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Effects of nutritional interventions on BDNF concentrations in humans: a systematic review

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ABSTRACT

Objectives: Brain-derived neurotrophic factor (BDNF) plays an essential role in brain and metabolic health. The fact that higher concentrations are associated with improved cognitive performance has resulted in numerous intervention trials that aim at elevating BDNF levels. This systematic review provides an overview of the relation between various nutritional factors and BDNF concentrations in controlled human intervention studies.

Methods: A systematic search in May 2020 identified 48 articles that examined the effects of dietary patterns or foods ($n = 3$), diets based on energy intake ($n = 7$), vitamins and minerals ($n = 7$), polyphenols ($n = 11$), long-chain omega-3 polyunsaturated fatty acids ($n = 5$), probiotics ($n = 8$), and miscellaneous food supplements ($n = 7$).

Results: In particular, studies with dietary patterns or foods showed increased peripheral BDNF concentrations. There are also strong indications that polyphenols tend to have a positive effect on BDNF concentrations. Four of the 11 included studies with a polyphenol intervention showed a significant increase in BDNF concentrations, one study showed an increase but this was not statistically analyzed, and two studies showed a trend to an increase.

Discussion: The two polyphenol classes, phenolic acids, and other phenolic compounds were responsible for the significant effects. No clear effect was found for the other dietary factors, which might also be related to whether serum or plasma was used for BDNF analysis. More work is needed to understand the relation between peripheral and central BDNF concentrations.

KEYWORDS

brain-derived neurotrophic factor; human interventions; diet; foods; vitamins and minerals; polyphenols; long-chain omega-3 polyunsaturated fatty acids; probiotics; food supplements; systematic review


Introduction

Brain-derived neurotrophic factor (BDNF) is a protein that is mainly produced in the central nervous system [1]. Its function depends on the stage of brain development. In early life, BDNF plays an important role in neural development and functioning, whereas in adult life it is involved in processes such as synaptic transmission and synaptic plasticity, which contribute to cognitive function [2]. Indeed, previous studies have shown that lower BDNF concentrations are associated with cognitive impairment [3] and higher BDNF concentrations with improved cognitive performance [4]. It is well-known that lifestyle factors such as diet are contributing to mental and cognitive health [5]. Therefore, specific dietary changes could be an effective way to exert an effect on BDNF and thereby preserving and improving cognitive and metabolic health. In more detail, it seems that dietary factors can influence cognition via pathways

related to energy metabolism and synaptic plasticity [6], in which BDNF could play a role.

BDNF can also be found in the periphery since it can cross the blood–brain barrier, albeit this has only been demonstrated in animal studies [7]. However, this circulating peripheral BDNF is not only brain-derived since it can also be produced by peripheral tissues including muscle, thymus, heart, liver, vascular smooth muscle cells, lung, and spleen [8]. This peripheral BDNF production seems to be similar between animals and humans [9]. In the periphery, the majority of BDNF is stored in platelets while the rest circulates in plasma [8]. There are indications that peripheral and central BDNF concentrations are positively associated [10], which suggests that concentrations of BDNF in the blood can be regarded as indicative of concentrations of BDNF in the central nervous system, though this conclusion remains open for discussion.

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Although it has received the most attention, BDNF is not only relevant from the cognitive health perspective as evidence is also growing that BDNF also plays a role in other more peripheral oriented processes. Lower peripheral BDNF concentrations are not only associated with an impaired cognitive performance [11], but, for example, also with a higher body weight [12]. In this context, a combined central and peripheral role for BDNF was found in energy homeostasis, a finding which was first demonstrated in rats [13]. In that study, intraventricularly administered BDNF resulted in decreased energy intake and consequently body weight loss. More recently, it has been suggested that BDNF also acts as a metabolic modulator in humans by controlling and affecting patterns of food intake, physical activity, and glucose metabolism [14]. Moreover, BDNF mediates energy metabolism not only via the brain but also via peripheral neurons and target organs that are involved in maintaining energy balance. These various sites of action and functions imply that BDNF could influence appetite, insulin sensitivity, and parasympathetic cardiovascular tone. If that is indeed the case, then there is a possibility that elevated BDNF concentrations could counteract the development of obesity and the metabolic syndrome [15].

