

# *The relationship between B vitamin supplementation and pruritus incidence in adults a systematic review and meta-analysis*

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**Abstract:** We aim to assess the prevalence of pruritus or itching in adult patients taking Vitamin B supplementation. The method applied in this paper is a systemic search was conducted from electronic databases (PubMed/Medline, Cochrane Library, and Google Scholar) from inception to 30th October 2023. All statistical analyses were conducted in Review Manager 5.4.1. Studies meeting inclusion criteria were selected. A random-effect model was used when heterogeneity was seen to pool the studies, and the result was reported in prevalence and their corresponding 95% confidence interval (CI). Five studies (three randomized controlled trials and two observational studies) were included in our analysis. We analyzed the prevalence of vitamin B3 (niacin) and B12 (cyanocobalamin). There was a statistically significant prevalence of pruritus in participants treated with niacin (prevalence = 18% (9%, 26%);  $p < 0.0001$ ;  $I^2 = 98\%$ ) and cyanocobalamin (prevalence = 46% (32%, 60%);  $p < 0.00001$ ;  $I^2 = \text{Not applicable}$ ). Hence, the overall prevalence was (prevalence = 22% (14%, 31%);  $p < 0.00001$ ;  $I^2 = 98\%$ ). Our study showed that patients taking vitamin B3 supplementation and B12 supplementation had 18% and 46%, respectively, prevalence of pruritus. Overall, there was a 22% prevalence.

## 1. Introduction

Niacin, also known as vitamin B3, is available in two variants: nicotinamide or nicotinic acid (NA). However, Niacin is an important medication used to manage dyslipidemia; a condition characterized by abnormal levels of lipids in the blood<sup>[1]</sup>. It has been utilized for over 50 years and is recognized as being one of the first medications proven to reduce CVD events and mortality rates<sup>[2]</sup>. Niacin offers multiple clinical benefits; however, its most beneficial effect is increasing HDL-C (high-density lipoprotein cholesterol)<sup>[3]</sup>. This rise in HDL-C helps protect against CVD risk factors such as atherosclerosis, coronary artery disease, stroke, and heart attack<sup>[2][3]</sup>. Additionally, niacin reduces low-density lipoprotein cholesterol (LDL-C) levels while raising triglycerides which can further help protect cardiovascular health<sup>[3]</sup>. This makes niacin an essential part of many treatment plans for those living with high cholesterol or heart health issues.

While nicotinic acid provides various positive effects on the lipid profile, its most remarkable and valuable property is its ability to elevate the amount and effectiveness of HDL-C levels. Furthermore,

the liver is responsible for synthesizing triglycerides, very low-density lipoproteins (VLDL), Lipoprotein (a), and Low-Density Lipoprotein Cholesterol (LDL-C)<sup>[4]</sup>. NA gets attached to and antagonizes the hydroxycarboxylic acid-2 receptor of hepatocytes. This inhibits a hepatic microsomal enzyme (diacylglycerol acyltransferase 2) that is necessary for the final step in the production of those lipids. NA not only reduces beta-lipoproteins that are involved in the formation of LDL-C but also reduces the atherogenic small dense LDL-C particles<sup>[5]</sup>.

Nicotinic acid is generally well-tolerated, but some side effects may occur. These side effects are typically reversible and can be minimized or eliminated by adjusting the dosage or administration method<sup>[6]</sup>. The recommended maintenance dose corresponds to 1-2 g/day. However, the predominant side effect of NA includes flushing which occurs mostly due to immediate-release nicotinic acid (IRNA) and the initial doses of extended-release nicotinic acid (ERNA)<sup>[5]</sup>. Flushing occurs when the body releases prostaglandin D2 and prostaglandin E2 from cells called Langerhans cells, which is found in the skin, as well as macrophages<sup>[7]</sup>.

The management of niacin-induced skin flushing includes aspirin or non-steroidal anti-inflammatory drugs before niacin treatment, using extended-release niacin formulations, and decreasing the niacin dosage<sup>[8]</sup>. Studies have demonstrated that aspirin treatment can alleviate the symptoms of flushing and tingling linked to niacin usage<sup>[9]</sup>.

