European Journal of Clinical Nutrition (2019) 72:18–25
https://doi.org/10.1038/s41430-018-0305-9

REVIEW ARTICLE

A review of factors that affect carotenoid concentrations in human plasma: differences between Mediterranean and Northern diets

María Marhuenda-Muñoz[1,2,3] · Sara Hurtado-Barroso[1,2,3] · Anna Tresserra-Rimbau[3,4] · Rosa Maria Lamuela-Raventós[1,2,3]

Published online: 28 November 2018

Abstract

Carotenoids are naturally occurring pigments of autotroph organisms that have been related to many health benefits and this is not only because some of them are precursors of vitamin A. Individual or whole carotenoid consumption has been associated with a lower risk of developing cancer, cardiovascular and metabolic diseases among others. However, the blood levels of carotenoids vary largely from person to person due to different factors. Diet is the most important one because of the dietary patterns that different populations follow, the time of the year of consumption or the personal preferences. Nevertheless, the intrinsic host factors such as the absorption, distribution, metabolism and excretion genetic polymorphisms, the volume of distribution and the person's microbiota and others such as carotenoid interactions are also inducing this so called inter-individual variability. Besides, culinary methods and processing produce changes in the foods that directly affect carotenoid content and hence their blood profile. Different types of studies have been performed to understand the between-subject variation of the carotenoid profile in human plasma. This research is focused on this matter as levels of carotenoids in human plasma could be useful for the prediction of some diseases. The Mediterranean diet is probably the most carotenoid rich diet stemming from its high proportion of fruits and vegetables. Its differences with other diets and the effect on the carotenoid blood profile of the consumers are currently a very interesting topic of study.

Introduction

Carotenoids are a numerous class of naturally occurring pigments synthesized by autotrophs (plants, algae and photosynthetic bacteria) that are associated with the yellow, orange and red colors of many plants [1]. They are mainly present in vegetable products but might be also found in animal origin foods depending on the livestock diet [2]. There are more than 700 carotenoids in nature; however, only a few, from fruits and vegetables, are ingested in sufficient quantity to be detected in human plasma; the most abundant being lycopene, β-carotene, lutein, α-carotene, β-cryptoxanthin, and zeaxanthin, along with their more common *cis*-isomers and some degradation products. Fig. 1 shows the chemical structures of the major carotenoids that are present in human plasma (see Fig. 1). Approximately 10% of them can be converted by the body to retinol, provitamin A, mainly α-carotene and β-carotene and some xanthophylls such as β-cryptoxanthin; and some apo-carotenoids are provitamin A, having β-carotene the greatest vitamin A activity [2]. Other carotenoids cannot produce retinoids (i.e., zeaxanthin and lycopene). However, they all have in common a long carbon chain terminated at each end by an ionone ring, with the exception of lycopene, that has not the terminal rings [3].

Consumption of carotenoid-rich foods is important since vitamin A deficiency is associated with blindness, reduced immune function [4] and increased risk of mortality [5].

✉ Rosa Maria Lamuela-Raventós
lamuela@ub.edu

1 Department of Nutrition, Food Sciences, and Gastronomy, School of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain

2 Biomedical Research Networking Centres in Physiopathology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain

3 Nutrition and Food Safety Research Institute (INSA-UB), University of Barcelona, Barcelona, Spain

4 Human Nutrition Unit, Faculty of Medicine and Health Sciences, Department of Biochemistry and Biotechnology, Pere Virgili Health Research Center, University Hospital of Sant Joan de Reus, Universitat Rovira i Virgili, Reus, Spain

