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Bioavailability of Fat-Soluble Vitamins and Phytochemicals in Humans: Effects of Genetic Variation

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Abstract

Recent data have shown that interindividual variability in the bioavailability of vitamins A (β-carotene), D, and E, and carotenoids (lutein and lycopene), as well as that of phytosterols, is modulated by single nucleotide polymorphisms (SNPs). The identified SNPs are in or near genes involved in intestinal uptake or efflux of these compounds, as well as in genes involved in their metabolism and transport. The phenotypic effect of each SNP is usually low, but combinations of SNPs can explain a significant part of the variability. Nevertheless, results from these studies should be considered preliminary since they have not been validated in other cohorts. Guidelines for future studies are provided to ensure that sound associations are elucidated that can be used to build consolidated genetic scores that may allow recommended dietary allowances to be tailored to individuals or groups by taking into account the multiloci genotypic signature of people of different ethnic origin or even of individuals.

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1. INTRODUCTION

Vitamins are micronutrients: They are essential in minute amounts (<1 g/day) for the normal development, growth, and functioning of the body. These organic compounds cannot be endogenously synthesized, or at least not in adequate amounts, and thus must be obtained from the diet. Vitamins are divided into two classes: water-soluble and fat-soluble. The latter class contains four groups of compounds:

- vitamin A (preformed vitamin A, i.e., retinol and its esters, and provitamin A carotenoids, i.e., mainly β-carotene, α-carotene, and β-cryptoxanthin)
- vitamin D (cholecalciferol and ergocalciferol)
- vitamin E (tocopherols and tocotrienols)
- vitamin K (phylloquinone and menaquinones)

Phytochemicals are naturally occurring plant chemicals. Thousands are commonly found in the human diet, usually in minute amounts (<1 g/day). However, they are not considered micronutrients since their essentiality has not been demonstrated. Nevertheless, some can exert biological actions and some are assumed to have beneficial effects on human health. Among phytochemicals, terpenoids, also known as isoprenoids, constitute a large and diverse class of fat-soluble organic compounds derived from five-carbon isoprene units. They can be divided into six groups: terpenes, diterpenes, triterpenes, phytosterols (PS), saponins, and carotenoids.

PS: phytosterol

Among these groups, carotenoids and PS have received much attention, and there is now a wealth of studies linking the intake or the blood concentration of these compounds with parameters of human health or specific diseases (see 108 and 111 for reviews).

Fat-soluble vitamins and terpenoids are lipids, and as such, their fate in the gastrointestinal tract during digestion and their absorption by enterocytes share some common mechanisms (2, 69). The discovery of the involvement of proteins in the uptake and absorption of these compounds by the human body (112, 131) has led to new hypotheses aimed at explaining the relatively wide-ranging interindividual variability in their bioavailability and health effects. Indeed, the numerous proteins involved in their bioavailability have led to suggestions that variations in the genes encoding for these proteins could modulate the expression or activity of these proteins and could, in turn, affect the bioavailability of these compounds. Therefore, this review aims to present what is known about the effects of genetic variation on the bioavailability of fat-soluble vitamins and phytochemicals in humans and to discuss how future studies might be carried out, as well as the potential applications of this fast-moving field. We focus on the compounds for which there are sufficient data, that is, vitamins A [β-carotene (βC)], D, and E, the carotenoids lycopene and lutein, and PS.

βC: β-carotene

VE: vitamin E

RDA: recommended dietary allowance

EARs: estimated average requirements

2. SUMMARY OF FAT-SOLUBLE VITAMINS AND PHYTOCHEMICALS

2.1. Vitamin E

Vitamin E (VE) is the generic term that refers to compounds exhibiting qualitatively the biological activity of α-tocopherol. These include eight naturally occurring molecules: four tocopherols (α, β, γ, and δ) and four tocotrienols (α, β, γ, and δ) (**Figure 1**). Naturally occurring and chemically synthetized tocopherols are not identical: Synthetic tocopherol is usually a racemic mixture of eight stereoisomers and is named all-*rac*-tocopherol, whereas natural tocopherols exist only in the *RRR* configuration. Additionally, synthetic tocopherol is often provided as an ester to protect the phenol group against oxidation and thus increase its shelf life (126).

The most abundant forms of VE in diets in developed countries are α- and γ-tocopherol, and they are found at the highest concentrations in human blood and tissues (144). VE is found at relatively high concentrations in vegetable oils and nuts, but it is also present in other food matrices. In the United States, approximately 70% of VE intake is accounted for by γ-tocopherol due to the high consumption of food sources rich in γ-tocopherol in the typical diet (e.g., soybean oil, corn oil) (71). The current United States recommended dietary allowance (RDA) of VE for healthy adults is 15 mg/day, but it is estimated that >90% of men and >96% women in the United States do not consume the estimated average requirements (EARs) (125). Data from a study published in 2012 point to similar inadequacies in several European countries (127). A systematic review of global α-tocopherol status has pointed to a relatively high prevalence of VE deficiency, with 13% of the participants exhibiting serum α-tocopherol concentrations <12 μmol/L, which has been proposed as a criterion for VE deficiency (66), and only 21% of the participants reaching serum α-tocopherol concentrations >30 μmol/L (107), which has been proposed as a criterion for VE adequacy (91).

VE is quantitatively the main lipid-soluble antioxidant in mammalian blood and tissues (27). It acts as a chain-breaking antioxidant, especially against peroxyl radicals, and is thus essential in maintaining the integrity of the long-chain polyunsaturated fatty acids found in cell membranes (27). Within the past 15 years, it has also been shown to exert nonantioxidant activities (146): modulation of gene expression (78, 145), inhibition of cell proliferation (72), and regulation of bone mass (51). Since oxidative stress has been implicated in the etiology of several diseases, for

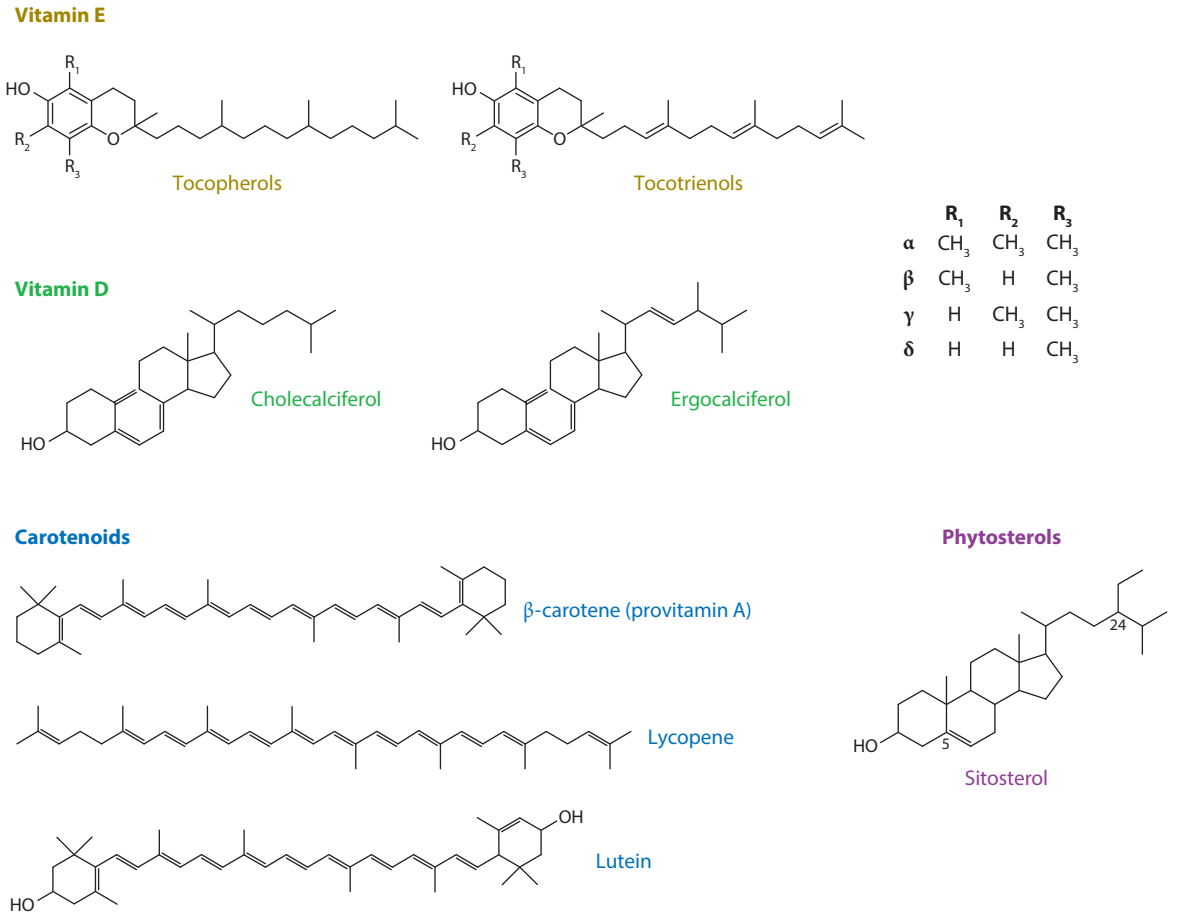


Figure 1

Chemical structures of the fat-soluble vitamins and phytochemicals discussed in this review. For the sake of space, only sitosterol is presented to illustrate the general structure of phytosterols. Δ^5-sterols are unsaturated at position 5 in the sterol ring, whereas 5α-sterols are saturated in the sterol ring. For example, sitostanol is structurally identical to sitosterol except for the unsaturated B ring. Moreover, phytosterols also differ regarding the side chain at C24.

example, cardiovascular diseases and cancers, numerous epidemiological studies have investigated the association between VE dietary intake or status and the incidence of these diseases, and these studies have reported beneficial associations (97, 106, 110). However, most randomized controlled trials have failed to show a benefit of VE supplementation on the incidence of these diseases (29, 124). Several explanations have been put forward, including an absence of an effect of VE supplementation on these diseases (56), a negative effect of α-tocopherol supplementation on the bioavailability of other VE vitamers (36), and the absence of population stratification by VE status or oxidative stress (124). It has also been suggested that high interindividual variability of α-tocopherol bioavailability may have interfered with the effects of VE supplementation (25) and that the ability to benefit from VE supplementation depends on a participant's genotype (15, 93, 147).