Atopic dermatitis, also called eczema, is a long-lasting, itchy inflammatory skin disorder that commonly impacts the face, neck, arms, and legs but typically does not affect the palms and soles<sup>[10]</sup>. The inflammatory process in atopic dermatitis is complex but it is believed that activated T lymphocytes circulating in the bloodstream and residing in the skin contribute to the elevated production of inflammatory cytokines, including interleukin (IL)-1a, IL-2, IL-6, and interferon (IFN)-c<sup>[11]</sup>. Recent research indicates that the inflammation in atopic dermatitis doesn't just stem from T lymphocytes but also involves mast cells, eosinophils, and monocytes. This suggests a more complex involvement of various immune cells in the pathogenesis of atopic dermatitis, highlighting the multifaceted nature of the condition and possibly creating new opportunities for treatment<sup>[12]</sup>. Vitamin B12 or cyanocobalamin plays an important role in the body's immune system. It scavenges nitric oxide (NO) molecules, which are produced by inflammation and can inhibit normal cellular function<sup>[13]</sup>. Recent studies have shown that vitamin B12 (cyanocobalamin) could reduce the production of cytokines by T lymphocytes. Methyl-cyanocobalamin was found to inhibit the synthesis of IL-6 induced by phytohemagglutinin or concanavalin by 60–70%. Additionally, it enhanced cellular proliferation and the activity of T-helper (Th) cells, which is crucial for immunoglobulin synthesis of B cells by pokeweed mitogen. These findings suggest that the inhibition of cytokine production could be a key factor in the therapeutic effectiveness of vitamin B12 in treating atopic dermatitis<sup>[14]</sup>.

In this meta-analysis we aim to investigate the association between vitamin B supplementation and pruritis in adults, focusing on the comparative effects of niacin and cyanocobalamin on the incidence of pruritis.

## 2. Methods

### 2.1. Search strategy and databases

The Systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>[15]</sup>. An electronic search was done using Pubmed/Medline, Cochrane Trial Register, and Google Scholar from their inception to 30th October 2023. The following search string was used: (vitamin B1 supplementation OR B2 OR B3 OR B6 OR B5 OR B7 OR B9 OR B12 OR thiamine OR niacin OR riboflavin OR pyridoxine OR pantothenic acid OR biotin OR cobalamin OR folate OR folic acid) AND (pruritus OR itching) AND (adults OR

grownup OR person). We additionally searched the referenced articles of previously published meta-analyses, cohort studies, and review articles to identify any relevant studies.

## 2.2. Study selection criteria

Studies were selected if they followed our PECOS: P (Patients): Adult population taking vitamin B supplementation; E (Exposure): Pruritus; C (Control): None; O (Outcomes): prevalence of pruritus in the adult population taking vitamin B supplementation; S (Studies): Observational studies and Randomized Controlled Trials.

## 2.3. Data extraction and Quality assessment

Two reviewers screened the electronic databases. Studies were exported to EndNote Reference Library version 20.0.1 (Clarivate Analytics, London, UK) and duplicate articles were screened and removed. Two investigators entered the data extracted from the selected studies on a computer spreadsheet.

Quality assessment and bias assessment were done using the New Ottawa Scale (NOS) score for observational studies and the Cochrane Collaboration Tool for clinical trials. NOS score of 1-5 was considered a high risk for bias, 6-7 was moderate, and a score >7 was considered a low risk for bias.

Seven domains were assessed by The Cochrane Collaboration's tool: adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and free of other bias. The individual domains and overall risk-of-bias judgment were expressed on one of three levels: high risk of bias, unclear risk of bias, and low risk of bias. Based on these factors, the overall quality of evidence was deemed as high, moderate, or low risk of bias.

## 2.4. Statistical Analysis

Review Manager (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020) was used for all statistical analyses. The data from studies were pooled using a random-effects model when heterogeneity was seen. Analysis of results was done by calculating the inverse variance (IV) with respective 95% confidence intervals (CI). The chi-square test was performed to assess any differences between the subgroups. Sensitivity analysis was done to see if any individual study was driving the results and to explore reasons for high heterogeneity. As per the Cochrane Handbook, the scale for heterogeneity was considered as follows: I<sup>2</sup> = 25–60% – moderate; 50–90% – substantial; 75–100% – considerable heterogeneity, and P < 0.1 indicated significant heterogeneity<sup>[16]</sup>. A P < 0.05 was considered significant for all analyses.

