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Review Article

Vitamins, the gut microbiome and gastrointestinal health in humans ☆

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ABSTRACT

The gut microbiome plays important roles in the maintenance of host health and the pathogenesis of many diseases. Diet is a key modulator of the gut microbiome. There is increasing evidence that nutrients other than fermentable fiber affect the gut microbial composition. In this review, we discuss the effects of vitamins on the gut microbiome, and related gastrointestinal health, based on *in vitro*, animal and human studies. Some vitamins, when provided in large doses or when delivered to the large intestine, have been shown to beneficially modulate the gut microbiome by increasing the abundance of presumed commensals (vitamins A, B_2, D, E, and beta-carotene), increasing or maintaining microbial diversity (vitamins A, B_2, B_3, C, K) and richness (vitamin D), increasing short chain fatty acid production (vitamin C), or increasing the abundance of short chain fatty acid producers (vitamins B_2, E). Others, such as vitamins A and D, modulate the gut immune response or barrier function, thus, indirectly influencing gastrointestinal health or the microbiome. Future research is needed to explore these potential effects and to elucidate the underlying mechanisms and host health benefits.

1. Introduction

Gastrointestinal health is a broad term that includes the normal functioning of the gut immune, neuroendocrine, barrier, motor, and digestive systems. More recently, the gut microbiome has been shown to modulate each of these functions, highlighting its importance in the maintenance of host health and the pathogenesis of many diseases [1–5].

Recent research has suggested that environmental factors, particularly diet, are potent modulators of the gut microbiome [6–10], with a clear focus on dietary fibers as fuel for gut microbes [11]. However, nutrients and ingested compounds other than fermentable dietary fibers also affect the composition of

☆ *Abbreviations*: CD, Crohn's Disease; CF, cystic fibrosis; FFQ, food frequency questionnaires; IBD, inflammatory bowel disease; RDA, recommended daily allowance; ROS, reactive oxygen species; UC, ulcerative colitis; VDR, vitamin D receptor

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the microbiome or the biological functions of the gastrointestinal tract [12–16]. To use an extreme example, antibiotics have acute effects on the gut microbiota composition and its functions that depend on the type, dose, spectrum, duration and route of administration used [17]. Micronutrients and other dietary components consumed in small quantities such as vitamins, minerals, specific fatty acids and phytochemicals may also elicit changes in the microbiome.

Microbiome modulation can occur either directly through actions of dietary components on the composition of the microbiome or its metabolic processes, or indirectly through altering the physiology of the gut to change the intestinal lumen environment, thereby producing changes in the microbiome. Vitamins are candidates for microbiome-modulators via several mechanisms. Vitamins represent a diverse array of molecules with many functions in the body, and are categorized into fat-soluble and water-soluble vitamins. Fat-soluble vitamins are absorbed and transported in the body similarly to fats, and are integral cell membrane components, while the water-soluble vitamins are generally coenzymes in metabolic reactions that carry chemical groups and electrons [18]. Some have direct anti-microbial actions *in vitro* or *in vivo*, such as vitamins A, B6, C and E, with immediate effects on the gut microbiome, reflected by changes to the fecal microbiome [19–22]. Vitamins that are co-factors in energy generation reactions participate in energy metabolism in bacteria, and can directly support certain types of microbes, increasing their prevalence or supporting biological functions [23]. Indirect effects include modifying the host immune response or susceptibility to infection, especially in the gut [24–26]. The microbiome is also a producer of vitamins, thus contributing to micronutrient sufficiency and the stability of bacterial communities in the gut [27]. Therefore, vitamins may have bi-directional, direct or indirect effects on the gut microbiome without being used as an energy source.

In this narrative review, we aimed to summarize research concerning the effects of vitamins on the gut microbiome and related gastrointestinal health, with a focus particularly on human clinical studies.

1.1. *Vitamin A*

Vitamin A plays a crucial role in vision, gene expression, reproduction, embryonic development, growth, and immune function. The two primary sources of vitamin A are retinol from meat and fish, and pro-vitamin A carotenoids from fruits and vegetables. Intestinal absorption of retinol occurs in the lumen of the small intestine and is high, with an absorption efficiency in the range of 70% to 90% [28, 29]. One study reported the median retinol recovered in the feces of healthy subjects was 1.8% of intake [30]. Carotenoids with vitamin A activity are absorbed intact, or cleaved to form vitamin A primarily in the intestinal mucosa prior to secretion into the lymph [31]. Absorption of carotenoids ranges from 5% to 65% depending on factors related to carotenoid type, food matrix and host factors [32]. At intakes above 20 mg, absorption of carotenoids appears to be limited [33, 34]. Carotenoids that are not absorbed in the small intestine are excreted in the feces [35].

1.1.1. *Vitamin A effects on the gut microbiome*

Retinoids have functions in every cell of the body, with mucin production, cell growth and cell differentiation most important in the gut as these factors maintain the normal barrier function of the intestines. Dysfunction of the intestinal mucosa alters the permeability of the intestinal epithelium and modifies the production of biochemical factors that interact with gut microbes. Therefore, vitamin A status may affect the gut microbiome via changes to the intestinal mucosal barrier.

Several interventional studies have investigated the direct effects of vitamin A supplementation on the fecal microbiome composition in humans, as summarized in Table 1. A study in 306 infants in Bangladesh randomized to receive a single high dose of vitamin A or placebo within 48 hour of birth showed that boys receiving vitamin A had a higher abundance of fecal *Bifidobacterium* than boys receiving placebo, however, this difference was not seen in girls. For girls in late infancy, a positive association of plasma retinol with *Actinobacteria* (the phylum containing *Bifidobacterium*) and the commensal *Akkermansia* was found. However, there were no differences seen in the study population overall for *Bifidobacterium* and *Proteobacteria* [36]. In a single-blind, non-controlled pilot study, children with autism spectrum disorders completed a vitamin A intervention consisting of a single high dose (intended to prevent deficiency over a period of 4 to 6 months in young children), including gut microbe analyses at baseline and after 6 months in a subset of 20 participants [37]. At follow-up, there were a number of changes, including an increase in *Bacteroidales* order, *Bacteroidia* class, and *Bacteroidetes* phylum, and decrease in *Proteobacteria, Actinobacteria, Enterobacter, Escherichia-Shigella, Clostridium*, and *Bifidobacterium* compared to baseline. Although these findings are from an uncontrolled study, they suggest potential roles of vitamin A in modulating the gut microbiota in children with autism spectrum disorders [37].

Several observational studies support these findings and have found associations between dietary intake or plasma concentrations of vitamin A and the gut microbiota composition [38–42]. LV and coworkers examined changes in the gut microbiota of Chinese infants with persistent diarrhea [38]. Participants were divided into a vitamin A-deficient and a vitamin A-sufficient group based on serum retinol levels. Although gut microbiota richness (Chao) did not differ between groups, the investigators found a significantly lower diversity (Shannon and Simpson index) of the gut microbiota in the vitamin A-deficient group compared with the vitamin A-sufficient group. Additionally, they also found that *Escherichia-Shigella* and *Clostridia* were the key phylotypes in the sufficient group, whereas *Enterococcaceae*, including the common enteropathogen *Enterococcus faecalis*, dominated in the deficient group [38]. These findings are consistent with the requirement for vitamin A in maintaining a healthy gut microbial composition by protecting against pathogens and maintaining healthy mucosal barriers [43, 44]. However, this study does not include information concerning dietary and food supplements such as prebiotics and probiotics, which may contribute to the observed effects. In another study, the fecal microbiota of 16 adults with cystic fibrosis (CF) were profiled by 16S rRNA gene sequencing, and associations between UniFrac distances of fe-

Table 1 – Summary of articles describing direct effects of vitamins on the human gut microbiome