2.2. Vitamin D

Vitamin D (VD) is the generic term that refers to compounds exhibiting antirachitic activity. The two main VD vitamers are cholecalciferol [vitamin D_3 (VD_3)] and ergocalciferol [vitamin D_2 (VD_2)] (**Figure 1**). In animals, VD_3 is synthesized by the exposure of 7-dehydrocholesterol in the skin to UVB light, whereas in fungi, VD_2 is synthesized by the exposure of ergosterol to UVB light. In humans, VD photosynthesis varies widely and depends on many factors, for example, the duration of sun exposure, time of day, latitude, season, atmosphere composition, clothing, sunscreen use, and skin pigmentation, but a majority of individuals require some dietary VD, either from VD-rich foods or from supplements, to reach an adequate VD status. VD_3 is the main dietary source of VD and is obtained in significant amounts from food, such as milk and dairy products, fatty fish, meat, and eggs (61). The US RDA for healthy adults is 15 μg/day (assuming minimal sun exposure), and data point to dietary intakes below recommended levels for >75% of the population in several developed countries (127). According to the findings of the National Health and Nutrition Examination Survey 2005–2006, 37% of the US population uses a dietary supplement containing VD (9).

VD: vitamin D

DBP: vitamin D binding protein

VDR: vitamin D receptor

VD is a prohormone that needs two hydroxylations to become active. In the liver, it is converted by cytochrome P450 (CYP) family 2 subfamily R member 1 (CYP2R1) to 25-hydroxycholecalciferol [25(OH)D], which is the main circulating VD form, the concentration of which is measured to assess VD status. Following its transport via the bloodstream bound to vitamin D binding protein (DBP), it is converted in the kidney by CYP family 27 subfamily B member 1 (CYP27B1) to 1,25-dihydroxycholecalciferol [$1,25(OH)_2D$] (34). This metabolite exerts both nongenomic and genomic effects via the vitamin D receptor (VDR), and far more than 1,000 target genes have been identified (30). VD is essential for bone health and for regulating blood calcium and phosphate concentrations, but it is also involved in other biological functions, such as immunity, cell proliferation, and apoptosis. In a Mendelian randomization analysis, VD status was negatively associated with all-cause and cancer mortality (3).

2.3. Carotenoids

Carotenoids are lipid phytochemicals belonging to the tetraterpene family. There are two classes: carotenes that are nonoxygenated carotenoids (e.g., α- and β-carotene, lycopene) and xanthophylls that are oxygenated carotenoids (e.g., lutein, zeaxanthin, β-cryptoxanthin). Carotenoids are natural pigments, with colors ranging from red to yellow, and are produced in all photosynthetic organisms (bacteria, algae, and plants), as well as in some nonphotosynthetic bacteria and fungi. They are involved in many biological functions, such as photosynthesis, photoprotection, photomorphogenesis, development, and hormone synthesis (102), and they also participate in enhancing the visual attraction of these organisms.

More than 700 different carotenoids have been identified, but only about 40 are present in significant amounts in the human diet. Total and individual carotenoid intake is highly variable both within and between populations, and it largely reflects fruit and vegetable consumption. Data from 37,846 European inhabitants reported a mean total carotenoid intake of 10 ± 4 mg/day (119). The six carotenoids found in the highest concentrations in human blood are those found in the highest quantities in the human diet, that is, βC, lycopene, and lutein (**Figure 1**), as well as β-cryptoxanthin, α-carotene, and zeaxanthin (77). Although there are no RDAs for carotenoids, higher consumption is usually recommended.

Following enzymatic cleavage by β-carotene oxygenase 1 (BCO1), α- and β-carotene, and β-cryptoxanthin, can be converted to retinol in the human body and hence are referred to as provitamin A (proVA) carotenoids. The RDA for VA in France is 600- and 800-μg retinol activity

equivalents (RAE) per day for, respectively, women and men (US RDA, 700 and 900 μg/day, respectively). RAE have been established to account for the variability in carotenoid bioavailability, depending on the food matrix in which they are incorporated and the efficiency of their conversion to retinol following their enzymatic cleavage (56). Current RAE are as follows: 1-μg RAE = 1-μg retinol = 2-μg all-*trans*-βC from supplements = 12-μg all-*trans*-βC from food = 24-μg α-carotene or β-cryptoxanthin from food.

BCO1: β-carotene oxygenase 1

RAE: retinol activity equivalents

The contribution of proVA carotenoids as a source of VA depends on dietary habits, but a meta-analysis has shown that they represent 35% of total VA intake in developed countries (βC, 86%; α-carotene, 10%; β-cryptoxanthin, 4%) (135). Although frank VA deficiency is rare in developed countries, data point to dietary intakes below recommended levels in large parts of the population of several developed countries (127). Nevertheless, VA deficiency remains a public health problem in developing countries, mainly due to inadequate VA intake caused by insufficient access to VA-rich foods (i.e., animal products). It is estimated that about one-third of children are affected (90), but women of reproductive age are also at risk of deficiency. VA deficiency compromises the immune system, thus worsening the outcomes of common childhood infections (e.g., measles, malaria). The earliest symptom of VA deficiency is impaired night vision, which in extreme cases leads to irreversible blindness. According to the World Health Organization, night blindness is estimated to affect 250,000–500,000 children each year, 50% of whom die within the following year.

The xanthophylls lutein and zeaxanthin are present at high concentrations in the human macula lutea (the yellow spot of the retina), and there is a growing body of evidence suggesting that they exert a specific biological function in the eye. Several studies have demonstrated that they increase visual acuity and can quench 400–450-nm incident blue light, which is harmful to photoreceptors (87). Several other studies have also suggested that their consumption diminishes the incidence of cataract and age-related macular degeneration (6, 13).

Lycopene is the pigment responsible for the red color of tomatoes and tomato products. Both dietary intake and higher blood concentrations have been negatively associated with the risk of prostate cancer (32, 133) and cardiovascular disease (33). Since oxidative stress has been implicated in the etiology of these diseases, lycopene has been suggested to exert its protective effects through its antioxidant properties, which have been well characterized in vitro (75). However, lycopene also exhibits biological activity independent of its antioxidant effects: It modulates inflammation (49, 55, 86) and reduces the efficiency of cholesterol absorption (148), and several studies suggest that its metabolic products also exert nonantioxidant biological effects (8, 54, 55, 92).

2.4. Phytosterols

PS are plant-derived sterols with structural similarities to cholesterol, but with side chain modifications and ring saturations. PS are divided into two classes: Sterols, also known as Δ^5-sterols, are unsaturated at position 5 in the sterol ring, whereas stanols, also known as 5α-sterols, have a saturated sterol ring (**Figure 1**) (105). PS are found in fruits, vegetables, nuts, and oils, with Δ^5-sterols the most abundant class.

The intake of PS is between 200 and 400 mg/day in the typical diet in developed countries, depending on dietary habits, which is close to the average cholesterol intake. Most ingested PS are Δ^5-sterols, with the most abundant being sitosterol. High concentrations of PS are found in oils, such as corn and sunflower oils, and also in almonds, beans, corn, and wheat.

Due to their structural similarity, PS and cholesterol compete for incorporation into mixed micelles and subsequent uptake by the enterocyte. Overall, several meta-analyses have shown that PS added to food lead to a significant decrease in low-density lipoprotein (LDL) cholesterol (73, 108). No significant differences in terms of effect were observed between Δ^5-sterols and 5α-sterols.

3. BIOAVAILABILITY OF FAT-SOLUBLE VITAMINS AND PHYTOCHEMICALS

ABCG5: ATP binding cassette subfamily G member 5

ABCG8: ATP binding cassette subfamily G member 8

The bioavailability of an ingested molecule is usually defined as the relative amount of the molecule or one of its metabolites that reaches the systemic circulation or its site of action. In practice, biologists use different methods to assess it. For example, pharmacologists usually estimate the bioavailability of an orally administered drug by measuring the postprandial blood concentration of the drug or one of its metabolites. Nutritionists use this method as well as alternative methods. Indeed, they also estimate the bioavailability of a molecule by measuring the increase in its fasting blood concentration following either acute or chronic supplementation. They also estimate bioavailability by measuring the increase in concentration in a tissue where it is assumed to exert its biological action, for example, measuring carotenoids in the skin. Additionally, they estimate tissue bioavailability by quantifying a marker, the level of which correlates with the tissue concentration of the studied molecule, for example, measuring macular pigment optical density, which is used as a marker of xanthophyll concentration in the macula lutea. Techniques using stable isotopes of fat-soluble vitamins and phytochemicals allow nutritionists to measure more accurately the amount of these absorbed through the diet (95, 128). It should be emphasized that most approaches, with the exception of the last mentioned, measure only the relative bioavailability of fat-soluble vitamins and phytochemicals.