Interventions aimed at increasing BDNF concentrations seem an attractive target to maintain or even improve cognitive performance as well as metabolic health. Despite numerous observations that specific dietary ingredients affect BDNF concentrations, the question remains whether these dietary factors indeed modulate BDNF concentrations. In this systematic review, we provide an overview of the potential relation between the consumption of different dietary factors and BDNF concentrations in controlled human intervention studies.

Methods

Search strategy

The systematic review was based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist [16]. This systematic review was not pre-registered with PROSPERO. A systematic literature search was performed on May 27th 2020 in three databases: Cochrane Central Register of Clinical Trials, Ovid MEDLINE, and Embase. Search terms consisted of (brain-derived neurotrophic factor or BDNF) combined with (diet or dietary or food or nutrient or nutrition or nutritional or supplement or supplements or supplementation or intake). Duplicates were removed and those studies that only included human

were filtered out. However, this filter was impossible in Cochrane where all records had to be retained.

Selection criteria

The first phase of the selection procedure consisted of screening the titles and abstracts. This selection was performed independently by two researchers. When inconclusive, articles' eligibility was discussed by both researchers until agreement was reached. Articles were included if they met the following criteria: (1) intervention studies performed in human adult subjects (aged ≥ 18 years); (2) intervention with a nutritional component; (3) plasma or serum concentrations of BDNF are provided; (4) original research (i.e. no letters, conference proceedings or reviews); (5) written in English; (6) no duplicates. The second phase of the selection procedure consisted of reading full texts to assess their eligibility. Articles were excluded when no control group had been used.

Data collection

The data from the selected articles were extracted to create an overview that included: publication information (year of publication, first author); study and subject characteristics (design, sample size, specification of subgroups, mean age, gender); characteristics of the BDNF measurement (assay, unit, plasma or serum); and specifications of the intervention. If BDNF concentrations were expressed in ng/ml, units were converted to pg/ml. A software caliper package was used when data were only displayed in graphs (Onde Rulers; Ondesoft, Beijing, China). The intervention effect of studies with parallel designs was defined as the difference between the changes from baseline and intervention in the experimental and placebo groups. The intervention effect of crossover studies was defined as the difference between values obtained at the end of the experimental and control periods. In order to assess the methodological quality of the selected intervention studies, the Jadad score was calculated [17]. This five-point scale reviews the randomization process, blinding and the description of withdrawals (Supplemental Table 1).

Results

Search results

The literature search retrieved 3641 articles from the selected databases. Screening of titles and abstracts resulted in the exclusion of 2974 articles based on the predefined selection criteria. After reviewing the full

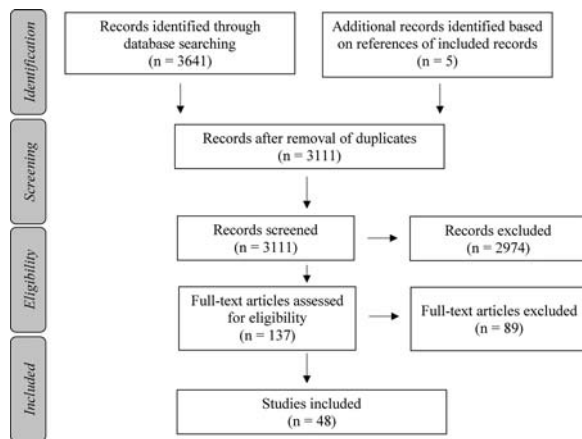


Figure 1. PRISMA flowchart of the selection process.

texts of the remaining 132 articles, another 89 articles were excluded as they did not meet the selection criteria. Based on a search through references of the included articles five additional articles were included. Ultimately 48 articles met the inclusion criteria (Figure 1), which were then clustered based on the type of nutritional intervention. This resulted in the following clusters: dietary patterns or foods ($n = 3$); diets based on energy intake ($n = 7$); and supplements ($n = 38$). The latter category was further divided into the following sub-clusters: vitamins and minerals ($n = 7$); polyphenols ($n = 11$); long-chain omega-3 polyunsaturated fatty acids ($n = 5$); probiotics ($n = 8$); and miscellaneous: protein (extracts) or lipids ($n = 7$).