Vitamin	Population	Country	Number of patients	Study type	Dose/intake	Microbiome measurement technology	Effect (relative change)	Reference
A	Healthy newborns and toddlers	Bangladesh	306	Double-blind, randomized controlled trial	50,000 IU vitamin A as a single dose	16S rRNA gene (Terminal restriction fragment-length polymorphism assay)	*Bifidobacteria* ↔ *Proteobacteria* ↔ (sex-specific associations found)	[36]
A	Young children with autism spectrum disorders	China	64	Single-blind, intervention pilot study	200,000 IU vitamin A as a single dose, follow-up after 6 mo	16S rRNA gene (amplicon sequencing)	Ace, Chao, Shannon, and Simpson indices ↔ *Bacteroidetes* ↑ (+46%) *Proteobacteria* ↓ (-28%) *Actinobacteria* ↓ (-82%) *Enterobacter* ↓ (-94%) *Escherichia-Shigella* ↓ (-51%) *Clostridium* ↓ (-94%) *Bifidobacterium* ↓ (-90%)	[37]
A	Infants with persistent diarrhea	China	59	Observational study	Vitamin A deficient compared to sufficient children (serum retinol <0.7 μmol/L	16S rRNA gene (amplicon sequencing)	Chao richness ↔ Shannon eveness ↓ Simpson diversity ↑ *Enterococcus* ↑ *Escherichia-Shigella* ↓ *Enterococcaceae* ↑ (+50%) *Lactobacillales* ↑ (+36%)	[38]
A	Adults with cystic fibrosis	Australia	16	Observational study	Vitamin A and beta-carotene intakes via 3-day food diary	16S rRNA gene (amplicon sequencing)	*Clostridium* ↑ *Gemellales* ↑ *Bacteroidetes/Bacteroidia/Bacteroidales* ↓	[40]
A	Healthy adults	USA	98	Observational study	Retinol and retinol-equivalent intakes via FFQ	16S rDNA gene sequencing	78 taxa that had abundance ≥0.2% in at least one sample ↔	[39]
A	Pregnant women	Norway	60	Observational study	Retinol intakes via FFQ; median retinol 822.5 μg and beta-carotene 1894 μg	16S rRNA gene (amplicon sequencing)	Whole tree phylo-genetic diversity ↓ (-5.6%) *Proteobacteria/Actinobacteria* ↑ *Proteobacteria/Firmicutes* ↑	[41]
Beta-carotene	Lactating women	USA	20	Observational study	Vitamin A & beta-carotene intake via 24h dietary recall	16S rRNA gene (amplicon sequencing)	Beta-carotene: *Firmicutes* ↑ Vitamin A: *Dialister* ↓	[42]
A	Hospitalized infants	South Africa	34	Observational (case-control) study	Vitamin A sup-plementation (yes/no)	16S rRNA gene (amplicon sequencing)	Alpha diversity ↔ Beta diversity ↓	[45]
A	Healthy adults	Ireland	12	Double-blind, randomized placebo-controlled pilot study	250 μg retinol equivalents	Shotgun metagenomic sequencing	*Lachnospiraceae* ↑ (+15%) Alpha diversity ↔ *Proteobacteria, Firmicutes, Actinobacteria* ↔	[46]
D	Healthy adults	Ireland	12	Double-blind, randomized placebo-controlled pilot study	60 μg cholecalciferol	Shotgun metagenomic sequencing	*Coriobacteriaceae* ↑ (+52%) *Desulfovibrionaceae* ↓ (-65%) *Odoribacter* ↓ (-100%) *Streptococcus salivarius* ↓ (-100%) *Dorea longicatena* ↑ (+89%) *Bifidobacterium longum* ↑ (+118%) *Coprococcus comes* ↑ (+102%)	[46]

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Table 1 (*continued*)

Vitamin	Population	Country	Number of patients	Study type	Dose/intake	Microbiome measurement technology	Effect (relative change)	Reference
D	Healthy adults	Austria	16	Interventional open-label pilot study	34,300-68,600 IU cholecalciferol per week	16S rRNA gene (amplicon sequencing)	Bacterial richness ↑ *Gammaproteobacteria* ↓	[83]
D	Adolescent girls	Iran	50	Intervention study	50,000 IU cholecalciferol per week	16S rRNA gene (TaqMan assays)	*Enterococcus* ↔ *Bacteroidetes* ↓ (-72%) *Lactobacillus* ↓ (-24%) *Firmicutes* ↑ (+50%) *Bifidobacterium* ↑ (+20%)	[84]
D	Pregnant women	Norway	60	Observational study	Vitamin D intakes by FFQ. Median 3.13 μg/d	16S rRNA gene (amplicon sequencing)	Whole tree phylogenetic diversity ↓ (-7.8 %) Shannon diversity ↓ (-5.1 %) *Actinobacter/Proteobacteria* ↑ *Proteobacteria/Firmicutes* ↑ *Other/Bacteroidetes* ↑ *Staphylococcus* ↑	[41]
D	Healthy young adults	Brazil	150	Observational study	Vitamin D intake tertiles by FFQ, blood 25OHD tertiles	16S rRNA gene (amplicon sequencing)	*Prevotella* ↑ *Haemophilus* ↓ *Veillonella* ↓	[85]
D	Overweight and obese vitamin D-deficient adults	Australia	26	Double-blind, randomized placebo-controlled trial	100,000 IU cholecalciferol loading and 4,000 IU cholecalciferol per day or placebo maintenance	16S rRNA gene (amplicon sequencing)	Shannon diversity ↔ *Lachnospira* ↑ *Blautia* ↓	[86]
D	1-mo old infants	The Netherlands	913	Observational study	Infant Vitamin D supplementation (yes/no)	16S rRNA gene (Real time polymerase chain reaction)	*Bifidobacterium* ↓ *Bacteroides fragilis* ↑ *Clostridium difficile* ↓ (in infants whose mothers adhered to an alternative lifestyle)	[87]
D	Mother-infant pairs	Canada	1,157	Cohort study	FFQ, supplement questionaire	16S rRNA (amplicon sequencing)	Infants: Megamonas ↓ Breastfed infants: *Bilophila* ↓ Lachnospiraceae ↓ *Haemophilus* ↑ Mothers: *Clostridium difficile* ↓	[88]
D	3 - 6-mo old infants	USA	261	Observational study (nested in a double-blind, placebo controlled, randomized, clinical trial of vitamin D in pregnancy)	Cord blood vitamin D, mean 22.7 ± 11.9 ng/mL	16S rRNA gene (amplicon sequencing)	Shannon diversity ↔ *Lachnobacterium* ↑ *Lactococcus* ↓	[89]
D	Multiple sclerosis patients and healthy controls	USA	15	Interventional open-label pilot study	5,000 IU cholecalciferol per day	16S rRNA gene (DNA microarray)	*Akkermansia* ↑ *Faecalibacterium* ↑ *Coprococcus* ↑ *(all in untreated multiple sclerosis patients)*	[91]

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Table 1 (*continued*)

