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The effect of dietary interventions on brain-derived neurotrophic factor (BDNF) levels in adults: a systematic review of clinical trials

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Abstract

Background Brain-derived neurotrophic factor (BDNF) is crucial for brain development, neuronal function, and metabolism. This systematic review aims to comprehensively examine the impact of various diets on BDNF levels, addressing gaps in understanding diet's influence on BDNF's role in neuroprotection and metabolism.

Method This systematic review was conducted in accordance with PRISMA 2020 guidelines. An extensive search was conducted in PubMed, Web of Science, and Scopus up to April 2024, using terms related to diet and BDNF. Relevant clinical trials involving adults were included. Data extraction covered study design, participant details, and outcomes, with quality assessed using the Cochrane method. Clarifications from authors were sought as needed to ensure comprehensive analysis.

Results This review examined 7633 articles to assess the impact of various diets on BDNF levels, narrowing down to 13 studies. The study found varying effects: intermittent fasting and ketogenic diets generally increased BDNF, while other diets showed minimal or no impact. The review highlights diverse outcomes and the need for further research on dietary effects on BDNF.

Conclusion The review found that fasting and calorie restriction diets generally increase BDNF levels, while other dietary interventions showed inconsistent effects. Further research is needed to better understand these dietary impacts on BDNF and to develop optimized strategies for enhancing cognitive health and managing obesity.

Keywords Brain-derived neurotrophic factor (BDNF), Dietary interventions, Obesity and overweight, Systematic review

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Introduction

Brain-Derived Neurotrophic Factor (BDNF) is a pivotal neurotrophin that plays an essential role in neuronal survival, differentiation, and synaptic plasticity, thereby contributing critically to cognitive functions such as learning and memory [1, 2]. Beyond its neurological importance, BDNF is increasingly recognized for its involvement in metabolic regulation, including energy homeostasis and appetite control. Higher circulating BDNF levels have been associated with healthier lifestyle patterns, while lower levels have been linked to metabolic risk factors, obesity, and eating disorders [3]. BDNF signaling is influenced by a variety of factors, including age, body weight, stress, physical activity, environmental exposures, lifestyle behaviors, and dietary intake [4].

Given this connection, dietary interventions have been explored as potential modulators of BDNF levels, aiming to leverage their benefits for both neurological and metabolic health. Nutritional strategies—including adherence to specific dietary patterns and the use of bioactive compound supplementation—have demonstrated variable effects on BDNF concentrations. For example, polyphenol-rich diets have been associated with increased peripheral BDNF levels, indicating potential neuroprotective effects. Additionally, experimental evidence suggests that certain dietary components, such as omega-3 fatty acids, flavonols, and vitamin E, can modulate BDNF expression, at least in animal models [5–7]. In contrast, high-fat diets and refined sugar intake have been shown to reduce BDNF levels, whereas caloric restriction may enhance them [5]. Several human studies have also investigated the impact of different dietary interventions on BDNF concentrations [8]. For instance, Harvie et al. reported no significant difference in BDNF levels between intermittent and continuous energy restriction over a six-month period in overweight premenopausal women [9]. Similarly, in a randomized pilot study comparing zero-calorie alternate-day fasting (ADF) with daily caloric restriction (CR) in adults with obesity, no significant changes in BDNF were observed from baseline to week 8; however, trends toward increased BDNF in the ADF group and decreased BDNF in the CR group were noted by week 32 [10]. In another study, a three-month calorie-restricted diet (CRD) led to an increase in BDNF concentrations among overweight and obese individuals [11]. Evidence regarding the effects of ketogenic diets on BDNF remains limited and inconclusive. However, in a crossover trial involving overweight/obese men, postprandial BDNF concentrations did not significantly differ following meals rich in fat, carbohydrates, or protein [12].

To the best of our knowledge, no previous systematic review has comprehensively assessed the effects of various dietary interventions on circulating BDNF levels in adults. Therefore, the present systematic review aims to synthesize and evaluate existing evidence on the effect of various dietary interventions on circulating BDNF levels in adults.