Prevalence was calculated through raw data. This along with other extracted information was used to find standard errors using the formula:

$$SE = \sqrt{\frac{p \times (1 - p)}{n}}$$

Where "p" was the prevalence and "n" was the number of patients taking Vitamin B supplementation. The prevalence and standard error of each study were then input into the Review manager through the inverse variance method to compute pooled prevalence along with a 95% confidence interval.

Risk factors were analyzed qualitatively as appropriate data was not available to analyze this outcome.

### 3. Results

#### 3.1. Literature Search Results

The initial literature search of this study using three electronic databases showed 338 potential studies. After removing duplicates, 277 articles remained. 93 articles were selected for full article reading. 5 studies were selected for our article. A Prisma flow chart (Figure 1) is also provided.

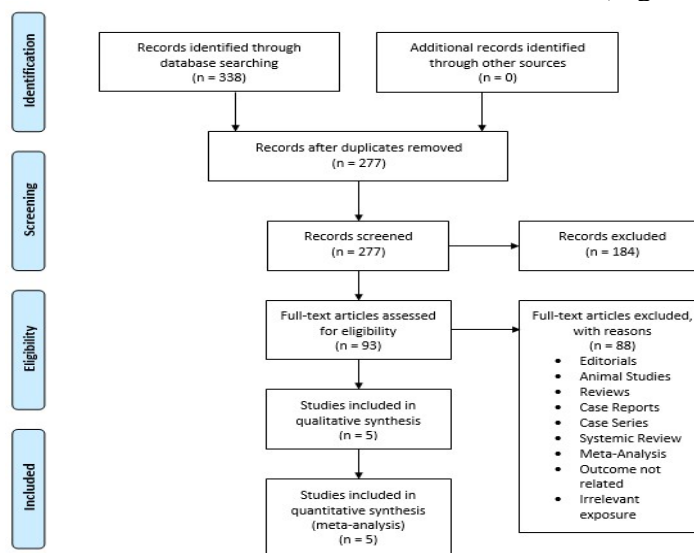


Figure 1: PRISMA flow diagram.

#### 3.2. Study Characteristics

Table 1 provides the demographic and clinical data of the selected studies<sup>[17][18][19][20][21]</sup>. The analysis included three published RCTs and two observational studies, with a patient population of 2090. The average age of the patients in these studies was 45.4 years (Table 1).

Table 1: Baseline Characteristics of the included studies.

Name	Study design	Country	Total Patients (n)	Female (%)	Mean Age (years)	Type of Vitamin B used	Net risk of bias
<b>Birjmohun et al. (2007)</b>	Prospective Multicenter Observational Study	Netherland	480	20.7	58.4	Niacin	Low risk
<b>Kashyap et al. (2002)</b>	Open-label clinical trial	USA	814	36	59	Niacin	Low risk
<b>Norquist et al. (2007)</b>	Randomized placebo-controlled clinical trial	USA	142	58	48.8	Niacin	Low risk
<b>Mills et al. (2003)</b>	Randomized placebo-controlled clinical trial	Canada	33	26	27.3	Niacin	Low risk
<b>Stucker et al. (2004)</b>	Randomized placebo-controlled clinical trial	Germany	49	67.34	33.6	Cyanocobalamin	Low risk

#### 3.3. Publication Bias and Quality Assessment

Publication bias cannot be assessed since the number of included studies was less than 10. All studies had a low risk of bias (Table 2, 3).

Table 2: Quality assessment of randomized controlled trials using the Cochrane collaboration tool.

	Sequence generation	Allocation concealment	Blinding of participants, etc.	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Net risk
Norquist et al., 2007	Low	Low	Low	Low	Low	Low	Unclear	Low
Mills et al., 2003	Low	Low	Low	Low	Low	Low	Unclean	Low
Stucker et al., 2004	Low	Low	Low	Low	Low	Low	Low	Low

Table 3: Quality assessment of observational studies using the New Ottawa Scale.

Study	Selection				Comparability	Outcome			Total Score
	Representation of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at the start of this study		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Birjmohun et al., 2007	1	1	1	1	1	1	1	1	8
Kashyap et al., 2001	1	1	1	1	2	1	1	1	9

### 3.4. Results of meta-analysis

Five studies were selected to outline the incidence of pruritis in adults supplemented with vitamin B<sup>[17][18][19][20][21]</sup>. The studies were split into two subgroups; one was treated with niacin and the other was given cyanocobalamin (Figure 2).

