Cell Host & Microbe

Minireview

Navigating the B vitamins: Dietary diversity, microbial synthesis, and human health

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SUMMARY

B vitamins are intricately involved in various physiological processes vital for health. Their significance is complicated by the heterogeneous landscape of B vitamin distribution in diets and the contributions of the gut microbiota. Here, we delve into the impact of these factors on B vitamins and introduce strategies, with a focus on microbiota-based therapeutic options, to enhance their availability for improved well-being. Additionally, we provide an ecological and evolutionary perspective on the importance of B vitamins to human-microbiota interactions. In the dynamic realms of nutrition and microbiome science, these essential micronutrients continue to play a fundamental role in our understanding of disease development.

INTRODUCTION

Accumulating evidence underscores the crucial role of microbial biosynthesis of different B vitamins in health and disease, such as the pathogenesis and development of various cardiometabolic diseases.[1–3] Recently, B vitamins have also gained recognition as significant contributors to host-microbiota symbiosis.[4] However, the generation and functions of B vitamins are complex. Distinct mechanisms regulate the bacterial biosynthesis of each B vitamin, and the mere capacity of gut microbes to produce them does not ensure an adequate supply to the host. Here, we delve into the pivotal role of B vitamins in human health and disease, while exploring strategies to optimize their availability in the context of diet-microbiota interactions. We aim to explore the interplay between B vitamin metabolism, diet, and the microbiota to inform the development of microbiota-directed therapeutic options that consider these micronutrients.

B GROUP VITAMINS IN HUMAN HEALTH AND DISEASES

B vitamins represent a vital group of micronutrients, serving as indispensable cofactors for numerous enzymes or directly participating in host metabolism, as illustrated in Figure 1A. Their impact extends across a wide spectrum of physiological processes within the human body, encompassing aspects from energy production to immune regulation.[5] The importance of these vitamins for human well-being cannot be overstated. Deficiencies in these micronutrients, each characterized by substantial inter-individual heterogeneity in our circulation[1–3,5,6] (Figure 1B), are often referred to as a form of "hidden hunger," which affects millions of people worldwide.[7]

To elucidate the significance of different B vitamins, it is essential to consider their potential implications in disease. For example, B1 (thiamin) deficiency is intricately linked to conditions such as beriberi and heart failure.[8] In fact, most B vitamins, when insufficient, can contribute to cardiac dysfunction and related metabolic issues due to their vital roles in energy production and metabolic pathways.[8,9] A shortage of B2 (riboflavin), a precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), may lead to multi-system disorders such as type 2 diabetes (T2D) and cancer.[10,11] B3 (niacin), a component of nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), is primarily linked to cognitive decline and T2D,[12,13] whereas deficiencies in B5 (pantothenic acid), despite its role as a fundamental component of coenzyme A (CoA) and acyl-carrier protein, are uncommon.[14] Deficiencies in both B6 (pyridoxine), a vitamer of the biologically active pyridoxal phosphate coenzyme, and B7 (biotin) play pivotal roles in cardiometabolic diseases,[1] with the former condition being associated with a broader spectrum of diseases.[15,16] The intricate relationship between B9 (folate) and B12 (cobalamin) stands out as a significant factor in hepatic disorders, notably contributing to the development of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) when levels are insufficient.[17,18] Strikingly, early-life B12 deficiency may even set the stage for diabetes and obesity later in life.[19]

FACTORS INFLUENCING B VITAMIN STATUS

Diet and gut microbiota are key factors that influence the circulating levels of B vitamins, alongside other factors such as alcohol,[5] medications,[3,20] exercise,[21] and bariatric surgery.[1] By