Vitamin	Population	Country	Number of patients	Study type	Dose/intake	Microbiome measurement technology	Effect (relative change)	Reference
E	Adults with cystic fibrosis	Australia	18	Observational study	3-d food diary	16S rRNA gene (amplicon sequencing)	*Tissierellaceae* ↑ *Firmicutes* ↑ *Bacteroidales/ Bacteroidia/ Bacteroidetes* ↓	[40]
E	Pregnant women	Norway	60	Observational study	Vitamin E intake via FFQ, median 9.5 mg/d	16S rRNA gene (amplicon sequencing)	*Proteobacter* ↓ *Firmicutes* ↓ *Other/Bacteroidetes* ↑	[41]
E	Lactating women	USA	20	Observational study	Vitamin E intake via 24h dietary recall	16S rRNA gene (amplicon sequencing)	*Firmicutes* ↑	[42]
E	Iron-deficient infants and toddlers	USA	36	Double-blind, randomized placebo-controlled trial	Vitamin E (18mg/d alpha-tocopherol) in addition to iron therapy	16S rRNA gene (amplicon sequencing)	*Bacteroidetes* ↓ (-10%) *Firmicutes* ↑ (+12%) *Actinobacteria* ↔ *Proteobacteria* ↔	[130]
K	Young healthy women	Japan	28	Observational study	3-d weighted food record. Mean = 102 ± 31 μg/1000 kcal	16S rRNA gene (T-RFLP)	*Bifidobacterium* ↑ *Lactobacillales* ↑ *Bacteroides* ↓	[149]
B2	Healthy adults	Ireland	12	Double-blind, randomized placebo-controlled pilot study	75 mg riboflavin	Shotgun metagenomic sequencing	Observed number of species ↑ *Clostridiaceae/Clostridium* ↑ *Veillonellaceae* ↓ *(-44%)* *Faecalibacterium* ↓ *(-35%)* *Eubacterium hallii* ↓ *(-39%)* *Alistipes shahii* ↑ *(+126%)*	[46]
B2	Healthy adults	The Netherlands	11	Single arm pilot study, pre- vs post-test	100 mg riboflavin	Fluorescence in situ hybridization	*Faecalibacterium* ↑ *Roseburia* ↑ *Escherichia coli* ↓	[13]
B2	Lactating women	USA	20	Observational study	24h dietary recall	16S rRNA gene (amplicon sequencing)	*Prevotella* ↑ *Bacteroides* ↓	[42]
B3	Healthy subjects	Germany	10	Intervention study	Delayed release nicotinic acid at increasing doses 30 mg - 300 mg	16S rRNA gene (amplicon sequencing)	*Bacteroidetes* ↑	[165]
B2	Adults with cystic fibrosis	Australia	18	Observational study	Riboflavin intakes via 3-d food diary	16S rRNA gene (amplicon sequencing)	*Bacteroidetes* ↓	[40]
B2	Crohn's Disease patients	Netherlands	70	Intervention study	100 mg riboflavin	16 S rRNA based fluorescent in situ hybridisation:; and metagenomic shotgun sequencing	Species' relative abundance ↔ *Enterobacteriaceae* ↓	[175]
B5	Lactating women	USA	20	Observational study	24h dietary recall	16S rRNA gene (amplicon sequencing)	*Actinobacteria* ↑ *Prevotella* ↑ *Bacteroides* ↓	[42]
B12	Lactating women	USA	20	Observational study	24hr dietary recall, mean = 3.6 ± 3.5 μg/d at 6 months	16S rRNA gene (amplicon sequencing)	*Prevotella* ↑	[42]
C	Healthy adults	Ireland	12	Double-blind, randomized placebo-controlled pilot study	500 mg ascorbic acid	Shotgun metagenomic sequencing	Alpha diversity (evenness) ↑ *Bacteroidetes* ↔	[46]

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Table 1 (*continued*)

Vitamin	Population	Country	Number of patients	Study type	Dose/intake	Microbiome measurement technology	Effect (relative change)	Reference
C	Adults with cystic fibrosis	Australia	18	Observational study	Vitamin C intakes via 3-d food diary	16S rRNA gene (amplicon sequencing)	*Bacteroidetes/Bacteroidia/ Bacteroidales* ↓	[40]

Description of symbols: ↑ significant increase; ↓ significant decrease; ↔ no change. T-RLFP=terminal restriction fragment length polymorphism.

cal microbiota and time-dependent micronutrient intake assessed by food diary were evaluated [40]. The investigators found that the intake of beta-carotene equivalents was negatively correlated with the phylum *Bacteroides* and positively correlated with *Firmicutes* and its lower taxa, including *Clostridium* [40]. The authors hypothesized that the supplemented vitamins may influence the gut microbiota through modification of the gut environment, particularly mucus production. Median micronutrient intakes were likely higher than the dietary intakes of the general population because most of the CF population received vitamin supplements, therefore the results may not be applicable to a healthy population. Likewise, an association study in 98 healthy individuals aiming to link long term dietary patterns with gut microbial enterotypes revealed no significant correlations between vitamin A intake and gut microbial taxa [39].

The associations between the intake of dietary macro- and micronutrients during pregnancy and the observed taxonomic differences in their gut microbiota, as measured in the stool after delivery, were investigated by Mandal et al. [41]. The authors found that there were significant associations between three vitamins D, E, and A, and the microbial composition at the phylum level. Increases in retinol intake were found to be related to increased *Proteobacteria: Actinobacteria* and *Proteobacteria: Firmicutes* ratios. Moreover, retinol intake was inversely associated with whole-tree phylogenetic diversity, although this result was not significant when evaluated using Shannon's diversity [41]. Consistent with this, Carrothers and coworkers collected repeated fecal samples up to 6 months postpartum from 20 lactating women and investigated associations with nutrient intakes [42]. The investigators reported significant positive associations between intakes of vitamin A and beta-carotene with the relative abundances of classes *Negativicutes* and *Erysipelotrichia* and genus *Dialister* [42]. Furthermore, in a South African case-control study conducted in 34 infants, a history of vitamin A supplementation was associated with reduced beta diversity, and there was no change in alpha diversity [45]. On the other hand, a study in healthy Irish adults using colon-delivered vitamin A failed to show a significant difference in the abundance of *Proteobacteria, Actinobacteria* and *Firmicutes*, and alpha diversity did not change, although *Lachnospiraceae* increased significantly [46].

Animal models link vitamin A to changes in the intestinal mucosa. A murine model showed that retinoic acid at 1-5 μM reduced intestinal mucus production in a dose-dependent manner and induced changes in intestinal mucosa thickness, which coincided with changes in the gut microbiota composition [40, 47]. In another study using gnotobiotic mice investigating the modulatory effect of different micronutrients on the gut microbiota, vitamin A deficiency had the largest effect on the structure of microbial communities and their metatranscriptome. In particular, *Bacteroides vulgatus* increased significantly during the vitamin A deficiency phase and decreased significantly when mice were transitioned back to the sufficient diet [48], which has implications for bile salt deconjugation [49].

In summary, several studies suggest an effect of vitamin A on microbial composition while some report that a replete vitamin A status may be associated with increased microbial diversity. The effects of vitamin A on mucus production could be responsible for these modulatory effects, as has been found in animal studies. However, diverse patient groups and the observational study designs used limit the current evidence base, which could be improved with clinical studies with a more rigorous design.

1.2. *Vitamin A effects on gastrointestinal infectious diseases*

Effects of vitamin A on gastrointestinal infections is suggested by several clinical findings. Episodes of diarrhea have been shown to correlate with an increased prevalence of vitamin A deficiency [38, 50], and a number of studies have shown that vitamin A supplementation reduces diarrhea incidence in children aged from 6 months to 5 years [51–56]. The underlying mechanisms are thought to relate to the maintenance of the intestinal epithelial lining and the regeneration of damaged mucosal epithelial cells [57]. As a result of damage to the intestinal epithelial tissues, diarrhea increases the body's requirement for vitamin A, thereby draining reserves of the vitamin. However, the extent of involvement of the gut microbiome is unknown [38, 51-56, 58, 59].

Vitamin A is also important for the intestinal immune response to pathogens and tolerance to food-derived antigens [16]. Moreover, vitamin A regulates the gene expression of anti-microbial peptides [60]. In a study in children aged 5-15 months from Mexico, vitamin A supplementation increased the duration of enteropathogenic *Escherichia coli* infections, possibly by decreasing interleukin-8 and monocyte chemoattractant protein-1 concentrations. On the other hand, vitamin A supplemented children showed shorter enterotoxigenic *Escherichia coli* infections in association with fecal tumor necrosis factor-alpha and interleukin-6 concentrations [61].

Although not fully conclusive, together these findings corroborate that impairment of helper T cell-2 response when vitamin A is deficient (while favoring the helper T cell-1 profile) may harm the response against extracellular bacterial infections [56].

Vitamin A supplementation may further affect norovirus infection. In a randomized, placebo-controlled trial, 127 Mexican infants and toddlers were supplemented with either 20,000 IU retinol (children <12 months) or 45,000 IU retinol (children >12 months) at baseline and every 2 months thereafter [58]. Stool samples were collected every 2 weeks, screened for norovirus, and characterized at the norovirus genogroup level (G1 and G2) after diarrheal episodes. The authors found that vitamin A supplementation reduced the prevalence of norovirus G2 but not G1 or overall norovirus infections. Moreover, vitamin A supplementation increased the length of norovirus shedding and decreased norovirus-associated diarrhea prevalence [58]. Accordingly, using *in vitro* and *in vivo* models, the authors showed that treatment with vitamin A inhibited murine norovirus replication and significantly altered intestinal microbiome profiles. In particular, bacterial species belonging to *Lactobacillaceae* families were increased and the antiviral effects of *Lactobacillus* were demonstrated using an *in vitro* model [58, 62].

