. The scale's development included both patients and healthy individuals as research subjects, ensuring its applicability across diverse groups.

Finally, the scale consists of 14 items, which is a moderate number that helps minimize the fatigue effect in participants. The four-level scoring system of the neuroticism scale discourages compromise answers and significantly improves the scale's effective utilization rate. Efforts to streamline personality inventories have demonstrated that it is possible to reduce the number of items without compromising validity and reliability. For example, McCrae and Costa[31] effectively condensed the NEO-PI-R into the more manageable NEO-FFI. Similarly, Francis *et al*.[32] successfully reduced the EPQ to the EPQR-A while maintaining essential psychometric properties.

4.2. Limitations of the scale

While this study had several advantages, there are three major limitations that should be noted. First, the age range of the subjects was narrow, limiting the generalizability of the findings across different age groups. Second, the study did not incorporate a well-designed structural interview. Finally, the study relied solely on self-evaluation scales, without peer assessments or other external evaluations, which would have allowed for a more comprehensive, multifaceted assessment.

5. Conclusion

The neuroticism scale includes four dimensions: low self-esteem, excessive emotional sensitivity, unstable mood, and excessive worry, with scores ranging from 1 to 4. The scale demonstrates good reliability and validity, making it a valuable tool for both research studies and clinical diagnosis.

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Conflict of interest

Yonggui Yuan and Wenhao Jiang are the Editor-in-Chief and the Associate Editor of the journal, respectively, but were not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Wenhao Jiang
Investigation: Qingfei Liu, Linlin You
Methodology: Qingfei Liu, Linlin You, Wenhao Jiang
Writing – original draft: Qingfei Liu, Linlin You
Writing – review & editing: Yonggui Yuan, Wenhao Jiang

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee for Clinical Research of Zhongda Hospital, affiliated with Southeast University, and informed consent was obtained from all participants.

Consent for publication

Informed consent of participants was obtained for publishing their data in this paper.

Availability of data

The raw/processed data required to derive these findings cannot be shared at this time as the data also form part of an ongoing study.

References

1. Huang Y, Zhou R, Wu M. Neurophysiological mechanism of neuroticism. *Adv Psychol Sci*. 2015;23(4):602-613.

   doi: 10.3724/SP.J.1042.2015.00602

2. Lahey BB. Public health significance of neuroticism. *Am Psychol*. 2009;64(4):241-256.

   doi: 10.1037/a0015309

3. Ding JL, Tian H. A review of Honey's neurosis theory. *Med Philos (Humanit Soc Med)*. 2007(6);28:43-45.

4. Mats BK. Eysenck's theory of personality and the role of background music in cognitive task performance: A mini-review of conflicting findings and a new perspective. *Front Psychol*. 2017;14(8):1991.

   doi: 10.3389/fpsyg.2017.01991

5. McCrae RR, Sutin AR. A five-factor theory perspective on causal analysis. *Eur J Pers*. 2018;32(3):151-166.

   doi: 10.1002/per.2134

6. Gu SQ, Xi XN, Cheng ZH, Wu ZG, Wang GQ. The relationship between personality and mental health in college students. *Chin J Clin Psychol*. 2014;22(2):354-356.

7. Rydberg Sterner T, Gudmundsson P, Sigström R, *et al*.

Depression and neuroticism decrease among women but not among men between 1976 and 2016 in Swedish septuagenarians. *Acta Psychiatr Scand*. 2019;139(4):381-394.

doi: 10.1111/acps.13005

8. O'Loughlin, RE, Fryer JW, Zuckerman M. Mindfulness and stress appraisals mediate the effect of neuroticism on physical health. *Pers Individ Differ*. 2019;142:122-131.

doi: 10.1016/j.paid.2019.01.019

9. García Herrero AM, Sánchez-Meca J, Álvarez Muñoz FJ, Rubio-Aparicio M, Navarro-Mateu F. Neuroticism and suicidal thoughts: A meta-analytic study. *Rev Esp Salud Publica*. 2018;92:e201808049.

10. Mohiyeddini C, Bauer S, Semple S. Neuroticism and stress: The role of displacement behavior. *Anxiety Stress Coping*. 2015;28(4):391-407.

doi: 10.1080 / 10615806.2014.1000878

11. Ferrando PJ. The measurement of neuroticism using MMQ, MPI, EPI and EPQ items: A psychometric analysis based on item response theory. *Pers Individ Differ*. 2001;30:641-656.

doi: 10.1016/s0191-8869(00)00062-3

12. Uliaszek AA, Hauner KK, Zinbarg RE, *et al*. An examination of content overlap and disorder-specific predictions in the associations of neuroticism with anxiety and depression. *J Res Pers*. 2009;43(5):785-794.

doi: 10.1016/j.jrp.2009.05.009

13. Costa PT, McCrae RR. Stability and change in personality assessment: The revised NEO personality inventory in the year 2000. *J Pers Assess*. 1997;68(1):86-94.

doi: 10.1207/s15327752jpa6801_7

14. Keuthen NJ, Tung ES, Tung MG, Curley EE, Flessner CA. NEO-FFI personality clusters in trichotillomania. *Psychiatry Res*. 2016;239:196-203.

doi: 10.1016/j.psychres.2016.03.011

15. Uliaszek AA, Al-Dajani N, Sellbom M, Bagby RM. Cross-validation of the demoralization construct in the revised NEO personality inventory. *Psychol Assess*. 2019;31(2):159-166.

doi: 10.1037/pas0000655

16. Zhang WP. *Preparation of Neurotic Questionnaire for College Students and Its Relationship with Physical and Mental Health*. China: Southwest University; 2011.

17. Bu T, Liu HJ. Preparation of family resilience questionnaire. *Psychol Technol Appl*. 2019;7(3):173-182.

18. Xi C, Zhong MT, Lei XX, *et al*. The reliability and validity of the full and simple subscales of neuroticism on the big five personality scale. *Chin J Clin Psychol*. 2017;25(3):453-456.

19. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.

doi: 10.1046/j.1525-1497.2001.016009606.x

20. Manea L, Gilbody S, McMillan D. A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. *Gen Hosp Psychiatry*. 2015;37(1):67-75.

doi: 10.1016/j.genhosppsych.2014.09.009

21. Hinz A, Klein AM, Brähler E, *et al*. Psychometric evaluation of the generalized anxiety disorder screener GAD-7, based on a large German general population sample. *J Affect Disord*. 2016;210:338-344.

doi: 10.1016/j.jad.2016.12.012

22. Löwe B, Decker O, Müller S, *et al*. Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the general population. *Med Care*. 2008;46(3):266-274.

doi: 10.1097/MLR.0b013e318160d093

23. Wu ML. *Questionnaire Statistical Analysis Practice: SPSS Operation and Application*. China: Chongqing University Press; 2010.

24. Wang MC, Bi XY. Regression hybrid model: Method progress and software implementation. *Adv Psychol Sci*. 2018;26(12):2272-2280.

25. Bolger N, Schilling EA. Personality and the problems of everyday life: The role of neuroticism in exposure and reactivity to daily stressors. *J Pers*. 1991;59(3):355-386.

doi: 10.1111/j.1467-6494.1991.tb00253.x

26. Riccelli R, Indovina I, Staab JP, *et al*. Neuroticism modulates brain visuo-vestibular and anxiety systems during a virtual rollercoaster task. *Hum Brain Mapp*. 2017;38(2):715-726.

doi:10.1002/hbm.23411

27. Erin D. Anxiety. *Nurs Stand*. 2016;30(46):15.

doi: 10.7748/ns.30.46.15.s17

28. Hagger-Johnson G, Roberts B, Boniface D, *et al*. Neuroticism and cardiovascular disease mortality: Socioeconomic status modifies the risk in women (UK Health and Lifestyle Survey). *Psychosom Med*. 2012;74(6):596-603.

doi: 10.1097/PSY.0b013e31825c85ca

29. Smith EM, Reynolds S, Orchard F, Whalley HC, Chan SW. Cognitive biases predict symptoms of depression, anxiety and wellbeing above and beyond neuroticism in adolescence. *J Affect Disord*. 2018;241:446-453.

doi: 10.1016/j.jad.2018.08.051.

30. Subica AM, Allen JG, Frueh BC, Elhai JD, Fowler JC. Disentangling depression and anxiety in relation to neuroticism, extraversion, suicide, and self-harm among adult psychiatric inpatients with serious mental illness. *Br J*

Clin Psychol. 2016;55(4):349-370.

doi: 10.1111/bjc.12098

31. McCrae RR, Costa PT Jr. A contemplated revision of the NEO five-factor inventory. *Pers Individ Differ*. 2004;36(3):587-596.

doi: 10.1016/S0191-8869(03)00118-1

32. Francis LJ, Brown LB, Philipchalk R. The development of an abbreviated form of the revised Eysenck personality questionnaire (EPQR-A): Its use among students in England, Canada, the USA and Australia. *Pers Individ Differ*. 1992;13(4):443-449.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Association of high-density lipoprotein-related inflammatory markers with suicidal ideation: Data from the NHANES 2015 – 2023 survey

Zhonghua Sun[1], Sen Chen[1], Yameng Xu[2], and Chen Qu[1]*

[1]Department of Geriatrics, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

[2]Department of Epidemiology, School of Public Health of Nanjing Medical University, Nanjing, Jiangsu, China

Abstract

Suicidal ideation (SI) is a strong predictor of suicide risk. High-density lipoprotein (HDL)-related inflammatory indicators, which combine HDL cholesterol (HDL-C) with other inflammation-related markers, provide a comprehensive assessment of the body's inflammatory, immune, and metabolic states. However, limited research has examined the association between HDL-related inflammatory indicators and SI. This study analyzed data from 14,554 participants, including 588 individuals with SI, using information from the 2015 – 2023 National Health and Nutrition Examination Survey. SI was evaluated using the ninth item of the Patient Health Questionnaire-9. A weighted approach was applied to logistic regression, restricted cubic spline, and subgroup analyses to explore the relationship between six HDL-related inflammatory indicators and SI. In addition, weighted quantile sum regression was employed to account for the interactions among inflammatory markers and their influence on the outcomes. Among the various single-marker models, only high-sensitivity C-reactive protein/HDL-C (CHR) consistently demonstrated a significant linear association with SI. In Model 3 of the logistic regression analysis, the odds ratio with a 95% confidence interval was 1.11 (1.02, 1.21). Mixture analyses further identified CHR as the primary factor contributing to the increased prevalence of SI. This study provides the first epidemiological evidence linking multiple novel inflammatory markers to SI, identifying CHR as the most critical factor. Further prospective studies are needed to confirm this causal relationship.

Keywords: Suicidal ideation; Patient Health Questionnaire-9; High-density lipoprotein-related inflammatory indicators; National Health and Nutrition Examination Survey

***Corresponding author:**
Chen Qu
(quchen@njmu.edu.cn)

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1. Introduction

Globally, suicide remains a major cause of death, with approximately 800,000 fatalities annually, accounting for 57% of all violent deaths.[1] Although global suicide rates have declined since 1990, suicide remains among the top 10 leading causes of age-standardized years of life lost, including in the United States (U.S.).[2] Suicidal ideation (SI) substantially increases the risk of suicide across diverse populations and serves as a critical warning sign of suicide mortality.[3,4] Numerous studies have demonstrated a strong association

between the pathogenesis of SI and various biomarkers, including high-sensitivity C-reactive protein (hs-CRP),[5] monocytes,[6] and high-density lipoprotein cholesterol (HDL-C).[7] Recent research has further underscored the complex interplay among inflammatory, immune, and lipid biomarkers.[8-12]

High-density lipoprotein (HDL), among lipid biomarkers, has attracted significant attention due to its multifunctional roles, including anti-inflammatory, antioxidant, immune-regulating, and reverse cholesterol transport functions.[13,14] In recent years, novel HDL-related inflammatory indicators have been developed by combining HDL-C levels with other blood components, such as white blood cell (WBC), lymphocyte (LYM), monocyte (MONO), and neutrophil (NEU) counts as well as hs-CRP and platelet (PLT) levels.[15-17] These HDL-associated markers simultaneously reflect inflammation, immune responses, and metabolic states, allowing for a more comprehensive evaluation of how these risk factors collectively influence health. However, research on the relationship between HDL-associated markers and SI remains extremely limited.

The Centers for Disease Control and Prevention (CDC) administers the National Health and Nutrition Examination Survey (NHANES), which provides comprehensive data on biochemical markers. This study aimed to analyze NHANES data to explore the association between HDL-related inflammatory markers and SI in U.S. adults. We hypothesize that elevated levels of these HDL-related inflammatory markers are significantly associated with an increased prevalence of SI among adults.

2. Methods

2.1. Study population

Data were collected from three NHANES cycles: 2015 – 2016, 2017 – March 2020, and August 2021 – August 2023. During these cycles, data on both HDL-related inflammatory indicators and SI were collected simultaneously. As illustrated in Figure 1, the study initially included 37,464 individuals from the NHANES dataset. Through a stepwise exclusion process, 18,510 individuals missing SI data, 1,464 individuals missing biochemical parameter data (HDL-C, WBC, NEU, LYM, MONO, hs-CRP, and PLT), and 2,729 individuals missing demographic data (gender, age, race/ethnicity, marital status, education level, and poverty income ratio [PIR]) were removed. In addition, 35 individuals missing lifestyle factor data (smoking status and alcohol consumption) and 172 individuals missing health condition data (hypertension, diabetes, stroke, and kidney disease) were excluded. Ultimately, 14,554 adult individuals with complete data were included, enabling a comprehensive analysis of the association between HDL-related inflammatory indicators and SI.

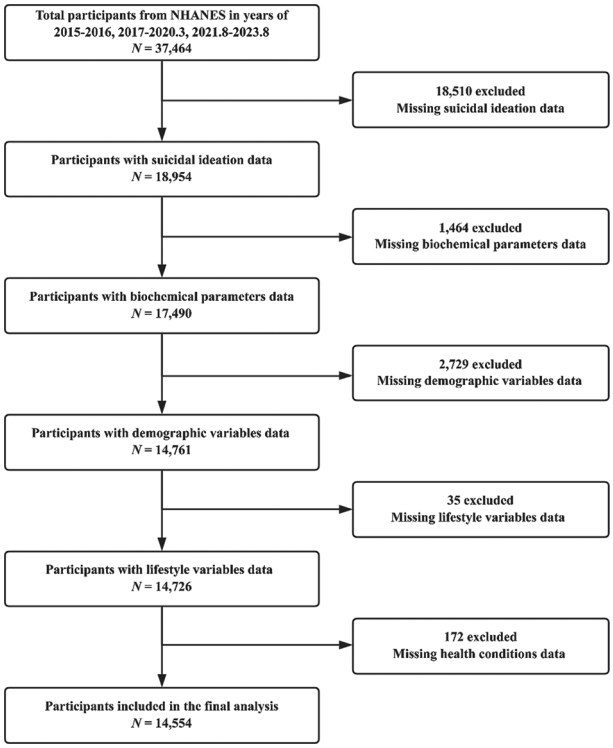

Figure 1. Flowchart depicting the participant selection process
Abbreviation: NHANES: National Health and Nutrition Examination Survey.

2.2. Exposure variable

Seven biochemical parameters from the NHANES database were used to calculate HDL-related inflammatory indicators: HDL-C, WBC, NEU, LYM, MONO, hs-CRP, and PLT. The following formulas were applied to derive the HDL-related inflammatory indicators: WBC-to-HDL-C ratio (WHR): WBC/HDL-C; NEU-to-HDL-C ratio (NHR): NEU/HDL-C; LYM-to-HDL-C ratio (LHR): LYM/HDL-C; MONO-to-HDL-C ratio (MHR): MONO/HDL-C; hs-CRP-to-HDL-C ratio (CHR): hs-CRP/HDL-C; and PLT-to-HDL-C ratio (PHR): PLT/HDL-C. Due to the non-normal distribution of these indicators, a natural log transformation was performed to achieve a normal distribution.[18,19]

2.3. Definition of SI

SI was assessed using the ninth item of the Patient Health Questionnaire-9 (PHQ-9), which inquires about thoughts of self-harm or death over the past 2 weeks. Responses were scored on a scale where 0 indicated "not at all" and 3 represented "nearly every day." Participants with a score of 1 – 3 were classified as having SI, whereas those scoring 0 were considered not to have SI.[20]

2.4. Covariates

To account for potential confounders in the association between HDL-related inflammatory indicators and SI, several covariates were adjusted based on previous studies and available NHANES data.[8,21] These covariates were carefully selected to control for demographic, lifestyle, and health-related variables that could influence both inflammation and SI, thereby ensuring the validity and robustness of our findings.