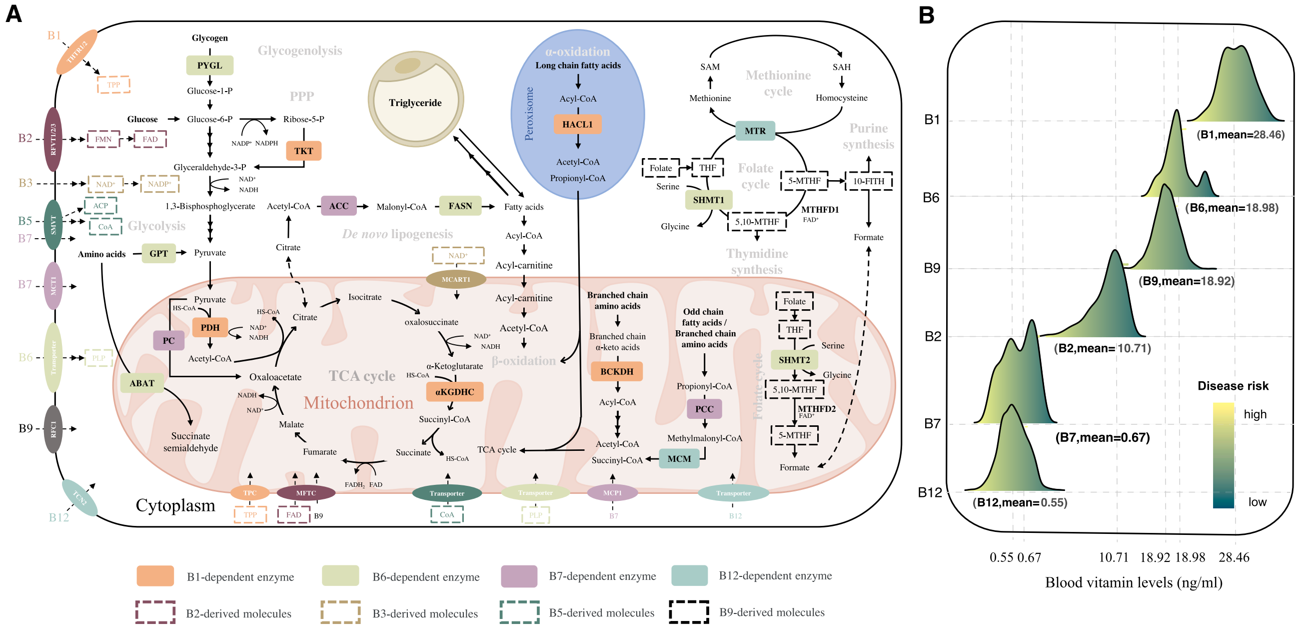

Figure 1. Importance of B group vitamins to health and diseases
(A) Representative enzymes or pathways for each B vitamin.
(B) Ridgeline plot showing inter-individual differences in B vitamins in the circulation (with mean circulating levels of each B vitamin indicated on the x axis) and associated disease risks in cases of deficiency.[1–3,5,6]

delving into the impact of these factors on B vitamin status, we can formulate more precise and tailored approaches to optimize their supply and ultimately promote better health and well-being.

Dietary intake

B vitamins are integral components of the unmapped complexity of our diet,[22] with their presence varying significantly across common food items[23] (Figure 2A; Table S1). Consequently, B vitamins play a pivotal role in distinguishing dietary patterns, such as omnivorous, vegan, and vegetarian diets.[24,25] For instance, omnivores generally acquire higher levels of B12 from meat sources, whereas vegans typically exhibit increased folate intake from vegetables.[25] Suboptimal dietary preferences, which also exhibit disparities in B vitamin content, have been estimated to explain as much as 70% of new T2D cases, according to recent estimations.[26]

In accordance, notable reductions in daily intake of B6, B9, and B12 have been documented by the UK National Diet and Nutrition Survey over the past decade[27] (from 2008 to 2019; Figure 2B). In contrast, daily intake of B1 and B7 saw an increase, likely attributed to food fortification practices for these two vitamins.[5,29] Additionally, the varied health effects associated with popular dietary regimes can be partially attributed to differences in B vitamin profiles. For instance, the well-established metabolic advantages associated with the Mediterranean diet[30] are partly linked to its rich supply of B vitamins.[31] Further estimations have confirmed that following this dietary pattern ensures a more sufficient intake of these micronutrients compared with westernized diets (based on nutritional data from UK[27] and Sweden[2]; Table S2), which are often characterized by energy-dense and highly processed foods and thus elevated risk of metabolic disorders.[32] Of note, a diet resembling that of hunter-gatherers[33] even surpass Mediterranean diet in terms of the B vitamin availability (Table S2) and have been observed with rapid metabolic effects in clinical trials.[34]