Table 1 PICOS crieteria

Population	Adults (≥ 18 years)
Intervention	Dietary interventions including specific dietary patterns (e.g., Mediterranean, ketogenic, low-fat) or caloric modifications
Comparison	Control groups receiving usual diet, standard care, or alternative dietary interventions
Outcome	Changes in circulating levels of brain-derived neurotrophic factor (BDNF)
Study Design	Randomized controlled trials (RCTs) and non-randomized interventional studies
Time Frame	No minimum duration required

Materials and methods

Protocol and reporting guidelines

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility criteria

Studies were included if they met the following criteria: [1] randomized and non-randomized trials (parallel or crossover) examining the effects of broad dietary patterns or structured dietary strategies on circulating BDNF levels; [2] interventions conducted in adults (≥ 18 years); [3] BDNF levels assessed both at baseline and post-intervention.

We excluded studies based on the following criteria: [1] non-human studies, observational designs, reviews, editorials, case reports, ecological studies, and book chapters; [2] studies that investigated the effects of dietary supplements (e.g., isolated vitamins, minerals, or herbal products); and [3] studies examining the effects of single food items or ingredients (e.g., olive oil, specific fruits or vegetables) rather than structured dietary interventions. To ensure clarity and transparency in the selection process, the inclusion and exclusion criteria were structured using the PICOS (Population, Intervention, Comparison, Outcomes, Study design) format. A summary of the PICOS criteria is provided in Table 1.

Information sources and search strategy

A comprehensive search strategy was developed and applied to five electronic databases: PubMed, Scopus, Web of Science, Embase, and ProQuest, from inception through April 18, 2024. Searches combined Medical Subject Headings (MeSH) and free-text terms tailored to each database. The keywords used (either individually or in combination) included: "*diet*", "*dietary intervention*", "*intermittent fasting*", "*alternate-day fasting*",

"*time-restricted eating*", "*intermittent energy restriction*", "*caloric restriction*", "*ketogenic diet*", "*Mediterranean diet*", "*vegetarian*", "*low-fat diet*", "*hypocaloric diet*", "*high-fat diet*", "*high-protein diet*", *combined with "brain-derived neurotrophic factor" or "BDNF."*.

Searches were not restricted by language or publication date. To enhance comprehensiveness, we also searched the grey literature, including Google Scholar, preprints, and conference proceedings. Additionally, reference lists of included studies and relevant reviews were manually screened for further eligible articles.

The full electronic search strategies for each database are provided in Supplementary File 1.

Selection process

All records were imported into EndNote reference management software, and duplicates were removed. Two independent reviewers screened the titles and abstracts, followed by full-text screening of potentially eligible studies. Any disagreements were resolved through discussion until consensus was reached. Although inter-rater reliability (e.g., Cohen's kappa) was not calculated, agreement was achieved in all cases.

Data items

The eligibility of studies was first assessed based on their titles and abstracts. Studies deemed potentially relevant were then reviewed in full to determine their suitability for inclusion in this systematic review. The following information was extracted from the included studies: the first author's name, publication year, study location and design, the number of participants in each group, participant details such as mean age and gender, the type of dietary intervention used, the duration of the intervention, the main study outcomes, and the health status of both the intervention and control groups.

Risk of bias assessment

Two researchers independently assessed the risk of bias of included studies using the Cochrane Risk of Bias Tool for randomized trials [13]. The tool evaluates the following domains: [1] random sequence generation [2], allocation concealment [3], blinding of participants and personnel [4], blinding of outcome assessment [5], incomplete outcome data [6], selective outcome reporting, and [7] other sources of bias. Each domain was rated as "low," "unclear," or "high" risk of bias. Discrepancies were resolved through discussion, and if necessary, by contacting study authors for clarification.

Results

Figure 1 illustrates the flow diagram of PRISMA. Initially, 8450 articles were attained by searching electronic databases [Scopus ($n = 3627$), Web of Sciences ($n = 2033$), and PubMed ($n = 1973$), Embase ($n = 612$), ProQuest ($n = 205$)]. The remaining 4885 articles were screened entirely by title and abstract after removing the duplicates. Finally, 13 studies were included in the current systematic review.

Although 19 studies appeared relevant based on their titles and abstracts, they were excluded after full-text evaluation due to reasons such as the absence of a control group [14–16], being a study protocol without results [17], combining diet and exercise [18–20], involving dietary supplements [21–30], or inclusion of pediatric/adolescent populations [31, 32], which did not align with our eligibility criteria.