The use of retinoids on specific enteric infections was tested recently also using both *in vitro* and *in vivo* approaches. Cabrera and colleagues, using a murine model of Shiga toxin-producing *Escherichia coli* infection, found that vitamin A deficiency improved survival, despite increasing intestinal damage during infection. Possibly, vitamin A triggered an increased population of polymorphonuclear cells, thus enhancing Shiga toxin effects [63]. Similarly, mice deficient in vitamin A that survived infection with *Citrobacter rodentium* become asymptomatically colonized with the pathogen, suggesting that pathogen clearance was enhanced via retinoic acid supplementation [64].

Taken together, evidence on vitamin A and gastrointestinal infectious diseases suggests that vitamin A exerts multiple effect on gut immunity that can modulate intestinal epithelia and mucosal fitness, and thus the response to intestinal pathogens. This includes effects on the barrier function of the intestinal mucosa [65]. Even mild vitamin A deficiency is associated with infectious diseases of the respiratory and intestinal tracts, particularly in children, due to reduced barrier competence. The impaired mucosal response stemming from vitamin A deficiency, with decreased mucin and defensin-6 expression, may allow easier penetration of pathogenic bacteria through the intestinal barrier [65]. To what extent the gut microbiome is involved, however, remains unknown and requires further research.

1.3. *Vitamin D*

The primary role of vitamin D in bone formation and resorption is mediated through increased intestinal calcium absorption [66, 67]. Dietary vitamin D is efficiently absorbed along with dietary fat in the small intestine. Bile acids initiate the emulsification of lipids, pancreatic lipase hydrolyzes the triglycerides, and bile acids support the formation of lipid- and vitamin D-containing micelles, which enter into the enterocytes [68–70].

Vitamin D deficiency is associated with several diseases of the gastrointestinal tract, such as inflammatory bowel disease (IBD) [71–78]. Emerging research has focused on the roles of vitamin D and the vitamin D receptor (VDR) on the gut microbiome and inflammation [79, 80].

1.3.1. *Vitamin D effects on the gut microbiome*

There is growing clinical evidence supporting the microbiome-modulatory effects of vitamin D [39, 80, 81]. Several observational and interventional studies have found associations between vitamin D and the microbiome, as summarized in Table 1.

A recent double-blind, placebo-controlled parallel group study investigated the effect of vitamin D as one of 6 vitamin treatments administered using a colonic delivery form [46]. Ninty-six healthy adult volunteers were randomized to each vitamin treatment (12 volunteers per vitamin), or placebo (24 volunteers) for 4 weeks. The 6 vitamin combinations tested were vitamins A, B2, C, D, and E, and a combination of B2 and C. A dose of 60 μg cholecalciferol was used as the vitamin D treatment, which was formulated for colonic delivery via a hard gelatin capsule coated with a pH-dependent polymer Eudragit S100 [82]. Vitamin D caused changes in the fecal microbiome at family and species level: an increase in *Coriobacteriaceae*, a decrease in *Desulfovibrionaceae* and *Odoribacter*, and an increase in *Streptococcus salivarius, Dorea longicatena, Bifidobacterium longum*, and *Coprococcus comes*. The authors suggest that part of the effect may be related to activation of the VDR, given the VDR gene has been identified as a vital host factor that can shape the gut microbiome at the genetic level [46, 79].

The effects of high-dose oral vitamin D supplementation on the human mucosa-associated and fecal microbiome were also studied in an open-label pilot study [83]. 16 healthy volunteers were endoscopically examined. Mucosal biopsies and stool samples were obtained from the stomach, small bowel, and colon before and 8 weeks after oral supplementation. The investigators found that vitamin D supplementation modulated the microbiome of the upper gastrointestinal tract by reducing the relative abundance of *Gammaproteobacteria*, including *Pseudomonas* and *Escherichia/Shigella* species, and by increasing bacterial richness. There were no changes in the microbiome composition in the lower gastrointestinal tract or stool samples [83].

Another recent study also suggested that high dose supplementation of vitamin D alters the microbiome composition of adolescent girls. 50 girls were supplemented with 50,000 IU cholecalciferol weekly for 9 weeks. In this population, *Bacteroidetes* and *Lactobacillus* decreased, whilst *Firmicutes* and *Bifidobacterium* increased after supplementation [84]. In a cross-sectional study in 150 healthy adults, associations between dietary vitamin D3 intakes and circulating 25(OH)D with the gut microbiota and inflammatory markers were investigated [85]. Participants were stratified into tertiles of intake and status. In participants with the highest vitamin D intake, *Prevotella* was more abundant, whereas *Haemophilus* and *Veillonella* were less abundant. Furthermore, there were inverse associations between circulating 25(OH)D concentrations and inflammatory

markers. The investigators concluded that the role of vitamin D in maintaining immune homeostasis may involve interactions with the gut microbiota [85]. In an association study in 60 pregnant women, vitamin D intake derived from FFQs showed a strong inverse association with microbial alpha diversity, and was found to be associated with higher levels of *Proteobacteria*, a phylum known to contain multiple pathogens, and a higher relative abundance of *Staphylococcus*. It was concluded that these associations may be explained by the antimicrobial properties of vitamin D, with higher dietary intake resulting in the suppression of certain groups of bacteria and thereby leading to relative increases in possible pathogenic groups [41]. This assumes that vitamin D reaches the large intestine where it can affect gut microbial communities, which was not investigated in this study. We are not aware of clinical studies that have investigated changes to the microbiome where the effects of vitamin D in the intestinal lumen are compared to systemic vitamin D concentrations.

In another randomized, placebo-controlled trial conducted in 26 overweight or obese yet otherwise healthy vitamin D-deficient adults, supplementation with a loading dose of 100,000 IU vitamin D3 and 4,000 IU vitamin D3 daily for 15 weeks caused changes to the fecal microbiome. The group supplemented with vitamin D increased their abundance of *Lachnospira* and decreased *Blautia* abundance. Participants' microbiomes were also analyzed according to vitamin D status at follow-up. Deficient subjects had a greater abundance of family *Clostridiaceae* and genus *Ruminococcus*, whilst high vitamin D subjects had a higher proportion of *Coprococcus* species, especially *Coproccous eutactus* [86].

Two large cohort studies also suggest that vitamin D influences the infant gut microbiota. In 913 one-month old infants in the prospective KOALA Birth Cohort Study, the effect of vitamin D supplementation on certain bacterial species in fecal samples was investigated. Overall, maternal dietary and plasma vitamin D were associated with lower counts of *Bifidobacterium* and higher counts of *Bacteriodes fragilis*, while in infants of mothers following an alternative lifestyle vitamin D supplementation was associated with lower counts of *Clostridium difficile* [87]. In 1,157 mother-infant pairs in the Canadian Healthy Infant Longitudinal Development Cohort Study, maternal consumption of vitamin-D fortified milk reduced the likelihood of *Clostridium difficile* colonization in infants [88]. In an ancillary analysis of a randomized controlled trial with vitamin D supplementation during pregnancy, the fecal microbiome of infants was investigated [89, 90]. The investigators showed that higher concentrations of cord blood vitamin D were linked with increased *Lachnobacterium* and decreased *Lactococcus* in infant stool samples, suggesting that vitamin D levels *in utero* and shortly after birth may influence the microbial community that colonizes the infant gut [89]. A further case-control study conducted in 15 multiple sclerosis patients and healthy controls supplemented with 5,000 IU vitamin D showed some post-treatment differences. Compared to baseline, *Faecalibacterium* and *Enterobacteriaceae* increased in abundance while *Ruminococcus* decreased after vitamin D supplementation. There were other significant differences found according to case-control group and the use of medication in multiple sclerosis patients, however the results are difficult to interpret due to the low sample size [91].