Gut microbiota

The gut microbiota possesses remarkable capability to synthesize and utilize B vitamins, thus serving as a significant alternative factor regulating these essential micronutrients. However, this capacity, much like the inter-bacterial variations in relative abundances, exhibits substantial diversity and heterogenicity among common gut microbes[28] (Figure 2C). Approximately 12.5% of gut bacteria, most of which belong to Bacteroides, were predicted to produce all eight B vitamins, according to one estimation.[28] Yet, only a subset of bacteria within the gut have been experimentally validated for their capacity to synthesize B1[35] and B12,[36] and these vitamin producers consequently support non-vitamin-producing microbial counterparts, highlighting the essential role of B vitamins for not only the host as discussed above[5,37] but also the gut microbes themselves.[38,39] As a result, the synthesis and utilization of these vitamins display a mosaic pattern,[40] where B vitamins act as essential mediators of bacteria-bacteria cross-feeding,[41,42] further influencing the gut ecosystem, as illustrated for B12.[43] Another case in point is that commensal-derived B6, for instance, can counteract the enhanced fitness of pathogenic bacterial strains during infection.[44] Conversely, deficiencies in these vitamins can also exert significant effects on gut microbiota composition.[45] It is important to note that, although the gut microbiota has the capacity to produce B vitamins, microbial production does not necessarily guarantee meeting the daily recommended intake levels in humans. The underlying reasons may be 2-fold.

First, estimations suggest that only B3, B6, B9, and B12 synthesized by gut microbes might provide sufficient amounts for

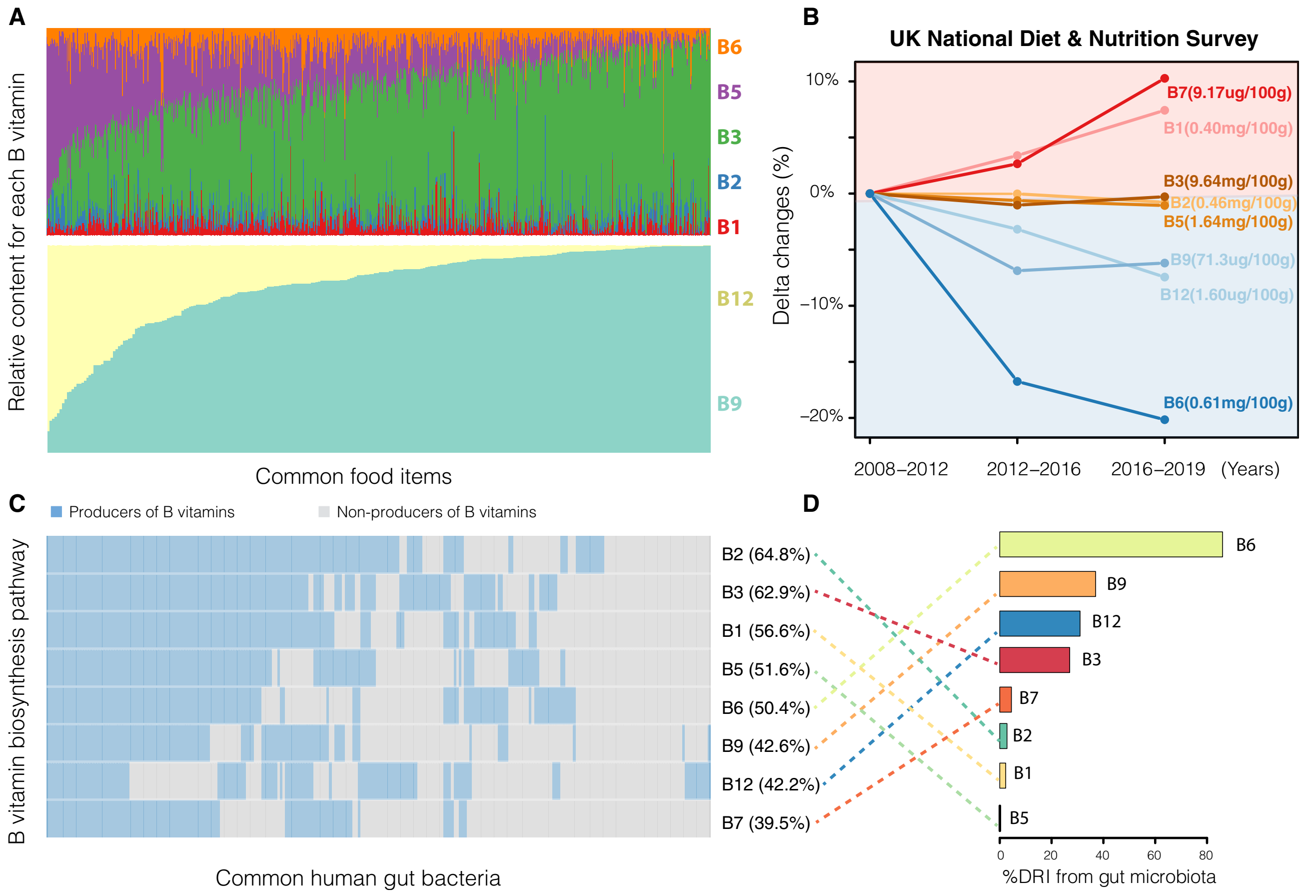

Figure 2. Variability of B vitamins across diets and the gut microbiota

(A) Relative B1 to B6 contents in nearly 800 common food items (upper panel, mg/100 g food) and B9 to B12 in nearly 300 food items (lower panel, µg/100 g food); raw absolute B vitamin levels in each food item were provided in Table S1.[23]