2.4.1. Demographic variables

(i) Age group: Age was categorized into three groups (20 – 39, 40 – 64, or ≥65) to explore potential age-related heterogeneity in the association between HDL-related inflammatory indicators and SI. Age was recorded in NHANES using the variable "RIDAGEYR," reported in years. This categorization allowed us to investigate whether certain age cohorts exhibited stronger or weaker associations with SI, considering that inflammation and lipid metabolism may vary by age. In addition, SI has been shown to differ significantly across age groups, necessitating this stratification

(ii) Gender: Gender (female or male) was determined using the NHANES variable "RIAGENDR." Given the known differences in both suicide rates and biological responses to inflammation between men and women, gender was an essential covariate. Previous studies have demonstrated that women tend to exhibit higher rates of SI but lower rates of completed suicide compared to men, potentially due to biological, psychological, and social factors

(iii) Race: Race was categorized into five groups – other Hispanic, non-Hispanic Black, non-Hispanic White, Mexican American, and other race – as captured by the NHANES variable "RIDRETH1"

(iv) Marital status: Marital status was classified into three categories – married/living with a partner, separated/divorced/widowed, and never married – using the NHANES variables "DMDMARTL" and "DMDMARTZ"

(v) Education level: Educational attainment was grouped into three levels – less than high school, high school, and greater than high school – using the NHANES variables "DMDEDUC2" and "DMDEDUC3"

(vi) PIR: Socioeconomic status, as measured using the PIR, was categorized into three groups – <1.3, 1.3 – 3.5, and ≥3.5 – using the NHANES variable "INDFMPIR."

2.4.2. Lifestyle variables

(i) Smoking status: Smoking status was determined based on responses to the NHANES question "SMQ020." Participants were categorized as "Yes" or "No." Those who reported having smoked ≥100 cigarettes in their lifetime were classified as smokers

(ii) Alcohol consumption: Alcohol consumption was categorized as "No" or "Yes" based on responses to the NHANES questions "ALQ101" and "ALQ111." Participants who reported consuming more than a 12-ounce beer, a 5-ounce serving of wine, or 1.5 ounces of liquor were classified as alcohol consumers.

2.4.3. Health condition variables

(i) Hypertension: Hypertension was identified through a combination of self-reported physician diagnoses, systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medication

(ii) Diabetes: Diabetes was identified based on self-reported physician diagnoses, an A1c level ≥6.5%, the use of insulin or diabetes medications, fasting glucose levels ≥7.0 mmol/L, random glucose levels >11.1 mmol/L, or oral glucose tolerance test results ≥11.1 mmol/L

(iii) Stroke: Stroke was identified based on participants' responses to the NHANES question "MCQ160f," which asked whether they had been previously diagnosed with a stroke by a doctor or other health-care professional

(iv) Kidney disease: Kidney disease was identified using the NHANES question "KIQ022," which asked participants if they had been diagnosed with weak or failing kidneys by a physician.

2.5. Statistical analysis

A weighting strategy (WTMEC2YR) was employed to strengthen the reliability of our results while examining the relationship between HDL-related inflammatory markers and SI.[22] For continuous variables, data were reported as weighted medians with interquartile ranges, and differences between groups were analyzed using the weighted Wilcoxon rank-sum test. For categorical variables, data are presented as weighted percentages, and differences among groups were evaluated using the weighted Chi-square test. In addition, Spearman's rank correlation was used to assess associations among the different inflammatory markers.

Weighted logistic regression was performed to analyze the association between HDL-related inflammatory indicators and SI, categorizing these indicators into tertiles to strengthen the robustness of our conclusions.[23] Weighted restricted cubic spline (RCS) analysis with three-knot points was used to investigate the dose–response relationship between HDL-related inflammatory indicators and SI.[24] To address the high correlations among inflammatory

markers, weighted quantile sum (WQS) regression was applied to identify the most influential marker within the mixture affecting SI prevalence.[25,26] Subgroup analyses were also conducted to explore potential heterogeneity in the association between HDL-related inflammatory indicators and SI across various population subgroups.

All analyses were performed using R software (version 4.1.0), with a two-sided $P < 0.05$ considered statistically significant.

3. Results

3.1. General characteristics

The analysis included 14,554 individuals with a median age of 48 years, of whom approximately 4.04% reported experiencing SI. Compared to individuals without SI, those with SI were generally younger and more likely to identify as Mexican American, other Hispanic, or other race. They were also more likely to be unmarried, have lower levels of education, live in poverty, smoke, and have a history of stroke or kidney disease. Notably, participants with SI exhibited higher levels of inflammatory markers, including WBC, NEU, hs-CRP, and various HDL-related inflammatory indicators (WHR, NHR, MHR, CHR, and PHR), while showing lower levels of HDL-C (Table 1). Furthermore, 13 inflammation-related indicators were found to display significantly right-skewed pairwise correlations (Figure A1).

3.2. Association between HDL-related inflammatory indicators and SI

The results of the weighted logistic regression indicated a potential relationship between CHR and SI. In Model 3, the odds ratio with 95% confidence interval was 1.11 (1.02, 1.21). This positive correlation remained consistent across other adjusted and quantile models. However, no significant associations were observed between other HDL-related inflammatory indicators and SI (Table 2).

3.3. RCS analysis

RCS analysis revealed a linear dose–response relationship between CHR and SI ($p_{nonlinear} = 0.419$, $p_{overall} = 0.011$). No

Table 1. Characteristics of participants by SI status

Characteristics	Total	No SI	SI	*P*-value
	N=14,554	*N*=13,966	*N*=588	
Age (year), median (IQR)	48.00 (34.00,62.00)	49.00 (34.00,62.00)	46.00 (30.00,59.00)	0.001
Age group, (%)				0.017
20 – 39	34.29	34.03	40.90	
40 – 64	44.79	44.88	42.33	
≥65	20.93	21.09	16.76	
Gender, (%)				0.929
Female	50.98	50.99	50.76	
Male	49.02	49.01	49.24	
Race, (%)				0.006
Non-Hispanic White	65.97	66.12	62.24	
Non-Hispanic Black	9.94	10.01	8.34	
Mexican American	7.64	7.63	7.94	
Other Hispanic	6.92	6.76	11.02	
Other race	9.52	9.49	10.45	
Marital status, (%)				<0.001
Married/living with a partner	63.27	64.07	43.03	
Divorced/separated/widowed	18.54	18.22	26.7	
Never married	18.19	17.72	30.27	
Education level, (%)				<0.001
<High school	10.32	10.05	17.12	
High school	23.9	23.75	27.72	
>High school	65.78	66.19	55.16	

(Cont'd...)

Table 1. ***(Continued)***

Characteristics	Total	No SI	SI	*P*-value
	N=14,554	*N*=13,966	*N*=588	
PIR, (%)				<0.001
<1.3	18.44	17.89	32.43	
1.3 – 3.5	36.34	36.05	43.61	
≥3.5	45.23	46.06	23.96	
Smoking, (%)				< 0.001
No	57.92	58.43	44.89	
Yes	42.08	41.57	55.11	
Drinking, (%)				0.246
No	12.53	12.61	10.54	
Yes	87.47	87.39	89.46	
Hypertension, (%)				0.902
No	61.57	61.58	61.27	
Yes	38.43	38.42	38.73	
Diabetes, (%)				0.059
No	84.42	84.54	81.51	
Yes	15.58	15.46	18.49	
Stroke, (%)				0.033
No	96.93	96.99	95.41	
Yes	3.07	3.01	4.59	
Kidney diseases, (%)				0.010
No	96.92	97.00	94.78	
Yes	3.08	3.00	5.22	
HDL-C (mmol/L), Median (IQR)	1.34 (1.09, 1.63)	1.34 (1.09, 1.63)	1.29 (1.06, 1.58)	0.024
WBC (10^9/l), Median (IQR)	6.90 (5.70, 8.30)	6.80 (5.70, 8.30)	7.20 (6.10, 8.70)	<0.001
NEU (10^9/l), Median (IQR)	4.00 (3.10, 5.10)	4.00 (3.10, 5.00)	4.40 (3.40, 5.60)	<0.001
LYM (10^9/l), Median (IQR)	2.00 (1.60, 2.50)	2.00 (1.60, 2.50)	2.10 (1.60, 2.50)	0.667
MONO (10^9/l), Median (IQR)	0.50 (0.40, 0.70)	0.50 (0.40, 0.70)	0.60 (0.50, 0.70)	0.285
hs-CRP (mg/l), Median (IQR)	1.80 (0.78, 4.20)	1.78 (0.77, 4.20)	2.42 (0.90, 4.90)	<0.001
PLT (10^9/l), Median (IQR)	240.00 (205.00, 280.00)	240.00 (205.00, 280.00)	242.00 (208.00, 281.00)	0.192
WHR (10^9/mmol), Median (IQR)	5.15 (3.80, 6.97)	5.14 (3.79, 6.93)	5.38 (4.21, 7.86)	<0.001
NHR (10^9/mmol), Median (IQR)	2.97 (2.08, 4.17)	2.95 (2.07, 4.15)	3.33 (2.39, 4.66)	<0.001
LHR (10^9/mmol), Median (IQR)	1.50 (1.09, 2.07)	1.50 (1.09, 2.05)	1.55 (1.11, 2.24)	0.237
MHR (10^9/mmol), Median (IQR)	0.40 (0.30, 0.55)	0.40 (0.30, 0.55)	0.42 (0.31, 0.61)	0.021
CHR (mg/mmol), Median (IQR)	1.34 (0.53, 3.40)	1.32 (0.52, 3.37)	1.91 (0.71, 4.32)	<0.001
PHR (10^9/mmol), Median (IQR)	178.36 (138.07, 230.11)	177.98 (137.69, 229.55)	189.11 (147.10, 244.88)	0.009

Abbreviations: CHR: High-sensitivity C-reactive protein-to-high-density lipoprotein cholesterol ratio; HDL-C: High-density lipoprotein cholesterol; hs-CRP: High-sensitivity C-reactive protein; IQR: Interquartile range; LHR: Lymphocyte-to-high-density lipoprotein cholesterol ratio; LYM: Lymphocyte count; MHR: Monocyte-to-high-density lipoprotein cholesterol ratio; MONO: Monocyte count; NHR: Neutrophil-to-high-density lipoprotein cholesterol ratio; NEU: Neutrophil count; PHR: Platelet-to-high-density lipoprotein cholesterol ratio; PIR: Poverty income ratio; PLT: Platelet count; SI: Suicidal ideation; WBC: White blood cell count; WHR: White blood cell-to-high-density lipoprotein cholesterol ratio.

Table 2. Results of weighted logistic regression analysis examining the association between high-density lipoprotein-related inflammatory indicators and suicidal ideation

	Range	Model 1		Model 2		Model 3	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
WHR							
T1	(0.62, 4.21)	Reference		Reference		Reference	
T2	(4.21, 6.27)	1.45 (1.12, 1.89)	0.006	1.31 (1.00, 1.71)	0.051	1.27 (0.98, 1.66)	0.075
T3	(6.27, 396.04)	1.58 (1.23, 2.04)	**<0.001**	1.31 (1.01, 1.69)	0.040	1.21 (0.93, 1.59)	0.155
P for trend			**<0.001**		0.050		0.193
Per ln(unit) increase		1.55 (1.22, 1.97)	**<0.001**	1.27 (0.99, 1.65)	0.063	1.18 (0.90, 1.54)	0.229
NHR							
T1	(0.13, 2.36)	Reference		Reference		Reference	
T2	(2.36, 3.66)	1.42 (1.03, 1.94)	**0.032**	1.31 (0.95, 1.81)	0.096	1.29 (0.94, 1.77)	0.117
T3	(3.66, 34.85)	1.63 (1.25, 2.13)	**<0.001**	1.37 (1.04, 1.79)	**0.024**	1.27 (0.96, 1.67)	0.091
P for trend			**<0.001**		**0.024**		0.102
Per ln(unit) increase		1.54 (1.22, 1.94)	**<0.001**	1.30 (1.03, 1.65)	**0.029**	1.22 (0.95, 1.56)	0.113
LHR							
T1	(0.12, 1.24)	Reference		Reference		Reference	
T2	(1.24, 1.87)	0.90 (0.66, 1.22)	0.482	0.81 (0.58, 1.12)	0.190	0.79 (0.57, 1.10)	0.151
T3	(1.87, 355.25)	1.12 (0.80, 1.56)	0.490	0.92 (0.65, 1.29)	0.611	0.86 (0.61, 1.23)	0.408
P for trend			0.500		0.645		0.440
Per ln(unit) increase		1.19 (0.95, 1.49)	0.131	0.99 (0.79, 1.26)	0.965	0.94 (0.74, 1.21)	0.639
MHR							
T1	(0.04, 0.33)	Reference		Reference		Reference	
T2	(0.33, 0.50)	1.18 (0.89, 1.56)	0.254	1.06 (0.78, 1.44)	0.721	1.02 (0.76, 1.39)	0.872
T3	(0.50, 3.61)	1.17 (0.92, 1.48)	0.189	0.99 (0.77, 1.29)	0.964	0.91 (0.70, 1.18)	0.480
P for trend			0.188		0.945		0.455
Per ln(unit) increase		1.35 (1.09, 1.68)	**0.008**	1.17 (0.92, 1.48)	0.206	1.09 (0.85, 1.39)	0.485
CHR							
T1	(0.02, 0.79)	Reference		Reference		Reference	
T2	(0.79, 2.63)	1.34 (0.96, 1.86)	0.085	1.31 (0.93, 1.86)	0.123	1.27 (0.90, 1.80)	0.168
T3	(2.63, 308.58)	1.72 (1.39, 2.13)	**<0.001**	1.57 (1.23, 2.01)	**<0.001**	1.48 (1.14,1.93)	**0.004**
P for trend			**<0.001**		**<0.001**		**0.005**
Per ln(unit) increase		1.17 (1.09, 1.26)	**<0.001**	1.13 (1.05, 1.23)	**0.003**	1.11 (1.02, 1.21)	**0.020**
PHR							
T1	(10, 151.38)	Reference		Reference		Reference	
T2	(151.38, 210.89)	1.13 (0.81, 1.59)	0.459	1.02 (0.73, 1.44)	0.887	1.01 (0.72, 1.41)	0.970
T3	(210.89, 1711.54)	1.35 (1.00, 1.81)	**0.048**	1.14 (0.85, 1.53)	0.380	1.08 (0.80, 1.46)	0.610
P for trend			**0.049**		0.373		0.601
Per ln(unit) increase		1.42 (1.02, 1.97)	**0.036**	1.15 (0.84, 1.57)	0.387	1.09 (0.79, 1.49)	0.596

Notes: Bold font indicates *P*-value < 0.05.

Model 1 did not adjust for any confounding factors.

Model 2 adjusted for gender, age group, race, marital status, education level, and poverty income ratio.

Model 3 adjusted for all covariates.

Abbreviations: CHR: High-sensitivity C-reactive protein-to-high-density lipoprotein cholesterol ratio; CI: Confidence interval; LHR: Lymphocyte-to-high-density lipoprotein cholesterol ratio; MHR: Monocyte-to-high-density lipoprotein cholesterol ratio; NHR: Neutrophil-to-high-density lipoprotein cholesterol ratio; OR: Odds ratio; PHR: Platelet-to-high-density lipoprotein cholesterol ratio; WHR: White blood cell-to-high-density lipoprotein cholesterol ratio.

significant dose–response relationships were observed between other HDL-related inflammatory indicators and SI (Figure 2).

3.4. Associations between co-exposure to inflammatory indicators and SI

The WQS regression identified CHR, NEU, and HDL-C as the inflammatory indicators most closely associated with SI. Notably, elevated CHR levels emerged as the primary contributor to the increased prevalence of SI, exerting a more pronounced influence than elevated NEU levels (Figure A2).

3.5. Subgroup analysis

Subgroup analyses revealed a consistent positive association between CHR and SI across all subgroups, including those defined by age group, gender, race, marital status, PIR, education level, alcohol consumption, smoking status, hypertension, diabetes, stroke, and kidney disease ($p_{\text{interaction}} > 0.05$) (Table 3).

4. Discussion

In this cross-sectional study involving 14,554 U.S. adults conducted between 2015 and 2023, we examined the association between HDL-related inflammatory indicators and SI. Our findings revealed that elevated levels of CHR were significantly associated with a higher prevalence of SI. Regulating blood CHR levels could potentially serve as an effective strategy to reduce SI prevalence, thereby alleviating the substantial public health burden associated with suicide.