Table 2 presents the characteristics of the eligible articles in the present study. All the included studies were published until January 2024 and conducted in countries like Germany, Sweden, the United States, Denmark, Netherlands, Iran, Italy, Maryland, Korea, Qatar, Lithuania, Spain, the UK, and New Zealand. In all studies, the effects of diets on BDNF were evaluated. Most studies have used RCT with different arms. The duration of the studies varied from 3 days to 2 years among the studies.

In this systematic review, the effects of different diets on BDNF were evaluated, and the results were presented separately in the following section. The current study demonstrated a BDNF increase induced by dietary restriction in intermittent fasting (IF) [33] and alternate-day fasting (ADF) [13]. The effects of caloric restriction on memory performance in healthy elderly subjects were not affected by brain-derived neurotrophic factors [34]. In addition, BDNF was not significantly affected by meal frequency (Reduced Meal Frequency Without Caloric Restriction) [35]. Intermittent or continuous energy restriction did not cause any significant changes in young overweight women [9]. A significant reduction in BDNF levels was observed in women but not in men in the diet-only (DIO: eight weeks of deficient energy diet (VLED 600 kcal/day)) and diet and exercise (DEX) groups [4]. Postprandial BDNF concentrations in serum significantly decreased after the high-fat and high-carbohydrate meals. A decreasing trend was demonstrated after the high-protein meal in healthy overweight/obese male participants [12]. A reduced-calorie diet did not affect plasma BDNF in overweight/obese subjects with cardiovascular risk factors [36]. A low-calorie diet with time-restricted feeding (TRF) is more effective in improving BDNF levels in overweight/obese women with food addiction [37]. The ketogenic diet (KD) in competitive natural bodybuilders can increase BDNF [38]. Supplementation with a mixed-grain diet benefits plasma BDNF levels in high school students [39]. BDNF levels in overweight and obese women remained unchanged by combining aerobic exercise and calorie restriction (CR).