The niacin subgroup included four studies with a patient population of 2041. Two studies recruited patients with a high risk of cardiovascular events<sup>[17][18]</sup>, one study had patients previously exposed to niacin<sup>[19]</sup>, and one included healthy volunteers<sup>[20]</sup>. There was a statistically significant prevalence of pruritis in participants treated with niacin (prevalence = 18% (9%, 26%);  $p < 0.0001$ ;  $I^2 = 98\%$ ) (Figure 2). The cyanocobalamin subgroup included one study with a patient population of 49<sup>[21]</sup>. In this randomized trial, patients with atopic dermatitis were supplemented with either topical vitamin B12 or placebo. Results of the meta-analysis showed a significant incidence of pruritis with the use of topical cyanocobalamin (prevalence = 46% (32%, 60%);  $p < 0.00001$ ;  $I^2 = \text{Not applicable}$ ). The overall prevalence of pruritis in patients subjected to vitamin B was statistically significant (prevalence = 22% (14%, 31%);  $p < 0.00001$ ;  $I^2 = 98\%$ ).

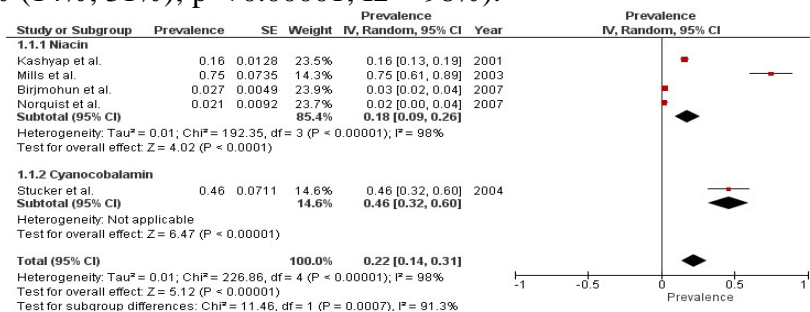


Figure 2: Forest plot illustrating the prevalence of pruritis secondary to niacin or cyanocobalamin.

## 4. Discussion

The meta-analysis conducted on five selected studies assessing the incidence of pruritis in adults

supplemented with vitamin B yielded important insights into two distinct subgroups: niacin and cyanocobalamin.

In four studies involving a large sample size of 2041 participants, a diverse group of individuals was included in the niacin subgroup<sup>[17][18][19][20]</sup>. This group encompassed individuals at high risk for cardiovascular events, those with prior niacin exposure, and even healthy volunteers. The findings revealed a statistically significant prevalence of pruritus among niacin-treated participants, with a remarkable prevalence rate of 18% (confidence interval: 9% to 26%). The observed statistical significance, along with a high I2 value of 98%, indicates substantial heterogeneity among the studies.

Niacin-induced cutaneous flushing, which includes redness, warmth, tingling, or itching in the skin of patients taking this therapy can significantly impact their acceptance or willingness to continue with it<sup>[8]</sup>. Researchers are continually developing new products intending to optimize and improve upon current niacin therapies in terms of their flushing profiles<sup>[22]</sup>. However, a study by Norquist 2007 et al. collected data through the Flushing Symptom Questionnaire (FSQ), According to the study, a significant number of patients who were treated initially with niacin or switched from placebo to niacin during later phases showed signs of facial flushing<sup>[19]</sup>. Pruritus, or itching, is a frequently reported side effect of niacin therapy, along with other side effects such as skin flushing, headache, and gastrointestinal problems<sup>[5]</sup>. Recent advancements in niacin therapy, including extended-release (ER) niacin formulations and prostaglandin inhibitors, have demonstrated reduced flushing and improved patient tolerability to niacin therapy<sup>[22]</sup>. According to a study by Davidson et al., Extended-release (ER) niacin formulations gradually release niacin into the bloodstream over time, minimizing the intensity and frequency of flushing<sup>[8]</sup>. However, prostaglandin inhibitors have been studied as a potential means for reducing the skin flushing response to niacin, offering a promising approach to addressing this side effect<sup>[23][24]</sup>.

Based on the results of our study, healthcare providers should initiate niacin treatment with low-dose or time-released formulations to assess tolerance. Although clinicians are typically knowledgeable about these approaches to mitigate niacin's side effects, individuals purchasing immediate-release niacin over the counter (OTC) may lack awareness of how to prevent these adverse reactions.