Dietary patterns & foods

One study evaluated changes in BDNF concentrations based on dietary patterns, while two studies evaluated changes based on whole foods (Table 1). In a study by Sánchez-Villegas et al. [18], subjects with a high cardiovascular risk consumed a Mediterranean diet supplemented with virgin olive oil or mixed nuts or a low-fat control diet. Energy intake was not controlled for and subjects were divided into two groups according to the observed weight changes. No significant differences in plasma BDNF concentrations were observed between the three diets, and these effects did not depend on changes in body weight. In a second study, Sandberg et al. [19] showed that consuming a whole grain rye kernel-based bread increased plasma BDNF concentrations in apparently healthy subjects when compared with white wheat flour-based control bread. Finally, a study in mild cognitively impaired women revealed that consuming mold-fermented cheese as compared with non-mold-fermented cheese led to a significant increase in serum BDNF concentrations [20].

Energy intake

In seven studies, energy intake was changed by various types of fasting and caloric restrictions (Table 1). The interventions were conducted in apparently healthy subjects [21–23], subjects with overweight [24] or obesity [25,26], and subjects with a mental disorder [27]. Only in this last study did a hypocaloric diet significantly increase serum BDNF concentrations, with the other six studies observing no effects.

Supplements

Vitamins and minerals

Seven studies were identified that had evaluated the effects of supplementation with either vitamins or minerals (Table 1). Four studies examined the effects of zinc but all in different populations: in women with premenstrual syndrome [28], diabetic subjects [29], subjects diagnosed with depression [30], and obese subjects [31]. Zinc supplementation showed a significant increase in serum BDNF concentrations in the premenstrual syndrome and obese population, while the other two populations did not appear to respond significantly to zinc. Two studies examined the effect of vitamin D3 in apparently healthy subjects. No significant differences between the intervention and control groups were found by Pirotta et al. [32], but a significant decrease in serum BDNF concentrations was observed in the supplemented group in the study by Walentukiewicz et al. [33]. In the latter study, however, the difference in changes between the intervention and control arms was not statistically analyzed. Finally, one study examined the separate and combined effects of both zinc and vitamin D3 in subjects with depressive symptoms [34]. Here, both the zinc arm and the combined zinc and vitamin D3 arm showed a trend to decreased serum BDNF concentrations, but again the study, unfortunately, did not statistically analyze the difference in changes between the groups.

Polyphenols

The 11 studies included in the polyphenol cluster investigated the effect of supplementation of foods or supplements rich in phenols or flavonols (Table 1). Therefore, the type of polyphenols studied was markedly different. One study examined polyphenols from *Eriobotrya japonica* Lindley [35], two studies seaweed rich in polyphenols [36,37], two studies resveratrol [38,39], one study ellagic acid [40], two studies (nano-)curcumin [41,42], one study *Ginkgo Biloba* [43], one study green tea [44], and one study dark chocolate [45]. A combination of resveratrol and quercetin

Table 1. Characteristics of the studies included per cluster in the systematic review.