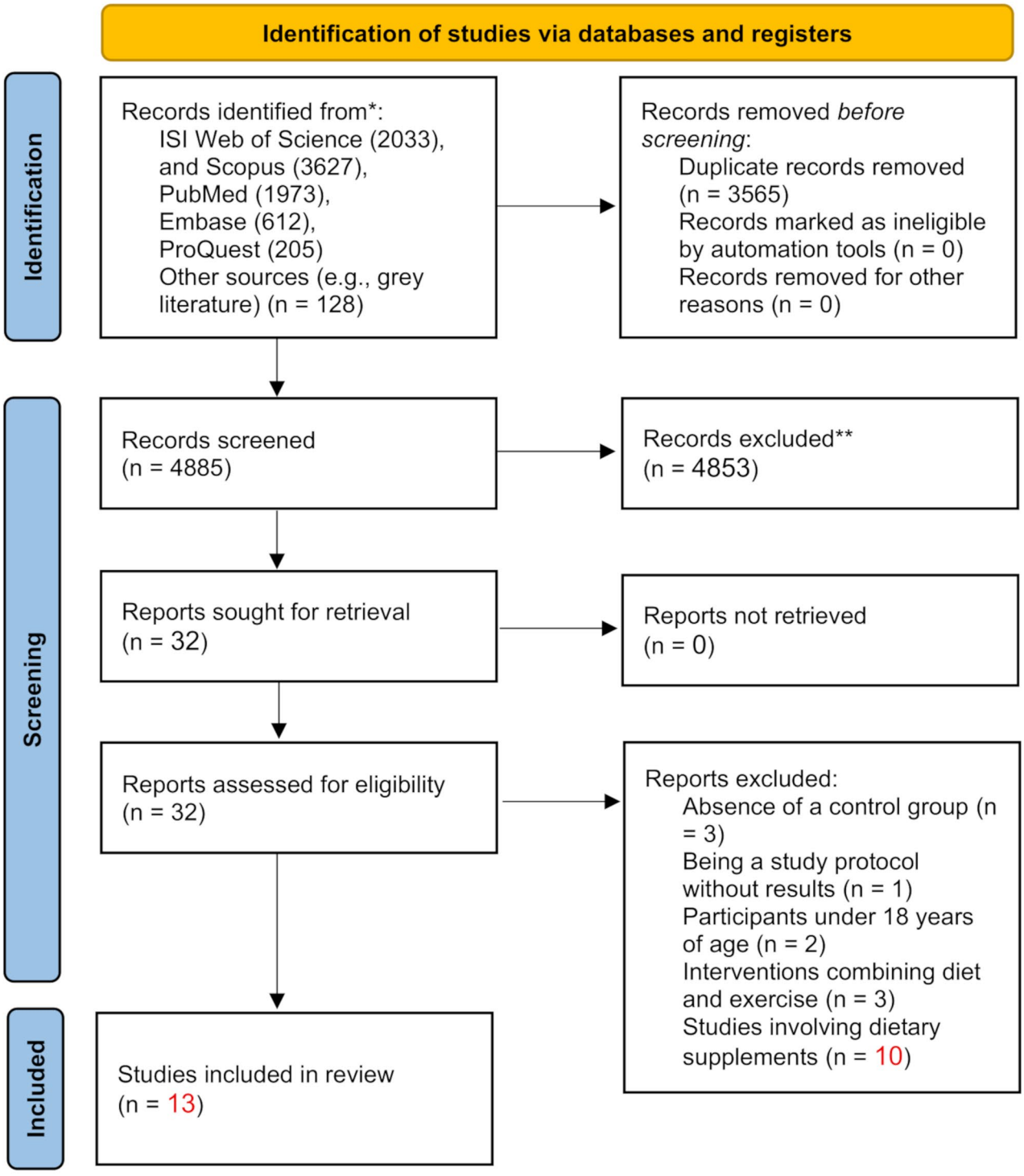

Fig. 1 Flow chart of study selection for included studies in the systematic review

Table 2 Studies evaluating the effects of different diet types on BDNF levels.

	Study Lead author (year), country (ref)	Study design, duration	diet	Sample size	Age, y	BMI	Results	Health status	BDNF Assessment Method
1	Kessler et al., 2015, Germany.	nonrandomized controlled clinical trial, follow up:baseline, 8w, 6 m	**Intermittent fasting**	**-fasting group**: 22 (7 male, 15 female), **-control group**: 14 (7 male, 7 female)	18–65 y	22.2	No statistically significant increase in BDNF levels following intermittent fasting compared to the control group.	Healthy adults. **Intervention**: One fasting day per week for 8 weeks, consisting of abstinence from solid food (00:00 to 23:59) and a maximum intake of 300 kcal from defined fasting beverages; supervised vegetable broth lunch on fasting days. **Control Group**: Regular healthy diet maintained over 8 weeks.	ND
2	Catenacci et al, 2016 USA	Randomized Follow up:8 w And 24 weeks of unsupervised follow-up Pilot Study	Alternate-Day Fasting	CR: 12 (3 Male, 9 Female) ADF: 13 (3 Male, 10 Female)	CR 42.7 (7.9) ADF 39.6 (9.5)	37.6	No difference in BDNF change between groups at 8 weeks; by week 32, BDNF increased in ADF group and decreased in CR group, with a significant between-group difference.	Adults with obesity. **Intervention**: ADF for 8 weeks: complete fasting on alternate days, with energy-matched meals on fed days; standardized weight maintenance advice provided post-intervention. **Control Group**: Continuous CR of approximately 400 kcal/day for 8 weeks.	ELISA
3	Witte et al. 2008 Germany	Randomized Follow up: 3M	caloric restriction	50 (21 Male, 29 Female)	60.5 years ± 7.6 SD	28	BDNF levels remained unchanged across all groups; no significant memory changes were observed.	Healthy adults aged 50–58 years with BMI > 21. **Interventions**: CR group: 30% reduction in caloric intake over 3 months. Unsaturated Fatty Acids Enhancement group: 20% increase in UFA intake over 3 months. **Control Group**: No change in habitual diet over 3 months.	ND
4	Glud et al. Denmark 2019	Randomized Controlled 12W	three groups: exercise-only, low energy diet, diet and exercise	50 (24 Male, 26 Female)	F 36.4 ± 7.9 M 38.0 ± 5.9	35.7	BDNF levels decreased significantly in women in both DIO and DEX groups; EXO group showed a 22% BDNF reduction in men. No significant BDNF changes were observed in men in DIO or DEX.	Overweight or obese but otherwise healthy adults. **Interventions**: • **EXO**: 12 weeks of aerobic exercise + isocaloric diet. • **DIO**: 8 weeks of very low energy diet (600 kcal/day) + 4-week maintenance. • **DEX**: 12 weeks of aerobic exercise + 8-week VLED (800 kcal/day) + 4-week maintenance. **Control**: No separate control group; comparisons made between intervention arms.	ELISA
5	Gravesteijn et al. Netherlands 2017	randomized, double-blind, cross-over trial three test days with 1 week washout periods	high-fat or high-carbohydrate or high-protein meal	18 (18 Male, 0 Female)	18–70 year	30.5	Serum BDNF concentrations were higher than plasma levels. Postprandial serum BDNF decreased significantly after high-fat and high-carbohydrate meals, with a trend toward decrease after high-protein meal; no significant differences between meals. Plasma BDNF remained unchanged.	Healthy overweight or obese men. **Intervention**: Participants consumed high-fat, high-carbohydrate, and high-protein meals on three separate test days with 1-week washouts; BDNF measured at baseline, 60, and 240 minutes postprandially. **Control**: Each participant served as their own control across different meal conditions.	ELISA