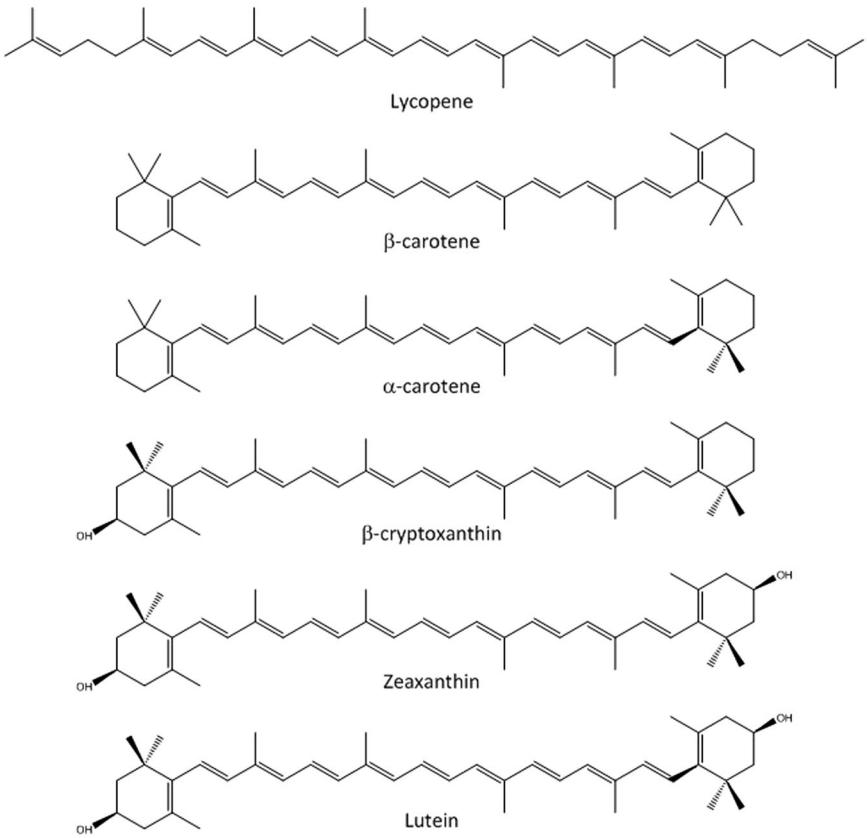

Fig. 1 Chemical structures of the major carotenoids present in human plasma

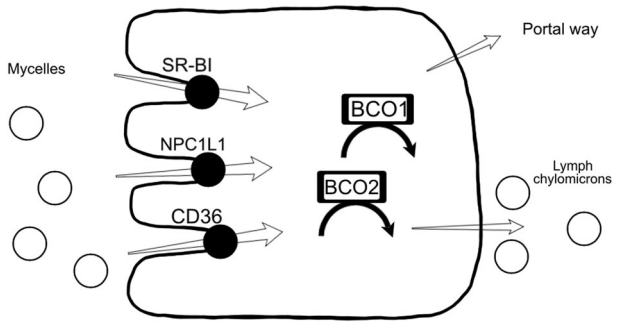

Fig. 2 Proteins involved in carotenoid transport across the human enterocyte

Through other mechanisms, zeaxanthin and lutein also contribute to maintain eye health and they can prevent age-related macular degeneration [6]. Besides the provitamin classification, carotenoids can be also divided into two groups: carotenes and xanthophylls. Xanthophylls, but not carotenes, have oxygen atoms in their molecular structure and so, they are more polar [7]. Most carotenoids are found in food in all-*trans* form; however, processing and cooking can result in the formation of other isomers. Due to their association with proteins in the plant matrix, their bioavailability is relatively low. It can be increased, though, by common culinary methods such as chopping, homogenizing and cooking [8–10]. Their lipophilic profile is also a determinant on the bioavailability, which is why using oil when cooking is also very positive.

Carotenoids are absorbed intestinally after their incorporation into mixed micelles that are composed by bile salts secreted by the liver and several types of lipids coming from the meal. The rate and extent of the absorption appear to be influenced not only by the type and amount of carotenoids but also by the type of fat (medium-chain vs. long-chain triglycerides) and the presence of soluble fiber [11]. The absorption takes place by passive diffusion and also by active uptake by the Scavenger Receptor-class B type I (SR-BI), Niemann-Pick C1-Like 1 (NPC1L1) and the Cluster Determinant 36 (CD36), the three of them being fat transporters [12].

Within the enterocytes, carotenoids can be cleaved by oxygenase enzymes: β-carotene 15,15′-oxygenase 1 (BCO1), which shows a higher affinity for provitamin A carotenoids, and β-carotene 9′,10′-oxygenase 2 (BCO2), whose affinity is higher toward non provitamin A carotenoids [1]. The products of the cleavage and the remaining uncleaved carotenoids are incorporated in the chylomicrons, the lipoproteins that distribute dietary fat and lipophilic vitamins to the different tissues. All of them reach the liver in the chylomicron remnants but more hydrophilic molecules such as apocarotenal can travel directly through the portal blood system. In the liver, they can undergo