Taken together, these studies suggest that despite design heterogeneity, there is evidence supporting vitamin D as a modulator of the gut microbiome [81]. However, the current results are scattered: changes to the human microbiome that are consistent across studies have not yet been found, although broad changes such as increases in the *Bacteroides* phylum are consistent in mouse models [81].

1.3.2. *Vitamin D effects on Inflammatory Bowel Disease*

A link between vitamin D and IBD has been found in several association studies, which have revealed a high prevalence of vitamin D deficiency among patients with IBD [92–98]. For example, low plasma levels of 25(OH)D are associated with an increased risk of IBD-related surgery and hospitalization, whereas normalization of vitamin D status reduces the risk of surgery related to Crohn's Disease (CD) [97]. Furthermore, low vitamin D status is associated with higher disease activity and lower health-related quality of life in patients with CD [93]. Additionally, in patients with CD, vitamin D status is lower in patients with active disease than in patients in remission [98]. These association studies indicate that vitamin D status may play a role in the pathogenesis of IBD. However, further studies are necessary to examine the impact of vitamin D supplementation on disease course. Factors contributing to vitamin D deficiency in IBD are thought to include decreased sun exposure, reduced dietary intake, and reduced intestinal absorption [74, 78, 96, 99].

There are also several controlled clinical trials that have investigated the impact of vitamin D supplementation on disease relapse or symptoms in patients with either CD [100–104] or ulcerative colitis (UC) [105, 106]. These findings suggest that vitamin D supplementation may be of therapeutic benefit for IBD patients in terms of helping to prevent relapse and to lower activity scores when low vitamin D status is present, and the results are indicative of the involvement of the microbiome. However, further research is needed to improve our understanding of the underlying mechanisms, including the involvement of the intestinal microbiota. Overall, three different potential mechanisms have been proposed for the effect of vitamin D on IBD [107]: (1) through alterations in the immune response, especially through reduced VDR signalling [74, 100, 102, 103, 108-117]; (2) by improving intestinal epithelial barrier function [107, 118, 119]; (3) controlling the gut microbial composition by regulating the secretion of antimicrobial peptides, or via direct immune modulating effects [80, 107, 116, 120-122].

1.4. *Vitamin E*

Vitamin E is a fat-soluble dietary antioxidant that promotes plasma membrane repair [31, 123]. Vitamin E may have positive effects on intestinal epithelial barrier integrity; however, this effect has not been studied sufficiently in humans [124, 125]. The rate of intestinal vitamin E absorption has been estimated to be 51% to86% [31, 126, 127]. Vitamin E absorption from the intestinal lumen is dependent on biliary and pancreatic secretions, micelle formation, uptake into enterocytes, and chylomicron secretion [31]. All the different forms of vitamin E studied, including *all rac*-alpha-tocopherols, have been shown to exhibit similar apparent efficiencies of intestinal absorption and subsequent secretion in chylomicrons [31, 128].

Interestingly, a study analyzing colonic biopsies showed that the impact of diet on colon tocopherols appears to be limited [129]. Colon alpha-tocopherol concentrations at baseline were 687±95 pmol/mg and 775±95 pmol/mg in the healthy eating group and Mediterranean group, respectively.

1.4.1. *Vitamin E effects on the gut microbiome*

Several human intervention studies in various populations have found potential interactions between vitamin E and the gut microbiome (Table 1). In a cohort of adults with CF, Li and coworkers found a significant positive association of vitamin E intake with the phylum *Firmicutes* and its lower taxa (e.g., *Tissierellaceae*) and a significant negative association with the phylum *Bacteroidetes* [40]. The positive association between vitamin E and *Firmicutes* was also seen in an observational study conducted in lactating women in the USA [42]. In an association study in pregnant women, Mandal and coworkers found that a higher intake of vitamin E was associated with a decrease in *Proteobacteria*, a phylum known to contain multiple pathogens and to have pro-inflammatory properties [41]. Conversely, an association study of long-term dietary patterns and gut microbial enterotypes in healthy adults revealed no significant correlations between vitamin E intake and gut microbial taxa [39].

Tang and coworkers conducted an 8-week randomized controlled trial in infants and toddlers in the USA to investigate the potential microbiota-modifying effects of adding vitamin E to iron therapy [130]. A high proportion of supplemented iron is not absorbed and reaches the colon, where it is thought to act as a growth factor for enteric gram-negative bacteria [131–133]. Several human intervention studies have demonstrated unfavorable effects of iron supplementation on the fecal microbiome [134–136]. Tang and colleagues found that intervention groups given iron, or iron plus vitamin E, exhibited significantly different changes in the microbiome composition over time, particularly in the *Bacteroides* and *Firmicutes* phyla. In the group receiving iron plus vitamin E, there was a decrease in *Bacteroides* and an increase in *Firmicutes,* notably and increase in *Roseburia* abundance, compared to the group given iron alone [130]. *Roseburia* is a butyrate producer, and short-chain fatty acids have been reported to have beneficial effects on gut mucosal barrier function [137–139]. Thus, the investigators concluded that adding vitamin E to therapeutic iron supplementation may create a more favorable gut microbiome profile by promoting the growth of butyrate-producing bacteria, although a limitation to this conclusion is that the researchers did not measure butyrate in the study [130].

Taken together, the evidence base for effects of vitamin E on the gut microbiome is limited and should be improved by further pre-clinical and clinical research. Tocopherols show anti-microbial activity and therefore may impact the gut microbiome by this or other mechanism such as changing the gut redox potential. *In vitro* vitamin E could prevent biofilm formation in several human pathogens, particularly *Staphylococcus aureus* and *Staphylococcus epidermidis* [19]. Moreover, in the absence of vitamin E, the pathogenicity of *Citrobacter* in the intestinal tract of mice was enhanced [26]. These effect should be further explored in clinical studies.

1.5. *Vitamin K*

Vitamin K is an essential cofactor necessary for blood clotting and may be involved in the development of venous thrombosis [140, 141], vascular calcification [142, 143] and may affect bone health [144]. Vitamin K intake from food sources is predominantly in the form of phylloquinone from green leafy vegetables and some plant oils. However, vitamin K can also be obtained in the form of menaquinones in fermented foods, or via biosynthesis by the gut microbiota [145]. Approximately 10% to 50% of the human vitamin K requirement is met by endogenous synthesis [16, 140, 146, 147].

1.5.1. *Vitamin K effects on the gut microbiome*

Sparse research has investigated the effect of vitamin K on the microbiome (Table 1). In one *in vitro* study, "helper" and "dependent" pairs of bacteria were identified from a human stool sample. "Helper" bacteria contained a co-factor that supported the growth of the "dependent" strain. The "dependent" bacteria were screened to determine their reliance on menaquinone, ubiquinone and their metabolic precursors. The authors found several bacteria that require menaquinones as co-factors for growth, suggesting that vitamin K supports bacterial diversity in the gut microbiome [148]. These results could potentially explain differences in the gut microbial population of Japanese women with a high vitamin K diet, as assessed by a 3-day food diary. The microbiome analysis allowed the women to be divided into two clusters. One cluster was typified by a high relative abundance of *Ruminococcaceae* (previously classified as *Clostridium* cluster IV) and *Bacteroides*, and this group had significantly lower intakes of vitamin K. The other cluster had a high relative abundance of *Bifidobacterium* and *Lactobacillales*, and also greater vitamin K intakes [149]. Potentially, diet may have caused this shift in bacterial populations in the gut microbiome.

Only a few studies have investigated the menaquinone contents of the human gut and the health effects of menaquinone on the gut microbiota [150, 151]. Karl and colleagues assessed fecal and serum menaquinone concentrations with fecal microbiota composition in a randomized, parallel-group study [150]. Participants were randomly assigned to consume a diet high in either wholegrain or refined grain for 6 weeks. Fecal concentrations of different menaquinone forms exhibited substantial intra- and interindividual variability, which was associated with variability in microbiota composition, such as changes in the relative abundances of *Bacteroides* and *Prevotella*. Interindividual variability in fecal menaquinone concentrations rather than diet group partitioned individuals into two distinct groups. However, menaquinones were not detected in serum samples. The median total daily excretion of menaquinones in feces was 850 nmol/d but was highly variable. Furthermore, no associations between fecal menaquinones and serum markers of inflammation were observed. No conclusions from this study could be drawn regarding the contribution of microbiota-derived menaquinones to vitamin K or health status [150].

