

## Vitamin B6 in anxiety: sleep and immune function

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### Abstract

**Objective:** This scoping review aims to explore the role of vitamin B6 in sleep duration and immune function in individuals with anxiety disorders. **Methods:** A search was conducted on scientific databases such as PubMed, Science Direct, and Google Scholar using the keywords "vitamin B6", "sleep", "immune system," and "anxiety disorders." Only articles published in Indonesian or English between 2017-2023 were included. **Result:** The findings of this review suggest that individuals with anxiety disorders experience shorter sleep duration and lower immune function compared to those without anxiety disorders. Previous studies have shown that short sleep duration can increase stress and inflammation in adolescents and adults. Vitamin B6 synthesizes neurotransmitters, which significantly regulate sleep and anxiety symptoms. Additionally, previous research has suggested that vitamin B6 plays a vital role in the immune system by reducing cytokine production and inflammation responses in many signaling pathways. **Conclusion:** This scoping review provides preliminary evidence of the association between vitamin B6, sleep duration, and immune function, particularly in individuals with anxiety disorders. Further research is required to elucidate the mechanisms involved in this relationship. The findings of this review can support further research on the potential benefits of vitamin B6 for sleep duration and immune function.

**Keywords:** vitamin B6; sleep duration; immune system; anxiety disorders

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## INTRODUCTION

Anxiety disorders are common mental health disorders characterized by excessive fear, anxiety, or avoidance of perceived threats [1]. The global prevalence of anxiety disorders has risen by up to 25% since the onset of the COVID-19 pandemic [2]. These disorders significantly burden individuals and society, decreasing productivity and quality of life. According to Disability Adjusted Life Year (DALY) analysis, anxiety disorders globally account for about 28.68 years of lost productivity due to disability. The Health Ministry of

Indonesia also stated that anxiety disorders in Indonesia rank second in terms of prevalence among mental disorders, following depressive disorders [3]. Another study showed that during the COVID-19 pandemic, 20.2% of Indonesians experienced significant anxiety symptoms [4].

Anxiety disorders can have adverse effects on sleep duration and immune function. Individuals with mental disorders more commonly experience insomnia compared to healthy individuals, especially among female sufferers. A previous study found that 59% of women with anxiety disorders experience insomnia,

and 74.2% of men with eating disorders also experience insomnia [5]. Some article reviews reported that the prevalence of people sleeping less than 6 hours ranges from 22.1% to 53.3%, based on previous cohort studies [6-8]. Another study also showed that 52.57% of the global population affected by the COVID-19 pandemic experienced insomnia [9].

Moreover, stress has been identified as a trigger for inflammation due to the body's maladaptive response to extreme or chronic stress [10]. Previous research has indicated that individuals diagnosed with anxiety disorders or mental health disorders related to stress are associated with increased C-reactive protein (CRP) levels. Specifically, individuals diagnosed with "other anxiety disorders" are 1.1 times more likely to have elevated CRP compared to those without anxiety disorders [11]. Also, people with generalized anxiety disorder (GAD) are 1.2 times more likely than people in the control group to have higher levels of interleukin-6 (IL-6) and 1.5 times more likely to have higher levels of soluble urokinase plasminogen activator receptor (suPAR) [12].

Vitamin B6 is one of the nutrients the body requires, circulating through pyridoxine, pyridoxal, and pyridoxamine. It is a water-soluble nutrient that plays various vital roles in the body, including enhancing sleep quality, reducing anxiety symptoms, and strengthening the immune system. Previous research has looked extensively at the advantages of vitamin B6. However, a review that consolidates evidence from a scoping review is yet to be conducted to address the following inquiries: a) What evidence exists regarding the role of vitamin B6 in improving sleep duration and immune function among individuals with anxiety disorders? b) Is there a correlation between vitamin B6 intake and anxiety symptoms in individuals with anxiety disorders? c) How does vitamin B6 affect sleep duration and immune function in individuals with anxiety disorders?

## METHODS

This scoping review follows the PRISMA Extension for Scoping Review framework guidelines developed by the Joanna Briggs Institute [13,14]. The PRISMA guidelines can be accessed at the [link](#), and an explanation regarding these guidelines is provided in the article in the [ACP journal](#).