Inflammatory responses, immune function, and lipid metabolism are critical mechanisms in the development of many diseases, including SI.[7,27-29] Previous studies have highlighted the complex interactions between HDL-C and

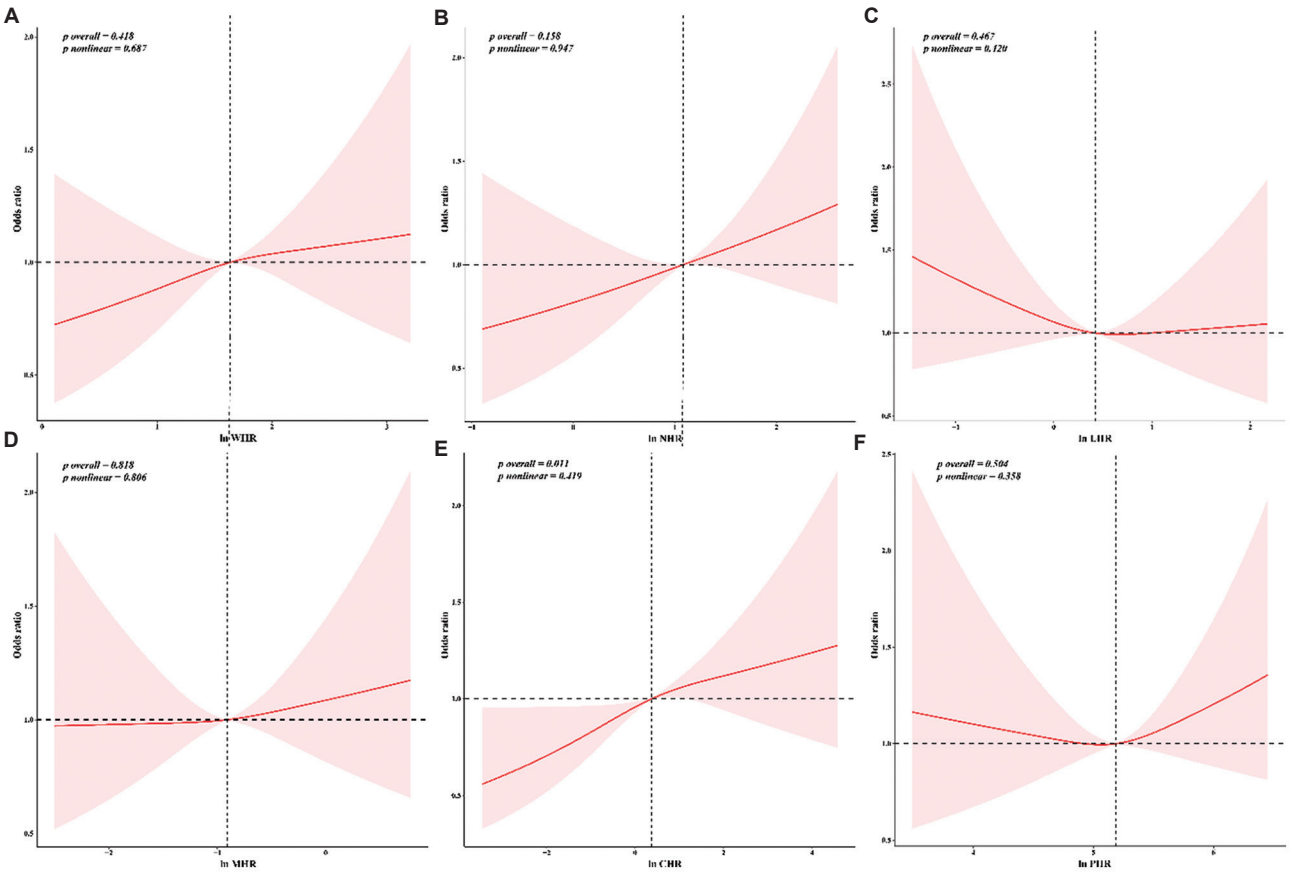

Figure 2. Restricted cubic spline analysis of high-density lipoprotein-related inflammatory indicators and SI. (A) WHR and SI dose–response relationship; (B) NHR and SI dose–response relationship; (C) LHR and SI dose–response relationship; (D) MHR and SI dose–response relationship; (E) CHR and SI dose–response relationship; (F) PHR and SI dose–response relationship. The analysis was adjusted for gender, age group, race, marital status, education level, poverty income ratio, smoking, drinking, hypertension, diabetes, stroke, and kidney disease. Reference values were defined as the median.
Abbreviations: CHR: High-sensitivity C-reactive protein-to-high-density lipoprotein cholesterol ratio; LHR: Lymphocyte-to-high-density lipoprotein cholesterol ratio; MHR: Monocyte-to-high-density lipoprotein cholesterol ratio; NHR: Neutrophil-to-high-density lipoprotein cholesterol ratio; PHR: Platelet-to-high-density lipoprotein cholesterol ratio; WHR: White blood cell-to-high-density lipoprotein cholesterol ratio; SI: Suicidal ideation.

Table 3. Subgroup analysis on the associations between high-sensitivity C-reactive protein-to-high-density lipoprotein cholesterol ratio and suicidal ideation

Characteristics	T1	T2	T3	$P_{interaction}$
Age group				0.967
20 – 39	Reference	1.31 (0.75, 2.29)	1.59 (0.95, 2.67)	
40 – 64	Reference	1.26 (0.82, 1.93)	1.35 (0.87, 2.12)	
≥65	Reference	1.09 (0.63, 1.87)	1.50 (0.83, 2.74)	
Gender	Reference			0.194
Female	Reference	1.24 (0.78, 1.99)	1.17 (0.84, 1.64)	
Male	Reference	1.30 (0.88, 1.93)	1.87 (1.30, 2.69)	
Race	Reference			0.186
Non-Hispanic White	Reference	1.53 (0.96, 2.42)	1.69 (1.17, 2.42)	
Non-Hispanic Black	Reference	1.29 (0.55, 2.98)	1.28 (0.66, 2.51)	
Mexican American	Reference	0.99 (0.36, 2.72)	1.31 (0.50, 3.45)	
Other Hispanic	Reference	0.68 (0.33, 1.41)	1.75 (0.80, 3.83)	
Other race	Reference	0.91 (0.46, 1.80)	0.83 (0.36, 1.89)	
Marital status	Reference			0.877
Married/living with a partner	Reference	1.32 (0.80, 2.20)	1.54 (1.01, 2.35)	
Divorced/separated/widowed	Reference	1.03 (0.56, 1.89)	1.18 (0.69, 2.00)	
Never married	Reference	1.35 (0.77, 2.34)	1.56 (0.83, 2.93)	
Education level	Reference			0.092
<High school	Reference	0.88 (0.47, 1.68)	0.74 (0.43, 1.27)	
High school	Reference	1.33 (0.80, 2.19)	1.30 (0.78, 2.17)	
>High school	Reference	1.32 (0.74, 2.37)	1.93 (1.33, 2.81)	
PIR	Reference			0.944
<1.3	Reference	1.11 (0.65, 1.87)	1.51 (1.04, 2.19)	
1.3 – 3.5	Reference	1.36 (0.78, 2.38)	1.53 (0.91, 2.57)	
≥3.5	Reference	1.28 (0.68, 2.39)	1.43 (0.72, 2.84)	
Smoking	Reference			0.133
No	Reference	1.03 (0.57, 1.87)	1.81 (1.28, 2.57)	
Yes	Reference	1.46 (0.98, 2.18)	1.26 (0.89, 1.78)	
Drinking	Reference			0.258
No	Reference	0.73 (0.31, 1.69)	0.81 (0.31, 2.08)	
Yes	Reference	1.35 (0.92, 1.98)	1.60 (1.23, 2.08)	
Hypertension	Reference			0.639
No	Reference	1.16 (0.77, 1.75)	1.32 (0.91, 1.91)	
Yes	Reference	1.52 (0.96, 2.41)	1.80 (1.27, 2.55)	
Diabetes	Reference			0.549
No	Reference	1.21 (0.82, 1.79)	1.49 (1.09, 2.02)	
Yes	Reference	1.58 (0.76, 3.29)	1.61 (0.89, 2.94)	
Stroke	Reference			0.806
No	Reference	1.28 (0.89, 1.84)	1.50 (1.13, 1.99)	
Yes	Reference	1.07 (0.35, 3.22)	1.05 (0.35, 3.16)	
Kidney diseases	Reference			0.290
No	Reference	1.31 (0.92, 1.86)	1.54 (1.15, 2.06)	
Yes	Reference	0.50 (0.20, 1.25)	0.64 (0.22, 1.92)	

Abbreviations: OR: Odds ratio; CI: Confidence interval; PIR: Poverty income ratio.

various blood components, such as blood cells, immune cells, CRP, and PLT.[8,30-32] HDL-related inflammatory biomarkers, which are novel indicators derived by combining HDL-C with other inflammatory or immune markers, provide a comprehensive reflection of the body's inflammatory and immune status.[8,33] However, research on the relationship between HDL-related inflammatory biomarkers and SI remains limited. Using data from this large cross-sectional NHANES study, we found that among six HDL-related inflammatory biomarkers, CHR demonstrated the strongest association with SI, exhibiting a linear relationship. To further assess CHR's role within the context of co-exposure to other inflammatory markers, we included all markers in a WQS regression model. The results confirmed that even after accounting for interactions among inflammatory markers, CHR remained the primary factor influencing SI prevalence. As an easily accessible clinical marker, CHR demonstrates a linear and stable influence on SI, remaining unaffected by other biochemical indicators. This highlights its potential for broad clinical application in the future.

Previous studies have demonstrated a significant association between lower HDL-C levels, higher CRP levels, and increased SI prevalence.[34-37] However, to our knowledge, no prior research has specifically examined the relationship between CHR and SI. We hypothesize that CHR may influence SI prevalence for the following reasons: (1) HDL can exert anti-inflammatory effects through the transcriptional regulator ATF3.[13,38] Individuals with higher HDL levels tend to have lower inflammation (which decreases CHR), thereby reducing the likelihood of SI; (2) Under conditions of inflammatory stimuli, HDL may undergo oxidative or enzymatic modifications.[32] In individuals with higher levels of inflammation, HDL function may become impaired or exacerbate inflammation (resulting in elevated CHR), ultimately promoting the occurrence of SI; (3) Compared to other inflammatory markers, hs-CRP is sensitive to lower levels of chronic inflammation and serves as a distinctive indicator of susceptibility to suicide.[5,37,39]

This study has several notable strengths. First, compared to traditional inflammatory markers, the novel inflammatory markers used in this research offer higher sensitivity and account for the combined effects of metabolic and immune factors. Despite limited research on the association between these novel markers and SI, this study is the first to simultaneously evaluate the relationship between multiple HDL-related inflammatory indicators and SI prevalence. Advanced mixture machine learning methods were employed to assess the stability of CHR under complex co-exposure conditions. Second, we categorized inflammatory marker values into both continuous and quantile-based groups, fitting regression models for each. In addition, we used RCS and subgroup analyses to enhance the robustness and consistency of our key findings. Finally, we applied weighted strategies to all statistical analyses, significantly improving the representativeness of our sample and allowing our findings to more accurately reflect the health status of the U.S. population.

However, this study also has some limitations. First, although we accounted for various confounding factors, such as demographic, lifestyle, and health conditions, we cannot entirely rule out the influence of unmeasured confounders on our findings. Nonetheless, the use of multiple statistical models likely reduced the probability of false-positive results to some extent. Second, the cross-sectional design limits our ability to infer a causal relationship between CHR and SI. However, conducting this analysis based on a large cross-sectional study is still valuable, as the findings provide important insights and directions for future prospective research. Third, the findings are based on data from the U.S. population, which necessitates further validation in other regions to confirm their generalizability.

5. Conclusion

This study is the first to simultaneously evaluate the relationship between multiple HDL-related inflammatory indicators and the prevalence of SI among adults in the U.S. Notably, CHR exhibited the strongest association with SI in both individual and mixed exposure models. Further prospective studies are needed to confirm this causal relationship.

Acknowledgments

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Conflict of interest

Chen Qu is an Editorial Board Member of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Zhonghua Sun, Chen Qu
Formal analysis: Chen Qu
Investigation: Zhonghua Sun, Sen Chen
Methodology: Zhonghua Sun, Yameng Xu
Writing – original draft: Zhonghua Sun
Writing – review & editing: Chen Qu

Ethics approval and consent to participate

Ethical review and approval were waived for this study due to the fact that NHANES surveys were previously reviewed and approved by the CDC and Prevention National Center for Health Statistics Research Ethics Review Board (https://www.cdc.gov/nchs/nhanes/irba98.htm). All participants had provided informed consent before taking part in the survey. Since the data were de-identified, no additional consent or ethical approval was required for this study.

Consent for publication

Not applicable.

Availability of data

The NHANES public data used in this study can be freely accessed at the website (https://www.cdc.gov/nchs/nhanes/index.htm).

References

1. Bachmann S. Epidemiology of suicide and the psychiatric perspective. *Int J Environ Res Public Health*. 2018;15(7):1425.
doi: 10.3390/ijerph15071425

2. Naghavi M. Global, regional, and national burden of suicide mortality 1990 to 2016: Systematic analysis for the Global Burden of Disease Study 2016. *BMJ*. 2019;364:l94.
doi: 10.1136/bmj.l94

3. Large MM, Nielssen O. Suicidal ideation and later suicide. *Am J Psychiatry*. 2012;169(6):662; author reply 663.
doi: 10.1176/appi.ajp.2012.11111674

4. Hubers AAM, Moaddine S, Peersmann SHM, *et al*. Suicidal ideation and subsequent completed suicide in both psychiatric and non-psychiatric populations: A meta-analysis. *Epidemiol Psychiatr Sci*. 2018;27(2):186-198.
doi: 10.1017/s2045796016001049

5. Courtet P, Jaussent I, Genty C, *et al.* Increased CRP levels may be a trait marker of suicidal attempt. *Eur Neuropsychopharmacol*. 2015;25(10):1824-1831.
doi: 10.1016/j.euroneuro.2015.05.003

6. Steiner J, Gos T, Bogerts B, Bielau H, Drexhage HA, Bernstein HG. Possible impact of microglial cells and the monocyte-macrophage system on suicidal behavior. *CNS Neurol Disord Drug Targets*. 2013;12(7):971-979.
doi: 10.2174/18715273113129990099

7. Zhang J, McKeown RE, Hussey JR, Thompson SJ, Woods JR, Ainsworth BE. Low HDL cholesterol is associated with suicide attempt among young healthy women: The Third National Health and Nutrition Examination Survey. *J Affect Disord*. 2005;89(1-3):25-33.
doi: 10.1016/j.jad.2005.05.021

8. Zhao J, Zheng Q, Ying Y, *et al.* Association between high-density lipoprotein-related inflammation index and periodontitis: Insights from NHANES 2009-2014. *Lipids Health Dis*. 2024;23(1):321.
doi: 10.1186/s12944-024-02312-9

9. Gao J, Lu J, Sha W, *et al.* Relationship between the neutrophil to high-density lipoprotein cholesterol ratio and severity of coronary artery disease in patients with stable coronary artery disease. *Front Cardiovasc Med*. 2022;9:1015398.
doi: 10.3389/fcvm.2022.1015398

10. Fu YW, Li XX, Xu HZ, Gong YQ, Yang Y. Effects of periodontal therapy on serum lipid profile and proinflammatory cytokines in patients with hyperlipidemia: A randomized controlled trial. *Clin Oral Investig*. 2016;20(6):1263-1269.
doi: 10.1007/s00784-015-1621-2

11. Lu CF, Cang XM, Liu WS, *et al*. Association between the platelet/high-density lipoprotein cholesterol ratio and nonalcoholic fatty liver disease: Results from NHANES 2017-2020. *Lipids Health Dis*. 2023;22(1):130.
doi: 10.1186/s12944-023-01861-9

12. Atehortua L, Davidson WS, Chougnet CA. Interactions Between HDL and CD4+ T Cells: A Novel Understanding of HDL Anti-Inflammatory Properties. *Arterioscler Thromb Vasc Biol*. 2024;44(6):1191-1201.
doi: 10.1161/atvbaha.124.320851

13. De Nardo D, Labzin LI, Kono H, *et al.* High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. *Nat Immunol*. 2014;15(2):152-160.
doi: 10.1038/ni.2784

14. Sorci-Thomas MG, Thomas MJ. High density lipoprotein biogenesis, cholesterol efflux, and immune cell function. *Arterioscler Thromb Vasc Biol*. 2012;32(11):2561-2565.
doi: 10.1161/atvbaha.112.300135

15. Guo X, Shen R, Su Y, Ma L. High-density lipoprotein-related inflammatory indices predict repeat revascularization in coronary drug-eluting stenting. *Biomark Med*. 2023;17(22):959-969.
doi: 10.2217/bmm-2023-0399

16. Huang Y, Ding K, Dai Z, *et al.* The relationship of low-density-lipoprotein to lymphocyte ratio with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2175-2185.

doi: 10.2147/copd.S369161

17. Cândido FG, da Silva A, Zanirate GA, Oliveira N, Hermsdorff HHM. Lymphocyte to high-density lipoprotein cholesterol ratio is positively associated with pre-diabetes, metabolic syndrome, and non-traditional cardiometabolic risk markers: A cross-sectional study at secondary health care. *Inflammation*. 2024.

doi: 10.1007/s10753-024-02063-w

18. Guo B, Liu X, Si Q, *et al.* Associations of CBC-derived inflammatory indicators with sarcopenia and mortality in adults: Evidence from Nhanes 1999 ~ 2006. *BMC Geriatr*. 2024;24(1):432.

doi: 10.1186/s12877-024-05012-2

19. Huang H, Wei L, Chen X, *et al.* Cord serum elementomics profiling of 56 elements depicts risk of preterm birth: Evidence from a prospective birth cohort in rural Bangladesh. *Environ Int*. 2021;156:106731.

doi: 10.1016/j.envint.2021.106731

20. Huang D, Zhong S, Yan H, Lai S, Lam M, Jia Y. Association between serum zinc levels and suicidal ideation in US adults: A population-based cross-sectional study. *J Affect Disord*. 2023;329:359-368.