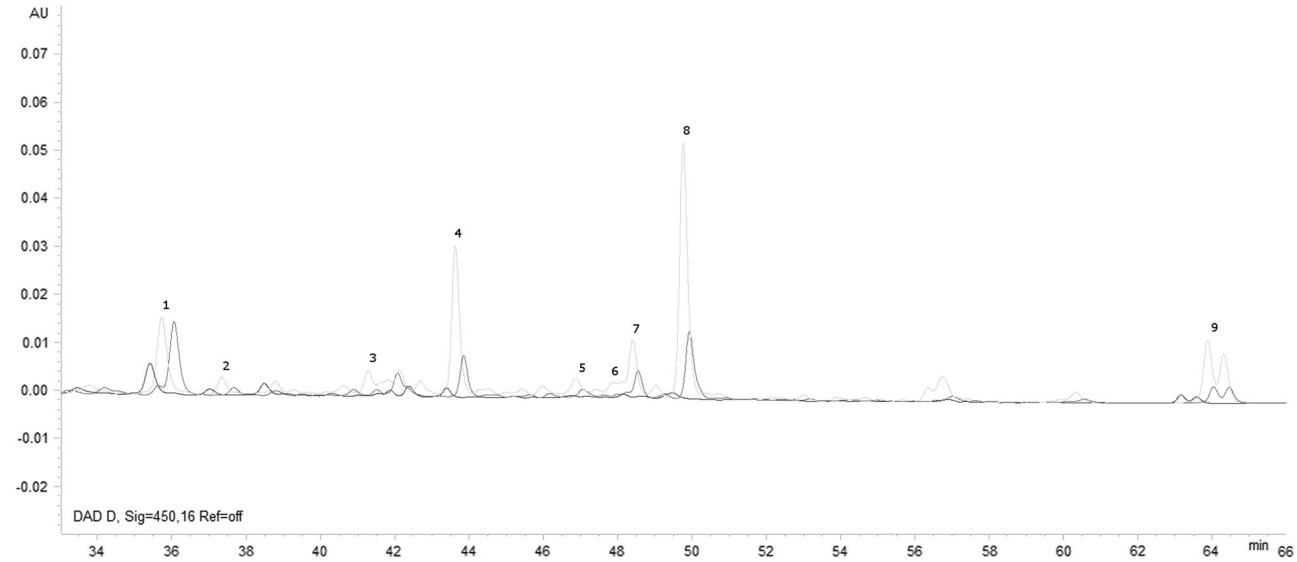

Fig. 3 HPLC chromatograms of random samples of carotenoids extracted from human plasma. 1–Astaxanthin; 2–Zeaxanthin; 3–*E*-*β*-apo-8′-carotenal; 4– Cryptoxanthin; 5–13-*Z*-*β*-carotene; 6–*α*-carotene; 7–*β*-carotene; 8–9-*Z*-*β*-carotene; 9–Lycopene

further or new cleavage and then are distributed to extra-hepatic tissues [3]. Figure 2 shows a very schematic representation of these mechanisms (see Fig. 2).

Provitamin A carotenoid uptake and conversion to retinol —the active form of vitamin A—is, in part, controlled by the intestine-specific homeobox (ISX) transcription factor, which is under the control of retinoic acid receptor (RAR)-dependent mechanisms [1]. Thus, when vitamin A stores are high, ISX is activated and represses the expression of SR-BI and BCO1, and the contrary occurs when the stores are low.

Genetic differences among individuals are supposed to be the cause of the inter-individual variations in concentrations of carotenoids in blood and tissues. Three chromatograms demonstrating great differences among carotenoid peak areas between the individuals are represented in Fig. 3 (see Fig. 3). These chromatograms were obtained from the carotenoid plasma extraction of healthy volunteers (*non-published results*), the carotenoids were separated by HPLC and detected at 450 nm, using the validated method developed by our research group [13]. A number of single nucleotide polymorphisms (SNPs) have been identified in genes that code for proteins that are involved in carotenoid intestinal uptake, transport and metabolism [14, 15]. The lipophilic profile of the carotenoids makes their volume of distribution in the body quite high and so, only to some extent will plasma concentrations reflect tissue levels [14].

In the last few years, several studies and systematic reviews have been focused on the effect that carotenoids have on human health. Antioxidant activity and capacity of carotenoids have been described and related with reduced risk of some types of cancer and enhancement of the immune system [16, 17]. But also evidences indicate that carotenoids are inhibitors of pro-inflammatory and pro-thrombotic factors and can reduce the risk of cardiovascular and other chronic diseases [18–20]. Because of their anti-oxidant and anti-inflammatory activities, carotenoids could also reduce the risk of metabolic syndrome [21]. Carotenoid consumption has been associated with the prevention and treatment of Type 2 Diabetes Mellitus and some of its complications such as nephropathy, retinopathy and neuropathy [22]. This effect is thought to be achieved by the antioxidant capacity of these compounds, that reduces the oxidative stress and inflammation involved in the triggering and progression of the complications [22]. This reduction in reactive oxygen species (ROS) and reactive nitrogen species (RNS), and probably the modulation of inflammation might, as well, be the explanation for the carotenoid ability of reducing the risk for cardiovascular diseases [18, 19]. Carotenoids and carotenoid conversion products inhibit adipogenesis and fat storage capacity by suppressing PPARɣ. Lower serum levels of carotenoids have been found in overweight and obese individuals [23]. Also obese subjects could have a reduced capacity of conversion from carotenoids to retinoids [24]. A prospective study suggests a positive effect on children adiposity and BMI concomitant with carotenoid supplementation [25]. Lifestyle of subjects and antioxidant activity from carotenoids could explain this fact, but also, it is important to highlight that adipose tissue is one of the main storages of carotenoids and retinoids [26]. There are other studies that focus on particular compounds, a cardioprotective profile has been delineated for lycopene and some potential mechanisms have been described for its

anti-atherogenic effect [20] and it has also been shown to be inversely associated with the positive prostate cancer risk [27]. Cerhan et al. showed a lower risk of rheumatoid arthritis when levels of β-cryptoxanthin in body were higher [28]; however, this relationship was not found by other authors [29]. Moreover, other conditions related with oxidative stress like Alzheimer disease have been associated with low concentration of carotenoids in subjects [30, 31]. Although some results are discordant or require further research, the positive health effect of high carotenoid intake through the diet is clearly demonstrated [21].