Different approaches can be used to assess the bioavailability of the same molecule. For example, lutein bioavailability can be estimated by measuring postprandial chylomicron concentrations (24), plasma concentrations after a lutein-rich test meal, the long-term plasma lutein response to daily lutein supplementation (58), or variation in macular pigment optical density after long-term lutein supplementation (19). The relative weights of the metabolic processes modulating the bioavailability of fat-soluble vitamins and phytochemicals differ according to the assessment method used. Thus, studies investigating genetic variations associated with variability in the bioavailability of fat-soluble vitamins and phytochemicals are likely to yield different results if different bioavailability assessment methods are used.

The bioavailability of fat-soluble vitamins and phytochemicals depends on several successive steps, from their transfer from the food or supplement through which they are ingested to the tissues where their concentration is measured. To put into perspective some of the genetic associations discussed in this review, we briefly describe these steps, focusing on the proteins that can significantly impact the bioavailability of fat-soluble vitamins and phytochemicals. (Readers can find more detailed information in the reviews in References 16, 18, 20, 21, 40, and 112.) The first step is to extract the compounds from food or supplements and transfer them to mixed micelles; that is, they undergo micellization (**Figure 2**). The efficiency of this step is only partial, and the fraction of fat-soluble vitamins and phytochemicals that is thus made potentially available for absorption is referred as the bioaccessible fraction. The second step is the uptake of these compounds or their metabolites, produced during digestion, by the enterocyte (**Figure 3**). A third step is their resecretion in the intestinal lumen. This process can be quantitatively important for some fat-soluble vitamins and phytochemicals, for example, PS, which are excreted from the enterocyte by the ATP (adenosine triphosphate) binding cassette subfamily G members 5 and 8 (ABCG5 and ABCG8) heterodimer. The compounds that remain in the intestinal cell are then transported across the enterocyte to be secreted at the basolateral side, mostly in chylomicrons but also in intestinal high-density lipoprotein (HDL). Parent fat-soluble vitamins and phytochemicals and their metabolites are mostly secreted in the lymph fluid, but some less apolar metabolites are also secreted in the portal vein. Following their uptake, metabolism, and secretion into the bloodstream by the liver, the blood metabolism of different fat-soluble vitamins and phytochemicals

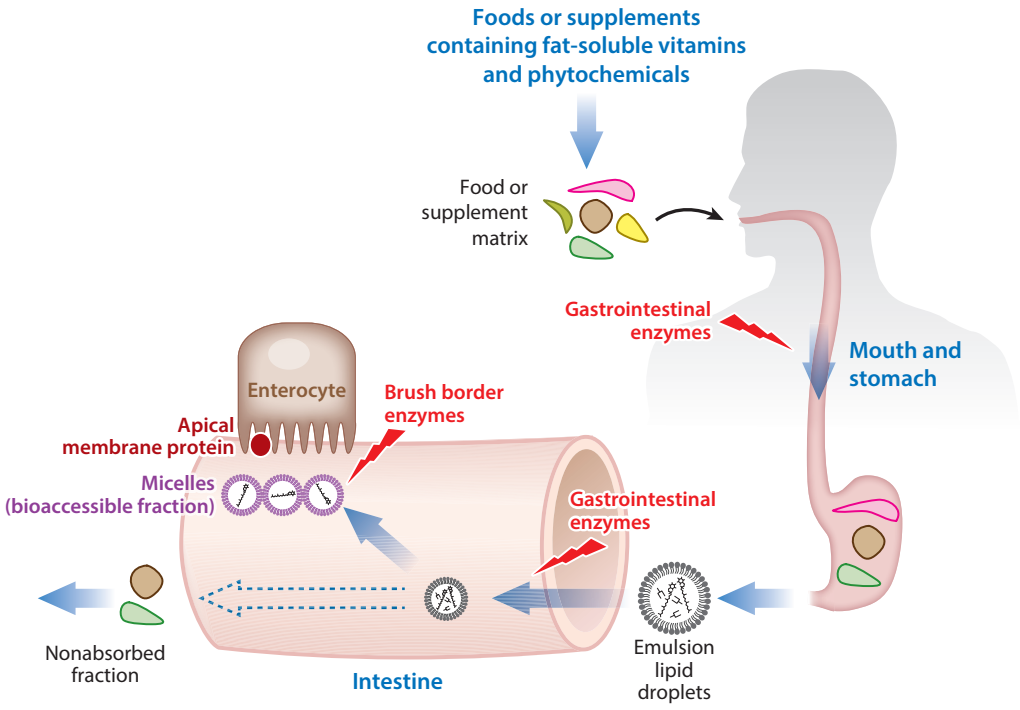


Figure 2

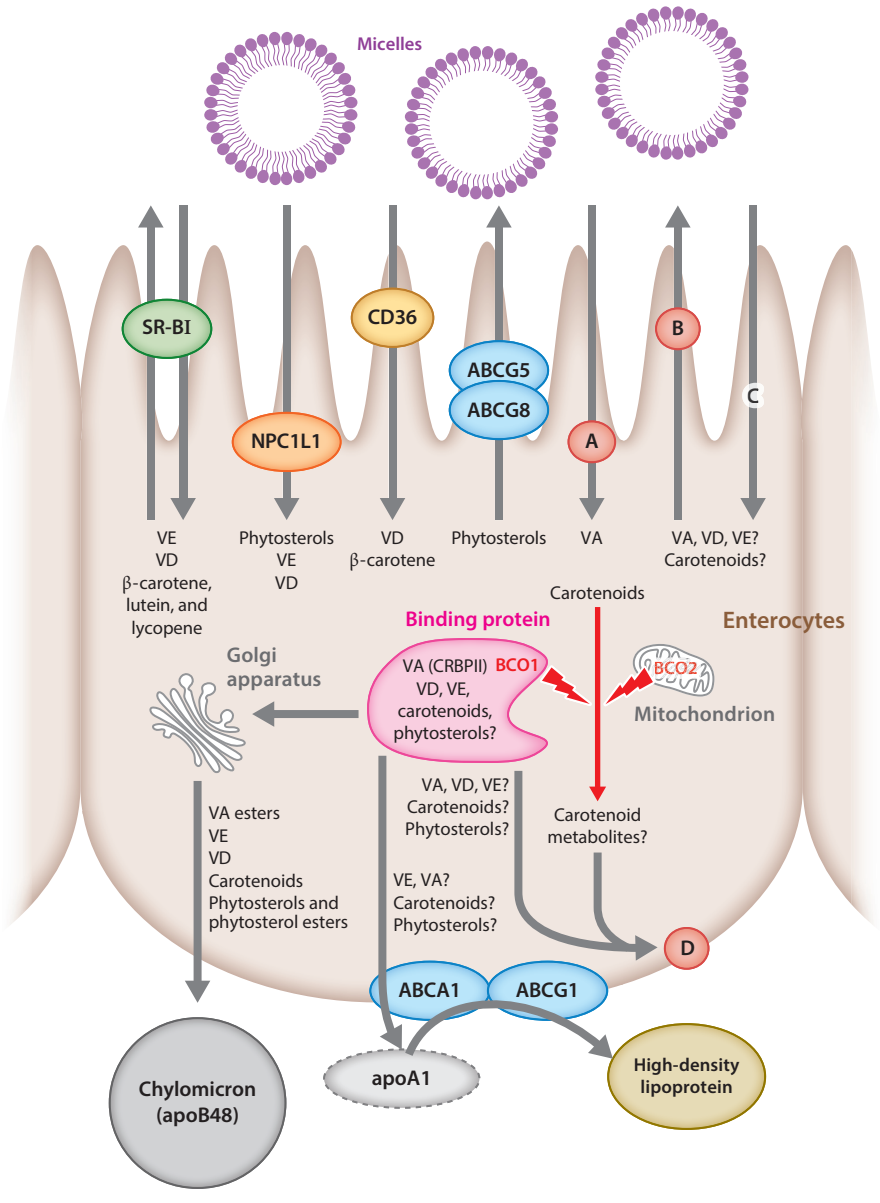
The fate of fat-soluble vitamins and phytochemicals in the lumen of the upper gastrointestinal tract during digestion. Shown are the different vehicles assumed to transport these compounds in the human upper gastrointestinal lumen.

and their metabolites differs because some—such as VE, carotenoids, and PS—are transported in lipoproteins, while others are transported by specific proteins; for example, retinol is transported by the retinol binding protein 4–transthyretin complex (RBP4–TTR) and 25(OH)D by DBP. Several different factors can affect these processes, and furthermore, the fact that numerous proteins are implicated in the bioavailability of fat-soluble vitamins and phytochemicals (**Figure 3**) likely explains the high interindividual variability that has been observed for all of those that have been studied. Indeed, after standardized test meals rich in fat-soluble vitamins and phytochemicals were given to a group of healthy participants, the coefficient of variation of the blood response, which was used as a marker of their bioavailability, ranged from 47% for VD given as a supplement to 137% for lutein given in tomato puree (22–25, 41).