First author (year)	Population	Experimental group/control (N)	Intervention	Duration	Effects on BDNF*
Dietary Patterns & Foods					
Sánchez-Villegas (2011)	At high cardiovascular risk	91/77	Mediterranean diet with virgin olive oil	3 y	=
		75/77	Mediterranean diet with mixed nuts		=
Sandberg (2018)	Healthy	19	Whole grain rye kernel-based bread	1–3 d	↑
Suzuki (2019)	Mild cognitive impaired	35	Mold fermented cheese	12 wks	↑
Diets Based on Energy Intake					
Carlson (2007)	Healthy	21	Reduced meal frequency	8 wks	=
Catenacci (2016)	Obese	15/14	Zero-calorie alternate-day fasting	8 wks	=
Cherif (2017)	Healthy	22	Islamic intermittent fasting	3 d	=
Khoshandam Ghashang (2019)	Healthy	25/25	Ramadan fasting	29 d	=
Guimaraes (2008)	Schizophrenic	25/42	Hypocaloric diet	11.5–26 mo	↑
Harvie (2011)	Obese	54/53	Continuous energy restriction	26 wks	=
Schübel (2018)	Overweight	47/51	Intermittent calorie restriction	12 wks	=
		46/51	Continuous calorie restriction		=
Supplements					
<i>Vitamins & Minerals</i>					
Jafari (2019)	Premenstrual syndrome	27/30	Zinc gluconate	12 wks	↑
Kheirouri (2018)	Diabetic	25/25	Zinc gluconate	12 wks	=
Pirotta (2014)	Healthy	13/13	Vitamin D3	10 wks	=
Ranjbar (2014)	Depressed	22/22	Zinc sulfate	12 wks	=
Solati (2015)	Obese	24/26	Zinc gluconate	12 wks	↑
Walentukiewicz (2018)	Healthy	27/30	Vitamin D3	12 wks	–
Yosae (2020)	Depressed	24/22	Zinc gluconate	12 wks	–
		27/22	Vitamin D3		–
		25/22	Zinc gluconate + vitamin D3		–
<i>Polyphenols</i>					
Choi (2016)	Healthy	40/40	<i>Eriobotrya japonica</i> Lindley	12 wks	=
Choi (2016)	Healthy	10/11	Fermented <i>Laminaria japonica</i>	8 wks	↑
Huhn (2018)	Healthy	30/30	Resveratrol	26 wks	=
Liu (2018)	Healthy	37/39	Ellagic acid	12 wks	=
	Overweight	38/36			↑
Osali (2020)	Metabolic syndrome	11/11 ^a	Nano-curcumin	6 wks	–
Reid (2018)	Healthy	32/28	Fermented <i>Laminaria japonica</i> A.	6 wks	↑
Sadowska-Krepa (2017)	Healthy	9 / 9	<i>Ginkgo biloba</i> extract	6 wks	=
Sadowska-Krepa (2019)	Healthy	8/8	Green tea extract	6 wks	–
Sumiyoshi (2019)	Healthy	10/8	Dark chocolate	4 wks	=
Witte (2014)	Overweight	23/23	Resveratrol	26 wks	=
Yu (2015)	Depressed	50/50	Curcumin	6 wks	↑
<i>Long-Chain Omega-3 Polyunsaturated Fatty Acids</i>					
Bot (2011)	Diabetic	13/12	E-EPA	12 wks	=
Burg, van der (2019)	Depressed	42/41	EPA + DHA	8 wks	=
Matsuoka (2015)	Traumatized	53/57	EPA + DHA	12 wks	=
Sedláček (2018)	Overweight	11/10	EPA + DHA	12 wks	=
Witte (2014)	Healthy	40/40	LC-n3-FA	26 wks	–
<i>Probiotics</i>					
Chung (2014)	Healthy	26/10	<i>L. helveticus</i> IDCC3801-fermented milk	12 wks	=
Haghighat (2019)	Hemodialysis + depressed	25/25	Prebiotics + <i>L. acidophilus</i> T16, <i>B. bifidum</i> BIA-6, <i>B. lactis</i> BIA-7, <i>B. longum</i> BIA-8	12 wks	↑
		25/25	<i>L. acidophilus</i> T16, <i>B. bifidum</i> BIA-6, <i>B. lactis</i> BIA-7, <i>B. longum</i> BIA-8		=
Hwang (2019)	Mild cognitive impaired	50/50	<i>L. plantarum</i> C29-fermented soybean	12 wks	–
Kim (2020)	Healthy	63	<i>B. bifidum</i> BGN4 + <i>B. longum</i> BORI	12 wks	↑
Pinto-Sanchez (2017)	Irritable bowel syndrome	22/22	<i>B. longum</i> NCC3001	6 wks	=
Riezzo (2018)	Constipated	28/28	<i>L. reuteri</i> DSM-17938	15 wks	–
Romijn (2017)	Depressed	28/36	<i>L. helveticus</i> + <i>B. longum</i>	8 wks	=
West (2014)	Healthy	46/51	<i>B. animalis</i> subsp. <i>lactis</i> BI-04	21 wks	=
		47/51	<i>L. acidophilus</i> NCFM + <i>B. animalis</i> subsp. <i>lactis</i> BI-07		=
<i>Miscellaneous: Protein (Extracts) & Lipids</i>					
Almeida, de (2019)	Healthy + depressed	35/34	Ayahuasca	1 d	↑
Chui (2014)	Healthy	24/24	LD-1227 marine nutraceutical	9 wks	↑
Kim (2015)	Frail elderly	32/33	Milk fat globule membrane	13 wks	=
Petelin (2019)	Overweight	30/30	Royal jelly	8 wks	=
Sarris (2019)	Depressed	81/77	S-adenosyl methionine + folinic acid + EPA + DHA + 5-HTP + zinc picolinate + co-factor vitamins	8 wks	=
Stringham (2019)	Healthy	49/10	Macular xanthophyll	26 wks	↑
Varanoske (2020)	Healthy	10/9	β-alanine	2 wks	=