### Eligibility criteria

The articles included in this scoping review are scientific articles that mention the research results about the relationship or effect of vitamin B6 on sleep regulation, the immune system, and anxiety symptoms. Other inclusions are articles published between 2017

and 2023, written in English or Indonesian, and not review articles. Articles that involved humans or animals as subjects are included to assess the extent of vitamin B6 research.

### Resources

This article uses Medical Subject Headings (MeSH) to determine suitable and topic-specific keywords. These keywords are then combined to form English queries entered into the Science Direct, PubMed, and Google Scholar databases. English and Indonesian queries are used in the Google Scholar database. Additionally, researchers conducted supplementary searches using the Google search engine. The article search process was conducted on May 3, 2023.

### Search

The search process combines several MeSH keywords such as "vitamin B6," "sleep," "immune system," and "anxiety disorders" to be entered into various search engines, with restrictions on the year of publication, language, and excluding review articles.

### Selection of sources of evidence

All findings are entered into Mendeley, an application that assists in the article selection process. During the screening process, Mendeley helps identify and remove duplicate articles. Subsequently, article selection is performed manually to exclude articles not meeting the inclusion criteria.

### Data charting process

The data mapping process is carried out to classify findings into subsections that align with the objectives of composing a scoping review article. The data mapping process is conducted through collaborative discussions with the reviewing team to determine titles for each subsection, which can subsequently address the questions within this scoping review article.

### Data items

Classifying the articles' characteristics was the basis for all subsequent findings. Article characteristics include author names, article publication year, research design, variables, objectives, quantity and characteristics of the sample, research location, intervention groups (if applicable), intervention duration (if applicable), and research outcomes.

### Synthesis of result

The entire article selection process is presented in a chart depicting the number of articles initially found and the number of articles that underwent reduction due to not meeting inclusion criteria. The collection of articles that have undergone the selection and mapping process will then be presented in a table.

## RESULTS

Figure 1 shows the selection process of the articles. Total of 2,260 research articles. The screening process removed 86 duplicate articles, resulting in 2,174 articles. At the eligibility stage, 2,148 articles were excluded due to the articles not being written in English or Indonesian, not mentioning vitamin B6, or not being scientific articles. Subsequently, 27 research articles underwent a full-text review, of which 17 were excluded: 9 were unrelated to the scoping review topic, and the remaining 8 were review articles. 10 articles remain for further discussion in the scoping review.

Table 1 provides a summary of each study. The ten articles that passed the selection process were eight experimental and two cross-sectional. 1 of 8 experimental studies was carried out on experimental animals, and the rest were carried out on humans. All articles that passed the selection process were divided into three: the effectiveness of vitamin B6 on sleep, the immune system, and anxiety disorders.