In this review, we aim to go through the different factors that influence the high inter-individual variability of carotenoid levels in human plasma.

Matherials and methods

Literature search and selection

A comprehensive literature search about plasma carotenoid level variability was performed between May and August 2017 through the database Pubmed. The search terms included "carotenoid" in combination with "variability", "plasma levels", "Mediterranean diet" or "Northern diet". After the removal of duplicates and articles with only abstract in English available the articles were selected by title and through links of related articles and references. Then, studies with no relevant outcome or data were eliminated as well.

Results

Factors influencing carotenoid levels in human plasma

The concentration of carotenoids found in human plasma after the same meal may not be equal in different subjects. There is a high inter-individual variability that might be due to very different causes (see Table 1).

Not only diet, but also biological activity depends on bioavailability that is mainly determined by bioaccesibility.

Table 1 Causes for plasma carotnoid inter-individual variability

Carotenoid interactions	
Culinary factors and processing	
Dietary habits	
Intrinsic host factors	ADME
	Volume of distribution
	Microbiota

ADME absorption, distribution, metabolism and excretion

Food matrix, dietary fat, dietary fiber, interaction between carotenoids and interaction between factors affect bioaccesibility, while passive diffusion and facilitated transport of carotenoids determine their bioavailability.

Mediterranean diet

When talking about inter-individual variability, the main cause is, certainly, the diet. It is difficult, in large studies where volunteers are asked to follow a particular diet, to control dietary habits of the participants to the extent of measuring the exact amount of carotenoids or carotenoid containing foods. In this way, although the participants may not change significantly their habits from one intervention to the other, very different practices from one person to another might occur and these differences could be crucial.

Globally, differences between populations are explained through diet. Mediterranean and Northern diet are typical European diets. Mediterranean diet is the typical diet from Mediterranean countries (Spain, Greece, France, Italy, Portugal…), whereas the countries from northern Europe, like UK and Republic of Ireland have another diet commonly known as Northern diet. The Mediterranean diet is probably the most carotenoid bearing diet for its richness in fruits and vegetables [32]. Because of this, it would be understandable that people that follow this type of diet are more likely to have higher content of carotenoids in their plasma.

A good example of this is an exchange list diet study performed in the United States in 2009. A group of healthy women were asked to follow a Greek-Mediterranean diet for 6 months after which, plasma carotenoids and fatty acids among other parameters were measured. As a result of the intervention the carotenoids in plasma were doubled, reflecting the larger fruit and vegetable consumption [33].

Other studies that have assessed the properties of the Mediterranean diet show that the consumption of this diet leads to an increase of the carotenoid content in plasma [34, 35].

A report from the European Prospective Investigation into Cancer and Nutrition was able to differentiate people from different European regions according to their carotenoid profile in plasma. Total carotenoids were higher in Southern regions, same as individual carotenoids, with the exception of carotenes, that showed no clear north-south difference [36]. Mediterranean population have higher amount of carotenoids present in plasma than anglo saxon population, especially for lycopene [37]. This fact can be explained by the large intake of tomatoes in the Mediterranean diet [38]. O'Neill et al. carried a study in which five European countries participated (Spain, The Netherlands, Finland, France, Republic of Ireland). With 80 subjects per country higher levels of lycopene and lutein and two-to-three-fold more β-cryptoxanthin in Spain, regarding

to other European countries, were found. There was, though, a similar concentration of α-carotene and β-carotene [38].

Another study described blood concentrations of different biomarkers of fruit and vegetables intake, namely carotenoids, tocopherols, ascorbic acid and retinol in young and healthy people from five European countries (France, UK (Northern Ireland), Republic of Ireland, The Netherlands and Spain). The serum concentrations of the cited biomarkers were considered "reference values" for these populations due to the study design. The authors found differences in the xanthophylls to carotenes ratio, being double in Spain compared to the northern countries (Northern Ireland and Republic of Ireland). The Spanish cohort also had higher levels of lutein, zeaxanthin and β-cryptoxanthin. The study concluded that some carotenoids (lutein, zeaxanthin, β-cryptoxanthin) and total xanthophylls in human plasma could be markers of the Mediterranean diet adherence [37].