De Pee & West (39) were the first to propose a systematic review of the factors assumed to affect the bioavailability of carotenoids. These factors have also been suggested to affect, although differently, the bioavailability of other fat-soluble vitamins and PS (17), and are summarized by the acronym SLAMENGHI (136). Each letter stands for one factor, for example, S is for molecular species, L for molecular linkage, etc. Among all these factors, three are linked with the effects of the individual: N, which stands for the nutrient status of the host and explains, for example, the effect of vitamin A status on βC bioavailability and bioconversion (82); G, which stands for the effects of genetic factors; and H, which stands for host-related effects, for example, sex, age, and disease. It is assumed that the genetic factors are particularly important with regard to the interindividual variability of the bioavailability of fat-soluble vitamins and phytochemicals (16). The

effect of genetic factors on this interindividual variability was first demonstrated for PS. Indeed, Berge et al. (11) showed that mutations in *ABCG5* and *ABCG8* led to the accumulation of PS, which can cause sitosterolemia, because the membrane transporters encoded by these genes are responsible for sterol excretion in enterocytes and hepatocytes. Further study has shown that single nucleotide polymorphisms (SNPs) can also have significant effects on blood concentrations of PS (57), showing for the first time that genetic polymorphisms can significantly affect the bioavailability of fat-soluble vitamins and phytochemicals. Nevertheless, the effect of genetic variations on the bioavailability of other fat-soluble vitamins and phytochemicals was addressed only recently.

SNP: single nucleotide polymorphism



(Caption appears on following page)

Figure 3 (*Figure appears on preceding page*)

Proteins involved in the uptake, transport, and secretion pathways of fat-soluble vitamins and phytochemicals (VA, VD, and VE; carotenoids; and phytosterols) across enterocytes. VD and VE, carotenoids, and phytosterols are taken up from mixed micelles by the apical membrane proteins SR-BI, NPC1L1, and CD36. The apical membrane protein (or proteins) involved in apical uptake of preformed VA (retinol) has not been identified. Most phytosterols are effluxed back to the intestinal lumen by the heterodimer ABCG5–ABCG8. A fraction of vitamins and carotenoids might be effluxed back to the intestinal lumen via apical membrane transporters (SR-BI and possibly others). The noneffluxed fraction of micronutrients is transported to the site where they are incorporated into chylomicrons. It is hypothesized that proteins are involved in the intracellular transport of these non-water-soluble compounds, although only CRBPII, which carries retinol, has clearly been identified. Nonmetabolized vitamins, carotenoids, and phytosterols are mostly secreted in the lymph fluid into chylomicrons (through the apoB pathway), either as free or esterified molecules, while part of the more polar vitamins and carotenoid metabolites may be secreted via the portal route. It has been shown that a minor fraction of VE can also be secreted at the basolateral side via ABCA1 and also possibly ABCG1, but it is not known whether this apoA1 pathway is also involved in the secretion of a fraction of the other micronutrients. Abbreviations: ?, putative pathway; A, putative retinol-specific transporter; ABCA1, ATP binding cassette subfamily A member 1; ABCG, ATP binding cassette subfamily G; apo, apolipoprotein; B, unidentified apical efflux transporter; BCO, β-carotene oxygenase; C, passive diffusion; CD36, CD36 molecule; CRBPII, cellular retinol binding protein type II; D, unidentified basolateral efflux transporter; NPC1L1, NPC1 like intracellular cholesterol transporter 1; SR-BI, scavenger receptor class B type I; V, vitamin. **Figure 3** adapted with permission from Reference 112.

This is probably because the absorption of these compounds was thought to occur through simple passive diffusion. However, as reviewed in 2011, several studies have now clearly demonstrated that intestinal cell proteins are involved in the absorption of these compounds (**Figure 3**) (112). This discovery, together with the emergence of affordable genotyping technologies, has led to the first studies investigating the association of genetic variations with the bioavailability of fat-soluble vitamins and phytochemicals other than PS (22–25, 41, 88, 132).

4. GENETIC VARIATIONS ASSOCIATED WITH BIOAVAILABILITY OF FAT-SOLUBLE VITAMINS AND PHYTOCHEMICALS

4.1. Vitamin E

Three clinical trials identified genetic variations associated with variability in VE bioavailability, but two fairly different methods were used to evaluate bioavailability, thus leading to a potential source of result heterogeneity, as highlighted in the previous section. Both Major et al. (85) and Athinarayanan et al. (7) measured VE blood concentrations following VE supplementation. In the first study (85), 2,112 male smokers received 50 mg/day all-*rac*-α-tocopheryl acetate (68 IU) for 3 years. Using a genome-wide association study (GWAS) approach (549,989 SNPs analyzed), 3 independent SNPs were found to be significantly associated with the variability in VE response. The association with the SNP rs964184, which is located between the BUD13 homolog (*BUD13*) and zinc finger protein 259 (*ZNF259*), is likely due to a variation in apolipoprotein A5 (*APOA5*) because this SNP is located close to the *APOA1/C3/A4/A5* cluster, as suggested by Ferrucci et al. (50). Indeed, *ZNF259* and *BUD13* encode for proteins with no known role in VE metabolism. An association with a SNP (rs2108622) located in cytochrome P450 family 4 subfamily F member 2 (*CYP4F2*) was also significant. *CYP4F2* encodes for the rate-limiting enzyme responsible for hepatic VE ω-oxidation. Sodium/potassium transporting ATPase interacting 3 (*NKAIN3*) encodes for a plasma membrane–bound Na^+/K^+-ATPase, whose activity is critical to maintaining cell viability and sensitive to radicals produced during lipid peroxidation. The inhibitory effect of VE on lipid

GWAS: genome-wide association study

peroxidation could thus explain the association with a SNP (rs7834588) in this gene. In the second study (7), 247 adults with nonalcoholic steatohepatitis and 173 children with nonalcoholic fatty liver disease received VE (*RRR*-α-tocopherol, 800 IU) for 96 weeks. Of the two nonsynonymous SNPs investigated, a SNP in *CYP4F2* (rs2108622) was significantly associated with a higher VE response following supplementation for 48 weeks, but not after 96 weeks. In a clinical trial by our group (25), the association was assessed for SNPs in genes involved in VE absorption and metabolism (3,769 SNPs in 59 candidate genes) with variability in VE bioavailability, measured as the postprandial chylomicron VE concentration, in a group of 38 healthy adult men who received a meal containing 100-IU *RRR*-α-tocopheryl acetate. A combination of 28 SNPs in 11 candidate genes was shown to be significantly associated with this variability. Of those 11 genes, 7 had been previously associated with interindividual variability in the postprandial chylomicron triglyceride response in the same group of participants (43), while the remaining 4 encode for proteins that are more specifically involved in VE metabolism and transport. ATP binding cassette subfamily G member 1 (*ABCG1*) may be involved in the basolateral efflux of VE from enterocytes to HDL (99, 104). Pancreatic lipase is a critical enzyme for the intestinal hydrolysis of dietary triglycerides and thus participates in the transfer of VE from oil droplets of dietary lipid emulsions to mixed micelles, a necessary step for VE absorption. The apical sodium bile acid transporter (ASBT), encoded by solute carrier family 10 member 2 (*SLC10A2*), is responsible for the reuptake of luminal bile acids in the ileum (38). Since bile acids are essential for normal VE absorption (118), SNPs in this gene could affect VE bioavailability. Sterol regulatory element binding transcription factor 2 (*SREBF2*) encodes a transcription factor controlling the expression of many genes required for cholesterol synthesis (64) and also that of *SLC10A2* and NPC1 like intracellular cholesterol transporter 1 (*NPC1L1*) (4), which encodes the main protein involved in the apical uptake of cholesterol (5) and also α-tocopherol (96) into enterocytes.