Notes: *compared to control; ^aassuming that subjects were equally divided into groups; = no statistically significant effect; ↑ statistically significant increase; – significance level missing; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; E-EPA: ethyl-eicosapentaenoic acid; LC-n3-FA: long-chain omega-3 polyunsaturated fatty acids.

showed no effect on serum BDNF concentrations in overweight subjects [39]. The remaining interventions were mainly performed in apparently healthy subjects in whom again resveratrol [38], but also a *Ginkgo biloba* extract [43] showed no significant change in serum BDNF concentrations, neither did dark chocolate [45]. Although the study evaluating the effect of green tea did not statistically analyze the difference in changes between the groups, evaluating the data as such indicated that the intervention had no effect on serum BDNF concentrations [44]. In contrast, supplementation with a plant extract of leaves of *Eriobotrya japonica* Lindley in apparently healthy subjects [35] and supplementation with nano-curcumin in subjects with metabolic syndrome [41] showed a trend to increased serum and plasma BDNF concentrations, respectively. Furthermore, supplementation with seaweed in apparently healthy subjects resulted in a significant increase in serum BDNF concentrations [36,37]. Supplementation with ellagic acid significantly increased plasma BDNF concentrations in overweight subjects but not in healthy subjects [40]. Finally, curcumin supplementation was found to increase plasma BDNF concentrations in subjects with major depressive disorder [42].

Long-chain omega-3 polyunsaturated fatty acids

Five studies have been identified that examined the effects of long-chain omega-3 polyunsaturated fatty acid supplements (Table 1). No significant differences in serum BDNF concentrations were found after the interventions with the different long-chain omega-3 polyunsaturated fatty acids in subjects with diabetes [46], subjects with depression [47], trauma patients [48], and overweight subjects [49]. The study in apparently healthy subjects [50] did not statistically analyze the difference in changes between the intervention and control arms, but as the change in serum BDNF concentrations in both groups was similar and small in relation to the reported group averages and standard deviations, this would likely not have reached significance.

Probiotics

The eight studies in the probiotics cluster evaluated the effects of various bacterial supplements (Table 1). Pinto-Sanchez et al. [51] and Riezzo et al. [52] found no significant effects of a single strain *Bifidobacterium longum* NCC3001 or *Lactobacillus reuteri* DSM-17938 probiotic approach on serum BDNF concentrations in subjects with irritable bowel syndrome or constipation, respectively, though Riezzo et al. [52] did not statistically analyze the changes versus control. West et al. [53] investigated both the single strain (*Bifidobacterium animalis* subsp. *lactis* BI-04) and double strain

(*Lactobacillus acidophilus* NCFM and *Bifidobacterium animalis* subsp. *lactis* BI-07) probiotic approach in apparently healthy subjects, and similarly found no significant changes in plasma BDNF concentrations. Haghghat et al. [54] examined both synbiotics (prebiotics and probiotics) and probiotics in hemodialysis patients with depressive symptoms. However, only in the synbiotics supplemented group they did find a significant increase in serum BDNF concentrations. Probiotic supplementation with *Lactobacillus plantarum* C29 did not affect serum BDNF concentrations in mild cognitive impaired subjects, but again no statistical test was applied to compare the difference in change [55]. Probiotic supplementation with different doses of *Lactobacillus helveticus* IDCC3801-fermented milk showed no overall effect on plasma BDNF concentrations in apparently healthy subjects [56]. Finally, probiotic supplementation with *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI in apparently healthy subjects did result in a significant increase in serum BDNF concentrations [57], but supplementation with *Lactobacillus helveticus* and *Bifidobacterium longum* in subjects with depressive symptoms did not [58].