doi: 10.1016/j.jad.2023.02.039

21. Jia J, Sun Z, Tao X, *et al.* Association between oxidative balance score and heart failure in the older adults: Results from the NHANES 2005-2018. *Heart Lung*. 2024;68:107-115.

doi: 10.1016/j.hrtlng.2024.06.006

22. Li Y, Wang J, Cai Y, Chen H. Association of serum Vitamin D with periodontal disease. *Int Dent J*. 2023;73(5):777-783.

doi: 10.1016/j.identj.2023.06.004

23. Chen H, Du N, Wang L, Yang L. A higher risk for melanoma in patients with Parkinson's disease: Based on the results from National Health and Nutrition Examination Survey 2001 - 2004. *J Clin Basic Psychosom*. 2023;1(1):0571.

doi: 10.36922/jcbp.0571

24. Yin J, Wang H, Li S, *et al.* Nonlinear relationship between sleep midpoint and depression symptoms: A cross-sectional study of US adults. *BMC Psychiatry*. 2023;23(1):671.

doi: 10.1186/s12888-023-05130-y

25. Du X, Xu X, Yu H, *et al*. Thyrotoxic effects of mixed exposure to perfluorinated compounds: Integrating population-based, toxicogenomic, animal, and cellular evidence to elucidate molecular mechanisms and identify potential effector targets. *Environ Sci Technol*. 2024;58:18177-18189.

doi: 10.1021/acs.est.4c06287

26. Carrico C, Gennings C, Wheeler DC, Factor-Litvak P. Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. *J Agric Biol Environ Stat*. 2015;20(1):100-120.

doi: 10.1007/s13253-014-0180-3

27. Bergmans RS, Kelly KM, Mezuk B. Inflammation as a unique marker of suicide ideation distinct from depression syndrome among U.S. adults. *J Affect Disord*. 2019;245:1052-1060.

doi: 10.1016/j.jad.2018.11.046

28. Vasupanrajit A, Jirakran K, Tunvirachaisakul C, Solmi M, Maes M. Inflammation and nitro-oxidative stress in current suicidal attempts and current suicidal ideation: A systematic review and meta-analysis. *Mol Psychiatry*. 2022;27(3):1350-1361.

doi: 10.1038/s41380-021-01407-4

29. Courtet P, Giner L, Seneque M, Guillaume S, Olie E, Ducasse D. Neuroinflammation in suicide: Toward a comprehensive model. *World J Biol Psychiatry*. 2016;17(8):564-586.

doi: 10.3109/15622975.2015.1054879

30. Kim KI, Oh SW, Ahn S, *et al.* CRP level and HDL cholesterol concentration jointly predict mortality in a Korean population. *Am J Med*. 2012;125(8):787-795.e784.

doi: 10.1016/j.amjmed.2012.02.013

31. Tang H, Xiang Z, Li L, *et al.* Potential role of anti-inflammatory HDL subclasses in metabolic unhealth/obesity. *Artif Cells Nanomed Biotechnol*. 2021;49(1):565-575.

doi: 10.1080/21691401.2021.1961798

32. Tehrani DM, Gardin JM, Yanez D, *et al.* Impact of inflammatory biomarkers on relation of high density lipoprotein-cholesterol with incident coronary heart disease: Cardiovascular Health Study. *Atherosclerosis*. 2013;231(2):246-251.

doi: 10.1016/j.atherosclerosis.2013.08.036

33. Gao Y, Wang M, Wang R, *et al.* The predictive value of the hs-CRP/HDL-C ratio, an inflammation-lipid composite marker, for cardiovascular disease in middle-aged and elderly people: Evidence from a large national cohort study. *Lipids Health Dis*. 2024;23(1):66.

doi: 10.1186/s12944-024-02055-7

34. De Berardis D, Serroni N, Marini S, *et al*, Alexithymia, suicidal ideation, and serum lipid levels among drug-naïve outpatients with obsessive-compulsive disorder. *Braz J Psychiatry*. 2014;36(2):125-130.

doi: 10.1590/1516-4446-2013-1189

35. O'Donovan A, Rush G, Hoatam G, *et al.* Suicidal ideation is associated with elevated inflammation in patients with major depressive disorder. *Depress Anxiety*. 2013;30(4):307-314.

doi: 10.1002/da.22087

36. Lozupone M, Donghia R, Sardone R, *et al.* Apolipoprotein E genotype, inflammatory biomarkers, and non-psychiatric multimorbidity contribute to the suicidal ideation phenotype in older age. The Salus in Apulia Study. *J Affect Disord*. 2022;319:202-212.

    doi: 10.1016/j.jad.2022.09.046

37. Park RJ, Kim YH. Association between high sensitivity CRP and suicidal ideation in the Korean general population. *Eur Neuropsychopharmacol*. 2017;27(9):885-891.

    doi: 10.1016/j.euroneuro.2017.06.010

38. Zhang H, Reilly MP. Anti-inflammatory effects of high-density lipoprotein through activating transcription factor 3: Benefit beyond cholesterol transport-dependent processes. *Arterioscler Thromb Vasc Biol*. 2014;34(6):e11-e12.

    doi: 10.1161/atvbaha.114.303553

39. Aronson D, Avizohar O, Levy Y, Bartha P, Jacob G, Markiewicz W. Factor analysis of risk variables associated with low-grade inflammation. *Atherosclerosis*. 2008;200(1):206-212.

    doi: 10.1016/j.atherosclerosis.2007.12.008

Appendix

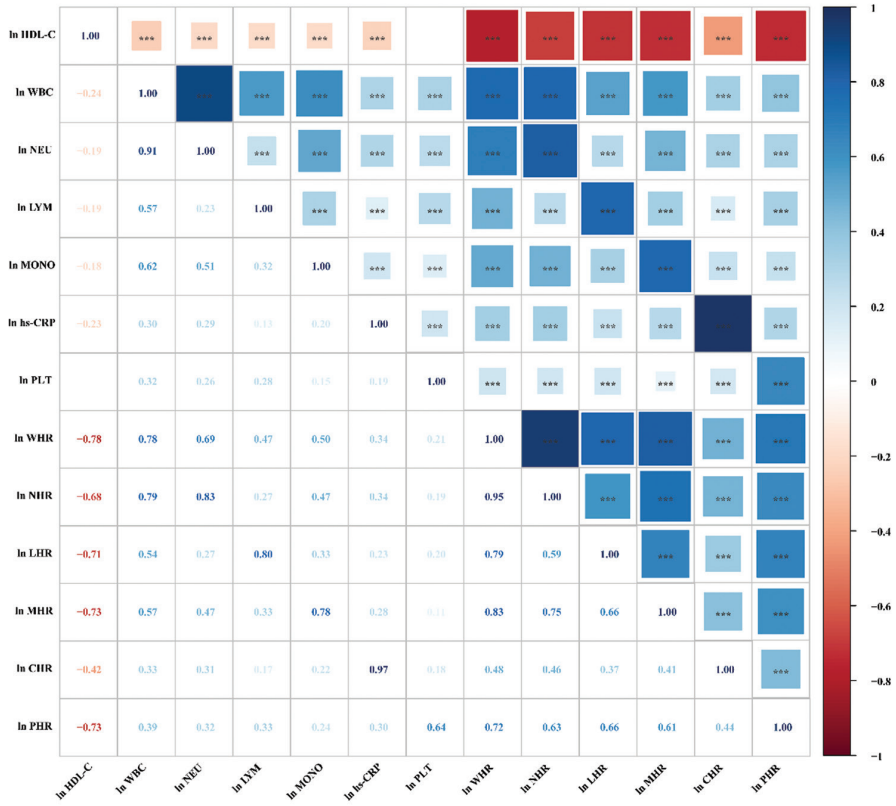

Figure A1. Plot of correlation coefficients for inflammation-related indicators. Blue and red points represent positive and negative correlations, respectively. The diameter of each square is proportional to the correlation coefficient.
Notes: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

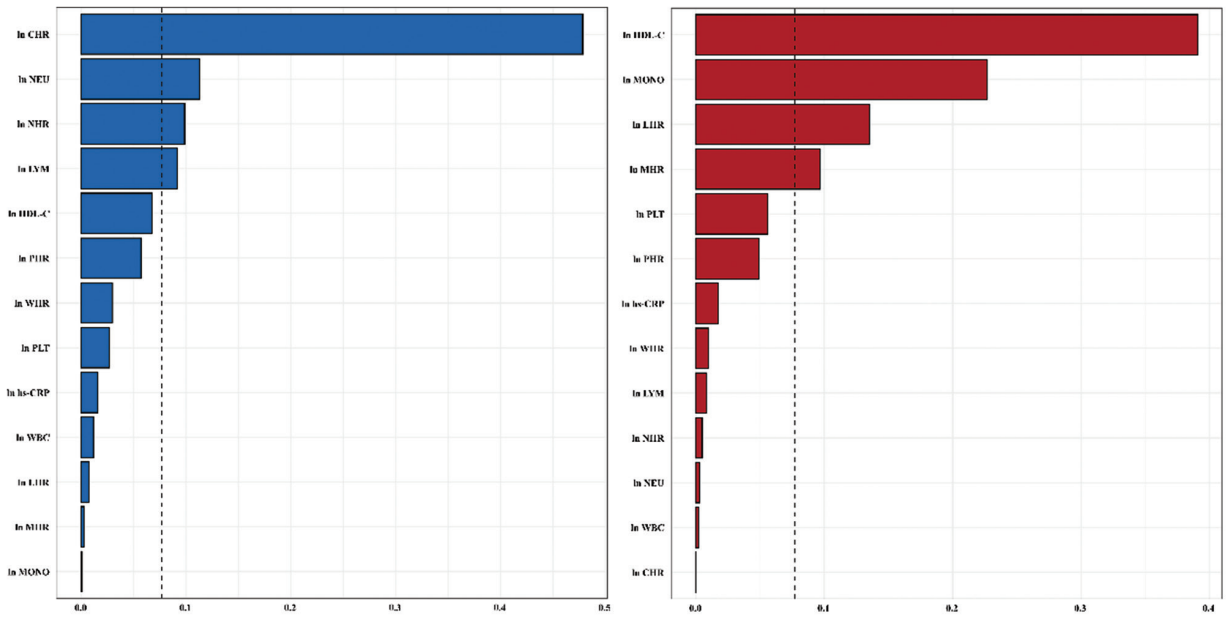

Figure A2. Results of weights from weighted quantile sum regression. Blue and red points represent positive and negative weights, respectively.

ACCSCIENCE PUBLISHING

Journal of Clinical and Basic Psychosomatics

ORIGINAL RESEARCH ARTICLE

Functional neurological movement disorders: Neuroimaging findings and methods of treatment

Peter Arlien-Søborg[1], Hans-Henrik Olsen[1], Josefin Agergaard[2], Jørgen Borup Hansen[3], and Bent Rosenbaum[3,4]*

[1]Department of Neurology, State University Hospital, Denmark

[2]State University Hospital, Clinic for Occupational Therapy and Physiotherapy, Denmark

[3]Psychiatric Centre Copenhagen, Copenhagen, Denmark

[4]Psychiatric Center Copenhagen & Institute of Psychology, University of Copenhagen, Denmark

Abstract

Results of neuroimaging can provide information concerning the cause of functional motor disorders. In this paper, we review the most important of these neuroimaging investigations indicating changes in activation patterns in several brain regions relevant to motor control. A new combined treatment approach has demonstrated more promising results than previous attempts where either psychological or physiotherapeutic interventions have been used. When physiotherapy focusing on relearning appropriate movement patterns is combined with psychodynamic psychotherapy, including personally adapted psychoeducation, the results are convincing and most often long-lasting. Few cases with relapse show remission after undergoing only a few additional sessions of this new treatment modality. Three cases presented in this paper illustrate such courses post-treatment, lending credence to the potential existence of a dialectic interaction between mind and brain processes. The cases underline the importance of a therapeutic alliance and the ability of the therapist to let painful emotional material emerge and be understood, all based on confidence between the patient and the treating team.

Keywords: Conversion disorders; Functional motor dysfunctions; Emotions; Neuroimaging; Treatment

***Corresponding author:** Bent Rosenbaum(bent.rosenbaum@dadlnet.dk)

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1. Introduction

Functional neurological symptoms are defined as symptoms that cannot be explained by known neurological or medical disorders. The most common manifestations include tremors, dystonia, paresis, and uncharacteristic gait disturbances, but speech problems, sensory symptoms, and even blindness may form part of the clinical picture. The presence of positive diagnostic findings such as Hoover's sign and diminishing symptoms during distraction is important for the diagnosis of functional movement disorder (FMD).[1] Individuals with FMD often have a previous history of physical or mental traumas but without premorbid or present psychiatric disorders detected through a systematic diagnostic approach.[2] Each of the FMD patients is associated

with a distinctive set of predisposing factors at play.[3] It has been reported that patients with psychogenic movement disorder reported higher rates of childhood trauma, specifically greater emotional abuse and physical neglect, greater fear associated with traumatic events, and a greater number of traumatic episodes compared with healthy volunteers.[2] However, ongoing physical or psychological traumas, infections, and medical disorders may precipitate functional disorders.[4,5] General cognitive functions are found to be normal in patients with functional movement disturbances in contrast to psychogenic non-epileptic seizures.[6,7] About 15% of patients referred to outpatient neurological clinics are suffering from neurological functional disorders.[8] These patients are often discovered to present additional symptoms from other organ systems such as the gastrointestinal system, heart, and lungs. Females are more often affected by FMD than males, and the symptoms may occur in children, adolescents, and adults.

Single-photon emission computed tomography (SPECT), functional magnetic resonance (fMR), and positron emission tomography scanning are useful tools for studying changes in activation patterns in different parts of the brain in healthy individuals and persons suffering from neuropsychiatric disorders. Several neuroimaging studies have shown that multiple brain structures, important for motor activation and control, are affected in patients suffering from neurological functional movement disturbances. Increased activation of neurons in a restricted area reflects an increase in metabolism, that is, oxygen consumption, which leads to an increase in blood flow. The motor cortex, prefrontal areas, right parietal lobe, amygdala, cerebellum and basal ganglia, cingulate gyrus, hippocampus, and thalamus, are, among others, activated in abnormal patterns (Figures 1 and 2).

Stone *et al.*[9] demonstrated reduced activation of the contralateral motor cortex during movement of weakened muscles and increased activation of a broad network comprising basal ganglia, insula, lingual gyri, and inferior frontal cortex. In an overview of neuroimaging results, mainly based on SPECT, Girouard *et al.*[10] found that hypoactivity at the frontal (46%), parietal (38%), and temporal parts (29%), as well as in basal ganglia (29%) and brain stem (17%). Specifically, Voon *et al.*[11] demonstrated lower activity in the left supplementary motor area (SMA), which is important for movement preparation, and greater activity in the right amygdala left anterior insula, and bilateral cingulate gyrus, which are associated with emotional processing. The motor intension is normal on the conscious level, but execution is inhibited by modulatory influences outside the conscious will.[12]

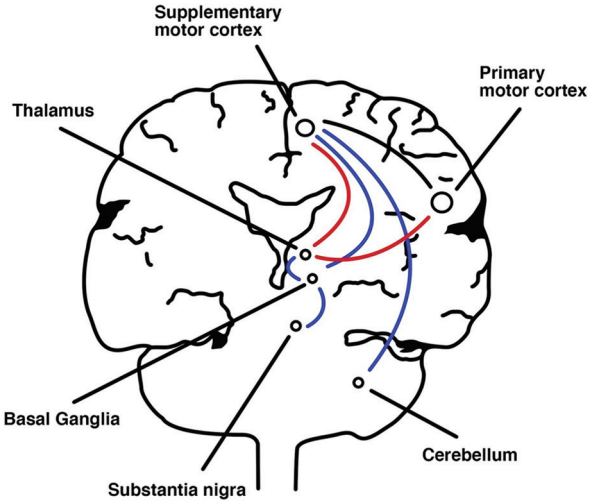

Figure 1. Coronal view of the brain. A voluntary movement is initiated in the supplementary motor cortex (SMC). The impulses are transmitted to the cerebellum, basal ganglia, and nigral substance (blue lines), which adjust the body movement, and returned through the thalamus to the SMC and primary motor cortex (red lines). This long circle may be influenced possibly at several locations by inhibitory impulses from the limbic system. Moreover, there is a reciprocal connection between SMC and the primary motor cortex.

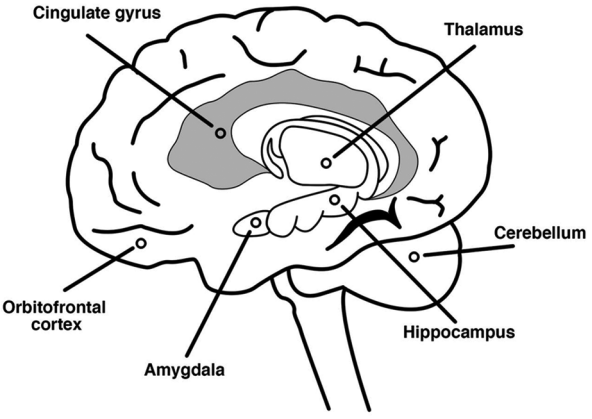

Figure 2. Sagittal view of the brain. Increased activity in parts of the limbic system (amygdala, cingulate gyrus, orbitofrontal cortex, and insula) may disturb normal motor function. Memory of unpleasant events may lead to reduced activity in the hippocampus, indicating a link between memory and limbic overload.