NPC1L1: NPC1 like intracellular cholesterol transporter 1

***GC* (gene):** vitamin D binding protein

4.2. Vitamin D

Several clinical trials have identified SNPs associated with variability in VD bioavailability, with all but one evaluating VD bioavailability as the circulating 25(OH)D concentration following VD supplementation, generally for several weeks. In summary, SNPs in *CYP2R1* (10, 44, 103, 114, 134, 139), cytochrome P450 family 24 subfamily A member 1 (*CYP24A1*) (10), *VDR* (10, 114, 139), vitamin D binding protein (*GC*) (44, 103, 139), calcium sensing receptor (*CASR*) (114), and retinoid X receptor alpha (*RXRA*) (141) have been associated with the 25(OH)D response following VD supplementation. *CYP2R1* encodes for a hepatic hydroxylase responsible for the conversion of VD to 25(OH)D (143). *CYP24A1* encodes for an enzyme that catalyzes the rate-limiting step in 25(OH)D and 1,25$(OH)_2$D catabolism in the kidney (34). *VDR* encodes for the nuclear receptor mediating the biological effects of 1,25$(OH)_2$D (34). *GC* encodes for VDR, which is responsible for the blood transport of all VD metabolites (34). *CASR* encodes for a plasma membrane G protein–coupled receptor that senses small changes in circulating calcium concentration. Although VD involvement in calcium homeostasis has been well described, and VD response elements have been identified in *CASR* (28), there is as yet no explanation why SNPs in this gene might affect VD bioavailability. *RXRA* encodes for one of the nuclear receptors that mediates the biological effects of retinoic acid, but no hypothesis has been put forward to explain the association of SNPs in this gene with VD bioavailability. Finally, Zhou et al. (142) have shown that the methylation levels of *CYP2R1* and *CYP24A1* are associated with the increase in serum 25(OH)D concentration following 12 months of VD supplementation. Only one study has investigated the association between SNPs and variability in the postprandial chylomicron VD concentration, which constitutes a more precise evaluation of VD bioavailability (41). In this study

ABCA1: ATP binding cassette subfamily A member 1

***SCARB1* (gene):** scavenger receptor class B member 1

SR-BI (protein): scavenger receptor class B member 1

from our group, 39 healthy adult men received a meal containing 5-mg VD_3 as a supplement, and the association was assessed between SNPs in genes involved in VD absorption and metabolism (3,791 SNPs in 61 candidate genes) and variability in VD response. A combination of 17 SNPs in 13 genes was shown to be significantly associated with this variability. Of those 13 genes, 5 [ATP binding cassette subfamily A member 1 (*ABCA1*), apolipoprotein B (*APOB*), Bet1 golgi vesicular membrane trafficking protein (*BET1*), lipoprotein lipase (*LPL*), and N-acetyltransferase 2 (*NAT2*)] had been previously associated with interindividual variability in the postprandial chylomicron triglyceride response in the same group (43). Additionally, eight genes that encode for proteins that are apparently more specifically involved in VD metabolism and transport were also associated with this variability: ATP binding cassette subfamily B member 1 (*ABCB1*), 7-dehydrocholesterol reductase (*DHCR7*), intestine specific homeobox (*ISX*), microtubule-associated protein RP/EB family member 2 (*MAPRE2*), pancreatic lipase (*PNLIP*), *SLC10A2*, *GC*, and scavenger receptor class B member 1 (*SCARB1*). Detailed explanations and hypotheses for these associations are discussed in the original paper (41), but it is interesting that SNPs were found in *ISX* and *SCARB1*: *ISX* has been shown to regulate *SCARB1* expression (137), and *SCARB1* encodes for an apical membrane protein, SR-BI, which has been shown to participate in VD uptake by enterocytes (113). Although ASBT, encoded by *SLC10A2*, had been proposed to facilitate VD apical uptake by enterocytes, we were not able to confirm this hypothesis in an in vitro study, and hence a more indirect effect, through its role in bile acid transport, should be considered (42).

4.3. Carotenoids

For fasting blood concentrations, data are available for only the three main carotenoids, but it is assumed that genetic variations also modulate the bioavailability of the other carotenoids found in human blood and tissue.

4.3.1. β-carotene. Four clinical trials were dedicated to identifying genetic variations associated with interindividual variability in βC bioavailability, which was first described 20 years ago (26). In the first study, Leung et al. (80) measured the postprandial concentrations of the triglyceride-rich lipoprotein βC and retinyl palmitate in 28 healthy adult women (nonsmokers) who received a meal supplemented with 120-mg βC. They observed that two common, nonsynonymous SNPs in *BCO1* (rs12934922 and rs7501331) were associated with a decrease in βC conversion capacity, as assessed by the retinyl palmitate:βC ratio in the triglyceride-rich lipoprotein fraction. These SNPs were also associated with an increase in fasting blood concentrations of βC. Hence, this study provided insights into the genetics of the poor βC converter phenotype. In another study of the same volunteers, Lietz et al. (81) observed a significant association among three of six SNPs upstream from *BCO1* (rs6420424, rs11645428, and rs6564851) and βC conversion capacity. Interestingly, as highlighted by the authors, these SNPs exhibit highly different genotype frequencies in 11 populations from the International HapMap (haplotype map) Project, possibly pointing to selection pressure related to VA status. Wang et al. (132) measured blood βC concentration in 23 healthy adults (nonsmokers) following 3 weeks' consumption of watermelon juice providing 2.5-mg βC per day. The two nonsynonymous SNPs previously investigated by Leung et al. (80) (rs12934922 and rs7501331) were found to be associated with the blood βC response, measured as strong ($n = 17$) versus weak ($n = 6$) following a cluster analysis. It should be noted that the supplement used in this study provided a βC dose closer to normal nutritional intakes than the pharmacological dose used in the previously discussed studies.

The association of SNPs with βC bioavailability in genes other than *BCO1* was investigated in only one study (22). In this clinical trial from our group, 33 healthy adult men received a

meal containing 100-g tomato puree providing 0.4-mg βC. The association was assessed between variability in the postprandial chylomicron βC concentration and genes involved in βC absorption and metabolism (2,172 SNPs in 54 candidate genes). A combination of 25 SNPs in 12 genes was shown to be associated with variability in the βC response. Four of these genes [*ABCA1; APOB;* lipase C, hepatic type (*LIPC*); transcription factor 7 like 2 (*TCF7L2*)] had been previously associated with interindividual variability in the postprandial chylomicron triglyceride response in the same group (43), while eight were more specifically associated with the βC response. Detailed explanations and hypotheses for these associations are discussed in the original paper (22), but two genes deserve closer attention. Three SNPs were found in *ISX*, which encodes for a transcription factor involved in βC intestinal absorption and conversion that regulates BCO1-mediated βC cleavage and SR-BI-mediated βC enterocyte apical uptake (137). Another study reported that a SNP in the ISX binding site in the *BCO1* promoter (rs6564851) was associated with a 50% decrease in conversion rates of βC and with increased fasting blood concentrations of βC (82). Hence, these data confirm the key role played by ISX in βC bioavailability (82). Additionally, a SNP in *BCO1* was found to be associated with βC response in these 33 participants. The second association of interest was found in *ELOVL2* (ELOVL fatty acid elongase 2). This gene encodes for an elongase responsible for the elongation of eicosapentaenoic acid to docosapentaenoic acid and subsequently the elongation of docosapentaenoic acid to docosahexaenoic acid. Although βC is not considered to be a substrate for this enzyme, this association is possibly due to the inhibitory effect of eicosapentaenoic acid on βC absorption (89).

ISX: intestine specific homeobox

ELOVL2: ELOVL fatty acid elongase 2

CD36: CD36 molecule

4.3.2. Lycopene. Only two clinical trials have been dedicated to identifying genetic variations associated with variability in lycopene bioavailability. Wang et al. (132) measured blood lycopene concentration in 23 healthy adults (nonsmokers) following 3 weeks' consumption of watermelon juice providing 20-mg lycopene per day. The association between lycopene concentrations and two nonsynonymous SNPs in *BCO1* was tested, but neither SNP had a significant effect. However, it should be noted that the sample size was small and that lycopene responsiveness was measured only as strong ($n = 17$) versus weak ($n = 6$) following a cluster analysis. In the second clinical trial (23), carried out by our group, the association was assessed between SNPs in genes involved in lycopene absorption and metabolism (1,885 SNPs in 49 candidate genes) and variability in the postprandial chylomicron lycopene concentration in a group of 33 healthy adult men who received tomato puree providing 9.7-mg all-*trans*-lycopene. A combination of 28 SNPs in 16 genes was shown to be associated with variability in the lycopene response. Seven of these genes [*ABCA1*, *LPL*, insulin induced gene 2 (*INSIG2*), solute carrier family 27 member 6 (*SLC27A6*), *LIPC*, CD36 molecule (*CD36*), and *APOB*] had been previously associated with interindividual variability in the postprandial chylomicron triglyceride response in the same group of participants (43). Four genes were more specifically associated with lycopene bioavailability, and the *p* values were significant following correction for multiple comparisons. *ABCB1* encodes for P-glycoprotein, an ATP-dependent drug efflux pump for xenobiotics with broad substrate specificity, which is highly expressed in enterocytes. This association suggests that P-glycoprotein may modulate lycopene absorption efficiency by causing excretion of a fraction of lycopene that is taken up into the intestinal lumen. The potential interaction of SNPs in *ELOVL2* with carotenoid bioavailability has been addressed in the previous discussion of βC. Microsomal triglyceride transfer protein (*MTTP*) encodes a protein that has a critical role in the assembly of chylomicrons. SOD2 [encoded by superoxide dismutase 2 (*SOD2*)] binds to the superoxide by-products of oxidative phosphorylation and converts them to hydrogen peroxide and diatomic oxygen. SNPs in *SOD2* have been associated with increased prostate cancer risk (74), and lycopene has been suggested to modify the deleterious

effect of these SNPs (123), possibly by quenching superoxide by-products, thereby leading to lycopene degradation.