Table 2 (continued)

	Study Lead author (year), country (ref)	Study design, duration	diet	Sample size	Age, y	BMI	Results	Health status	BDNF Assessment Method
6	Nasrollahzadeh et al. Iran 2023	parallel randomized controlled trial, 8W	Reduced-Calorie Diet	66 (29Male, 37 Female)	57.9 ± 7.9	30	No significant change in BDNF levels following the reduced-calorie diet.	Overweight or obese individuals with at least one cardiovascular risk factor. **Intervention**: Moderate calorie restriction: 75% of total energy requirements. **Control**: No calorie restriction.	ELISA
7	Irani et al. Ian 2023	randomized clinical trial 8W	Time restricted feeding	56 (0 Male, 56 Female)	TRF 43.56 ± 9.26 control 40.97 ± 8.33	31.3	BDNF levels significantly increased in the TRF group. BDNF was positively correlated with cognitive restriction scores, but not with food addiction severity.	Overweight or obese women with food addiction. **Intervention**: Time-restricted feeding (TRF): low-calorie diet with eating window from 10 AM to 8 PM; fasting hours allowed unsweetened coffee, tea, and water. **Control**: Low-calorie diet without time restriction.	ELISA
8	Paoli et al. Italy 2021	randomized clinical tria 8W	Low Carbohydrate Ketogenic Diet And western diet	19 (19 Male, 0 Female)	27.4 ± 10.5	26.8	BDNF levels increased in both groups, with significantly greater elevation in the KD group.	Healthy adults following isocaloric high-protein diets. **Intervention**: Ketogenic diet (KD): isocaloric intake of 45 kcal/kg muscle mass with 2.5 g/kg protein; carbohydrate intake < 5% daily (< 50 g/day). **Control**: Western diet (WD): isocaloric with same protein intake (2.5 g/kg), but carbohydrates at ∼55% of daily energy.	ND
9	Carlson et al. Maryland 2007	randomized cross-over 8W	Reduced Meal Frequency Without Caloric Restriction		40–50	18–25	Fasting BDNF levels were not significantly affected by meal frequency.	Normal-weight healthy middle-aged men and women. **Intervention**: One meal per day (all calories consumed between 5–9 PM) for 8 weeks. **Control**: Three meals per day for 8 weeks; randomized cross-over design with 11-week washout.	ELISA
10	Sánchez-Villegas et al. 2011 Spain	randomized clinical trial 3Y	Mediterranean diet	Control group (55 Male.22 Female) MeDiet + VOO (64 Male. 27 Female) MeDiet + Nuts (53 Male. 22 Female)	68.0 (6.1) 68.1 (6.1) 67.4 (5.7)	29.1	Plasma BDNF levels were higher but not significantly different in both MeDiet groups. However, the MeDiet + Nuts group had a significantly lower risk of low BDNF levels compared to control, especially among participants with baseline depression.	Adults participating in a dietary intervention trial comparing MeDiet and low-fat diets. **Interventions**: • **MeDiet + VOO**: Mediterranean diet supplemented with virgin olive oil. • **MeDiet + Nuts**: Mediterranean diet supplemented with nuts. **Control**: Low-fat diet.	ELISA
11	Kackley et al. 2022 U.S	ontrolled prospective feeding study was a placebo-controlled, double- blind trial. 6W	Ketogenic diets With and without exogeneous ketone salts	37 (18 male. 19 female)	KD + KS 24–60 KD + PL 25–55 LFD 25–57	31.1	No significant differences in BDNF levels between groups or over time.	Overweight or obese adults. **Intervention**: Hypocaloric ketogenic diet (∼ 75% of energy expenditure) combined with either ketone salt supplementation (KD + KS) or placebo (KD + PL). **Control**: Comparisons made between KD + KS and KD + PL groups; no separate non-ketogenic control group.	Electrochemiluminescence