Miscellaneous

The remaining cluster included seven studies with plant and protein extracts or supplements rich in lipids (Table 1). A single dose of ayahuasca increased serum BDNF concentrations in a combined population of apparently healthy subjects and depressed subjects [59]. A blend of high-purity caviar-derived DNA, collagen elastin and protein extracts from sturgeon did change serum BDNF concentrations in apparently healthy subjects [60]. Frail older persons who consumed milk fat globule membrane supplements showed no significant changes in serum BDNF concentrations [61]. Furthermore, supplementation with royal jelly did not significantly increase serum BDNF concentrations in overweight subjects [62], nor did the nutraceutical combination used in depressed subjects [63]. However, a study with two different doses of macular xanthophyll in apparently healthy subjects revealed a significant increase in serum BDNF concentrations when the two groups were combined [64]. Finally, another study in apparently healthy subjects found β -alanine supplementation to have no significant effect on plasma BDNF concentrations [65].

Risk of bias assessment

The assessment regarding the methodological quality of the studies resulted in sufficient Jadad scores for the

dietary patterns and foods cluster and poor Jadad scores for the energy intake cluster (Supplemental Table 1). Regarding the poor scores for the studies in these clusters, it should be taking into account that no points could be awarded for blinding regarding the intervention with dietary patterns or whole foods, or restriction in energy intake. Therefore, it can be questioned if this outcome is a real representation of quality for these particular clusters. The overall quality of the supplement studies in the vitamins and minerals sub-cluster is good, in the polyphenol sub-cluster sufficient to good with two studies scoring below average, in the long-chain omega-3 polyunsaturated fatty acids sub-cluster good except for one study, in the probiotics sub-cluster good, and in the miscellaneous sub-cluster one sufficient and the remaining studies good.

Discussion

Higher BDNF concentrations have been associated with both improved brain health [6] and metabolic health [14]. Therefore, interventions that could potentially elevate BDNF concentrations have attracted considerable attention. We have evaluated here the possible relation between consuming different nutrients and BDNF concentrations in controlled human intervention studies. To do so, we have categorized the available literature into seven (sub-)clusters. In general, two of three studies in the whole foods cluster and four of eleven studies in the polyphenol sub-cluster showed significant positive effects on BDNF concentrations. The studies in the cluster based on energy intake, and the supplement sub-clusters for vitamins and minerals, long-chain omega-3 polyunsaturated fatty acids, probiotics, and miscellaneous showed no consistent effects.

Four of the 11 studies in the polyphenol cluster showed a significant increase in BDNF concentrations, one study showed an increase in BDNF concentrations but did not statistically analyze this, and two studies showed a trend to an increase. The overall quality of the studies in this cluster was sufficient to good based on the Jadad scores (Supplemental Table 1). It thus seems that polyphenols are molecules of interest which could have a potentially positive effect on BDNF. Epidemiological studies and randomized controlled trials have indeed shown that an elevated intake of polyphenols can be linked to neuroprotective effects associated with improved cognitive function [66]. Based on polyphenols' chemical structure, they can be classified into flavonoids, phenolic acids, stilbenes, lignans, and other phenolic compounds [67]. Of the 11 polyphenol studies included here, four evaluated the effects of flavonoids (*Eriobotrya japonica* Lindley,

Ginkgo biloba, green tea, dark chocolate), one evaluated the effects of phenolic acids (ellagic acid), two evaluated the effects of stilbenes (resveratrol), and five evaluated the effects of other phenolic compounds (fermented *Laminaria japonica* A., (nano-)curcumin).

Phenolic acids and other phenolic compounds were responsible for the significant changes in BDNF concentrations. A potential mechanism underlying the beneficial effects of polyphenols might be a direct modulation of the cAMP-response element-binding protein (CREB) signaling pathways which are linked to BDNF expression [68]. However, activation of this CREB-mediated mechanism of action has generally been ascribed to flavonoids [69]. Although *Eriobotrya japonica* Lindley showed no significant effect on BDNF, it did show a trend to increased BDNF concentrations [35]. However, the other studies that applied the other flavonoids, *Ginkgo biloba*, green tea, and dark chocolate, showed no effect on BDNF concentrations [43,45]. The reason for this lack of an effect could be due to the low bioavailability of flavonoids in humans [70].