4.3.3. Lutein. Since higher blood lutein concentrations, together with those of another xanthophyll, zeaxanthin, have been associated with protection from age-related macular degeneration (52), studies investigating the association between genetic variations and variability in lutein bioavailability have measured lutein bioavailability in both blood and the macula lutea, that is, the site of lutein action. In a first study, Yonova-Doing et al. (140) measured macular pigment optical density in 310 Caucasian female twins aged 20–50 years before and after they received 54-mg lutein and 7.2-mg zeaxanthin daily for 6 months. The association was investigated between changes in macular pigment optical density and candidate SNPs (12 SNPs in eight genes), which had been previously associated with circulating and macular levels of carotenoids, and 4 SNPs were found to be significantly associated with the macular pigment optical density response to supplementation. The association with the SNP found in *ABCA1* (rs1929841) could be a consequence of the role of this membrane protein in lipid influx into the retinal pigment epithelium (45) or to enterocyte basolateral secretion of lutein in intestinal HDL (101), or both. A SNP in *SCARB1* (rs11057841) was associated with variability in the macular pigment optical density response, as well as with baseline serum lutein concentration. Fatty acid desaturase 1 (*FADS1*) encodes for a desaturase involved in the conversion of α-linolenic acid to eicosapentaenoic acid. The association of a SNP (rs174534) in this gene with variability in macular pigment optical density could be due to the inhibitory effect of eicosapentaenoic acid on carotenoid absorption, as mentioned in Section 4.3.1. *SCARB1* encodes for SR-BI, a protein expressed ubiquitously, that participates in the apical uptake of lutein into enterocytes (112) and also in the uptake of blood HDL, which carries lutein into retinal pigment epithelium, although it has been shown that lutein is preferentially taken up in this tissue from LDL via an LDL receptor–mediated mechanism (122).

Finally, a SNP in retinoid isomerohydrolase (*RPE65*) (rs4926339) was also associated with the macular pigment optical density response following lutein supplementation. This gene encodes a protein highly expressed in the retinal pigment epithelium, which works as a retinol isomerase of the visual cycle and is involved in visual pigment regeneration. Interestingly, this protein was also shown to act as an isomerase responsible for the production of *meso*-zeaxanthin (another xanthophyll found in the macula lutea) from lutein (117).

In another clinical trial from our group (24), the association was assessed of SNPs in genes involved in lutein absorption and metabolism (1,785 SNPs in 51 candidate genes) with variability in the postprandial chylomicron lutein concentration in a group of 39 healthy adult men who received a meal supplemented with 15-mg free lutein. A combination of 29 SNPs in 15 genes was shown to be associated with variability in the lutein response. Nine of these genes [*ABCA1*, *APOA1*, *APOB*, cordon-bleu WH2 repeat protein like 1 (*COBLL1*), *LIPC*, *INSIG2*, insulin receptor substrate 1 (*IRS1*), *LPL*, and melanocortin 4 receptor (*MC4R*)] had been previously associated with interindividual variability in the postprandial chylomicron triglyceride response in the same group of participants (43). Four genes were more specifically associated with lutein bioavailability, and the *p* values were significant following correction for multiple comparisons: ATP binding cassette subfamily G member 2 (*ABCG2*), *ELOVL2* , *ISX*, and *MTTP*. The potential association of the last three genes with carotenoid metabolism has been discussed above. *ABCG2* encodes for the breast cancer resistance protein (BCRP, also known as ABCG2), which is a multidrug transporter (98). This membrane protein has been suggested to be involved in lutein intestinal absorption, but no clear mechanism has been demonstrated.

4.4. Phytosterols

As mentioned in Section 3, studies searching for mutations causing sitosterolemia—a rare autosomal recessive disorder characterized by elevated blood PS concentration and pathological accumulation of PS in several tissues—were the first dedicated to identifying genetic variations associated with the bioavailability of fat-soluble vitamins and phytochemicals. These studies allowed researchers to link this disease to mutations in two genes, *ABCG5* and *ABCG8*, which encode for two ATP binding cassettes, sterolin-1 and sterolin-2, that work as hemitransporters (11, 79). These proteins are in charge of the excretion of PS, from enterocytes to the intestinal lumen and from hepatocytes to bile, normally a very efficient process. This discovery led to the hypothesis that genetic polymorphisms in these two genes could modulate PS bioavailability, albeit to a minor extent, that is, asymptomatically. This was confirmed by several association studies, including one GWAS, which showed that SNPs, located mainly in *ABCG8* for an unknown reason, are associated with fasting blood concentrations of PS (12, 57, 63, 65, 70, 94, 115, 121). Nevertheless, understanding the dual role of these transporters in PS metabolism—that is, in enterocytes and hepatocytes—these associations do not provide definite evidence that SNPs in these transporters affect PS intestinal absorption. Indeed, it is possible that the associations observed were mostly due to an effect of hepatocytes on PS excretion and not to an effect of enterocytes on PS excretion. Finally, Plat et al. (109) showed that SNPs in *ABCG8* could modulate changes in blood concentrations of PS after consumption of PS, providing additional evidence that SNPs in *ABCG8* likely affect the bioavailability of PS.

The bioavailability of PS is not only under the control of ABCG5 and ABCG8: Several other proteins and genes are involved directly or indirectly in transporting PS across the enterocyte and in the blood and other tissues. For example, at the enterocyte level, PS have been shown to be taken up, at least partly, by a process mediated by NPC1L1 (37). Thus, it is likely that genetic variations in genes other than *ABCG5* and *ABCG8* can modulate the bioavailability of PS. Yet candidate gene association studies have focused only on *NPC1L1* and *APOE*. These have confirmed what was expected, that is, that SNPs in *NPC1L1* modulate the bioavailability of PS (35, 83, 84). Concerning *APOE*, two studies observed that participants with the *APOE* 3/4 or 4/4 alleles absorbed PS more effectively than participants with the *APOE* 3/3 allele (83, 120). To the best of our knowledge, no biological mechanism has been suggested to explain how APOE can modulate the absorption of PS. Furthermore, although it was observed that intestinal cholesterol absorption, and thus possibly the absorption of PS, was related to the *APOE* genotype (76), another study did not confirm this finding (130). Thus, the elucidation of the role of genetic variation in *APOE* on the bioavailability of PS requires further investigation.

To be comprehensive, it should be mentioned that a SNP in a locus that was not expected to be involved in the metabolism of PS, the blood group *ABO* locus (alpha 1–3-N-acetylgalactosaminyltransferase and alpha 1–3-galactosyltransferase), was independently associated with fasting serum concentrations of PS in the only GWAS dedicated to identifying genetic variations associated with this phenotype (121). The authors have speculated that this association is perhaps related to the *N*-linked glycosylation of ABCG5 or ABCG8 protein, or both. Indeed, it has been hypothesized that these transporters may lose part of their activity when they are not glycosylated, as is the case with the blood *O* allele, leading to the loss of glycosyltransferase activity. In any case, it should be demonstrated whether SNPs in the *ABO* locus can modulate not only fasting blood concentrations of PS but also the bioavailability of PS.

5. FUTURE STUDIES

As highlighted in Section 4, the identification of genetic variations that can affect the bioavailability of fat-soluble vitamins and phytochemicals has been tackled only recently, and consequently, only

a few studies are available. Several validations are necessary in genetic association studies before definite conclusions can be drawn, so the results obtained to date should be considered preliminary. However, these studies serve as proof-of-concept studies, showing that methods and technologies are available to identify these genetic variations. In this section, we discuss the limits of the association studies and suggest some guidelines for future studies (**Figure 4**) to ensure that results can be translated into tailored dietary recommendations.