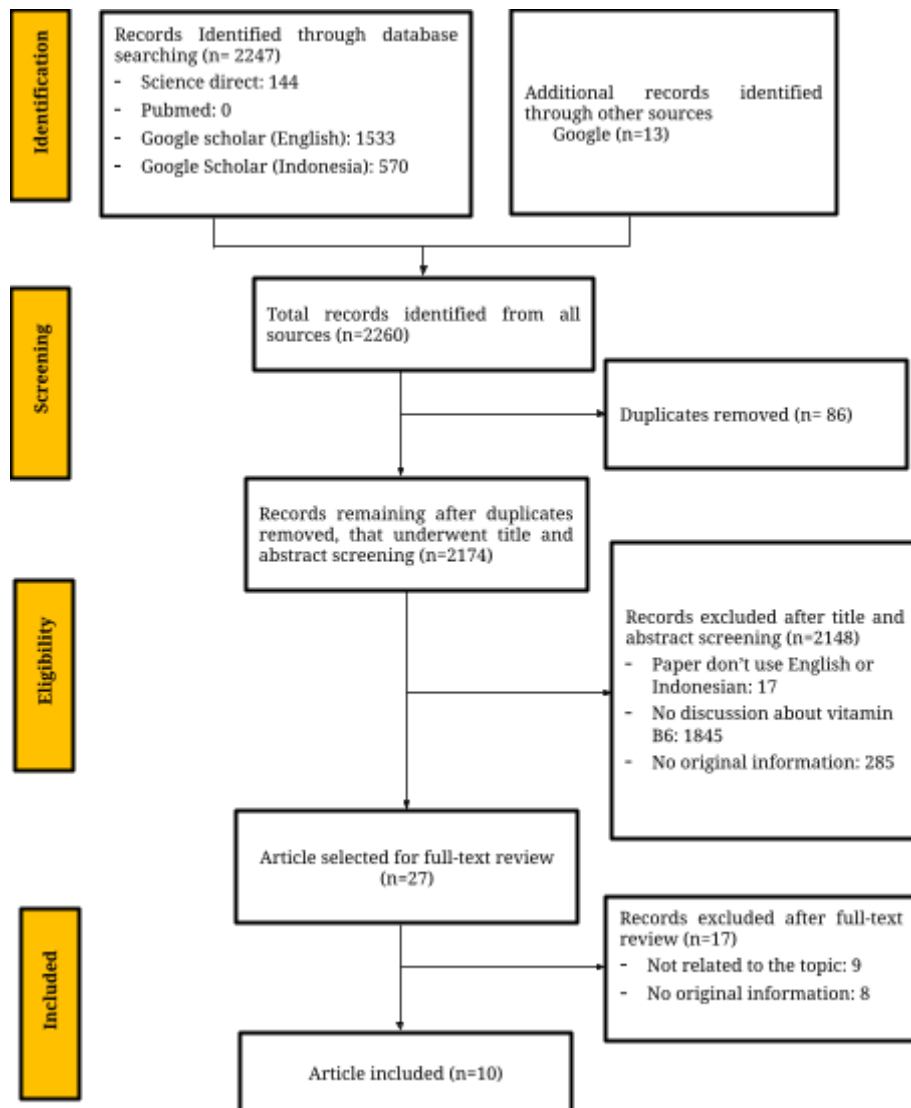


Figure 1. PRISMA Flow Diagram

**Tabel 1. Data characteristics**

*The effectiveness of vitamin B6 on sleep regulation*

Author, design and variable	Aim	Samples, place, and intervention	Results
<p>Author: Aspy <i>et al.</i>, 2018                      Design: Randomized, double-blind, placebo-controlled trial                      Variable:</p> <ul style="list-style-type: none"> <li>• Independent: Vitamin B6 vs Vitamin B complex</li> <li>• Dependent: Dreamin and Sleep</li> </ul>	<p>To analyze the effect of vitamin B6 supplementation on dreaming and sleep, while exploring the possibility of synergistic effects with other B vitamins to enhance dreams.</p>	<p>Samples and place:                      100 participants in University of Adelaide city                      Intervention:</p> <ul style="list-style-type: none"> <li>• Group 1: vitamin B6 (240 mg)</li> <li>• Group 2: vitamin B6 and B complex</li> <li>• Group 3: placebo</li> </ul> <p>Length of Intervention:                      5 days in a row</p>	<p>Vitamin B6 supplementation can significantly increase the number of dreams. However, it doesn't have a significant effect on the vividness, bizarreness, or color of dreams, nor doesn't significantly impact waking hours, sleep quality, or tiredness on waking. In comparison, the B complex group exhibited a decrease in sleep quality and an increase in tiredness on waking compared to the vitamin B6 group.</p>
<p>Author: Lemoine <i>et al.</i>, 2019                      Design: single-center, single-arm, open-label study                      Variable:</p> <ul style="list-style-type: none"> <li>• Independent: melatonin, vitamin B6, medical plant</li> <li>• Dependent: sleep quality, sleep onset latency, total sleep duration, sleep related daytime</li> </ul>	<p>To analyze the effectiveness of a combination of melatonin, vitamin B6, and medicinal plants in patients with moderate to severe insomnia.