The cyanocobalamin subgroup, which comprised just one study with 49 participants, was distinct from the niacin subgroup due to its focus on individuals with atopic dermatitis. The randomized trial compared the effects of topical vitamin B12 to those of a placebo<sup>[21]</sup>. The meta-analysis findings showed a remarkably high occurrence of itching when using topical cyanocobalamin, with a prevalence rate of 46%. Although there were few studies in this category, the strong effect size observed raises interesting inquiries about the possible link between cyanocobalamin supplementation and itching in people with atopic dermatitis. Topical cyanocobalamin, or vitamin B12, has also been shown to lead to skin irritations, like itching, burning, and redness, in some patients at the application site<sup>[25]</sup>. However, a study by Stucker et al. suggests topical vitamin B12 as a new therapeutic approach for Atopic Dermatitis, and the results indicate that there is significant superiority of Vitamin B12 cream when compared to placebo in reducing the extent and severity of atopic dermatitis<sup>[21]</sup>. On the other side, the efficacy of oral vitamin B12 supplementation in managing atopic dermatitis is still unknown, and the potential correlation between blood vitamin B12 levels and atopic dermatitis severity has not been investigated<sup>[26]</sup>. A case study of an 18-year-old male with severe refractory atopic dermatitis requiring continuous topical steroid therapy and 5-6 oral steroid trials per year to maintain control revealed a correlation between Vitamin B12 blood levels and atopic dermatitis severity. Moreover, Vitamin B12 oral supplementation resulted in a significant improvement in SCORAD scores<sup>[26]</sup>. While further research is needed to establish a definitive causal link between vitamin B12 deficiency and atopic dermatitis severity or relapse, the case study suggests that vitamin B12 levels should be evaluated in patients with difficult-to-control atopic dermatitis<sup>[26]</sup>. This highlights the potential therapeutic value of vitamin B12 oral supplementation.

In conclusion, this meta-analysis investigated the association between vitamin B supplementation and pruritus in adults, focusing on the comparative effects of niacin and cyanocobalamin. The results

revealed a significant prevalence of pruritus in adults supplemented with vitamin B, with distinct patterns observed between niacin and cyanocobalamin subgroups. Niacin, a well-established medication for managing dyslipidemia, showed a substantial prevalence of pruritus, emphasizing the importance of careful consideration and monitoring when initiating niacin therapy. On the other hand, the cyanocobalamin subgroup, focused on individuals with atopic dermatitis, demonstrated a notably high incidence of itching with topical cyanocobalamin use. While this suggests potential side effects of cyanocobalamin supplementation, it also raises intriguing questions about its role in managing atopic dermatitis. Further research is needed to elucidate the underlying mechanisms and establish the causal link between vitamin B supplementation and pruritus in different populations. Healthcare providers should be mindful of these findings when prescribing vitamin B supplements, and tailoring treatment plans based on individual patient characteristics and potential risk factors for pruritus.

## 5. Limitations

Our study has noteworthy limitations that warrant consideration. Firstly, a paucity of studies per subgroup, especially in the cyanocobalamin category, may limit the generalizability of our findings. The relatively modest total population size included in the analysis could impact the statistical power and precision of our results. Secondly, the presence of high heterogeneity among the niacin studies introduces complexity and potential sources of variation that may affect the reliability of our conclusions. Despite these limitations, the selected articles play a crucial role in our manuscript, providing essential insights into the relationship between vitamin B supplementation and pruritus in adults. While caution is necessary in extrapolating these findings, they contribute substantially to the existing literature and serve as a foundation for future investigations. Addressing these limitations through larger, diverse studies with standardized methodologies would further enhance our understanding of this association.

## 6. Conclusion

Our meta-analysis on vitamin B supplementation and pruritus in adults, while constrained by a limited number of studies, a modest population size, and high heterogeneity, reveals significant insights. Niacin demonstrated a noteworthy prevalence of pruritus, emphasizing careful consideration in clinical settings. The cyanocobalamin subgroup, though data-limited, suggests a potential link with itching, particularly in those with atopic dermatitis. These findings contribute substantially to existing literature, yet caution is advised in generalization. Future well-designed, larger-scale studies are imperative to address these limitations and comprehensively understand the intricate relationship between vitamin B supplementation and pruritus across diverse populations.

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