Taken together, the evidence regarding vitamin K and the gut microbiome is relatively meager. It appears that the menaquinones produced by the gut microbiome can be used both by the host and as a co-factor by certain microbiomes

that require it or its derivatives for growth. Given roles for vitamin K in bone and cardiovascular health, and the recent discovery that the gut microbiome interferes with the response of patients to anti-coagulant and vitamin K-antagonist, warfarin [152], an expansion of the evidence base is warranted.

1.6. *B-vitamins*

B-vitamins include vitamins B1 (thiamin), B2 (riboflavin), B3 (nicotinic acid/niacinamide), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate) and B12 (cobalamin) and are grouped together due to their water solubility, even though they are a diverse group of molecules with varied metabolic functions related to energy production, protein metabolism and hemopoiesis. Most B-vitamins are absorbed similarly: at low concentrations, an active transport system facilitates absorption, while passive diffusion occurs at higher concentrations, primarily in the small intestine [153]. Excess B-vitamin intake results in vitamins reaching the large intestine. The functions of the B-vitamins in the gut microbiome were recently reviewed and as the evidence base is limited, we will discuss them together [154].

B-vitamins are produced by the gut microbiome [23, 155, 156], however, the contribution of microbiome-produced B-vitamins to host requirements and status are largely unknown, and we only found one recent study evaluating this relationship [23]. Magnusdottir et al. estimated that 86% of the recommended daily allowance (RDA) of vitamin B6, 37% of the RDA of vitamin B9, 31% of the RDA of vitamin B12, and 27% of the RDA of vitamin B3 could be provided by the human gut microbiota [23]. For vitamin B2, only 3% of the RDA was estimated to be derived from the gut microbiome; these findings contradict earlier studies demonstrating that the large intestine plays a central role in regulating normal body homeostasis of this vitamin and that disruption of this function can lead to vitamin B2 deficiency [157]. Interestingly, microbiome-based production of vitamins has recently been shown to vary based on host health status: reduced intrinsic production was found in patients with IBD, malnutrition, and metabolic disorders, such as type 2 diabetes mellitus [156, 158, 159].

1.6.1. *B-vitamin effects on the gut microbiome*

Clinical trials investigating the effects of B-vitamin supplementation on the gut microbiome are limited (Table 1). The effect of vitamin B2 on the microbiome was tested in a study investigating the effects of several vitamins in a colonic delivery form, that we describe in more detail in the section on vitamin D [46]. After four weeks of a daily dose of 75 mg, the vitamin B2 content of the stool increased while vitamin B2 status did not change, indicating that vitamin B2 was released primarily in the large intestine. Vitamin B2 was found to have direct effects on the fecal microbiome, namely there was an increase in the observed number of species as well as in the genus *Alistipes* and *Clostridium* [46]. However, these results apply to high doses that are directly supplied to the large intestine, and may not be applicable to intake from foods or dietary supplements that are absorbed higher up in the digestive tract. Of note, in this study, fecal vitamin B2 concentrations were measured which may serve as a proxy for intestinal luminal content. As the authors measured an increase in fecal vitamin B2 when compared with baseline (419 µg/100g vs 169 µg/100g) while vitamin B2 status in plasma did not change, the results of this study support a direct effect of vitamins on gut microbial communities under the conditions tested.

Harmsen and coworkers investigated the effects of vitamin B2 supplementation on the fecal microbiome in 11 healthy adults in a pilot study [13]. Participants received a high dose of vitamin B2 (100 mg) intended to overcome intestinal absorption (estimated to be around 30 mg [160]) daily for 2 weeks. Investigators found an increase in the number of *Faecalibacterium prausnitzii* per gram of feces during 2 weeks of supplementation, and a decrease after supplementation, although concentrations did not return to baseline. *Faecalibacterium prausnitzii* has recently attracted interest as the major butyrate producer in the human microbiome, and because of its anti-inflammatory and gut barrier function-improving properties [161–163]. In addition to the findings for *Faecalibacterium prausnitzii*, an increase in *Roseburia* species and a decrease in *Escherichia coli* were observed, indicating improvement of the anaerobic conditions and redox status in the gut [13]. Vitamin B2 plays an essential role in cellular metabolism as a precursor of flavin mononucleotide and flavin adenine dinucleotide (FAD): both are co-enzymes required by glutathione reductase, which protects cells from the harmful effects of reactive oxygen species (ROS). Thus, vitamin B2 may act as an indirect antioxidant, modifying luminal microbiome conditions through a reduction in luminal ROS. This may create an environment that beneficially modulates the gut microbiome composition to favor *Faecalibacterium prausnitzii* and reduce *Escherichia coli*. Increasing *Faecalibacterium prausnitzii* relative to *Escherichia coli* counteracts pro-inflammatory processes and may have applications in the treatment of IBD. Indeed, Khan et al. further showed that *Faecalibacterium prausniztii* can use vitamin B2 as a mediator for extracellular electron transfer to the anode of microbial fuel cell systems. Furthermore, vitamin B2 can undergo fully reversible redox cycling under physiologically relevant conditions and can mediate the electrochemical oxidation of the main bacterial reducing equivalent NADH suggesting an important role as a redox mediator for bacterial extracellular electron transfer and growth in the human gut [164].

In support of these findings, an association study in 20 lactating women by Carrothers and coworkers found that increased intake of vitamins B2, B5, B6, and B12 were related to increased relative abundance of *Prevotella* and decreased relative abundance of *Bacteroides* in 120 fecal samples (collected on several occasions between 2 days and 6 months postpartum) [42]. In line with this are two observational studies. In one, vitamin B2 intake was associated with a decrease in *Bacteroidetes* in adults with CF. The other investigated the effects of vitamin B3 on the fecal microbiome in a two-part study [165]. Initially, 511 participants with different metabolic phenotypes were characterized according to their nicotinic acid status and the composition of their fecal microbiome. In participants with obesity, low dietary nicotinic acid intake was associated with reduced alpha-diversity and a lower *Bacteroidetes* abundance. Furthermore, low nicotinamide serum levels were significantly correlated with a reduced alpha diversity [165]. These correlations suggested that nicotinic acid may have favorable effects on the human gut microbiome [165].

Next, in a follow-up proof-of-concept study, 10 metabolically healthy volunteers received daily delayed-release microcapsules to deliver vitamin B3 (nicotinic acid and nicotinamide) to the ileocolonic region and directly target the gut microbiome. Supplementation lasted for 6 weeks, with a weekly increase in the dose of nicotinic acid (30 mg - 300 mg) and nicotinamide (900 mg - 3,000 mg). In the nicotinic acid group, a significant increase in *Bacteroidetes* abundance was observed over the 6-week period, whereas in the nicotinamide group, no significant changes were observed [165]. To explain the *Bacteroidetes* changes specific to nicotinic acid treatment, the authors discussed that the metabolization of nicotinamide depends on the presence of nicotinamidase (PncA) and nicotinamide phosphoribosyltransferase (NadV), and the limited representation of these enzymes in *Bacteroidetes* supports the observed difference in microbiome-modulating ability of nicotinic acid and nicotinamide [166]. *Firmicutes* and *Bacteroidetes* are the two most dominant bacterial phyla in the human gut microbiome. The *Firmicutes* to *Bacteroidetes* ratio is proposed to have an important role in maintaining intestinal homeostasis and host health such as obesity, diabetes and inflammatory bowel disease [167], however, the precise role is still in debate. Studies have shown mixed associations between the relative abundance of *Firmicutes:Bacteroidetes* and obesity [168]. Researchers note that these disparities could arise because of different methodological approaches employed in studies [168]. Thus it still remains unclear whether a high or low *Firmicutes:Bacteroidetes* ratio is beneficial in combating obesity [168]. Fangmann et al. suggested that the nicotinic acid may be a strong candidate for a targeted microbiome intervention, specially Bacteroidetes [165], which is further supported by the finding that biomarkers for insulin resistance were significantly improved in the nicotinic acid group, but not in the nicotinamide group [165].