</p>	<p>Samples and place: 40 participants in Polandia                      Intervention: Participants were asked to take 2 Novanult triple action capsules containing 1 mg melatonin, 0.42 mg vitamin B6, 8.4 mg California poppy extract, 150 mg passionflower extract                      240 mg lemon balm extract                      Length of intervention: 2 weeks</p>	<p>Significant improvements were observed in sleep quality, sleep onset latency, total sleep duration, and sleep-related daytime after 2 weeks.</p>
<p>Author: Ge <i>et al.</i>, 2022; Design: cross-sectional                      Variable:</p> <ul style="list-style-type: none"> <li>• Independent: vitamin B6 levels/Pyridoxal phosphate (PLP)</li> <li>• Dependent: sleep related problems such as sleep quality and sleep duration</li> </ul>	<p>To analyze the relationship between PLP concentration and sleep-related problems (sleep quality and sleep duration).</p>	<p>Samples and place:                      9710 participants assessed sleep quality and 15206 participants assessed sleep duration                      Intervention:                      No intervention</p>	<p>The relationship between variables is only significant in the male group. Serum PLP is negatively associated with the risk of very short, short, and long sleep duration. The average serum PLP is higher in individuals with normal sleep duration. PLP is negatively related to daytime sleepiness, and this relationship only occurs in the male group.</p>
<p>Author: Garcia <i>et al.</i>, 2021                      Design: RCT                      Variables:</p> <ul style="list-style-type: none"> <li>• Independent: poly-gamma-glutamiic acid (gamma-PGA) dan vitamin B6</li> <li>• Dependent: sleep status</li> </ul>	<p>To analyze the effectiveness of gamma PGA and vitamin B6 on sleep duration and sleep quality</p>	<p>Sample and place:                      47 adults in South Korea                      Intervention:</p> <ul style="list-style-type: none"> <li>• Group 1: gamma PGA (600 mg)</li> <li>• Group 2: vitamin B6 (100 mg)</li> <li>• Group 3: gamma PGA (60 mg) and vitamin B6 (100 mg)</li> </ul> <p>Length of intervention:                      12 weeks</p>	<p>Gamma PGA and vitamin B6 can increase sleep duration and sleep quality</p>