(B) Percent changes in the average daily intake of each B group vitamin from 2008 to 2019 based on UK National Diet and Nutrition Survey.[27]

(C) Predicted B vitamin producers and non-producers based on 256 common human gut bacterial genomes.[28]

(D) Estimated quantities of each B vitamin produced by the gut bacteria relative to the daily recommended intake (DRI) levels for humans.[28]

human utilization[28] (Figure 2D). Intriguingly, although B1, B2, and B5-producing bacteria are common, their prevalence does not guarantee sufficient production. In contrast, less common B6, B9, and B12 producers are likely high vitamin producers that meet human needs (Figures 2C and 2D). The reasons for these apparent discrepancies are multi-factorial. For example, microbial biosynthesis of B7 is an energy-expensive process and mainly occurs when environmental supplies fall short of bacterial requirements.[46] This could, at least partially, explain why there is an increased presence of the B7 biosynthesis pathway in individuals with prediabetes and diabetes.[47] In other words, those observations suggest that there might be an inadequate B7 supply in the gut for both the human host and gut microbes, leading to (1) decreased circulating B7 levels in individuals with T2D[48] and (2) increased B7 biosynthesis from gut bacteria for their own survival. Although it has been demonstrated in mice that the gut microbiota contributes to host B7 status, the effect seems to be more pronounced when mice are fed a chow diet as opposed to a high-fat diet.[1] Whether this increase in microbial B7 production plays physiologically significant roles in humans remains to be explored.

Second, variations in nutrition absorption rates along the gastrointestinal tract may constrain the supply of microbially produced B vitamins to humans, with the small intestine serving as the primary site for these water-soluble molecules.[49] Current evidence suggests that the colon, the primary breeding ground for microbially produced vitamins, may have a minor yet significant role in contributing to B vitamin status.[49] Accumulating studies indicate that physiologic doses of B vitamins, especially B9 and B12, can be absorbed from the colon in humans.[50,51] However, the extent to which microbially produced B vitamins from the colon, as opposed to the small intestine, contribute to circulating B vitamin levels remains largely unknown. This intricate interplay between the gastrointestinal tract, gut microbes, and B vitamins underscores the critical role of the microbiome in shaping the nutritional landscape and overall host health.

Diet-microbiota interactions: An evolutionary and ecological perspective

After bacterial land colonization,[52] these tiny microorganisms established extensive interactions with diverse host organisms.[53,54] Within this intricate web of relationships, the dietary