While this elegant study supports a role of B-vitamins on the gut microbiome, research has shown also a lack of association between the B-vitamins and the microbiome, as was found in a study in 60 pregnant women, which found no relationship between intakes of vitamins B1, B2, B3, B6, B9, or B12, and gut microbial composition [41].

Genomic studies of the human gut microbiota show that many microorganisms are able to absorb and transform vitamins but cannot produce them *de novo*. This suggests that they have evolved to use vitamin co-factors produced by other organisms, therefore the biosynthetic capability of the microbial community as a whole is important for individual species. A recent review highlights both the importance of B-vitamin acquisition for microbes in the gut environment and the diversity of mechanisms that microbes use to acquire these vitamins [169]. Aside from direct biosynthesis of vitamins to produce co-factors for various reactions, bacteria can also recover intermediates and obtain vitamins directly from other species. Different bacterial species use distinct metabolic pathways for the uptake or metabolism of vitamins [169]. These mechanisms were studied further by Magnusdottir and co-workers, who used a systematic genomic assessment to identify B-vitamin biosynthesis pathways in 256 common gut bacteria, with a broad aim of identifying cooperation between microorganisms. They found that all 8 B-vitamins are produced by normal inhabitants of the human gut microbiome, with the presence of all pathways, except for vitamin B12, observed in *Bacteroidetes, Firmicutes*, and *Proteobacteria*. The authors computed pairs of genomes that contained producers of certain B-vitamins with non-producers of the same vitamins and found double the number of inverse pairs in the gut microbes compared to microbes from other body sites, suggesting that the gut microbes have synergistic relationships in terms of B-vitamin supply [23].

To estimate microbiome micronutrient biosynthetic capabilities and requirements using available genomic data, Rodionov et al. performed an *in silico* reconstruction of biogenesis, salvage and uptake for eight B-vitamins (B1, B2, B3, B5, B6, B7, B9, and B12) over a reference set of 2,228 bacterial genomes representing 690 cultured species of the human gastrointestinal microbiota. Reference organisms were classified according their pathway variants, namely their prototrophic compared to auxotrophic phenotypes. Several conserved partial pathways were identified indicating that alternative routes of syntrophic metabolism exist. Using two large human cohorts, phenotypic profiles in regards to B-vitamin production were estimated [170]. The results of this *in silico* study were confirmed with humanized gnotobiotic mice and *in vitro* anaerobic fecal cultures. Media or chow containing a lack or excess of the vitamin did not substantially alter the relative abundance of auxotrophic bacteria within the microbiome in the test systems, indicating metabolic cooperation between microbes within the gut community [171].

Finally, the B-vitamin requirement of 15 human butyrate-producing gut bacterial strains was investigated recently using a combination of genome sequence analysis and *in vitro* growth experiments. Two abundant *Ruminococcaceae* species, *Faecalibacterium prausnitzii* and *Subdoligranulum variabile*, require B-vitamins for growth. Surprisingly, most species were prototrophic for several vitamins within the *Lachnospiraceae*, and vitamin B7 auxotrophy was widespread. Most *Eubacterium rectale* and *Roseburia* strains were auxotrophic for vitamins B1 and B9, but few other *Lachnospiraceae* were auxotrophic for these vitamins. Moreover, synthetic co-culture experiments between vitamin auxotrophs and prototrophs in the absence and presence of different vitamin concentrations demonstrated that cross-feeding between bacterial species takes place and that differences in cross-feeding efficiency between prototrophic strains occurs [172]. Taken together, these data indicate that several dominant butyrate producing bacteria depend upon B-vitamins supplied from the diet or via cross-feeding from other members of the microbial community, at least under the in vitro condition tested. We are not aware of similar experiments that have investigated in such comparative manner the role of vitamins on other functional microbial groups, such as propionate producing bacteria, lactate utilizing bacteria, or hydrogen utilizing bacteria.

1.6.2. *B-vitamin effects on inflammatory bowel disease*

Patients with IBD are prone to vitamin deficiencies, reflected by lower plasma concentrations of vitamins compared to healthy controls [122, 173]. Chronic inflammation of the intestine involving elevated concentrations of pro-inflammatory cytokines has been shown to lead to changes in the absorptive functions of the epithelium [157]. Accordingly, for vitamin B2, exposure of intestinal epithelial cells to the pro-inflammatory

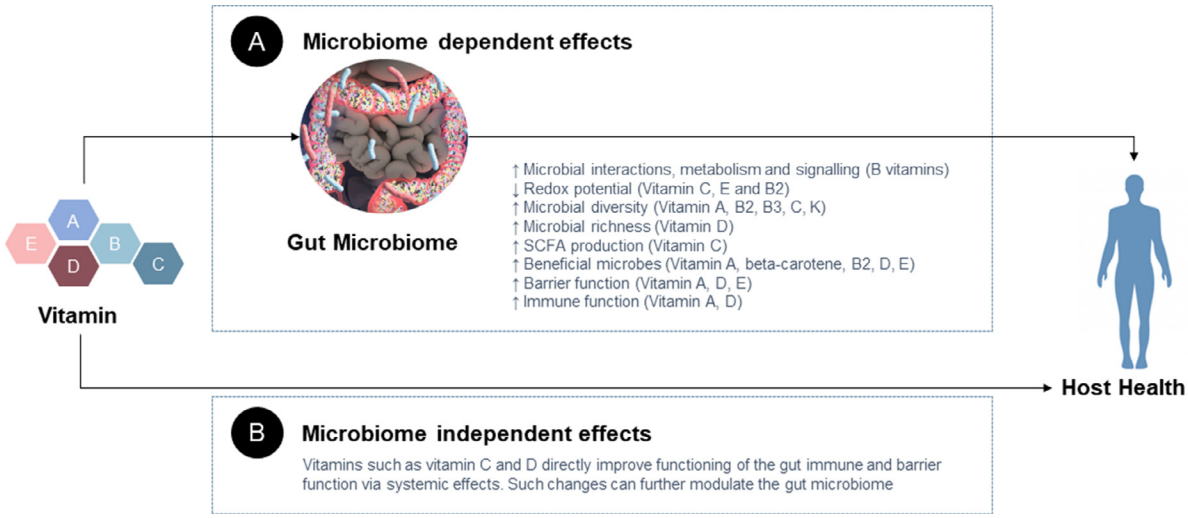

Fig. 1 – The effects of vitamins on host health. (a) Microbiome dependent effects of vitamin. For example, vitamins such as B vitamins are crucial for microbial interactions, metabolism and signaling. Vitamin C, E and B2 act as local antioxidants that impact the luminal redox balance. Some vitamins when provided in large doses or when delivered to the large intestine have been shown to beneficially modulate the gut microbiome by increasing the abundance of presumed commensals (vitamin A, beta-carotene, B2, D, E), increasing or maintaining microbial diversity (vitamins A, B2, B3, C, K) and richness (vitamin D), increasing short chain fatty acid production (vitamin C), or increasing the abundance of short chain fatty acid producers (vitamin B2, E). These changes will further beneficially modulate the gut immune response, or barrier and neuroendocrine function, thus, influencing host health. (B) Microbiome independent effects of vitamin. Vitamins such as vitamin C and D directly improve functioning of the gut immune and barrier function via systemic effects. Such changes can further modulate the gut microbiome.

cytokine tumor necrosis factor-alpha leads to significant inhibition of riboflavin uptake, which may explain the significantly low vitamin B2 concentrations observed in patients with IBD [157]. Accordingly, vitamin status in 24 patients with CD without micronutrient supplements was assessed and compared with that in 24 healthy controls. Although vitamins B1, B2, B6, and B9 were more depleted in patients with CD, vitamins B3, B7, and B12 were not different between the two groups, and vitamin B5 was increased in the CD group. Interestingly, vitamins B2 and B3 (nicotinic acid) further showed negative correlations with CD, suggesting that vitamin status of vitamins B2 and B3 may be markers of disease state [174].