Emotional overload may increase the activity in several parts of the limbic system, probably resulting in an inhibition of normal motor function.[13,14] Improvement of symptoms following treatment seems to be linked to a shift in amygdala connectivity from its relation to the posterior motor regions onto a dynamic relation with more anterior motor/prefrontal regions, which reflects better planning and self-agency.[15] Interestingly, activity in the hippocampus was reduced, indicating a link between

memory of unpleasant events and functional symptoms.[13,16] However, even in apparently resting conditions, fMR may reveal right temporoparietal hypoactivity. Furthermore, fMR shows decreased functional connectivity between the right temporoparietal junction and right sensorimotor cortex, bilateral SMA, vermis, and right insula indicating impaired self-agency.[17,18]

Very few studies have investigated the brain activation patterns following successful treatment. Some did find normalization of changes primarily prefrontally,[19,20] whereas others found normalization of brain activity in other important brain regions controlling motor function, along with improvement of symptoms.[21,22] There may be several explanations for changes in brain activation and connectivity in patients with FMD. Mental overloads increase the activity in the limbic system, which in turn may lead to inhibition of normal activation of prefrontal areas, thereby interfering with the planning and execution of motor function.[11] The inhibition may, however, take place at lower levels in certain brain parts such as the basal ganglia, cerebellum, thalamus, or hippocampus. On the other hand, the limbic system may not directly be responsible for the inhibition of the motor system but instead, the reduction of the activity of the motor response may be attributed to changes within different prefrontal and frontal motor areas.[9]

Several studies on this topic present a range of methodological limitations: (1) the study groups are small or inhomogeneous; (2) the nomenclature used is often varying; (3) some patients are on psychoactive drugs which may influence the brain activation patterns; and (4) many studies lack control groups.

The objective of the present study was to deepen our understanding of the mechanism of functional neurological symptoms. In this study, we collected relevant studies of neuroimaging and interpreted the findings obtained against the psychological hypothesis. The combined treatment of physiotherapy and personally adapted psychodynamic psychoeducation was also found to show positive results. The sole focus of this work was on FMD, without covering psychogenic non-epileptic seizures, a much more pathologically complex disease than FMD.

2. Methods of treatment

In the past, FMD was often associated with a bad prognosis.[23,24] In recent decades, however, a growing number of publications have shown successful treatment outcomes among FMD patients in outpatient[25,26] or inpatient settings.[27-31] All these studies reported treatment regimes comprising physiotherapy in combination with psychoeducation (Table 1).

We conducted a special kind of treatment consisting of a combined approach of physiotherapy in warm water swimming pools and training on the floor, and psychodynamic psychotherapy (including psychoeducation) in 42 consecutive patients.[32] This treatment was carried out as inpatient treatment for several weeks and in some cases, patients received psychotherapy as an outpatient regime.

The patients were examined by neurologists to disclose other possible neurological and medical disorders and evaluate paraclinical findings, which can be quite extensive for patients who had previously consulted multiple doctors. The diagnosis obtained was not the result of exclusions but was based on positive criteria, which are explained to the patient as part of general clinical information and psychoeducation. The patients were informed that symptoms are considered a result of the accumulation of different psychological burdens that disturb important brain motor programs and that we previously had seen similar cases and most often observed substantial improvement following treatment. To maximize the treatment effects, patients were recommended to be hospitalized in our department so that they could at least distance themselves from the routine interpersonal patterns in the outside world, which might be involved in the production and maintenance of their symptoms. To ensure mutual understanding and confirmation, there exists a collaboration between patients and the treating team.

Regarding physiotherapy, physiotherapeutic evaluation was conducted based on an analysis of physical functions combined with observations of movement patterns in the warm water swimming pool. The complexity and challenges of the physical exercises are gradually increased during training to keep the progress at an appropriate pace. The training revolves around relearning appropriate movement patterns in the water, followed by training on the floor. The self-confidence and belief in one's movement abilities are strengthened during physiotherapy, leading to gradual improvement in the ability to carry out daily activities. Thus, it can be said that physiotherapy is a method set to improve patients' balance rather than address or resolve their symptoms. Trust and emotionally responsive presence are keywords and crucial for a successful result.

Regarding the psychological method, the intervention is conceptually a psychodynamic mode of treatment,[32] based on the assumption that functional motor disturbances are pathogenetically linked with memorized and present mental strains, burdens, and/or conflicts. The emergence of physical symptoms may, in the patient's mind, subjectively be connected with social or

Table 1. In- and out-patient treatment regimes for functional motor disorders

	n	Duration of symptoms	Age (years)[a]	Treatment	Duration of rehabilitation	Effect of treatment	Follow up
Czarnecki *et al.*[26]	60	17 days (1 – 276); mixed motor disturbances	46 (17 – 79)	Outpatient regime; multidisciplinary team	5 days	Marked improvement in 75%	25 months; 60% still showed marked improvement
Nielsen *et al.*[25]	47	6 days (2 – 480); mixed motor disturbances	44 (21 – 85)	Outpatient regime; multidisciplinary team	5 days	Marked improvement in 65%	3 months; 55% still showed improvement
Jacobs *et al.*[27]	32	7.4 years (±10.3); mixed motor disturbances	49.1 ± 14.2	Inpatient regime; multidisciplinary team	1 week	86.7% of patients reported improvement; 59.1% improved on physician-rated videos	6 months; 69.2% showed improvement
McCormack *et al.*[29]	33	48.8 months (19 – 72); predominantly motor symptoms	40.8 (20 – 59)	Inpatient regime; multidisciplinary team	101 days (84 – 130)	Improvement: *Walking unaided*: 15.2% → 42.4%; *Walking aided*: 24.2% → 39.4%; *Wheelchair*: 60.6% → 18.2%	No follow up
Jordbru *et al.*[28]	60	1 – 48 months; gait disturbances	38 (19 – 62)	Inpatient regime; multidisciplinary team	28 days	Significant improvements in FMS, FIM, and SF-36	12 months; unchanged improvement
Saifee *et al.*[30]	26	>36 months; predominantly motor disturbances (in 63% of patients)	47 ± 9.5	Inpatient regime; multidisciplinary team	24 days (15 – 32)	58% showed some improvement; 35% showed no improvement	7 years; 58% showed some improvement
Arlien-Søborg *et al.*[31]	42	53 days (0 – 240); predominantly motor symptoms	39 (17 – 71)	Inpatient regime; multidisciplinary team	60 days	Moderate improvement in 28%; marked improvement in 67%; Unchanged in 4.7%	3 – 6 months; 14% showed moderate improvement; 79% showed marked improvement

Note: [a]Age is presented either as mean (range) or mean ± standard deviation.
Abbreviations: FIM: Functional independence measure; FMS: Functional mobility scale; SF-36: Short Form, 36-item.

interpersonal burdening situations that have affected the patient cognitively and emotionally as well as corporeally. The psychotherapy we administer is an individualized therapy divided into 2 weekly sessions. It started with an assessment followed by some psychoeducational communication concerning the nature of the pathological condition, some necessary changes in the present activities of the patient's life, and the aims of the therapy. The patients were encouraged to talk about significant emotional situations in the present life and present patterns that may be consciously or unconsciously connected with past, repressed experiences. Sometimes past patterns that have not been observed in the assessment sessions may surface later in the therapy. Symptoms are acknowledged as defensive manners to avoid burdening, painful emotions, and understanding the machinery of the brain's operations in these defensive manners is crucial for deciphering the emergence and persistence of symptoms.

3. Three illustrative case stories

3.1. Patient 1

This patient has no family history of neurological disorders. Her mother died from colon cancer when the patient was only 15 years of age. Her father suffered from depression and committed suicide when she was 24 years of age. A brother had severe coronary occlusions, and a brother-in-law died of a sudden coronary disorder 2 days before she became ill. The patient has been feeling unease of death since her mother died, and to compound this unpleasant feeling further, the illness and sudden death experienced by her brother-in-law became traumatizing events, leaving a great impact on her.

In June 2012, when she was 42 years of age, she suddenly experienced dizziness and ataxia of the left-side extremities. A stroke was suspected but neuroimaging was normal. She was treated with antithrombotic drugs and improved rapidly, but in November the symptoms

reappeared. Examinations revealed no somatic disorder. An attempt was made to rehabilitate her, including exercise in a warm water swimming pool, but the symptoms deteriorated. Subsequently, she was referred to a clinical psychologist for a few consultations, but no improvement was seen. She walked with a walker.

In January 2013, she was referred to our Neurological Functional Team, State University Hospital (NFTSUH). The neurological examination in a supine position and tests for coordination showed normal results, but as soon as she tried to walk, she was extremely unsteady in a very acrobatic and non-somatic manner. A walker, however, stabilized her gait, allowing her to walk short distances. Performing daily rehabilitation in a warm water swimming pool and using a walker, combined with psychotherapy with our psychologist (H.-H.O.) twice a week, had led to improvements, and after 2 – 3 weeks, she was able to walk short distances without support. At this time, she mentioned for the first time her sorrow related to her father's abnormal reactions following the death of his wife. Within another week, her gait had normalized. Two weeks later, the gait was stabilized further, and she was able to run and jump; she was discharged after 38 days of treatment.

We saw her 3 months after discharge at a planned follow-up. She was readmitted with symptoms similar to the first admission. After undergoing a few new rehabilitation sessions (physiotherapy and psychotherapy), her condition normalized within 3 weeks.

3.2. Patient 2

Patient 2 grew up as the third child and the only girl among five siblings. Both parents used to consume alcohol heavily, 1 – 2 times each month. While young, she and her siblings stayed with their grandmother until their parents became sober. She performed well in school. She was a leisure-time educator and later became a leader in a leisure-time institution.

She fell in November 2012 on an icy road and hit her head, when she was 40 years old. She immediately developed pain in the neck and dizziness and sought medical attention the following day. Five days after the fall she had nausea. Despite this, she continued working without taking leaves of any sort. Ten days after the fall, she observed paraesthesia in the left part of her face and reduced strength in the left-side extremities. Following the deterioration of the symptoms, she was admitted to a local hospital. Finally, she became wheelchair-dependent due to severe left-side hemiparesis. A magnetic resonance imaging (MRI) scan of her brain was normal.

She was referred to NFTSUH 2 months after the fall. At the time of the clinical neurological examination, she was fully awake and able to converse in her native language as well as Danish. She had severe left-side hemiparesis, normal tendon reflexes, and normal plantar reflexes. She was able to stand with support but with an abnormal gait. We found a positive Hoover's sign. All paraclinical examinations were normal, including repeated brain MRI and motor evoked potentials. We concluded that she was suffering from functional hemiparesis, and she started rehabilitation in our functional team.

One week after the rehabilitation had started, she was able to transfer from the wheelchair to bed and toilet. After another week, she was ambulatory and able to walk to the water basin by herself. This was the time point during the treatment course in which she expressed anger for unknown reasons at the fourth session with her psychologist. After 1 week, she walked with a high walker. Four weeks after the referral, she was able to climb the stairs a little. After another week, she walked with a walker and revealed her secret of being violently assaulted in her youth. In the following week, she was able to walk without any kind of support, yet with a discrete weakness of the left leg. The combined physio- and psycho-therapy lasted 6 weeks, and she was discharged to her home for further physiotherapy at a local clinic.

3.3. Patient 3

For this patient, an important part of the family history was that her mother suffered from multiple sclerosis and died from this in July 2011 when the patient was 13 years of age. According to the patient, her mother was a disabled person who needed help in almost all matters. The patient, as a child and adolescent, had suffered from guilt feelings for not being able to save her mother. Moreover, she was often told that she had a close physical resemblance to her mother. Owing to the death of her mother, the patient had a short series of consultations with a school psychologist. In her daily life, she has always been very active and interested in sports.

In November 2015, she fell on her neck and back during sports and immediately experienced pain in her neck, and she was admitted to a local hospital. MRI scan of the spines was normal and she was discharged once achieved improvement. However, a few days following discharge, she developed paresis of both legs and complained of paraesthesia from the feet to the hips. She could not walk. There were no problems with the urinary sphincter. She was readmitted to hospital. A repeated MRI of the spines showed normal findings.

She had a series of physiotherapy in different departments in local hospitals. She improved a little but could still only walk with two sticks, and her legs trembled

while walking. Thus, a FMD was suspected, and she was referred to a special unit for psychosomatic diseases. The psychiatric investigation found her moderately depressed, and she was treated with sertraline. She did not improve neurologically and was finally referred to our department (NFTSUH) late March in 2016.

At arrival, the patient was alert. The function of the cranial nerves was normal. The upper extremities were intact. The strength of the lower extremities was intact, and she had normal tendon and plantar reflexes. We only found mildly reduced sensibility in her left foot. Her gait was highly abnormal due to severe shaking and shivering of the legs. Her somatosensory evoked potentials and motor evoked potentials were both normal. We started graded physiotherapy for her in a warm water swimming pool combined with psychotherapy twice a week with a psychologist.

After 1 week of treatment, she was able to walk with a walker up to 200 m. At this point, she realized that she was angry with her father for his plan to marry his new girlfriend, and she was able to walk independently after another week of treatment. Yet she still experienced muscle cramps in the legs, but this issue normalized, and 5 days later she was able to ride a bicycle and was then discharged from the hospital at the end of April 2016, following 4 weeks of rehabilitation.

Five months later, she encountered a new, sports-related accident. She experienced pain in the back and disturbance of gait, and she was acutely referred to a local hospital. MRI of the spine was normal, and she was transferred to our department. After having brief contact with a psychologist and a neurologist in the NFTSUH, she attained a quick improvement and was discharged after 2 days with a normal gait. In the following 3 months, she still suffered from intermittent symptoms when she felt stressed until she had a confrontation with her father and stepmother in the 26th psychotherapy session. Three years after that session, she showed normal mental and physical abilities in the follow-up interviews. She has moved into her own flat and obtained her high school diploma.

4. Discussion

We have successfully treated a series of 42 patients with this combined method, achieving good results,[31] and later included patients who have not changed the results. The three cases presented herein are typical examples, chosen to illustrate how we understand the dialectic interactions between mind, body, and brain processes. The combined treatment contains therapeutic elements that work across the whole patient sample. The first part is the creation of a treatment alliance, taking place from the patients' first successive meetings with the neurologist, the physiotherapist, the psychologist/psychotherapist, and the nurses. It is important that in all four meetings, the patient's feelings are being heard, understood, respected, and given hope 24 h a day. The second part of the treatment involves training in a warm water swimming pool. Such training often surprises patients in a positive way that they have a bigger control of their bodies than expected, encouraging them to continue receiving treatment and moving through the more difficult part of the training. The third part of the treatment is building trust and a working alliance between the psychotherapist and the patients, which form the foundation to facilitate an open-minded presentation of the subjective experiences and life stories of the patients, including the emotionally disturbing experiences of conscious and unconscious traumatizing moments and the childhood-to-adulthood periods.

In the case of patient 1, important traumatizing elements in her life history were the early death of her mother and the subsequent failed mourning reactions of the father leading to inappropriate behavior toward both the patient and her best girlfriend. The emotions related to these events were brought to the surface in the 4th and 7th sessions, and after implementing the intervention, we observed changes in her physical training. A week later, she functioned normally and was discharged home.

In the case of patient 2, the psychotherapy sessions revealed a traumatizing, violent assault, and attempt to rape in her youth which had been neglected by the authorities, and almost totally repressed by the patient. After a few weeks, these memories, being triggered by the therapist's intervention, surfaced to her surprise in the 4th session, and she reacted in exasperation toward the therapist. A few days later, progress in the training was observed, and after a few weeks, she had improved to a point that she was able to walk normally and was therefore discharged so that she could achieve further stabilization at home.

The third patient had been through several unsuccessful treatment courses before being referred to our department. Warm water swimming pool training helped her in addition to the successive psychotherapeutic empathic exploration of her sorrow after losing her mother. Further improvement ensued after she expressed anger toward her father during the therapy, who had let her down psychologically. The improvements did not stabilize totally until she was guided to confront her father with her feelings of being neglected and let down during psychotherapy, which has since helped her gain a feeling of more freedom and more control over herself and her life. Since then, similar symptoms did not recur.

All these three patients suffered serious mental burdens that could result in an overload of the limbic system, which

subsequently could be responsible for their movement disorders. This could reflect a vulnerability in specific connections between the limbic system and hippocampus as well as changes in connectivity inside the prefrontal areas and other regions relevant to motor control. Unfortunately, we have no neuroimaging evidence to illustrate any changes in the patterns of brain activation of our treated patients.