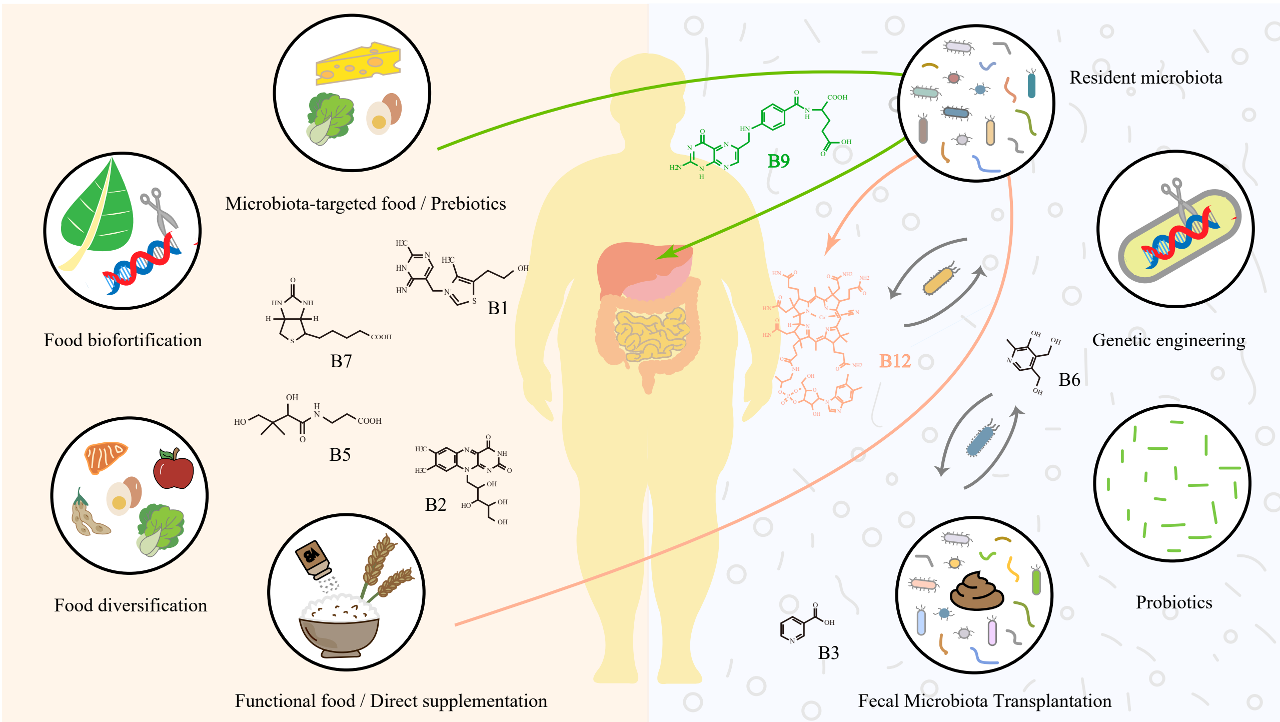

Figure 3. Balancing B vitamins through diet and gut microbiota

B vitamins are indispensable for both human health and the intricate gut ecosystem, consisting of trillions of microorganisms. Dietary approaches to elevate B vitamin levels encompass direct supplementation, consumption of functional foods, microbiota-directed foods or prebiotics, food biofortification, and dietary diversification. Notably, microbiota-directed foods and functional foods have proven effective in enhancing microbial production of B9 and B12, respectively. From a microbial standpoint, genetic engineering of gut bacteria, probiotics, and fecal microbiota transplantation show promise. This integrated approach underscores the potential synergy between dietary and microbial strategies in optimizing B vitamin status for overall human well-being.

niche of the host has emerged as a significant driver of coevolution and codiversification.[55,56] Recent research has shed light on the pivotal role of nutritional B vitamins as potential limiting factors linked to the evolution of obligate symbiosis in insects.[4] This insight is drawn from an extensive dataset comprising 1,850 microbe-insect symbiotic relationships spanning 402 insect families, accompanied by an analysis of nutrient composition within each insect family.

There is also emerging evidence to suggest that B vitamins may have played similar pivotal roles not only in their coevolution with the gut microbiota but also in human evolution, driven directly or indirectly by dietary shifts. Key transitional points contributing to human evolution include the advent of agriculture, industrialization, and the proliferation of westernized lifestyles, all of which have been accompanied by shifts in dietary practices.[57] Despite the challenge of fully reconstructing ancient microbial genomes from human paleofecal samples,[58] a comparison between the gut microbiomes of non-industrialized and industrialized populations reveals substantial perturbations in microbial composition and functionality induced by industrialized lifestyles. These alterations include the vanishing gut microbes and notable shifts in microbial biosynthesis of certain B vitamins.[59,60] This implies a potential role of diet and lifestyle changes in influencing microbial B vitamin production, collectively contributing to the coevolution between humans and their gut microbiota. Moreover, dietary shifts have also been demonstrated to be able to imprint genetic signatures in the evolution of the human genome.[57] However, whether the observed positive selection in human genes related to B1[61] and B9 metabolism,[62] for instance, is attributable to similar societal and dietary changes remains a topic that warrants further investigation. Nonetheless, dietary B vitamins are believed to play significant ecological roles in mediating host-microbiota interactions over evolutionary timescales.

BALANCING DIETARY AND BACTERIAL SOURCES FOR OPTIMAL HEALTH

To harness the benefits that B vitamins offer to our overall well-being, achieving an equilibrium between dietary intake and bacterial synthesis is crucial. Microbiota-directed therapeutic approaches have recently gained substantial attention, complementing traditional dietary strategies. This holistic approach not only recognizes the significance of dietary sources but also embraces the potential of our microbial allies in enhancing our health and nutritional outcomes.