*The effectiveness of vitamin B6 on the immune system*

Author, design and variable	Aim	Samples, place, and intervention	Results
<p>Author: Du <i>et al.</i>, 2020                      Design: In vivo and In vitro experiment</p>	<p>To analyze the impact of vitamin B6 on excessive inflammation through the</p>	<p>Sample and place:                      C57BL/6 mice 6-8 weeks, Guangzhou China</p>	<p>Vitamin B6 can suppress proinflammatory cytokines, slow cell death, and increasing the</p>

Variable: <ul style="list-style-type: none"> <li>Independent: vitamin B6 supplementation</li> <li>Dependent: pro inflammatory cytokine, sphingosine-1-phosphate lyase (SPL) enzym, sphingosine-1-phosphate (S1P).</li> </ul>	S1P and SPL-dependent mechanism in macrophages.	Intervention: <ul style="list-style-type: none"> <li>Group 1: Vitamin B6 supplementation</li> <li>Group 2: placebo</li> </ul> Length of intervention: 30 days	survival rate in response to inflammation. It stops proinflammatory cytokines from working through different signaling pathways and lowers the buildup of S1P by making SPL work harder.
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*The effectiveness of vitamin B6 against anxiety symptoms*

Author, design, and variable	Aim	Samples, places, and intervention	Results
Author: Field <i>et al.</i> , 2022 Design: RCT Variable: Independent: vitamin B6 supplementation, Dependent: anxiety level and visual surround suppression	To assess the effect of high doses of vitamins B6 and B12 compared to placebo on behavior.	Sample and place: 478 young adults in UK Intervention: Group 1: vitamin B6 (100 µg/day); Group 2: Vitamin B12; Group: placebo Length of intervention: 5 years	Vitamin B6 supplementation reduces anxiety symptoms and shows a tendency to decrease depression while also increasing surround suppression.
Author: Ghavidel <i>et al.</i> , 2022 Design: randomized double blind clinical trial Variable: <ul style="list-style-type: none"> <li>Independent: vitamin B6 supplementation</li> <li>Dependent: pain, disease severity, psychological profile</li> </ul>	To evaluate the impact of administering 80 mg of vitamin B6/day on pain, disease severity, and psychological profile.	Sample and place: 90 patients of fibromyalgia, Iran Intervention: Group 1: vitamin B6 (80 mg/day); Group 2: placebo Length of intervention: 6 weeks	There were improvements in disease severity, pain, and psychological outcomes observed in the treatment and placebo groups, but no significant differences were found between the two groups.
Author: Tsujita <i>et al.</i> , 2019 Design: RCT Variable: <ul style="list-style-type: none"> <li>Independent: Tryptophan (TRP), Vitamin B6, and Nicotinamide-containing supplement to be consumed between meals</li> <li>Dependent: mood and Autonomic Nervous System (ANS) activity</li> </ul>	To analyze the impact of TRP, vitamin B6, and nicotinamide-containing supplements taken between meals on mood and ANS activity.	Sample and place: 150 depressive young adults in Kyoto University divided into two groups based on Center for Epidemiologic Studies Depression Scale (CES-D): mild to moderate vs. severe depressive symptoms Intervention: Group 1: TRP (100 mg), vitamin B6 (4 mg) and nicotinamide (4 mg) containing supplement; Group 2: placebo (270 mg of lactate) Length of intervention: 7 days	There was an improvement in CESD score in both intervention group but only on the severe depression. group. Profile of Mood States (POMS) score was reduced in Group 1 intervention on the severe depression group.
Author: Pouteau <i>et al.</i> , 2018 Design: randomized, single-blind clinical trial Variable: <ul style="list-style-type: none"> <li>Independent: magnesium and vitamin B6</li> <li>Dependent: stress level</li> </ul>	To compare the effectiveness of a combination of magnesium and vitamin B6 versus magnesium alone on stressed adults with suboptimal serum magnesium concentrations using Depression Anxiety Stress Scale (DASS-42).	Sample and place: 264 stressed, healthy adults with low magnesium concentration Intervention: <ul style="list-style-type: none"> <li>Group 1: Mg (300 mg) + vitamin B6 (30 mg)</li> <li>Group 2: Mg (300 mg)</li> </ul> Length of intervention: 4 and 8 weeks	There was an improvement in stress levels in both treatment groups after 8 weeks, but there was no significant difference between the two treatment groups.
Author: Richards <i>et al.</i> , 2020 Design: cross-sectional Variable: Independent: vitamin B6, Dependent: depression levels	To examine the relationship between vitamin B6 levels and levels of depression.	Sample and place: 51 recipients of depot-medroxyprogesterone acetate (DMPA) hormonal contraception for 2 years in Indonesia. Intervention: No intervention	There is no significant relationship between vitamin B6 levels and depression levels

## DISCUSSION

Anxiety and sleep disorders have a two-way relationship that affects each other. Anxiety symptoms such as restlessness and fear can disrupt sleep by causing increased alertness and shorter sleep duration. Conversely, sleep disturbances can lead to unusual coping behaviors due to a failure to adapt to sleep disturbances. Prior research stated that anxiety and sleep disorders are directly or indirectly mediated by several neuromodulators, such as norepinephrine, serotonin, histamine, acetylcholine, dopamine, orexin, gamma-aminobutyric acid (GABA), the hypothalamic-pituitary-adrenal (HPA) axis, and corticotropin-releasing factor (CRF) [25, 26].

Previous research shows a relationship between anxiety disorders and immune function [27–30]. A previous study discovered that people who cannot handle stress, whether it is physical, psychosocial, or acute, can develop mental illnesses like depression, anxiety, or post-traumatic stress disorder (PTSD). This is because stress makes the body produce more proinflammatory cytokines and affects the immune system [10]. Another study stated that social stressors can disrupt the blood-brain barrier, thereby increasing the brain's inflammatory modulator, interleukin-6 (IL-6), and affecting attitudes and cognition [31].

### Role of Vitamin B6

Vitamin B6 is a coenzyme involved in synthesizing melatonin, a hormone promoting sleepiness and onset [17, 32]. Additionally, vitamin B6 synthesizes serotonin, serving as a melatonin precursor. Melatonin also helps regulate circadian rhythms, governing wakefulness and sleep patterns. Moreover, vitamin B6 plays an important coenzyme in synthesizing GABA, which regulates sleep and wakefulness through circadian rhythms. GABA responds to light stimulation and inhibits the release of melatonin in the morning, promoting alertness and wakefulness [32, 33]. Furthermore, GABA also regulates REM and NREM sleep stages, which can impact overall sleep duration [34–36].