5. Conclusion

This study presents a series of essential steps undertaken in the treatment of FMD, featuring a thorough neurological examination, the formation of a well-functioning team-patient treatment alliance, and a combined treatment merging physiotherapy and psychodynamic therapy supplemented with nursing support. Physiotherapy or psychological treatment, in isolation, will usually not lead to a successful clinical outcome. The psychological treatment shows results and adds its effect to the physiotherapeutic improvements when the traumatic memory elements are connected and reflected upon in the patient's conscious mind.

Functional neuroimaging demonstrating altered activation patterns and functional connectivity indicates changes in brain regions vital for normal voluntary motor function. Emotional overload may lead to increased activity in several parts of the limbic system, probably resulting in the inhibition of normal motor function. Roelofs *et al.*[33] found that increased functional connectivity between emotion- and movement-related brain regions is an important mechanism accounting for the appearance of functional movement symptoms. Furthermore, reduced activity in the hippocampus suggests active suppression of memory of unpleasant events, emphasizing the important link between the hippocampus and the limbic system, that is, between memory and emotions.

Several studies have indicated that abnormal activation patterns are normalized following recovery. However, despite all the promising findings, it is still difficult to deduce a common hypothesis from the neuroimaging results.[34,35] However, based on our clinical experiences and most of the available studies, we believe that the limbic system plays an important role in the disturbance of motor control and impaired self-agency in patients suffering from FMD.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Peter Arlien-Søborg, Hans Henrik Olsen, Bent Rosenbaum
Investigation: All authors
Methodology: Peter Arlien-Søborg, Bent Rosenbaum
Writing – original draft: Peter Arlien-Søborg, Hans-Henrik Olsen, Josefin Agergaard, Bent Rosenbaum
Writing – review & editing: Peter Arlien-Søborg, Bent Rosenbaum

Ethics approval and consent to participate

We have obtained informed consent from the reported patients.

Consent for publication

All the patients gave consent to publish their data in this study.

Availability of data

Data are available from the corresponding author upon reasonable request.

References

1. American Psychiatric Association. DSM-5. 5th ed. Arlington: American Psychiatric Association Publication; 2013.
2. Kranick S, Ekanayake V, Martinez V, Ameli R, Hallett M, Voon V. Psychopathology and psychogenic movement disorders. *Mov Disord.* 2011;26:1844-1850.
   doi: 10.1002/mds.23830
3. Fobian AD, Elliott L. A review of functional neurological symptom disorder, etiology and the integrated etiological summary model. *J Psychiatry Neurosci.* 2019;44(1):8-18.
   doi: 10.1503/jpn.170190
4. Pareés I, Kojovic M, Pires C, Rubio-Agusti I, Saifee TA, Sadnicka A. Physical precipitating factors in functional movement disorders. *J Neurol Sci.* 2014;338:174-177.
   doi: 10.1016/j.jns.2013.12.046
5. Carson AJ, Brown R, David AS, *et al.* Functional (conversion) neurological symptoms: Research since the millennium. *J Neurol Neurosurg Psychiatry.* 2012;83(8):842-850.
   doi: 10.1136/jnnp-2011-301860
6. Voon V, Ekanayake V, Wiggs E, *et al.* Response inhibition in motor conversion disorder. *Mov Disord.* 2013;28:612-618.
   doi: 10.1002/mds.25435
7. Kalogjera-Sackalleres D, Sackalleres JC. Intellectual and

neuropsychological features of patients with psychogenic pseudoseizures. *Psychiatry Res*. 1999;86(1):73-84.

doi: 10.1016/S0165-1781(99)00016-5

8. Stone J, Carson A, Duncan R, Roberts R, Warlow C, Hibberd C. Who is referred to neurology clinics? - The diagnoses made in 3781 new patients. *Clin Neurol Neurosurg*. 2010;112:747-751.

doi: 10.1016/j.clineuro.2010.05.011

9. Stone J, Zeman A, Simonotto E, *et al*. fMRI in patients with motor conversion symptoms and controls with simulated weakness. *Psychosom Med*. 2007;69:961-969.

doi: 10.1097/PSY.0b013e31815b6c14

10. Girouard E, Savoie I, Witkowski LC. Functional neurological symptom disorder: A diagnostic algorithm. *Hindawi Behav Neurol*. 2019;2019:3154849.

doi: 10.1155/2019/3154849

11. Voon V, Brezing C, Gallea C, Hallett M. Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder. *Mov Disord*. 2011;26(13):2396-2403.

doi: 10.1002/mds.23890

12. Cojan Y, Waber L, Carruzzo A, Vuilleumier P. Motor inhibition in hysterical conversion paralysis. *Neuroimage*. 2009;47:1026-1037.

doi: 10.1016/j.neuroimage.2009.05.023

13. Aybek S, Nicholson TR, Zelaya F, *et al*. Neural correlates of recall of life events in conversion disorder. *JAMA Psychiatry*. 2014;71:52-60.

doi: 10.1001/jamapsychiatry.2013.2842

14. Marshall JC, Halligan PW, Fink GR, Wade DT, Frackowiak RS. The functional anatomy of a hysterical paralysis. *Cognition*. 1997;64(1):B1-B8.

doi: 10.1016/S0010-0277(97)00020-6

15. Faul L, Knight LK, Espay AJ, Depue BE, LaFaver K. Neural activity in functional movement disorders after inpatient rehabilitation. *Psychiatry Res Neuroimaging*. 2020;303:1111125.

doi: 10.1016/j.psychresns.2020.111125

16. de Lange FP, Toni I, Roelofs K. Altered connectivity between prefrontal and sensorimotor cortex in conversion paralysis. *Neuropsychologia*. 2010;48:1782-1788.

doi: 10.1016//j.neuropsychologia.2010.02.029

17. Maurer CW, LaFaver K, Ameli R, Epstein SA, Hallett M, Horowitz SG. Impaired self-agency in functional movement disorders A resting-state fMRI study. *Neurology*. 2016;87:564-570.

doi: 10.1212/WNL.0000000000002940

18. Voon V, Gallea C, Hattori N, Bruno M, Ekanayake V, Hallet M. The involuntary nature of conversion disorder. *Neurology*. 2010;74:223-228.

doi: 10.1212/WN1.0b013e31181ca00e9

19. Tiihonen J, Kuikka J, Viinamaki M, Lehtonen J, Partanen J. Altered cerebral blood flow during hysterical paresthesia. *Biol Psychiatry*. 1995;37(2):134-135.

doi: 10.1016/0006-3223(94)00230-Z

20. Dogonowski AM, Andersen KW, Selleberg F, Schreiber K, Madsen KH, Siebner HR. Functional neuroimaging of recovery from motor conversion disorder: A case report. *Neuroimage*. 2019;190:269-274.

doi: 10.1016/j.neuroimage.2018.03.061

21. Vuilleumier P, Chicherio C, Assal F, Schwartz D, SlosmanD, Landis T. Functional neuroanatomical correlates of hysterical sensorimotor loss. *Brain*. 2001;124:1077-1090.

doi: 10.1093/brain/124.6.1077

22. Lafaver K, Faul L, Jacob A, Depue B. Functional neuroimaging of functional movement disorders (FMD) before and after a rehabilitation program. *Neurology*. 2018;90(15 Suppl):S30.006.

doi: 10.1212/WNL.90.15_supplement.S30.006

23. Stone J, Sharpe M, Rothwell PM, Warlow CP. The 12 year prognosis of unilateral functional weakness and sensory disturbance. *J Neurol Neurosurg Psychiatry*. 2003;74: 591-596.

doi: 10.1136/jnnp.74.5.591

24. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: A systematic review. *J Neurol Neurosurg Psychiatry*. 2014;85:220-226.

doi: 10.1136/jnnp-2013-305321

25. Nielsen G, Ricciardi L, Demartini B, Hunter R, Joyce E, Edwards MJ. Outcomes of a 5-day physiotherapy programme for functional (psychogenic) motor disorders. *J Neurol*. 2015;262:674-681.

doi: 10.1007/s00415-014-7631-1

26. Czarnecki K, Thompson JM, Seime R, Geda YE, Duffy JR, Ahlskog JE. Functional movement disorders: Successful treatment with a physical therapy rehabilitation protocol. *Park Relat Disord*. 2012;18:247-251.

doi: 10.1016/j.parkreldis.2011.10.011

27. Jacob AE. Kaelin DL, Roach AR, Ziegler CH, LaFaver K. Motor retraining (MoRe) for functional movement disorders: Outcomes from a 1-week multidisciplnary rehabilitation program. *Phys Med Rehabil*. 2018;10(11):1164-1172.

doi: 10.1016/j.pmrj.2018.05.011

28. Jordbru AA, Smedstad LM, Klungsøyr O, Martinsen EW. Psychogenic gait disorder: A randomized controlled trial

of physical rehabilitation with one-year follow-up. *J Rehabil Med*. 2014;48:181-187.

doi: 10.2340/16501977-1246

29. McCormack R, Moriarty J, Mellers JD, *et al*. Specialist inpatient treatment for severe motor conversion disorder: A retrospective comparative study. *J Neurol Neurosurg Psychiatry*. 2014;85:893-898.

doi: 10.1136/jnnp-2013-305716

30. Saifee TA, Kassavetis P, Parees I, *et al*. Inpatient treatment of functional motor symptoms: A long-term follow-up study. *J Neurol*. 2012;259:1958-1963.

doi: 10.1007/s00415-012-6530-6

31. Søborg PA, Albrechtsen L, Olsen HH, LaCour P. Functional neurological movement disorders. *Ugeskr Læger*. 2017;179:V04170295.

32. Della Selva PC. *Intensive Short-term Dynamic Psychotherapy: Theory and Technique*. London: Routledge; 2004.

33. Roelofs JJ, Teodoro T, Edwards MJ. Neuroimaging in functional movement disorders. *Curr Neurol Neurosci Rep.* 2019;19:12.

doi: 10.1007/s11910-019-0926-y

34. Dar ME, Kanaan RA. Uncovering the etiology of conversion disorder: Insights from functional neuroimaging. *Neuropsychiatr Dis Treat*. 2016;12:143-153.

doi: 10.2147/NDT.S65880

35. Conejero I, Thouvenot E, Abbar M, Mouchabac S, Courtet P, Olie E. Neuroanatomical of conversion disorder: Towards a network approach. *Rev Neurosci*. 2017;29(4):355-368.

doi: 10.1515/revneuro-2017-0041

ACCSCIENCE PUBLISHING

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CASE REPORT

Serotonin syndrome induced by the combined use of metaxalone, phentermine, and duloxetine: A case report

Gabrielle Rivera-Maldonado[1], Wenxin Song[2], Leenil Noel[2], and Adam J. Fusick[1,2,3]*

[1]Department of Psychiatry and Behavioral Neurosciences, University of South Florida Morsani College of Medicine, Tampa, Florida, United States of America

[2]Department of Psychiatry and Behavioral Neurosciences, University of South Florida Morsani College of Medicine, Tampa, Florida

[3]Mental Health and Behavioral Sciences Service, James A. Haley Veterans Hospital, Tampa, Florida, United States of America

Abstract

Serotonin syndrome is a potentially life-threatening condition caused by increased serotonergic activity. Although this condition is commonly associated with certain antidepressants, this report describes a case of serotonin syndrome induced by the combined use of metaxalone and phentermine with duloxetine and bupropion. Our patient developed serotonin syndrome following the administration of metaxalone for severe back spasms. Symptoms resolved following the discontinuation of these medications, provision of supportive care, and administration of lorazepam and cyproheptadine. This case report adds to the existing literature, as studies on metaxalone-induced serotonin syndrome are currently limited. This case report also highlights the importance of monitoring polypharmacy, especially when prescribing less common medications such as metaxalone as well as weight-loss medications such as phentermine.

Keywords: Serotonin syndrome; Serotonin toxicity; Metaxalone; Phentermine; Selective serotonin reuptake inhibitors; Polypharmacy

***Corresponding author:**
Adam J. Fusick
(adam.fusick@va.gov)

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1. Introduction

Serotonin syndrome is a toxic condition resulting from the overuse of one or more serotonergic drugs, which increases neurological serotonergic activity.[1] Its clinical manifestations exhibit a spectrum of severity proportional to levels of free serotonin. Mild-to-moderate symptoms include hyperreflexia, tremors, and gastrointestinal disturbances, whereas severe cases may result in profound autonomic hyperactivity, mental status changes, and sustained clonus/rigidity.[2] Serotonin syndrome is often diagnosed using a set of clinical indicators known as Hunter's criteria.[3]

The most common etiology is the combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs) with monoamine oxidase inhibitors (MAOIs), followed by the use of two MAOIs or other types of serotonergic polypharmacy. Combining medications with diverse mechanisms

of action has the greatest potential for lethality.[2] Duloxetine is a SNRI widely used for its combined antidepressant and neuropathic pain reduction properties, whereas bupropion is a norepinephrine and dopamine reuptake inhibitor with weak serotonergic activity.[4]

Metaxalone, an oxazolidinone analog used as a muscle relaxant, has been less extensively investigated but may possess serotonergic activity. Although its mechanism of action remains unknown, it is hypothesized that metaxalone acts as a reversible MAOI due to its comparable structure.[5] According to a previous case report, serotonin syndrome is caused by metaxalone overdose alone or metaxalone overdose along with a therapeutic dose of an SSRI.[6] Serotonin syndrome has been reported to manifest in a patient with cirrhosis receiving venlafaxine and quetiapine, upon initiation of metaxalone.[7]

Phentermine is a sympathomimetic medication employed for suppressing appetite and facilitating weight loss.[8] Although there are no published cases of serotonin syndrome associated with phentermine, the drug is known to inhibit serotonin metabolism through monoamine oxidase.[9] Overall, the literature on metaxalone and/or phentermine-induced serotonin syndrome is limited. However, there appears to be significant potential for increasing serotonergic activity through monoamine oxidase pathways.

This case report describes a patient on duloxetine, bupropion, and phentermine who developed serotonin syndrome following the administration of metaxalone. Several factors that potentially contributed to the development of serotonin syndrome in this patient will be reviewed.

2. Case presentation

A 56-year-old male with moderate, recurrent major depressive and adjustment disorders presented to the emergency department due to a 1-week history of progressive restlessness, abdominal pain, diaphoresis, nausea, and vomiting. He also had a history of medical comorbidities, including chronic myelogenous leukemia, peripheral neuropathy, chronic lumbar back pain (for which he was receiving oxycodone), and hypertension. Upon admission, he was conscious and oriented, afebrile, and hemodynamically stable but was restless, tremulous, and demonstrated akathisia. The urine drug screen was positive for oxycodone and negative for illicit substances. He was administered morphine (2 mg/mL) intravenous (IV) q6h for pain and lorazepam (0.5 mg/0.25 mL) IV q4h for acute agitation. Due to concerns regarding serotonin syndrome, he was admitted to the intensive care unit. He developed hypertension (159/89 mmHg), tachycardia (101 bpm), and a fever of 98.4°F following admission. Laboratory tests revealed a creatine phosphokinase level of 995 U/L. Physical examination was notable for clonus, nystagmus, and tremors.

A psychiatrist was consulted for investigating possible serotonin syndrome. The neurological examination demonstrated ocular vertical nystagmus, inducible clonus on the right foot, jerkiness, tremors, and akathisia but no brachial or patellar hyperreflexia. The patient discontinued his psychotropic medications 2 days before admission, as he believed that they were the cause of his symptoms. He was unable to provide additional information due to acute mental status changes.

The patient's wife reported that 5 days before admission, he began experiencing tremors, diaphoresis, diarrhea, abdominal pain, and temperature dysregulation and was "tense" while driving. Two days before admission, the patient experienced deterioration, as evidenced by increased restlessness and tremors, decreased sleep, diaphoresis, altered mental status, hypertension, and tachycardia, as determined by blood pressure measurement at home. Tremors were described as the patient's hands rhythmically oscillating up and down while holding the steering wheel as he was driving. The patient's wife, however, was unaware of the specific medications that the patient had received in the weeks preceding this event.

A review of the patient's medication regimen included duloxetine 60 mg daily, bupropion XL 150 mg daily, gabapentin 600 mg QID, metaxalone 800 mg BID PRN, pantoprazole 40mg daily, hydrochlorothiazide 12.5 mg daily, nilotinib 150 mg BID, cyclobenzaprine 10 mg TID PRN, oxycodone 15mg q4h PRN, and phentermine 37.5 mg daily.

The patient fulfilled Hunter's criteria for serotonin syndrome by exhibiting ocular clonus, inducible clonus, and use of serotonergic medications (such as duloxetine, metaxalone, and phentermine). Cyproheptadine administration was initiated after a psychiatric consultation. After 2 days of treatment with a 12 mg loading dose and a 2 mg Q2H dose of cyproheptadine for a maximum dose of 32 mg/day, the patient's mental status markedly improved. He acknowledged receiving phentermine "sparingly" but had resumed daily doses 5 days before symptom onset. Metaxalone was another agent he used PRN; however, he had also resumed taking this medication twice a day for 2 days before symptom onset. These two PRN agents were being used in addition to his regular scheduled medications.

On day 4, evaluation revealed that the vital signs were within normal limits. Neurological examination revealed

the absence of nystagmus, clonus, jerkiness, tremors, or akathisia. Furthermore, the mental status examination demonstrated considerable improvement, as evidenced by the return to baseline attention without agitation. Cyproheptadine was discontinued, and duloxetine was resumed at a dose of 30 mg on day 5. The patient continued to improve clinically and was discharged on day 6.