Dietary strategies

Numerous dietary strategies have been offered to enhance vitamin supplementation, including the development of functional food, direct supplementation, food biofortification, and food diversification (Figure 3). For instance, fortified foods now contribute to approximately 25% of B1 intake,[5,29] and direct supplementation of multivitamins is, indeed, associated with lower disease risks.[63] Promising therapeutic functional foods for treating dyslipidemia, such as whole grains, plant sterols, berberine, and silymarin, have been identified,[64] with some of these acting by improving B vitamin status.[3,65] Food biofortification, a process that relies on selective breeding or genetic engineering to boost the production of B vitamins in crops, has also undergone significant advancements.[66] However, promoting a diverse, healthful diet may be a preferred approach over direct supplementations.[37]

In addition, microbiota-directed dietary approaches, including the development of specific foods and prebiotics in addition to a healthy diet, hold significant promise. For instance, although the low-carbohydrate, high-protein, high-unsaturated fatty acid diet may contain lower B9 levels compared with the Mediterranean diet, it can enhance bacterial biosynthesis of this vitamin, thus complementing dietary sources to better serve the host.[2] Additionally, as recently shown, dietary fibers can enhance B3 production from *Parabacteroides distasonis*, improving glucose intolerance and insulin resistance.[13] Furthermore, undernourished children have exhibited a reduced representation of multiple pathways involved in B vitamin metabolism within their gut microbiome, and microbiota-targeted foods have demonstrated the potential to foster both gut community development and child growth.[67,68] These multifaceted dietary strategies, informed by the intricate dynamics of B vitamin metabolism, offer diverse pathways to optimize health and nutritional outcomes.

Microbial strategies

Expanding beyond the resident microbiota-directed dietary strategies discussed above, microbial interventions involving bacterial genetic engineering, supplementation of B vitamin-producing probiotics, and fecal microbiota transplantation (FMT) have all demonstrated promise in enhancing vitamin status (Figure 3). These efforts have led to the conceptualization of the gut microbiota as a new avenue for obtaining essential vitamins.[69] To illustrate, genetic manipulation has the potential to increase B12 production in *Escherichia coli* by more than 250-fold,[70] presenting a promising therapeutic option for treating B12 deficiency-related metabolic disorders. The protective properties of lactic acid bacteria, the most common probiotics, against inflammation have also been associated with its production of B2 and B9.[71] Moreover, some strains of *Akkermansia muciniphila*, representing a new generation of probiotics, are capable of B vitamin production. However, the extent to which B vitamin production contributes to their probiotic benefits remains a topic for further investigation. Some suggestions have even been made to use B vitamin-producing bacteria as preferable fortification agents over chemically synthesized pseudo-vitamins (which do not have the same physiological effects as the natural vitamins).[72,73] Last but not least, FMT has provided crucial mechanistic insights into improving various diseases, although its clinical application remains somewhat limited. For instance, FMT has demonstrated the potential to partially alleviate autism-like behaviors that was associated with disrupted intestinal B6 homeostasis in mouse models.[74]

Yet, the development of microbiota-based therapeutics is not without challenges. One such challenge is the existence of distinct regulatory mechanisms governing bacterial biosynthesis of different B vitamins. For example, B9 synthesis by bacteria may increase when dietary carbohydrates are insufficient, yet dietary protein levels are high. This dietary shift favors proteolytic bacteria, which metabolize amino acids to support B9 production.[2] However, B12, which plays an equally vital role, similar to B9, in hepatic one-carbon metabolism, is suggested to be regulated by gut redox potentials.[3] Therefore, methods to enhance the production of one B vitamin might not necessarily enhance the production of others. Another challenge is how to take the microbiota of both small intestine and colon into consideration when developing these therapeutics. Nonetheless, growing evidence indicates that it is time to rethink healthy eating in light of the microbiome science.[75]

CONCLUDING REMARKS

In summary, this review has explored the multifaceted roles of B vitamins in human health, the diverse factors influencing their status, and the evolving landscape of diet-microbiota interactions. The recognition of microbial biosynthesis as a crucial contributor to B vitamin dynamics adds a layer of complexity to our understanding, emphasizing the need for a holistic approach to optimize these essential micronutrients. As we navigate this complex interplay, future research should delve into elucidating microbial regulatory mechanisms, refining clinical applications, and conducting longitudinal studies to tailor interventions for personalized health outcomes. Overall, this review contributes to our understanding of B vitamins, providing insights that guide comprehensive approaches to tackle nutritional deficiencies and enhance overall well-being.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chom.2023.12.004.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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