Moreover, changes within Mediterranean diet consumers can be explained by seasonal variations [37–39]. For example, in Spanish diet higher β-cryptoxanthin and lycopene levels were found in winter and summer, respectively, because of the citrus fruits being more consumed in winter and tomatoes and watermelon in summer [39, 40]. Also, differences in some carotenoids and serum concentrations can take place because of the geographic, timing, demographic and cultural factors. In general, European countries from Mediterranean (southern) areas consume greater amounts of vegetables and fruits than northern countries [41, 42].

Intrinsic host factors

The distribution profile of carotenoids in the body is a more difficult aspect to assess due to the immense number of factors related not only to the food or carotenoid itself but maybe to the influence of host factors.

Earlier this year, Bohn et al. reviewed inter-individual discrepancies in host factors that might be affecting plasma carotenoid levels. Apart from dietary habits, health status including viral infections, micronutrient status, blood lipid profile, respiratory conditions and thyroid disorders are the main cause of variability according to, mostly, observational studies [14]. Other conditions related to the intestine length, permeability and function are obviously affecting overall absorption, not only carotenoid one. Other observational studies suggested other lifestyle habits such as smoking, alcohol consumption and physical activity also as sources of variability, as well as gender, age, weight, and ethnicity [14].

The volume of distribution of carotenoids is, as mentioned before, quite large in the body due to their lipophilic profile [14]. Because of this, and although it should not change intra-individually depending on the levels absorbed, the carotenoids could remain more or less constant in plasma but be higher in the different target tissues, accumulating in the adipose tissue, the skin, the liver and maybe other tissues. Besides, volume of distribution might not be the same in all individuals and can change according to health status. Plasma is one of the easiest samples that can be obtained in humans whereas tissue biopsies are quite invasive. A more expensive option would be to use isotopically labeled carotenoids and measure them in tissue [43].

In this matter, another reason that can make the profiles to vary is whether the volunteers are, or not, deficient in carotenoids (provitamin A or non provitamin A carotenoids). An intervention trial performed by Record et al. consistent in consumption of diets high or low in fruit and vegetables or following dietary supplementation with an antioxidant mixture detected a significant increase in α- and β-carotene, lutein and zeaxanthin [44]. When the studies are designed with a depletion period before the intervention, the absorption might be enhanced in order to replenish the body and not because of a different content of carotenoids in the foods.

Carotenoid absorption, distribution, metabolism and excretion (ADME), as every nutrient, non-nutrient or drug, can be affected by many reasons. In this case, some physiological parameters could be affecting carotenoid bioaccessibility. Some in vitro studies have been performed in order to assess them. Biehler et al. described that a low gastric pH would be degrading some carotenoids and thus, reducing their accessibility and absorption [45]. Periago et al. also found that high pepsin concentration facilitates the breakdown of protein-lycopene complexes increasing their availability [46]. In a study by Garret et al. and a posterior paper by Biehler et al. suggested that the concentrations of bile salts and pancreatic enzymes is critical for the micellization of carotenoids [47, 48]. A rather new approach to nutrition and metabolism, nutrigenomics, is starting to ease the explanation of ADME inter-individual variability following intervention trials. Two reviews have described a number of genes involved in the ADME processes whose different polymorphic variants could be the cause of the different outcomes [14, 15]. The genes mentioned vary from transport to –SR-BI, CD36, NPC1L1–, from –ATP binding cassette (ABC) proteins—and within the intestinal cells—fatty acid binding protein (FABP)–; to cleavage in intestinal and non-intestinal cells –BCO1 and 2–; transport in the circulatory system—the different apolipoproteins and the cholesterol ester transfer protein (CETP)—and elimination enzymes –cytochrome P450.

Lastly, although not much has been made clear in the area, the microbiota might have an influence on carotenoid

assimilation. Even though it seems that carotenoids are not very much absorbed in the large intestine, Karlsson et al. stated that the bacterial genus *Collinsella* was enriched in obese patients with atherosclerosis and that these same patients presented lower ß-carotene levels [49]. The authors suggested that the genome of this genus might not be favorable for the production of this carotenoid. These findings, though probably insufficient to state that microbiota has a critical function in carotenoid absorption, may hint an interesting role of the microbiome balance.

Interaction between carotenoids

Some studies have shown a competition of carotenoids to be micellized or absorbed [50]. There are evidences about the decrease of lutein when it is consumed along with lycopene or β-carotene [51–53] and of α-carotene and lycopene after β-carotene uptake [54], inversely to described by an Australian study [55].

Culinary factors and processing

Carotenoids are characterized by their high instability. During processing, due to their antioxidant capacities, some of the carotenoids are oxidized and degraded; however, isomerizations also occur. This degradation is induced by heat, light, oxygen, acids, transition metals, or interactions with radical species. Thermal processing causes the breakdown of the cellular matrix of the plant material and may also induce *trans* to *cis* isomerization due to the heating, increase in surface area, and agitation processes involved. The *cis* isoforms that are originated are more bioavailable because it seems that the packed structure of *cis*-isomers is more soluble in bile acid micelles and may be preferentially incorporated into chylomicrons. So, in processed foods and in human plasma and tissues, higher quantities of *cis*-isomers are found [56].