Another neurotrophic signaling pathway that can be modulated by polyphenols, in particular phenolic acids, is the Akt pathway, which ultimately leads to an increase in BDNF concentrations [71]. This pathway could be the mechanism of action of ellagic acid which showed an effect on BDNF concentrations, at least in overweight subjects [40]. Both the Akt and CREB pathway are stimulated by curcumin [72], resulting in an expected increase in BDNF concentration as observed in depressed subjects in the study by Yu et al. [42] and a trend to an increase in metabolic syndrome subjects in the study by Osali et al. [41]. Despite several studies highlighting the positive effect of resveratrol supplementation on cognitive improvement [73], it does not seem to be mediated via elevated BDNF concentrations [38,39].

Of the active polyphenol compounds responsible for the significant effect on BDNF concentration upon supplementation with fermented *Laminaria japonica* A. [36,37], the seaweed specific phlorotannins could play a role [67] as the same pathway is stimulated as is seen after flavonoid exposure [74]. However, since a specialized fermentation process had been applied to the seaweed, the supplements not only contained the phlorotannin polyphenols but were also enriched with gamma-aminobutyric acid (GABA; [75]). GABA has been recognized as stimulating BDNF expression via the same CREB mechanism, at least during early development [76]. It is possible therefore that besides the phlorotannin polyphenols, the GABA content in seaweed could also have played a role in increasing

BDNF concentrations, yet it has not been shown that GABA has the same effect on BDNF expression in adult life. Furthermore, the high fiber content in seaweed [77] may also have contributed to the positive effects on BDNF concentration, since Sandberg et al. [19], as presented in the dietary patterns and foods cluster, showed that a fiber-rich diet also elevated BDNF concentrations. Another mechanism that could be of importance is adult hippocampal neurogenesis since both BDNF and various dietary interventions have been shown to affect the level of neurogenesis in the adult hippocampus [78].

Regarding the dose of the polyphenol supplements used in the interventions, it is notable that those studies that did not show an effect on BDNF concentrations used a lower dose (38-575 mg) than the studies that did show an effect (>1000 mg; Supplemental Table 2). The doses in those studies that did show an effect were comparable to the average dietary polyphenol intake in Europe [79], suggesting that the negative findings in the other studies may have been related to the low doses used. In summary, based on the included studies in this cluster it can be postulated that polyphenols, more specifically the phenolic acids and other phenolic compounds, have a beneficial effect on neurotrophic factors such as BDNF. The underlying mechanisms, as far as evaluated in humans, appear to be similar to the CREB and Akt pathways as described in cell and animal studies [71].

As well as the polyphenol sub-cluster, interesting observations have also been found in the dietary patterns and foods cluster. The quality of the studies in this cluster was sufficient based on the Jadad scores (Supplemental Table 1), when taking into account no points could be awarded for blinding regarding the intervention with dietary patterns or whole foods. The intake of whole-grain rye kernel-based bread resulted in increased plasma BDNF concentrations despite the short duration of the intervention [19]. It could be that the gut-brain axis is involved in increasing BDNF, amongst others because the microbiota composition changed after rye kernel bread had been consumed, which was positively correlated with the increase in circulating BDNF concentrations [80]. This is supported by the increase in short-chain fatty acids in response to rye-based products [81], as well as by improved cognitive performance that is correlated to the amount of fiber in the diet [82]. Similarly, supplementation with a mixed-grain diet in adolescents has also been seen to result in increased plasma BDNF concentrations [83], though unfortunately changes in microbiota were not analyzed. The suggestion that changes in the diet could affect BDNF via modulating microbiota

composition is appealing and is supported by several studies that have shown a link between microbiota composition, BDNF concentrations [84], and cognition [85]. This link can also be seen in the respective studies from Haghghat et al. [54] and Kim et al. [57] where the microbiota populations changed upon supplementation. In this context, it is significant that the studies in the probiotics sub-cluster showed no significant changes in BDNF concentrations [51,53]. However, it should be acknowledged that in those interventions the microbiota profiles also remained stable [51], except for one genus [55].