3. Discussion

Serotonin syndrome is a potentially fatal condition resulting from excessive serotonergic activity. It is characterized by somatic, autonomic, and cognitive symptoms, including altered mental status, autonomic instability, and neuromuscular anomalies. Although frequently linked to MAOIs, SSRIs, and SNRIs, other agents, including muscle relaxants and weight reduction pills, have also been associated with its development.

The patient in the current case was receiving several medications that affect serotonin levels through diverse mechanisms. Duloxetine, an SNRI, increases serotonin and norepinephrine levels by inhibiting their reuptake.[10] Bupropion, primarily an NDRI with certain serotonergic effects, is a known risk factor.[11] Phentermine, a sympathomimetic amine used for weight loss, can indirectly enhance serotonin's release.[12] Although metaxalone is a muscle relaxant and its exact mechanism of action is not fully understood, it appears to have serotonergic properties that, when combined with other serotonergic agents, can cause serotonin syndrome.[6] Increasing evidence suggests that the mechanism of action of metaxalone comprises MAOI activity that becomes clinically relevant when given in large doses.[5,13] In addition, hepatic cytochrome P450 enzymes facilitate metaxalone metabolism. Specifically, CYP1A2 and CYP2D6 have been demonstrated to be the primary enzymes responsible for metabolism.[14] Our patient was receiving both duloxetine and bupropion, which are known CYP2D6 inhibitors.[15,16] Furthermore, duloxetine inhibits CYP1A2.[17] Even at therapeutic levels, this combination may have resulted in increased bioavailability of metaxalone, making its MAOI activity clinically relevant. We believe that these medications likely caused excess neurological serotonin formation, leading to dysregulation and patient's clinical manifestations.

One limitation of this case report was the other serotoninergic agents that the patient was concurrently receiving, specifically duloxetine, phentermine, and to some extent bupropion. Duloxetine is associated with serotonin syndrome; however, its incidence is low, and the time course of symptom onset appears to be more closely related to the use of metaxalone on an as-needed basis.[18] In addition, after resuming duloxetine during hospitalization, no adverse effects recurred, proving it less likely to be the primary cause of our patient's complaints. Phentermine may have affected this patient's serotonin levels; however, no evidence of serotonin syndrome occurring with phentermine administration currently exists.[9] This does exclude a theoretical mechanism, but phentermine is unlikely to be the primary offending agent. Given the patients' long-term compliance with bupropion before symptoms appeared, it is also unlikely to be the cause of the symptoms. To our knowledge, there are only three reported cases demonstrating serotonin syndrome in conjunction with bupropion toxicity, and none of these were caused by bupropion alone.[19] Finally, on the Naranjo Adverse Drug Reaction Probability Scale, our patient scored an 8, making metaxalones a "probable" cause of the medication reaction (Figure 1).[20] This case report emphasizes that understanding pharmacodynamic interactions is crucial, particularly in serotonergic polypharmacy.

It is essential that clinicians understand drug serotonergic potential. Medications not traditionally associated with serotonin syndrome, such as metaxalone or weight loss drugs, can still cause serotonin syndrome when coupled with other serotonergic drugs. Drug-drug interactions must be carefully considered when prescribing multiple neurotransmitter-affecting medications.[21] Early diagnosis of serotonin syndrome is crucial to prevent severe complications and improve outcomes. Management involves prompt cessation of all serotonergic agents and supportive care. Benzodiazepines are considered first-line drugs; serotonin antagonists such as cyproheptadine are reserved for severe cases in which there is minimal improvement with benzodiazepines.[22]

The patient's symptomatology was consistent with that of serotonin syndrome, as evidenced by his agitation, altered mental status, hyperreflexia, clonus, and autonomic

Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
TOTAL SCORE:				8

Figure 1. Naranjo Adverse Drug Reaction Probability Scale. Modified from Naranjo *et al.*[20]

instability. His rapid onset of symptoms after initiating metaxalone with concomitant phentermine use suggests a direct link to serotonin syndrome. After discontinuation of all serotonergic agents and the provision of supportive care, the patient still experienced altered mental status, autonomic instability, and muscle rigidity, requiring lorazepam and cyproheptadine administration. Consequently, the patient returned to his clinical baseline within 24 h.

4. Conclusion

This case highlights the importance of monitoring for serotonin syndrome in patients receiving multiple serotonergic medications, including metaxalone, which is not commonly linked to this condition. Health-care providers should maintain a high index of suspicion for this condition, especially when prescribing combinations of serotonergic medications. Additional research is warranted to better understand the serotonergic properties of metaxalone and similar drugs to enhance patient safety in the context of polypharmacy.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Investigation: All authors
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Verbal and written consent was obtained from the patient before participation

Consent for publication

The patient gave consent to publish his data in this study.

Availability of data

Data are available from the corresponding author upon reasonable request.

References

1. Scotton WJ, Hill LJ, Williams AC, Barnes NM. Serotonin syndrome: Pathophysiology, clinical features, management, and potential future directions. *Int J Tryptophan Res*. 2019;12:117864691987392.

   doi: 10.1177/1178646919873925

2. Talton CW. Serotonin syndrome/serotonin toxicity. *Fed Pract*. 2020;37(10):452-459.

   doi: 10.12788/fp.0042

3. Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9):635-642.

   doi: 10.1093/qjmed/hcg109

4. Huecker MR, Smiley A, Saadabadi A. Bupropion. In: *StatPearls*. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9554319 [Last accessed on 2024 Jul 22].

5. Bosak AR, Skolnik AB. Serotonin syndrome associated with metaxalone overdose. *J Med Toxicol*. 2014;10(4):402-405.

   doi: 10.1007/s13181-014-0404-5

6. Martini DI, Nacca N, Haswell D, Cobb T, Hodgman M. Serotonin syndrome following metaxalone overdose and therapeutic use of a selective serotonin reuptake inhibitor. *Clin Toxicol*. 2015;53(3):185-187.

   doi: 10.3109/15563650.2015.1009993

7. Surmaitis RM, Nappe TM, Cook MD. Serotonin syndrome associated with therapeutic metaxalone in a patient with cirrhosis. *Am J Emerg Med*. 2016;34(2):346.e5-e6.

   doi: 10.1016/j.ajem.2015.06.043

8. Suissa K, Schneeweiss S, Kim DW, Patorno E. Prescribing trends and clinical characteristics of patients starting antiobesity drugs in the United States. *Diabetes Obes Metab*. 2021;23(7):1542-1551.

   doi: 10.1111/dom.14367

9. Ulus IH, Maher TJ, Wurtman RJ. Characterization of phentermine and related compounds as monoamine oxidase (MAO) inhibitors. *Biochem Pharmacol*. 2000;59(12):1611-1621.

   doi: 10.1016/s0006-2952(00)00306-3

10. Westanmo AD, Gayken J, Haight R. Duloxetine: A balanced and selective norepinephrine- and serotonin-reuptake inhibitor. *Am J Health Syst Pharm*. 2005;62(23):2481-2490.

    doi: 10.2146/ajhp050006

11. Foley KF, DeSanty KP, Kast RE. Bupropion: Pharmacology and therapeutic applications. *Expert Rev Neurother*. 2006;6(9):1249-1265.

    doi: 10.1586/14737175.6.9.1249

12. Perez CI, Kalyanasundar B, Moreno MG, Gutierrez R. The triple combination phentermine plus 5-HTP/carbidopa leads to greater weight loss, with fewer psychomotor side effects than each drug alone. *Front Pharmacol*. 2019;10:1327.

doi: 10.3389/fphar.2019.01327

13. Gillman PK. New data on metaxalone (Skelaxin) and serotonin toxicity (serotonin syndrome): Warning of potential for fatalities if combined with serotonin re-uptake inhibitors. *Psycho Trop Commentaries*. 2018;6:22-32.

14. King Pharmaceuticals, Inc. Skelaxin (Metaxalone) Tablets: Prescribing Information (Rev. March 2018). U.S. Food and Drug Administration; 2018. Available from: https://www.fda.gov/drugsatfda [Last accessed on 2024 Jul 21].

15. Knadler MP, Lobo E, Chappell J, Bergstrom R. Duloxetine: Clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet*. 2011;50(5):281-294.

    doi: 10.2165/11539240-000000000-00000

16. Kotlyar M, Brauer LH, Tracy TS, *et al*. Inhibition of CYP2D6 activity by bupropion. *J Clin Psychopharmacol*. 25(3): 226-229.

    doi: 10.1097/01.jcp.0000162805.46453.e3

17. Lobo ED, Bergstrom RF, Reddy S, *et al*. *In vitro* and *in vivo* evaluations of cytochrome P450 1A2 interactions with duloxetine. *Clin Pharmacokinet*. 2008;47(3):191-202.

    doi: 10.2165/00003088-200847030-00005

18. Li L, Mi Q. Serotonin syndrome from duloxetine monotherapy: A case report. *Cureus*. 2023;15(6):e40933.

    doi: 10.7759/cureus.40933

19. Thorpe EL, Pizon AF, Lynch MJ, Boyer J. Bupropion induced serotonin syndrome: A case report. *J Med Toxicol*. 2010;6(2):168-171.

    doi: 10.1007/s13181-010-0021-x

20. Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.

    doi: 10.1038/clpt.1981.154

21. Möller HJ, Seemüller F, Schennach-Wolff R, Stübner S, Rüther E, Grohmann R. History, background, concepts and current use of comedication and polypharmacy in psychiatry. *Int J Neuropsychopharmacol*. 2014;17(7): 983-996.

    doi: 10.1017/S1461145713000837

22. Mikkelsen N, Damkier P, Pedersen SA. Serotonin syndrome-A focused review. *Basic Clin Pharmacol Toxicol*. 2023;133(2):124-129.

    doi: 10.1111/bcpt.13912

ACCSCIENCE PUBLISHING

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BRIEF REPORT

Association between concerns regarding COVID-19 mRNA vaccination and the adverse event rate among healthcare workers

Isabel Hach[1†*], Bunila-Yuwang Francisca[1,2†], Wolfgang Hitzl[3], Annette Sattler[4], Stephan Kolb[1], and Cosima Brucker[2]

[1]Department of Education and Science, Klinikum Nürnberg, Paracelsus Medical University, Nuremberg, Germany

[2]Clinic for Gynecology and Obstetrics, Klinikum Nürnberg, Paracelsus Medical University Nuremberg, Germany

[3]Department of Research and Innovation Management, Biostatistics and Publication of Clinical Trial Studies, Paracelsus Medical University, Salzburg, Austria

[4]Department of Hospital Pharmacy, Klinikum Nürnberg, Paracelsus Medical University, Nuremberg, Germany

†These authors contributed equally to this work.

***Corresponding author:**
Isabel Hach
(isabel.hach@klinikum-nuernberg.de)

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Abstract

Healthcare workers must be vaccinated regularly. However, vaccination-related side effects can lead to sick leaves and decreased willingness to be vaccinated. Negative expectations can cause nocebo effects, potentially increasing the rates of adverse events (AEs). Herein, we evaluated the relationship between concerns regarding the vaccination course and the prevalence rate of AEs after the first and second doses of mRNA vaccines in 982 healthcare workers from the Nuremberg Hospital. Most of our participants were women (78%). Fatigue and headache were the most common systemic AEs. Healthcare workers who were worried about the vaccination process reported significantly more AEs after the first vaccine dose than those who were not worried (80% vs. 68%, $P < 0.05$). Thus, strategies to minimize concerns could reduce vaccination-related side effects and improve willingness to be vaccinated.

Keywords: Nocebo effects; Self-fulfilling prophecy; Pharmacovigilance

1. Introduction

No vaccination in recent decades has been as eagerly anticipated as the one for COVID-19; however, this has been accompanied by fears of (unknown) side effects.[1] Although authorized vaccines are safe, precise information regarding their tolerability and safety can only be determined during the course of use.[2-5] The rates of side effects reported in observational studies conducted after vaccine authorization differ based on age, sex, vaccine type, and country.[2,5] Individuals working in the German healthcare system have expressed fears regarding the COVID-19 vaccination.[1] Negative expectations from vaccines or drugs can cause a nocebo (Latin for "I will harm") effect.[6-9] Nocebo effects are specific to the side effects discussed.[7,10] In clinical trials, the development of adverse events (AEs) in the placebo group, that is, patients who receive a preparation without the active substance, is considered a nocebo effect. In mRNA vaccine registration studies,

the AE rates in the placebo groups were high after the first dose.[2] In retrospect, the AEs that occurred during the registration trials were interpreted as being associated with nocebo effects.[11-13]

Nocebo effects are verifiable (neurophysiologically and clinically) and can lead to life-threatening situations.[6,10] Thus, downplaying nocebo effects as imaginary and not concerning is wrong and contrary to scientific knowledge. In non-interventional studies, the placebo arm is missing. Therefore, nocebo effects cannot be directly distinguished from side effects. Nocebo effects could change a vaccine's safety classification in clinical trials, which is highly relevant.[8,14] Placebo and nocebo effects are more likely to develop during treatment initiation.[6-9] The frequency of adverse events after COVID-19 vaccinations varied in studies, predictors for vaccination side effects could not be determined.[15,16] However, no study has investigated concerns regarding a nocebo effect before the first dose. Herein, we investigated the association between concerns regarding the course of an mRNA COVID-19 vaccine and the prevalence rate of AEs in healthcare workers (HCWs).

2. Methods

All employees of the Nuremberg Hospital – one of the largest municipal hospitals in Europe providing the highest care – who were vaccinated as of December 27, 2020 (start of COVID-19 vaccinations in prioritized individuals in Germany) were invited to volunteer in this pharmacovigilance study. There were no special inclusion or exclusion criteria. Questionnaires were available at the two vaccination centers of the hospital, as well as online, and included all previously identified AEs.[2] We analyzed the prevalence of AEs after the first dose of an mRNA vaccine (total n = 982; Comirnaty BNT162b2: n = 596). The participants were asked to report any AEs that developed within 1 week of the first dose. The participants selected the symptoms in the questionnaire that applied to them and classified them according to their intensity – mild, moderate, or severe. Completed questionnaires could either be physically submitted in prepared boxes or returned via internal mail. There were no special requests to fill out the questionnaires from memory, for example, 2 – 3 weeks after vaccination, to avoid recall bias. The questionnaire included an empty field for personal comments and perceived AEs not listed in the questionnaire. The questionnaire did not include questions regarding professional affiliation. Patients vaccinated with mRNA vaccines were predominantly medical professions (mostly nurses) directly involved in the care of patients with COVID-19. The participant's anamnestic data were collected, and they were asked if they were worried about the vaccination course (Answers: Yes or No). To assess the susceptibility to nocebo effects, we did not include the Q-No questionnaire. For example, the questionnaire asks whether patients read the summary of drug characteristics before consuming it.[16,17] This behavior may favor the development of nocebo effects or be considered normal by medical personnel and for new vaccines. Questionnaires completed by the same person were linked using a pseudonymization code. Once entered into a database, the data were completely anonymized and analyzed. The study has been registered with the Deutsches Register Klinischer Studien (German Register Clinical Studies, No: DRKS00027976) and was approved by the review board of PMU Nuremberg (No: IRB 2022_003; February 2, 2022).

2.1. Statistical analysis

Data were checked for incorrect entries. Fisher's exact and Pearson's Chi-square tests were used to analyze cross-tabulations. These tests were best suited to compare the frequency of side effects in different groups (our sample vs. registration study sample; subgroups of our sample).[18] The significance level was 5%. No correction was made for multiple testing. All analyses were performed using STATISTICA (version 13; Hill, T. & Lewicki, P. Statistics: Methods and Applications. StatSoft, Tulsa, OK, USA) and NCSS (version 2022; NCSS, LLC. Kaysville, UT, USA).

3. Results

Our cohort comprised 78% women (18 – 35 years: 25%; 36 – 50 years: 35%; and >51 years: 40%) and 22% men (18 – 35 years: 29%; 36 – 50 years: 29%; and > 51 years: 41%). Allergies were the most common pre-existing condition in both sexes (women: 53%; men: 50%), followed by cardiovascular (women: 11.5%; men: 12%) and thyroid (women: 11.5%; men: 2.8%) diseases. Mental illnesses were rarely reported (women: 1.5%; men: 1.7%). In total, 25% of the women and 20% of the men were smokers. The prevalence of obesity (body mass index >30 kg/m²) was 14% among women and 10% among men.

Fatigue, headache, and myalgia were the most common systemic AEs after the first vaccine dose. Fatigue, headache, chills, and vomiting developed significantly less frequently in patients aged <55 years in our study than in those in the registration study for Comirnaty (Table 1).

HCWs who reported concerns regarding the vaccination course (n = 180) were significantly more likely to exhibit systemic AEs (80% vs. 68%) after the first mRNA vaccine dose than those who reported no concerns (n = 605; Figure 1). Women were significantly more worried than men (27.5% vs. 10%, $P < 0.05$). After the second dose, the AE rates were not significantly different between the two groups.