Some mechanisms of carotenoid degradation in food have been studied. Vallverdú-Queralt et al. and Rinaldi de Alvarenga et al. [9, 10] recently described the effect that cooking time and ingredient synergism have on carotenoid levels and isomerization. An adequate processing time and temperature and the addition of extra virgin olive oil or onion to the mix improved the bioavailability of carotenoids. Small variations in this aspect could be, to some extent, responsible for the inter-individual variability of carotenoid content in plasma.

Conclusion

In general, it is known that carotenoids have an important role in prevention of several diseases. However, the absorption and transformation of these compounds are essential for these health benefits to take place. Different types of studies have been performed to decipher the causes of the variation of the carotenoid profile in human plasma from different subjects after the same type of meal. Factors such as age, region, diet and intrinsic factors from the host have been suggested as possible causes for this variability but some of them are not fully understood. The levels of carotenoids in human plasma could be useful for the prediction of some diseases if we knew exactly how and why they vary from person to person. Some research is already taking place in this matter; however, more studies are needed in order to use these molecules as predictors.

Funding This article is published as part of a supplement sponsored by the Mediterranean Diet Foundation and the Diputació de Barcelona. This work was supported by the CICYT (AGL2016-79113-R), and the Instituto de Salud Carlos III (ISCIII) (CIBEROBN) from the Ministerio de Economía, Industria y Competitividad (MEIC) (AEI/FEDER, UE) and Generalitat de Catalunya (GC) (2014 SGR 773). Anna Tresserra-Rimbau was supported by a Juan de la Cierva Formación postdoctoral fellowship from the Ministerio de Economía, Industria y Competitividad.

Compliance with ethical standards

Conflict of interest AT-R received grant funding from The European Foundation for Alcohol Research (ERAB); RLR received lecture fees from ERAB, Beer and Health o Centro de Información Cerveza y Salud (CICS) and grant support from the Ministry of Economy, Industry and Competitivity, Catalonia Government. The remaining authors declare that they have no conflict of interest.

References

1. Wang X-D. Carotenoids. (eds Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR). In: Modern nutrition in health and disease, 11th edn. pp 427-39 Lippincott Williams & Wilkins, 2014.
2. Ortega Anta RM, Mena Valverde M del C, Carvajales PA. Vitamina A. In: Gil Hernández Á, editors. Tratado de Nutrición, 2nd edn. Médica Panamericana; 2010. pp 756–87.
3. Delage B. Linus Pauling Institute, Oregon. Carotenoids. http://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/carotenoids Accessed 27 May 2017.
4. Sirisinha S. The pleiotropic role of vitamin A in regulating mucosal immunity. Asian Pac J Allergy Immunol. 2015;33:71–89.
5. Sommer A, Vyas KS. A global clinical view on vitamin A and carotenoids. Am J Clin Nutr. 2012;96:1204S–1206S.
6. Li B, Vachali P, Bernstein PS. Human ocular carotenoid-binding proteins. Photochem Photobiol Sci. 2010;9:1418.
7. Milani A, Basirnejad M, Shahbazi S, Bolhassani A. Carotenoids: biochemistry, pharmacology and treatment. Br J Pharmacol. 2017;174:1290–324.
8. van Het Hof KH, West CE, Weststrate JA, Hautvast JG. Dietary factors that affect the bioavailability of carotenoids. J Nutr. 2000;130:503–6.
9. Vallverdú-Queralt A, Regueiro J, de Alvarenga J, Torrado X, Lamuela-Raventos R. Carotenoid profile of tomato sauces: effect of cooking time and content of extra virgin olive oil. Int J Mol Sci. 2015;16:9588–99.