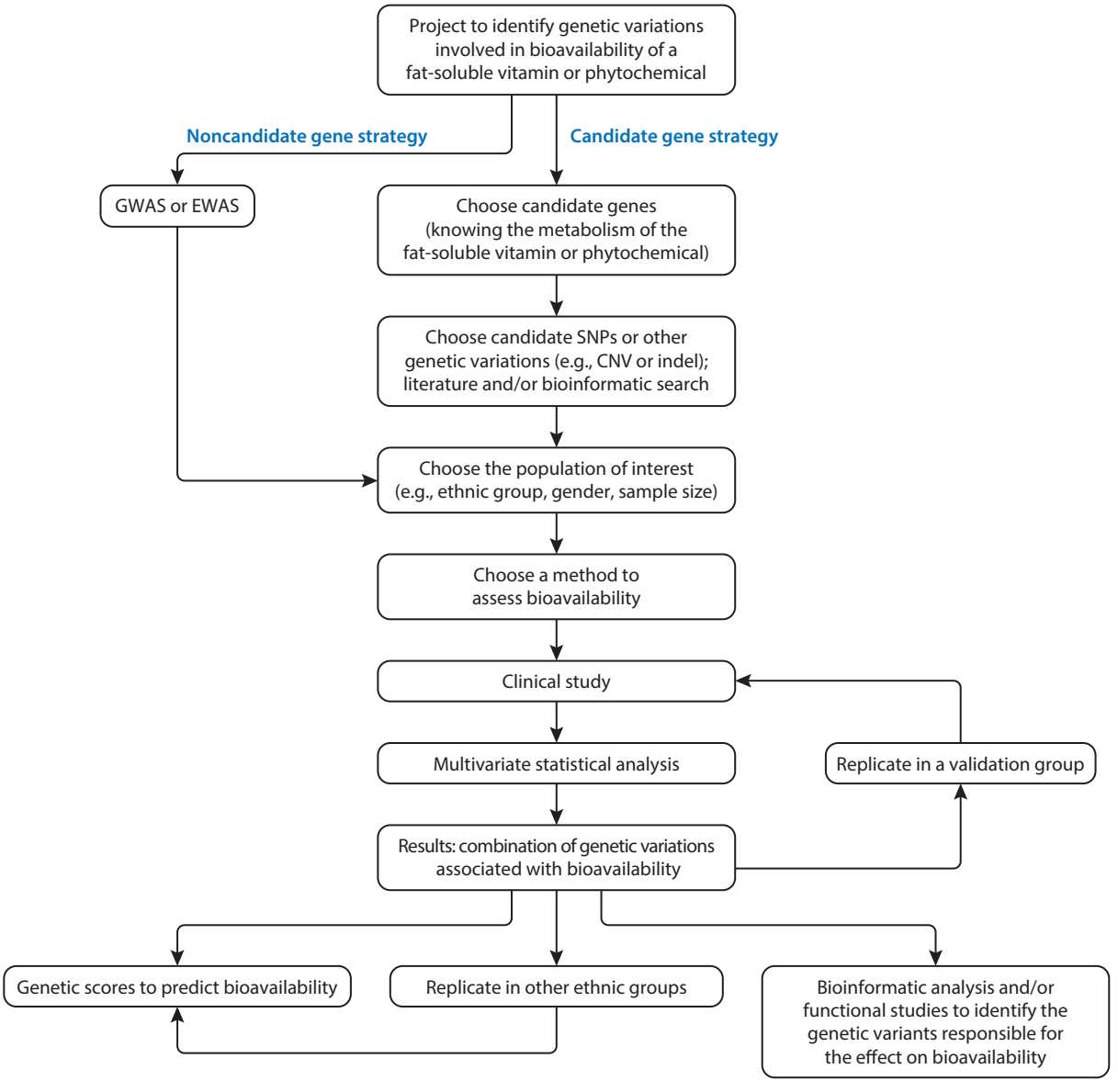


Figure 4

Procedure and guidelines for performing studies dedicated to identifying genetic variations involved in the bioavailability of fat-soluble vitamins and phytochemicals. Abbreviations: CNV, copy number variant; EWAS, exome-wide association study; GWAS, genome-wide association study; indel, insertion/deletion; SNPs, single nucleotide polymorphisms.

Association studies usually allow geneticists to conclude that an identified genetic variant modulates the phenotype of interest directly or is in linkage disequilibrium with some nearby genetic variant that affects the phenotype. Thus, to definitively demonstrate the involvement of a genetic variant, researchers must perform functional studies in which the effect of the different variant alleles on the studied phenotype can be evaluated, as was done in vitro to study the effects of *NPC1L1* variants on cholesterol absorption (47) or the effects of *BCO1* variants on βC absorption and cleavage (80). Nevertheless, because most genetic variations identified have only minor effects on bioavailability—that is, they modulate only a few percent of bioavailability—it is likely to be difficult to demonstrate significant biological effects in such studies. This is probably why we first observed that few studies have tried to study the biological effects of genetic variants. Nevertheless, we believe that priority should be given to building genetic scores that can accurately predict the phenotype of an individual or population group.

The second observation is that all studies dedicated to identifying genetic variants associated with the bioavailability of fat-soluble vitamins and phytochemicals followed a candidate gene approach. The advantage of this approach is that it does not require a large number of participants; thus it limits the risk of false-positive associations. However, many genes and SNPs that potentially have effects on the bioavailability of fat-soluble vitamins and phytochemicals are left out of the analyses. Thanks to progress made in high-throughput genotyping, GWAS investigations may be used to identify genetic variations associated with variability in the bioavailability of these compounds. GWAS investigations have the advantage of not making assumptions about the genetic variations that may affect the studied disease or phenotype, thus allowing researchers to identify unexpected associations. Nevertheless, GWAS investigations also have drawbacks. Since a very large number of genetic variations is investigated, the sample size required to limit false-positive associations is large (typically >10,000 participants). This can lead to false-negative associations, that is, the rejection of genetic variants that are marginally associated with the studied disease or phenotype. Another drawback of the large sample size inherent to a GWAS is the high cost. This is clearly a huge constraint if an accurate method is used to evaluate bioavailability, that is, when the cost of phenotyping largely exceeds that of genotyping. Thus, we suggest that the cost of phenotyping should be reduced, for example, by decreasing the number of postprandial blood samples that are drawn. Another point that deserves attention is that all studies of this topic looked at SNPs for which the minor allele frequency was at least 1% in the studied populations. Yet we hypothesize that SNPs that have a large effect on a phenotype are infrequent because they are under selective pressure due to the disadvantage they confer on the people who have them. Thus, an interesting approach might be to perform exome sequencing of key candidate genes involved in a phenotype, for example, intestinal transporters of fat-soluble vitamins and phytochemicals, and to assess whether some less frequently occurring SNPs are involved in the phenotype.

The third observation that arises from studies is that the methods used to evaluate the bioavailability of fat-soluble vitamins and phytochemicals were heterogeneous. As discussed in Section 3, this can have huge consequences for the observed associations because different genes might be involved in modulating the concentrations of the compounds that are actually measured. Thus, to compare or validate genetic associations observed in different studies, researchers must first check whether the studies used similar methods to evaluate bioavailability. Therefore, we advise that future genetic studies use the same standardized method to evaluate bioavailability. Measuring the postprandial chylomicron response at three to four postprandial intervals might be a good compromise between accuracy and cost and practicality.

The fourth observation is that no validation cohort was used in the studies. Yet genetic associations require observations of several independent groups of participants. This lack of

validation cohorts is likely due to the fact that measuring the bioavailability of fat-soluble vitamins and phytochemicals is complicated and costly compared with measuring, for example, fasting blood concentrations of them. Nevertheless, future studies need to meet the requirements of well-designed genetic association studies, and this includes the use of replication cohorts (62).

The fifth observation is that the participants in most studies were Caucasian males. Because some genetic associations depend on sex, it is advisable to include both females and males in studies to ensure that the associations observed apply to the whole population. Furthermore, genotyping of different ethnic groups has shown that genetic variants are not linked similarly, that is, haplotype blocks are not the same in different populations (67, 68, 116). Thus, it is possible that a polymorphism will be in linkage disequilibrium with a nearby allele that modulates the bioavailability of fat-soluble vitamins and phytochemicals in one population but not in another, leading to variable results in association studies. Moreover, SNPs involved in the variability of bioavailability might exhibit fairly different allele frequencies, depending on the ethnic group investigated. Thus, studies must be conducted with different ethnic groups to verify whether genetic variations are associated with bioavailability in these groups or to identify genetic variations that are specific to different groups.

Although it is assumed that SNPs explain most of the genetic variability between individuals, this is not the only kind of genetic variation that happens in the human genome. Indeed, there are also, for example, microsatellites, variable number tandem repeats, copy number variants, and insertion/deletion polymorphisms (1). There is no reason to believe that some of these genetic variations do not also affect the bioavailability of fat-soluble vitamins and phytochemicals. On the contrary, we hypothesize that the different numbers of copies of genes involved in the bioavailability of some of these compounds may have been selected for in some populations and thus allowed them to adapt to the dietary availability of some fat-soluble vitamins and phytochemicals, as has been reported in the case of the α-amylase genes (48).

Another kind of genetic variation that could modulate the bioavailability of fat-soluble vitamins and phytochemicals is epigenetic modification, which would add another level of complexity to the genetic regulation of bioavailability. For example, SNPs that increase the bioavailability of these compounds in one individual might have no effect in another individual due to epigenetic modifications that silence these genetic variations.

6. POTENTIAL APPLICATIONS: TAILORED NUTRITIONAL RECOMMENDATIONS

Recent years have witnessed remarkable progress in genotyping and sequencing technologies, leading to an increased number of investigations of genetic variations together with a decrease in analysis time. The price of these technologies has been dropping, making them affordable for individuals and allowing numerous companies to offer direct-to-consumer genetic testing. With the increase in the number of studies aiming to identify genetic variations associated with interindividual variability in the bioavailability of fat-soluble vitamins and phytochemicals, it is sensible to assume that the predictive quality of genetic scores combining these genetic variations will improve, that is, these genetic scores will be able to predict more reliably the bioavailability of these compounds in specific segments of the population or even at the level of the individual. Altogether, these advances open the possibility of tailoring nutritional recommendations to prevent deficiencies or to maximize the health benefits of these compounds in specific segments of the population or at the level of the individual. We discuss the modalities and objectives of these applications below.