Table 1. Comparison of prevalence of selected AEs after administration of the first dose of BNT162b2 (Comirnaty) (registration study cohort vs. our cohort)

AE	AE prevalence among <55-year-olds in registration study (n=10,889) (%)	AE prevalence among <55-year-olds in our study (n=453)[a] (%)	*P*-value (Fisher's exact test, two-sided)		AE prevalence among >55-year-olds in registration study (n=7,971) (%)	AE prevalence among >55-year-olds in our study (n=143)[a] (%)
Fatigue	47	175 (41)	0.008*	0.48**	34	45 (31)
Headache	42	123 (29)	0.000*	0.70**	25	33 (23)
Arthralgia	11	63 (15)	0.034*	0.053**	9	20 (14)
Chills	14	28 (7)	0.000*	0.48**	6	6 (4)
Vomiting	4	10 (2)	0.044*	0.004**	8	6 (4)

Notes: [a]: Data are presented as n (%); *: Comparison of AE prevalence among 16 – 55-year-olds (1) in the registration study versus 18 – 55-year-old HCWs in our study; **: Comparison of AE prevalence among >55-year-olds (1) in the registration study versus >55-year-old; HCWs in our study; The significance level was set at 5% ($P<0.05$).
Abbreviations: AE: Adverse event; HCW: Health care workers.

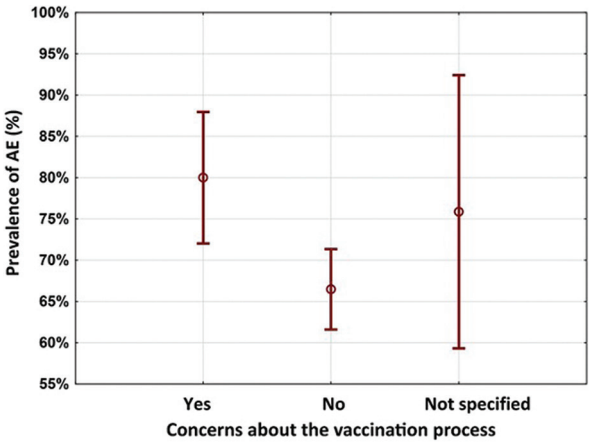

Figure 1. Prevalence of systemic AEs (after 1st mRNA vaccine dose, Comirnaty or Moderna) in relation to expressed concerns regarding the vaccination process. Image created by the author
Abbreviation: AE: adverse event.

4. Discussion

The sex distribution in our sample (78% women) is relatively typical for German hospital staff. A health report prepared by a large German health insurance company (Techniker Krankenkasse) stated that 75% of nursing staff are women[19] and compared the incapacity to work diagnosis of nursing staff with those of other occupational groups. Compared with the normal German population, our participants were less obese (women: 24% vs. 14%; men: 23% vs. 10%).[20] Our study and the GEDA 2019/2020-EHIS used self-reported data from participants, often leading to an underestimation of body weight compared with standard values. The male HCWs in our study smoked less frequently than those in the German general population (20.1% vs. 33.9%); similar data was obtained for women (25% vs. 24%).[20]

Similar to previous studies, our study partially demonstrated significantly lower AE rates than those in the pivotal study[2,5]; this was unexpected due to the high proportion of women in our sample and previous reports of greater prevalence of side effects in (younger) women than men.[16] The proportion of women and men was half in registration studies, and the results for both sexes are always published together.[2] Therefore, in samples such as ours, with a significantly higher proportion of women, the side effects should have been more than in samples with a 50/50 sex distribution. In a survey of German hospital staff, approximately 4.4% – 13.1% (vaccinated with Comirnaty and Moderna) of participants were sick for at least 1 day due to side effects after the first mRNA vaccine dose.[21] Thus, considering the high workload of hospital staff, measures should be taken to reduce the rate of side effects.[21,22] Our sample may have had high positive expectations of the vaccination because they were burdened by the pandemic.[22,23] Such positive expectations may have manifested as better tolerability to the vaccine (similar to a placebo effect).[9] Furthermore, our sample may have demonstrated a positive attitude toward the vaccinations and preventive measures or were used to them (e.g., annual flu vaccinations). At the beginning of the vaccination drive, only information regarding vaccine tolerability was available from registration studies.[2] However, information regarding side effects can significantly contribute to nocebo effects.[6-9] The lack of knowledge regarding the side effects could have protected against nocebo effects. Finally, the high proportion of women in our sample could influence the development of nocebo effects. However, previous studies have not yet established a clear influence of sex on the respective placebo or nocebo response in RCTs.[24,25] Approximately one-fifth of our patient sample expressed worries regarding the vaccination course; this is consistent with Holzmann-Littig *et al.*'s results, in which approximately 15% of the surveyed staff expressed fears of short-term side effects of the vaccination.[1] Herein, there was a clear association between existing concerns

regarding the vaccination process and the AE rate, which is consistent with previous data.[6-9]

Concerns regarding the (unknown) side effects of vaccinations can cause vaccination skepticism and refusal.[16,26,27] The significant association between concern and increased rate of side effects may be explained by self-fulfilling prophecy.[28,29] Negative expectations promote the emergence of feared and even unlikely developments in the future, among other things, by reinforcing certain predisposing behaviors. Pagnini *et al*. demonstrated that the expectation of colds in the summer is significantly associated with the development of flu-like symptoms in the winter.[30] They cited so-called nocebo effects, which are initiated by negative expectations, among other things, as a possible explanation for this association. However, determining these effects directly in non-interventional studies is not possible. Thus, the exact underlying mechanism remains unclear. However, increased self-attention might have a reinforcing effect.[31] People who are worried about the vaccination course may be more concerned about the possible side effects than those who are not worried. Furthermore, participants who want to accurately document their AEs (e.g., for pharmacovigilance) may experience more AEs because they specifically pay attention to the expected side effects.[14,26,29]

There are recommendations to reduce nocebo effects. These recommendations are partially aimed at reducing self-awareness by providing less information on insignificant side effects after counseling the patients regarding the nocebo phenomenon and obtaining their consent.[9] This prior consent is necessary to safeguard the patients' rights. Drawing attention to an unknown side effect is impossible. Whereas it is very difficult not to think about something that was previously announced. Providing focused information in observational studies would benefit pharmacovigilance because regardless of the reason for increased attention to expected side effects, a more objective reporting would be possible. Accordingly, we consider it unlikely that particularly detailed information on side effects, as suggested by some authors, would reduce fears and negative expectations, respectively.[1,11,21]

A limitation of our study is the use of real-world data in an observational setting. Clear evidence of nocebo effects cannot be obtained in this setting. In principle, our study participants may have had a positive attitude toward vaccination, resulting in lesser nocebo effects than that in the normal population.[16] However, our survey included medical professionals from different fields. Thus, vaccination expectations and knowledge regarding vaccinations may differ. We could only demonstrate the association between concerns regarding the vaccination process and higher AE prevalence. We could not prove causality. The pharmacovigilance behavior of our participants with an intensive AE registration could also have resulted in the higher AE rate. Nonetheless, regardless of the cause of increased AE rates, the underlying mechanism should be seriously considered and possible countermeasures should be initiated. Although studies into nocebo effects have recently increased, little is known about the influencing factors and measures to reduce them.[10,22,23] However, further studies are required to identify nocebo effects in clinical (e.g., RCTs) and observational (i.e., studies without a placebo group) studies. For example, sex- and gender-related expectations of vaccines as well as knowledge about health beliefs before a medical intervention (e.g., vaccination, drug therapy) may be examined. Subsequently, measures to reduce nocebo effects should be investigated and their effectiveness in clinical and observational studies should be examined. These results could help implement individual and population-based measures for personalized medicine and prevention.

5. Conclusion

Nocebo-like effects might have played a role in the AEs developed in our sample. Since high AE rates can contribute to vaccine hesitancy, as much as possible should be done to minimize nocebo effects.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Isabel Hach, Stephan Kolb
Formal analysis: Isabel Hach, Bunila-Yuwang Francisca, Wolfgang Hitzl
Investigation: Isabel Hach

Writing – original draft: Isabel Hach
Writing – review & editing: All authors

Ethics approval and consent to participate

The institutional review board of the PMU Nuremberg has evaluated the study approvingly (IRB 2022_003). The data protection officer of Klinikum Nuremberg confirmed that the study is general data protection regulation (GDPR)-compliant.

Consent for publication

Not applicable.

Availability of data

After completion of the study and 6 months after publication, we will make the raw data (excel file) available in completely anonymized form after request (ca. 05/25).

References

1. Holzmann-Littig C, Frank T, Schmaderer C, *et al*. COVID-19 vaccines: Fear of side effects among German health care workers. *Vaccines (Basel)*. 2022;10(5):689.

   doi: 10.3390/vaccines10050689

2. Polack FP, Thomas SJ, Kitchin N, *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615.

   doi: 10.1056/NEJMoa2034577

3. Yan Z, Yang M, Lai CL. COVID-19 vaccinations: A comprehensive review of their safety and efficacy in special populations. *Vaccines (Basel)*. 2021;9(10):1097.

   doi: 10.3390/vaccines9101097

4. Mallah SI, Alawadhi A, Jawad J, *et al*. Safety and efficacy of COVID-19 prime-boost vaccinations: Homologous BBIBP-CorV versus heterologous BNT162b2 boosters in BBIBP-CorV-primed individuals. *Vaccine*. 2023;41(12):1925-1933.

   doi: 10.1016/j.vaccine.2023.01.032

5. Cai C, Peng Y, Shen E, *et al*. A comprehensive analysis of the efficacy and safety of COVID-19 vaccines. *Mol Ther*. 2021;29(9):2794-2805.

   doi: 10.1016/j.ymthe.2021.08.001

6. Webster RK, Weinman J, Rubin GJ. A systematic review of factors that contribute to nocebo effects. *Health Psychol*. 2016;35(12):1334-1355.

   doi: 10.1037/hea0000416

7. Hutchinson P, Moerman DE. The meaning response, "placebo," and methods. *Perspect Biol Med*. 2018;61(3):361-378.

   doi: 10.1353/pbm.2018.0049

8. Okaïs C, Gay C, Seon F, Buchaille L, Chary E, Soubeyrand B. Disease-specific adverse events following nonlive vaccines: A paradoxical placebo effect or a nocebo phenomenon? *Vaccine*. 2011;29(37):6321-6326.

   doi: 10.1016/j.vaccine.2011.05.045

9. Colloca L, Barsky AJ. Placebo and nocebo effects. *N Engl J Med*. 2020;382(6):554-561.

   doi: 10.1056/NEJMra1907805

10. Colloca L. The nocebo effect. *Annu Rev Pharmacol Toxicol*. 2024;64:171-190.

    doi: 10.1146/annurev-pharmtox-022723-112425

11. Haas JW, Bender FL, Ballou S, *et al*. Frequency of adverse events in the placebo arms of COVID-19 vaccine trials: A systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(1):e2143955.

    doi: 10.1001/jamanetworkopen.2021.43955. Erratum in: *JAMA Netw Open*. 2022;5(2):e221277.

    doi: 10.1001/jamanetworkopen.2022.1277

12. Amanzio M, Mitsikostas DD, Giovannelli F, Bartoli M, Cipriani GE, Brown WA. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review. *Lancet Reg Health Eur*. 2022;12:100253.

    doi: 10.1016/j.lanepe.2021.100253

13. Lee YH, Song GG. Nocebo responses in randomized controlled trials of COVID-19 vaccines. *Int J Clin Pharmacol Ther*. 2022;60(1):5-12.

    doi: 10.5414/CP204028

14. Wartolowska K, Colloca L, Amanzio M. Editorial: The nocebo effect and its consequences for clinical trials and clinical practice. *Front Psychol*. 2023;13:1111324.

    doi: 10.3389/fpsyg.2022.1111324

15. Bashar MA, Kamble B, Kumar S, Nandekar SV, Mathur SK. Assessment of safety and adverse events following COVID-19 vaccination and their predictors in first 30 days among healthcare workers of a tertiary care teaching hospital in North India. *Vaccine X*. 2024;19:100522.

    doi: 10.1016/j.jvacx.2024.100522

16. Mitsikostas DD, Aravantinou-Fatorou K, Deligianni C, *et al*. Nocebo-prone behavior associated with SARS-CoV-2 vaccine hesitancy in healthcare workers. *Vaccines (Basel)*. 2021;9(10):1179.

    doi: 10.3390/vaccines9101179

17. Mitsikostas DD, Deligianni CI. Q-No: A questionnaire to predict nocebo in outpatients seeking neurological consultation. *Neurol Sci*. 2015;36(3):379-381.

    doi: 10.1007/s10072-014-1959-2

18. Du Prel JB, Röhrig B, Hommel G, Blettner M. Choosing statistical tests: part 12 of a series on evaluation of scientific publications. *Dtsch Arztebl Int*. 2010;107(19):343-348.

doi: 10.3238/arztebl.2010.0343

19. Grobe T, Steinmann S. *Gesundheitsreport 2019 - Pflegefall Pflegebranche? So geht's Deutschlands Pflegekräften*. Available from: https://www.gesundheitsreport-2019-data.pdf [Last accessed on 2024 Nov 28].

20. Damerow S, Rommel A, Prütz F, et al. Developments in the health situation in Germany during the initial stage of the COVID-19 pandemic for selected indicators of GEDA 2019/2020-EHIS. *J Health Monit*. 2020;5:3-20.

    doi: 10.25646/7172.2. Erratum in: *J Health Monit*. 2021;5(4):20.

    doi: 10.25646/8384

21. Nohl A, Brune B, Weichert V, Standl F, Stang A, Dudda M. COVID-19: Vaccination side effects and sick leave in frontline healthcare-workers-a web-based survey in Germany. *Vaccines (Basel)*. 2022;10(3):411.

    doi: 10.3390/vaccines10030411

22. Müller MM, Baillès E, Blanch J, *et al*. Burnout among hospital staff during the COVID-19 pandemic: Longitudinal results from the international Cope-Corona survey study. *J Psychosom Res*. 2023;164:111102.

    doi: 10.1016/j.jpsychores.2022.111102. Erratum in: *J Psychosom Res*. 2023;167:111205.

    doi: 10.1016/j.jpsychores.2023.111205

23. Schug C, Geiser F, Hiebel N, *et al*. Sick leave and intention to quit the job among nursing staff in German hospitals during the COVID-19 pandemic. *Int J Environ Res Public Health*. 2022;19(4):1947.

    doi: 10.3390/ijerph19041947

24. Shafir R, Olson E, Colloca L. The neglect of sex: A call to action for including sex as a biological variable in placebo and nocebo research. *Contemp Clin Trials*. 2022;116:106734.

    doi: 10.1016/j.cct.2022.106734

25. Enck P, Klosterhalfen S. Does sex/gender play a role in placebo and nocebo effects? Conflicting evidence from clinical trials and experimental studies. *Front Neurosci*. 2019;13:160.

    doi: 10.3389/fnins.2019.00160

26. Paul E, Steptoe A, Fancourt D. Attitudes towards vaccines and intention to vaccinate against COVID-19: Implications for public health communications. *Lancet Reg Health Eur*. 2021;1:100012.

    doi: 10.1016/j.lanepe.2020.100012

27. Chrissian AA, Oyoyo UE, Patel P, *et al*. Impact of COVID-19 vaccine-associated side effects on health care worker absenteeism and future booster vaccination. *Vaccine*. 2022;40(23):3174-3181.

    doi: 10.1016/j.vaccine.2022.04.046

28. Sternberg E. A self-fulfilling prophecy: Linking belief to behavior. *Ann N Y Acad Sci*. 2011;1234:98-99.

    doi: 10.1111/j.1749-6632.2011.06190.x

29. Mertens M. The self-fulfilling prophecy in medicine. *Theor Med Bioeth*. 2024;45(5):363-385.

    doi: 10.1007/s11017-024-09677-z

30. Pagnini F, Cavalera C, Volpato E, Banfi P. Illness expectations predict the development of influenza-like symptoms over the winter season. *Complement Ther Med*. 2020;50:102396.

    doi: 10.1016/j.ctim.2020.102396

31. Jepma M, Koban L, van Doorn J, Jones M, Wager TD. Behavioural and neural evidence for self-reinforcing expectancy effects on pain. *Nat Hum Behav*. 2018;2(11):838-855.

    doi: 10.1038/s41562-018-0455-8

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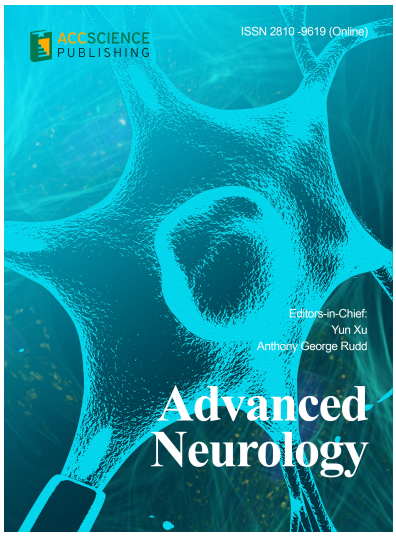

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