10. Rinaldi de Alvarenga JF, Tran C, Hurtado-Barroso S, Martinez-Huélamo M, Illan M, Lamuela-Raventos RM. Home cooking and ingredient synergism improve lycopene isomer production in Sofrito. Food Res Int. 2017;99:851–61.
11. Priyadarshani AMB. A review on factors influencing bioaccessibility and bioefficacy of carotenoids. Crit Rev Food Sci Nutr. 2017;57:1710–7.
12. Reboul E. Absorption of Vitamin A and carotenoids by the enterocyte: focus on transport proteins. Nutrients. 2013;5:3563–81.
13. Colmán-Martínez M, Martínez-Huélamo M, Miralles E, Estruch R, Lamuela-Raventos RM. A new method to simultaneously quantify the antioxidants: carotenes, xanthophylls, and vitamin A in human plasma. Oxid Med Cell Longev. 2016;2016:1–10.
14. Bohn T, Desmarchelier C, Dragsted LO, Nielsen CS, Stahl W, Rühl R, et al. Host-related factors explaining interindividual variability of carotenoid bioavailability and tissue concentrations in humans. Mol Nutr Food Res. 2017;61:1600685.
15. Borel P. Genetic variations involved in interindividual variability in carotenoid status. Mol Nutr Food Res. 2012;56:228–40.
16. Holick CN. Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study. Am J Epidemiol. 2002;156:536–47.
17. Herraiz LA, Hsieh W-C, Parker RS, Swanson JE, Bendich A, Roe DA. Effect of UV exposure and β-carotene supplementation on delayed-type hypersensitivity response in healthy older men. J Am Coll Nutr. 1998;17:617–24.
18. Müller L, Caris-Veyrat C, Lowe G, Böhm M. Lycopene and its antioxidant role in the prevention of cardiovascular diseases—a critical review. Crit Rev Food Sci Nutr. 2016;56:1868–79.
19. Wood AD, Strachan AA, Thies F, Aucott LS, Reid DM, Hardcastle AC, et al. Patterns of dietary intake and serum carotenoid and tocopherol status are associated with biomarkers of chronic low-grade systemic inflammation and cardiovascular risk. Br J Nutr. 2014;112:1341–52.
20. Thies F, Mills LM, Moir S, Masson LF. Cardiovascular benefits of lycopene: fantasy or reality? Proc Nutr Soc. 2017;76:122–9.
21. Cicero AFG, Colletti A. Effects of carotenoids on health: are all the same? results from clinical trials. Curr Pharm Des. 2017;23:1–1.
22. Roohbakhsh A, Karimi G, Iranshahi M. Carotenoids in the treatment of diabetes mellitus and its complications: a mechanistic review. Biomed Pharmacother Elsevier Mass SAS. 2017;91:31–42.
23. Burrows TL, Warren JM, Colyvas K, Garg ML, Collins CE. Validation of overweight children's fruit and vegetable intake using plasma carotenoids. Obesity. 2009;17:162–8.
24. Tang G, Qin J, Dolnikowski GG, Russell RM. Short-term (intestinal) and long-term (postintestinal) conversion of beta-carotene to retinol in adults as assessed by a stable-isotope reference method. Am J Clin Nutr. 2003;78:259–66.
25. Canas JA, Lochrie A, McGowan AG, Hossain J, Schettino C, Balagopal PB. Effects of mixed carotenoids on adipokines and abdominal adiposity in children: a pilot study. J Clin Endocrinol Metab. 2017;102:1983–90.
26. Andersen LF, Jacobs DR, Gross MD, Schreiner PJ, Dale Williams O, Lee D-H. Longitudinal associations between body mass index and serum carotenoids: the CARDIA study. Br J Nutr. 2006;95:358.
27. Nash SH, Till C, Song X, Lucia MS, Parnes HL, Thompson IM, et al. Serum retinol and carotenoid concentrations and prostate cancer risk: results from the prostate cancer prevention trial. Cancer Epidemiol Biomark Prev. 2015;24:1507–15.
28. Cerhan JR, Saag KG, Merlino LA, Mikuls TR, Criswell LA. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. Am J Epidemiol. 2003;157:345–54.
29. Costenbader KH, Kang JH, Karlson EW. Antioxidant intake and risks of rheumatoid arthritis and systemic lupus erythematosus in women. Am J Epidemiol. 2010;172:205–16.
30. Molina JA, Bustos F, Jiménez-Jiménez FJ, Esteban J, Guerrero-Sola A, Zurdo M, et al. Serum levels of beta-carotene, alpha-carotene, and vitamin A in patients with amyotrophic lateral sclerosis. Acta Neurol Scand. 1999;99:315–7.
31. Mecocci P, Polidori MC, Cherubini A, Ingegni T, Mattioli P, Catani M, et al. Lymphocyte oxidative DNA damage and plasma antioxidants in Alzheimer disease. Arch Neurol. 2002;59:794–8.
32. Stange C, editor. Carotenoids in nature. Vol. 79, Subcellular Biochemistry. Cham: Springer International Publishing; 2016. p. 457.
33. Djuric Z, Ren J, Blythe J, VanLoon G, Sen A. A Mediterranean dietary intervention in healthy American women changes plasma carotenoids and fatty acids in distinct clusters. Nutr Res. 2009;29:156–63.
34. Blum S, Aviram M, Ben-Amotz A, Levy Y. Effect of a mediterranean meal on postprandial carotenoids, paraoxonase activity and C-reactive protein levels. Ann Nutr Metab. 2006;50:20–4.
35. Itsiopoulos C, Brazionis L, Kaimakamis M, Cameron M, Best JD, O'Dea K, et al. Can the Mediterranean diet lower HbA1c in type 2 diabetes? Results from a randomized cross-over study. Nutr Metab Cardiovasc Dis. 2011;21:740–7.
36. Al-Delaimy WK, van Kappel AL, Ferrari P, Slimani N, Steghens J-P, Bingham S, et al. Plasma levels of six carotenoids in nine European countries: report from the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr. 2004;7:713–22.
37. Olmedilla B, Granado F, Southon S, Wright AJA, Blanco I, Gil-Martinez E, et al. Serum concentrations of carotenoids and vitamins A, E, and C in control subjects from five European countries. Br J Nutr. 2001;85:227.
38. O'Neill ME, Carroll Y, Corridan B, Olmedilla B, Granado F, Blanco I, et al. A European carotenoid database to assess carotenoid intakes and its use in a five-country comparative study. Br J Nutr. 2001;85:499.
39. Granado F, Olmedilla B, Blanco I, Rojas-Hidalgo E. Major fruit and vegetable contributors to the main serum carotenoids in the Spanish diet. Eur J Clin Nutr. 1996;50:246–50.
40. Granado F, Blázquez S, Olmedilla B. Changes in carotenoid intake from fruit and vegetables in the Spanish population over the period 1964–2004. Public Health Nutr. 2007;10:1018–23.
41. Byrd-Bredbenner C, Lagiou P, Trichopoulou A. A comparison of household food availability in 11 countries. J Hum Nutr Diet. 2000;13:197–204.
42. Elmadfa I, Weichselbaum E, editors. Energy and Nutrient Intake in the European Union. In: European Nutrition and Health Report 2004. Basel: KARGER; 2005. pp 19–46.
43. Yeum K-J, Russell RM. Carotenoid bioavailability and bioconversion. Annu Rev Nutr. 2002;22:483–504.
44. Record IR, Dreosti IE, McInerney JK. Changes in plasma antioxidant status following consumption of diets high or low in fruit and vegetables or following dietary supplementation with an antioxidant mixture. Br J Nutr. 2001;85:459.
45. Biehler E, Hoffmann L, Krause E, Bohn T. Divalent minerals decrease micellarization and uptake of carotenoids and digestion products into Caco-2 cells. J Nutr. 2011;141:1769–76.
46. Periago MJ, Bravo S, García-Alonso FJ, Rincón F. Detection of key factors affecting lycopene in vitro accessibility. J Agric Food Chem. 2013;61:3859–67.
47. Garrett DA, Failla ML, Sarama RJ. Development of an in vitro digestion method to assess carotenoid bioavailability from meals. J Agric Food Chem. 1999;47:4301–9.
48. Biehler E, Kaulmann A, Hoffmann L, Krause E, Bohn T. Dietary and host-related factors influencing carotenoid bioaccessibility