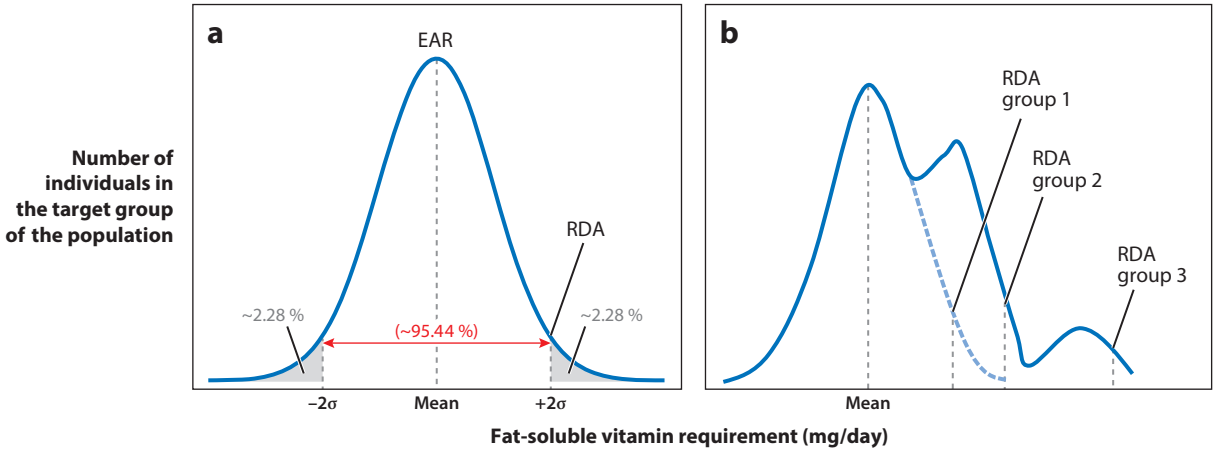


Figure 5

Current population-wide requirement curve and theoretical population-tailored recommended dietary allowance (RDA) curve. (*a*) The current population-wide requirement curve, which is assumed, owing to a lack of sufficient knowledge, to be normally distributed. The estimated average requirement (EAR) theoretically meets the requirements of half the population. The RDA is usually set at two standard deviations above the EAR, theoretically to meet the requirements of about 97.72% of the target group (e.g., healthy male adults, healthy pregnant females, children). Nevertheless, this also means that about 2.28% of the target group requires more than the RDA for the relevant nutrient. (*b*) The theoretical requirement if a single genetic variant significantly affects the bioavailability of a fat-soluble vitamin in a specific population. The proportion of individuals in the three parts of the curve reflects the proportion of the three alleles in the study group. In this hypothetical situation, new RDAs might be proposed to take into account the requirements of participants according to their genetic signature: RDA group 1 would cover the requirements of about 97.5% of individuals homozygous for the most frequent allele; RDA group 2 would cover the requirements of about 97.5% of heterozygous individuals; and RDA group 3 would cover the requirements of about 97.5% of individuals homozygous for the least frequent allele.

6.1. At the Population Level

By harnessing data from high-throughput genetic testing of several global populations, projects such as the International HapMap Project (67, 68, 116) and the 1000 Genomes Project (1) have allowed geneticists to provide us with insights into the genetic structure of the human genome, revealing the extent of genetic diversity between populations and differences in several hundred thousand SNPs that have a higher allele frequency. Populations differing in the allele frequency of variations in genes involved in the bioavailability of a fat-soluble vitamin or phytochemical may in turn exhibit different bioavailabilities of such compounds. RDAs have been established to cover the needs of 97.5% of specific segments of the population within one country, based on age, sex, and pregnancy and lactation status (**Figure 5**). Usually, RDAs are established in a sample of limited size, which obviously cannot account for population stratification. However, within a country, nutritional requirements might differ between segments of the population who are of different ethnic origin, for example, between Hispanic Americans and African Americans, which could partly be due to differences in nutrient bioavailability. Moreover, in many countries, no RDAs have been established, and RDAs established elsewhere, where the population's genetic makeup might be fairly different, are used. Of course, RDAs can be empirically adjusted to meet a population's requirement, but a priori knowledge of a population's ability to absorb a fat-soluble vitamin or phytochemical would save time and effort when tailoring an RDA. This might be absolutely crucial in countries with too few resources to empirically establish their own RDAs, in countries with segments of the population who are of different ancestry, or for phenotypes that have onset at older ages, for example, age-related macular degeneration.

A good example of applying population-tailored nutritional recommendations is illustrated by the fight against VA deficiency. In spite of the numerous programs implemented, VA deficiency is still a health issue in many developing countries: Although >80% of 1–5-year-old children in these countries receive VA supplements, the prevalence of VA deficiency has diminished by only 3% during the past 10 years (90). The World Health Organization recommends using a more diversified approach, including encouraging dietary modifications (e.g., the consumption of local crops with higher levels of proVA carotenoids), breastfeeding, food fortification, and supplementation. However, the bioavailability and conversion to VA of these carotenoids are very low and highly variable (59). We have shown that variability in the bioavailability of βC, and probably of other proVA carotenoids, is associated with a combination of SNPs (22). A theoretical calculation also allowed us to show that since the allele frequency of the genotypes involved in this bioavailability differs between ethnic groups, bioavailability is likely to vary between different ethnic groups. Moreover, it has been shown that proVA carotenoid conversion to VA is modulated by SNPs in the main conversion enzyme of these proVA carotenoids, BCO1 (50, 60, 80, 81, 138). The genotype frequency of these SNPs also varies among ethnic groups. Thus, we hypothesize that different ethnic groups likely exhibit different absorption and conversion capacities for these proVA carotenoids. This knowledge may allow policymakers to define the best nutritional strategy to fight VA deficiency in specific ethnic groups. For example, if the targeted ethnic group contains a significant proportion of individuals with genetic polymorphisms that impair the conversion of proVA carotenoids to VA, then it would be better to either recommend the consumption of foods rich in preformed VA or to provide this population with preformed VA supplements.

6.2. At the Individual Level

The effect of vitamin consumption on health parameters follows a well-known curve: At low levels, deficiency signs may occur, and if consumption increases, fat-soluble vitamins and phytochemicals may then exert essential metabolic functions. If intakes increase further, then the fat-soluble vitamins and phytochemicals may exert other beneficial biological effects, that is, they may prevent some diseases. At even higher intakes, harmful or toxic effects may appear (usually at supplementation levels). RDAs, which are defined to cover the requirements of 97.5% of the healthy population, are already enforced for specific subgroups (e.g., infants, children, elderly, pregnant women, breastfeeding women) (**Figure 5**), but these recommendations would be improved by taking into account more criteria in the segmentation of these subgroups. For example, this curve could be moved farther to the left or to the right depending on the absorption phenotype of an individual for a specific compound: An individual with a high capacity to absorb a specific fat-soluble vitamin or phytochemical would have a lower requirement compared with the general RDA, while an individual with a poor capacity for absorption would have a higher requirement compared with the general RDA (**Figure 5**). Most applications that come to mind involve personalizing nutritional recommendations to prevent deficiencies or to maximize the health benefits of a fat-soluble vitamin or phytochemical, but it should be emphasized that some of these compounds can also exert harmful effects, usually at chronic supplementation levels. For example, the use of βC and VE supplements has been reported to be associated with increased mortality (14). Thus, those who absorb these at high levels should be advised not to consume high doses of these for long durations. Using genetic scores that combine genetic variations associated with interindividual variability of bioavailability might help predict the absorption phenotype of an individual and thus could provide useful information for defining a more personalized RDA. Moreover, individuals' knowledge of their absorption phenotypes, and thus their personal RDA, may help improve dietary habits and encourage adherence (100). This approach has already been

proposed by several companies, albeit using predictions of the effects of single genetic variations, usually through direct-to-consumer genetic testing and personalized dietary or supplement recommendations. Although there has been tremendous progress in identifying genetic variations associated with variability in responses to dietary compounds, several critics still consider that the current knowledge base is too limited to offer practical, genotype-based nutritional recommendations (53). Additionally, other points require careful consideration and evaluation to define best practice; for example, there are ethical considerations (including how results are reported) and the analytical quality (31) must be considered, as well as the complexity of the information, and how practical guidance is offered.

7. CONCLUSIONS

In summary, there is now sufficient evidence to state that the bioavailability of fat-soluble vitamins and phytochemicals is partly modulated by genetic variations in several genes. Nevertheless, the bioavailability of some of these compounds, such as VA (as retinol or its esters) and vitamin K or other terpenoids, has not been well characterized, and while it may be that genetic variations are also involved in the variability of bioavailability of these compounds, genetic association studies are still lacking. Although much work remains to be done to identify a combination of genetic variations (SNPs, but also other kinds of genetic variations) that will allow us to confidently predict the bioavailability of fat-soluble vitamins and phytochemicals for different segments of the population or for an individual, the potential usefulness of this area of research is exciting in terms of developing personalized RDAs for these compounds. Nevertheless, it should be remembered that genetic variations represent only one of the factors that affect bioavailability, albeit they are stable over the life span, since other factors, such as epigenetic modifications or the factors described by the acronym SLAMENGHI (Section 3), also affect this phenotype. Thus, a DNA chip that can determine crucial genotypes and accurately predict the bioavailability of these compounds is unlikely to become a widespread and useful screening tool until numerous well-designed studies have provided validated genetic associations.

SUMMARY POINTS

1. Several factors are involved in the bioavailability of fat-soluble vitamins and phytochemicals, including an individual's genetic characteristics.
2. There is high interindividual variability in the bioavailability of these compounds in healthy people, and this is mainly assumed to be due to genetic variation.
3. Studies suggest that the bioavailability of fat-soluble vitamins and phytochemicals is modulated by combinations of genetic variations in genes involved in their metabolism and transport.
4. The method used to assess the bioavailability of these compounds can affect the results obtained, that is, the genetic variations associated with their bioavailability.
5. To date, only single nucleotide polymorphisms have been associated with the bioavailability of these compounds, but it is likely that other types of genetic variations, for example, copy number variants, are also involved.
6. Replication cohorts are required to support the associations observed so that in the future genetic scores can help to reliably predict the bioavailability of these compounds in a segment of the population or in an individual.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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