Previous research has suggested a connection between sleep disturbances and increased levels of proinflammatory cytokines [37, 38]. Another study mentioned that vitamin B6 can potentially influence sleep duration by reducing inflammation in the body [17, 39]. PLP (pyridoxal phosphate) is transported to the site of inflammation and regulates PLP-dependent enzymes and metabolic systems. Vitamin B6 or PLP can function as antioxidants, directly scavenging free radicals or participating in the glutathione-dependent antioxidant system, thereby protecting the body from oxidative stress.

Studies have explored the mechanisms by which vitamin B6 inhibits proinflammatory cytokines through *in vivo* and *in vitro* investigations [19]. Vitamin B6 has been shown to reduce the production of IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, which are cytokines that cause inflammation when low amounts of lipopolysaccharide (LPS) are present in the body. Also, vitamin B6 has effectively reduced inflammation in mice injected with high doses of LPS, stopping too much inflammation and endotoxic shock. Vitamin B6 can also help reduce inflammation. It stops NF- $\kappa$ B and MAPK signaling and lowers IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and iNOS levels at the mRNA level.

Besides, vitamin B6 can also alleviate inflammation through the sphingosine 1-phosphate (S1P) and sphingosine 1-phosphate lyase (SPL) mechanisms. S1P is a sphingolipid metabolite compound that is very important for controlling the immune system in the body. It activates NF- $\kappa$ B, MAPK, and other cell signaling pathways, such as those in macrophages [40]. Additionally, former research stated that increased levels of S1P are associated with heightened inflammation, which can lead to chronic inflammatory diseases such as inflammatory bowel disease (IBD) and multiple sclerosis [41]. The results of another study showed that SPL is an enzyme that depends on PLP and breaks down S1P into hexadecenal and phosphoethanolamine. SPL also controls the flow of S1P when everything is normal [42]. PLP intervention led to a significant increase in SPL activity and a significant decrease in S1P levels in the PLP treatment group [19]. The PLP group also showed that the production of the proinflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and NO was slowed down.

This scoping review revealed the role of vitamin B6 on anxiety disorder through neurotransmitter serotonin and GABA mechanisms [34, 43]. In the pathophysiology of anxiety disorders, fear stimuli enter the brain and are processed in the thalamus. Subsequently, interpretation and evaluation occur in the limbic system and medial prefrontal cortex. When the stimuli are interpreted as fear or anxiety, the hypothalamus and brainstem trigger a physical anxious response. Furthermore, an imbalance between excitatory and inhibitory neurons can also contribute to the development of anxiety disorders. Serotonin, acting as an excitatory neurotransmitter circulating in the brain, functions to reduce physical anxiety responses and process anxiety in the limbic system, particularly in the amygdala and hippocampus [34,44]. GABA is an inhibitory neurotransmitter that stops anxiety signals from getting to the amygdala. This shows how important it is to balance excited and inhibited neurons [45].

Decreased anxiety symptoms after administering vitamin B6 supplementation for five years [20]. This

effect is believed to be attributed to the involvement of vitamin B6 in the synthesis process of the neurotransmitter GABA. It is made from glutamate as a starting material with the help of glutamic acid decarboxylase enzymes and pyridoxal phosphate (PLP) as a coenzyme [32]. Vitamin B6 supplementation can alleviate symptoms of depression [22]. The theory also explains that vitamin B6 is vital as an enzyme cofactor in serotonin synthesis [32]. These are the enzymes that change tryptophan amino acid into serotonin. They do this with the help of pyridoxal phosphate (PLP), which works with the enzymes.

## CONCLUSION

The ten selected articles indicate that vitamin B6 has the potential to reduce anxiety symptoms significantly, improve sleep duration, and alleviate inflammation. Also, vitamin B6 shows promise for reducing anxiety symptoms and improving sleep duration by reducing inflammation in the body.

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