When evaluating the observed effects on BDNF concentrations in these intervention studies, it should be noted that a number of issues make interpreting the data complex. First, there is enormous variation in peripheral BDNF concentrations between studies, something which could depend on whether it was measured either in serum or in plasma (Supplemental Table 2). Since platelets release BDNF during the clotting process, serum contains higher concentrations of BDNF than plasma [8]. These differences in BDNF concentrations between serum and plasma can be up to 100- to 200-fold [86]. Moreover, clotting time also affects serum BDNF concentrations, whereas the centrifugation protocol also affects plasma BDNF concentrations [87]. Due to the low association between serum and plasma BDNF concentrations, it is difficult to generalize the findings of peripheral measurements [10]. Differences between plasma and serum BDNF analysis might also explain the rather unexpected finding that the studies in the long-chain omega-3 polyunsaturated fatty acid sub-cluster showed no effect on BDNF concentrations, even though omega-3 fatty acids have been found to have neuroprotective effects [88]. In addition, the expected link between dietary omega-3 fatty acid intake and BDNF concentrations has been shown in rat studies [89], and more recently in humans [90]. Interestingly, in the latter study, BDNF concentrations were measured in plasma unlike those interventions described in the sub-cluster where BDNF was always analyzed in serum. As fish oil lowers platelet aggregation [91], it could be that the BDNF stored in platelets was not secreted as easily during the clotting procedure after fish oil supplementation and, therefore, any potential increase in BDNF concentrations would not have become visible when analyzed in serum. Such a reduced BDNF release from platelets has also been shown upon an oral dose of the anticoagulant drug clopidogrel [92]. In addition to this potential serum effect, the absence of an effect in the reviewed fish oil intervention studies could also be related to the different populations studied. Fish oil supplements improved cognitive function in subjects with cognitive

decline but not in healthy subjects [93], which could explain why Witte et al. [50] found no changes in BDNF concentrations.

Second, the majority of the immunoassays used to analyze BDNF concentrations cannot distinguish between precursor BDNF (proBDNF) and mature BDNF (mBDNF; [94]), despite the fact that the two variants are functionally different [2]. Both are biologically active, yet proBDNF has a negative influence and mBDNF a positive influence on synaptic plasticity and, ultimately, memory and cognition. It could be that either one mediates the dietary effect on cognition [95]. For example, extracellular zinc activated metalloproteinase is involved in cleaving proBDNF into mBDNF [96].

Third, it is unclear whether peripheral BDNF concentrations as measured in the intervention studies included in this systematic review reflect central BDNF concentrations. There are certainly indications for such a relation since animal studies have shown positive correlations between peripheral and central BDNF concentrations, which was apparently evolutionary conserved across species [97]. However, from a structural and functional perspective, the blood–brain barrier in humans does not resemble those in animals [98]. Although evidence from human samples is limited, a positive correlation has been found between BDNF concentrations in cerebrospinal fluid and plasma in psychotic subjects [99]. Future research should focus on analyzing both peripheral (serum and plasma) and central BDNF to determine whether it is possible to estimate central BDNF from peripheral BDNF concentrations in other populations. There is also a pressing need to understand whether interventions induce similar changes in both compartments and whether there is a difference between peripheral plasma and serum concentrations in these correlations.

In conclusion, we have demonstrated that dietary interventions can elevate circulating BDNF concentrations. In particular, certain polyphenols, such as phenolic acids and phenolic compounds, seem to have this effect, which could be beneficial in improving metabolic and cognitive health. The effect of dietary ingredients from other (sub-)clusters was, however, inconsistent. Notwithstanding, it should be noted that reviewing studies that describe such effects on BDNF concentrations is highly complex, with findings varying depending on the type of material sampled for BDNF analysis and the BDNF variant measured. Further evaluations of nutritional interventions targeting an increase in BDNF concentrations, particularly focusing on the link between peripheral and central effects, are warranted.

Disclosure statement

No potential conflict of interest was reported by the authors.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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