In line with this, in a prospective clinical intervention study, patients with CD received 100 mg vitamin B2 daily for 3 weeks [175]. Clinical disease activity, serum biomarkers of inflammation and redox status, and fecal microbiome taxonomical composition and functionality were analyzed before and after the vitamin B2 intervention. The investigators found that vitamin B2 supplementation resulted in a reduction in systemic oxidative stress, some anti-inflammatory effects with a decrease of C-reactive protein, erythrocyte sedimentation rate, platelets, and IL-2, and a reduction in clinical symptoms. Fluorescence in situ hybridization analysis of fecal microbiota showed decreased fecal *Enterobacteriaceae* in patients with CD with low fecal calprotectin levels, although this was not observed in metagenomic analysis [175].

Klaassen *et al.* further showed that CD exacerbations were associated with decreases in the expression of microbial genes involved in the biosynthesis of anti-inflammatory mediators, including vitamins B1, B2, and B9 suggesting that increasing the intestinal abundance of these mediators may provide new treatment opportunities for patients with CD [176]. At the metagenomic level, Das et al. found that a part of the gene abundance profile for B-vitamins differed between healthy controls and patients with IBD [156]. Thus, it seems that there are differences in the microbiome of IBD patients, which may be modulated by B-vitamins, potentially through altering redox status.

1.7. *Vitamin C*

Vitamin C is a water-soluble antioxidant required for the synthesis of collagen, carnitine and norephinephrine. Intestinal absorption of ascorbic acid occurs through a saturable, dose- and sodium-dependent active transport process [177]. At low luminal ascorbate concentrations, active transport predominates, whereas simple diffusion occurs at high concentrations [31]. With usual dietary intake of ascorbic acid, approximately 70% to90% is absorbed; in contrast, absorption falls to approximately 50% or less as the dose increases to above 1 g/d [31, 178]. At high intakes, vitamin C in the large intestine is degraded by gut microbes to products such as D-arabo-ascorbic acid, lactate (as a transient product) and ribose [31, 179]. Similar to vitamin K and the B-vitamins, vitamin C can also be synthesized by intestinal microbes [180].

1.7.1. *Vitamin C effects on the gut microbiome*

Vitamin C has *in vitro* anti-microbial effects against various bacterial, fungal and viral targets [181] and may therefore be able to modulate intestinal microbial communities. We are

aware of only one recent clinical study that has investigated the direct effect of vitamin C on the gut microbiome, using a colon delivery form, as described above in the section on vitamin D [46]. With a dose of 500 mg per day for 4 weeks, Pham et al. found that vitamin C caused an increase in alpha-diversity (evenness) compared to baseline and placebo. While no significant changes in bacterial composition measured at the genus or species level were detected, there were increases in total SCFA, driven by greater concentrations of butyric and propionic acid after supplementation. There was no change in the *Bacteroidetes* composition with the vitamin C treatment, which was in contrast to an observational study showing that vitamin C intakes were associated with a decrease in *Bacteroidetes* in adults with CF [40].

A proposed mechanism for modulating the microbiome is similar to that of vitamin B_2: luminal conditions are improved through changing the redox potential and thus the anaerobic/aerotolerant balance in the digestive tract, hence selectively supporting microbial growth [182]. This mechanism was reinforced by a finding that the fecal pH and redox balance decreased in fecal samples of the vitamin C subgroup compared to placebo [46]. A similar link has been proposed by Million and co-workers, who found that aerobic growth of the three most odorous human gut microbes identified in their laboratory was possible with the addition of ascorbic acid, whilst no growth occurred without [183]. The latter findings are in line with a potential role in scavenging reactive oxidants in the gastric mucosa and have attracted research interest, particularly because of the suggested relationship with *Helicobacter pylori* [31, 184].

1.7.2. *Vitamin C intake and effects on inflammatory bowel disease*

Both CD and UC are characterized by recurrent intestinal inflammation that causes diarrhea and abdominal pain, therefore it has been speculated that the IBD phenotype may be affected by vitamin C through its effects on the immune response. However, no association was found between dietary vitamin C and the incidence of UC in participants from the EPIC observational study [185]. In contrast, in a case-control study in 239 Japanese patients with IBD, vitamin C intake was negatively related to UC risk [186]. Similarly, Buffinton and coworkers reported reduced ascorbate concentrations in the inflamed mucosa of patients with IBD [187, 188]. Additionally, in a Canadian IBD cohort of 311 participants, Shaghaghi and coworkers identified a genetic variant in the *SLC23A1* intestinal epithelium ascorbate transporter; this variant was associated with an increased risk of CD but not UC [188]. The investigators suggested that for individuals carrying the disease-associated genotype, supplementation with dehydroascorbate may increase intracellular vitamin C concentrations and may therefore be an opportunity for a personalized nutrition therapy [188]. However, this remains to be confirmed in additional studies.

2. Conclusions

Vitamins appear to modulate gastrointestinal health, either through modulating the composition and metabolic activity of the gut microbiome or by affecting the normal functioning of the gut barrier and immune system (Figure 1). A number of studies have supplied vitamins directly to the large bowel, which can be achieved via overdosing to exceed absorption in the small intestine or by using colon-targeted delivery systems. This includes promising new research on colon delivered vitamin B3 to increase the relative abundance of *Bacteroidetes*, associated with an improvement of biomarkers for systemic insulin sensitivity and metabolic inflammation [165], as well as high-dose vitamin B2 to reduce *Enterobacteriaceae* associated with improvements in clinical symptoms of IBD [175].

In addition, vitamins may impact gut microbiome composition and function indirectly via systemic effects as several clinical and association studies suggest [40, 106, 165]. For example, some of the effects of vitamin D on the gut microbiome may be related to activation of the VDR, given the VDR gene has been identified as a vital host factor that shapes the gut microbiome at the genetic level [79]. Moreover, the systemic effect of vitamins on gut immune and barrier function may underpin some of the effects that have been observed in many of the association studies. However, a known limitation of observational studies are confounding variables, such as dietary and food supplements, which may contribute to the microbiome modulatory effects, and this should be taken into account when attempting to ascribe a causal relationship between vitamins and gut microbiome composition. Furthermore, clinical studies using radiolabeled vitamins to investigate intestinal luminal and systemic concentrations of vitamins in response to oral interventions would generate valuable insights into the modes of action, particularly direct effects on intestinal microbes versus indirect effects such as via the immune or intestinal barrier function.

Interestingly, intrinsic, microbiome-based vitamin production has been shown to vary depending on host health status; these findings may facilitate the development of novel therapeutic approaches to counteract dysbiotic states and related host diseases or gastrointestinal diseases that arise independent of gut microbiome contributions [154]. The potential mechanisms of action for how vitamins impact gut microbiome composition and function may include local antioxidant effects that impact the luminal redox balance and therefore the relative abundances of facultative compared to strictly anaerobic species (e.g., an increased ratio of E*scherichia coli* versus *Faecalibacterium prausnitzii*, which is known to be associated with IBD) as could be the case for vitamin C [182]. Furthermore, B-vitamins act as essential co-factors in bacterial metabolism with synergistic relationships found between gut microbes in terms of B-vitamin supply [23].

It remains to be established whether and at which doses these local effects of vitamin supplementation on the gut microbiome will translate into host health benefits, including improvements in cognitive function, immunity, and the cure and prevention of diseases.

Author contributions

Author contributions were as follows:RES and SD conceptualized the study. SD wrote the original draft. JB, AR and VP re-

viewed and edited the manuscript. All authors reviewed and approved the manuscript.

Author Declarations

SD, AR, VP and RES are employees of DSM Nutritional Products Ltd., Kaiseraugst, Switzerland. Susanne Dold, Van T. Pham, Ateequr Rehman, Robert E. Steinert were employees of DSM Nutritional Products during the preparation of the manuscript. DSM Nutritional Products produces bulk vitamins used for human nutrition and other industries.

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