from spinach (Spinacia oleracea). Food Chem Elsevier Ltd. 2011;125:1328–34.
49. Karlsson FH, Fåk F, Nookaew I, Tremaroli V, Fagerberg B, Petranovic D, et al. Symptomatic atherosclerosis is associated with an altered gut metagenome. Nat Commun. 2012;3:1245.
50. Tyssandier V, Cardinault N, Caris-Veyrat C, Amiot M-J, Grolier P, Bouteloup C, et al. Vegetable-borne lutein, lycopene, and beta-carotene compete for incorporation into chylomicrons, with no adverse effect on the medium-term (3-wk) plasma status of carotenoids in humans. Am J Clin Nutr. 2002;75:526–34.
51. Reboul E, Abou L, Mikail C, Ghiringhelli O, André M, Portugal H, et al. Lutein transport by Caco-2 TC-7 cells occurs partly by a facilitated process involving the scavenger receptor class B type I (SR-BI). Biochem J. 2005;387(Pt 2):455–61.
52. Micozzi MS, Brown ED, Edwards BK, Bieri JG, Taylor PR, Khachik F, et al. Plasma carotenoid response to chronic intake of selected foods and beta-carotene supplements in men. Am J Clin Nutr. 1992;55:1120–5.
53. During A, Hussain MM, Morel DW, Harrison EH. Carotenoid uptake and secretion by CaCo-2 cells: beta-carotene isomer selectivity and carotenoid interactions. J Lipid Res. 2002;43:1086–95.
54. Wahlqvist ML, Wattanapenpaiboon N, Macrae FA, Lambert JR, MacLennan R, Hsu-Hage BH. Changes in serum carotenoids in subjects with colorectal adenomas after 24 mo of beta-carotene supplementation. Australian Polyp Prevention Project Investigators. Am J Clin Nutr. 1994;60:936–43.
55. Boileau aC, Merchen NR, Wasson K, Atkinson CA, Erdman JW. Cis-lycopene is more bioavailable than trans-lycopene in vitro and in vivo in lymph-cannulated ferrets. J Nutr. 1999;129:1176–81.
56. van den Berg H. Carotenoid interactions. Nutr Rev. 1999;57:1–10.