Table 2 (continued)

	Study Lead author (year), country (ref)	Study design, duration	diet	Sample size	Age, y	BMI	Results	Health status	BDNF Assessment Method
12	Harvie et al. 2011 UK	a randomised trial 6m	intermittent or continuous energy restriction	107 (0 male. 100 female)	30–45	30.6	No significant differences in BDNF levels between groups or over time.	Overweight or obese premenopausal women. **Intervention**: IER: ~2266 kJ/day for 2 days per week. **Control**: CER: ~6276 kJ/day for 7 days per week.	ELISA
13	Gibbons et al. New Zealand 2018	cross-over design	Intermittent fasting and exercise	12 (6 male. 6 female)	30 ± 10	ND	Fasting for 20 hours did not affect BDNF levels. Light cycling increased serum BDNF modestly (6%), mediated by increased platelets. High-intensity exercise significantly elevated plasma and serum BDNF and BDNF-per-platelet ratio 4–5 fold more than light exercise.	Aerobically fit healthy adults. **Intervention**: • 20-hour fasting • 90-minute light-intensity cycling at 25% VO_2peak • High-intensity interval cycling at 100% VO_2peak **Control**: Participants acted as their own control across fasting and exercise conditions.	ELISA

Abbriviations: CR: calorie restriction; BDNF: Brain-derived neurotrophic factor; BMI: body mass index; ADF: alternate-day fasting; IER: intermittent energy restriction; PA: physical activity; UFA: unsaturated fatty acid; VLED: very-low energy diet; EXO: exercise-only; DEX: diet and exercise; KD: ketogenic diet; MeDiet: mediterranean diet; CER: continuous energy restriction; ND: not determined

The methodological quality of the chosen and included studies was assessed using the Cochrane tool (Supplementary Table S1). Only two studies were high risk regarding "random sequence generation" and "allocation concealment." Regarding "selective reporting" and "blinding of participants and personnel," a high risk was observed in one study, but the level of risk was low or unclear in other sectors.

Discussion

This systematic review reveals that dietary interventions have inconsistent effects on BDNF levels in adults, in contrast to the more uniform responses seen with other lifestyle factors like exercise. A key observation is that intermittent fasting and ketogenic diets – interventions that impose a metabolic switch toward fat utilization and ketone production – were the ones most often associated with BDNF elevation. These regimens likely trigger adaptive cellular stress pathways that upregulate neurotrophic factors. Mechanistic studies support this concept: BDNF is known to mediate the beneficial effects of energetic challenges (such as vigorous exercise and fasting) on the brain and body [40]. During fasting or carbohydrate restriction, levels of the ketone body β-hydroxybutyrate (BHB) increase [41]; intriguingly, BHB can act as a signaling molecule that induces BDNF expression in the brain [42]. Sleiman et al. demonstrated in mice that exercise-induced elevations in BHB enhanced BDNF gene transcription in the hippocampus [43]. A ketogenic diet mimics some physiological aspects of exercise (e.g. increased BHB and altered energetic state), which may explain why Paoli et al.'s ketogenic diet trial showed a larger BDNF increase than a higher-carbohydrate diet [44]. Intermittent fasting, especially when extended beyond a few weeks (as in Catenacci et al.'s ADF study), might similarly engage these pathways by creating repeated bouts of metabolic stress followed by recovery, thereby stimulating BDNF production over time. In sum, diets that acutely lower blood glucose and elevate ketones or induce mild stress responses appear to have the greatest potential to boost BDNF, consistent with adaptive survival mechanisms observed in preclinical models.

On the other hand, many dietary interventions – particularly moderate continuous calorie reduction or standard healthy diets – did not elicit any change in BDNF, which invites scrutiny of possible reasons. One consideration is that peripheral BDNF homeostasis is tightly regulated and may only shift when a certain threshold of metabolic challenge is reached. For example, a daily 20–30% calorie deficit (as in Witte et al. and Nasrollahzadeh et al.) may improve metabolic markers but not enough to trigger BDNF changes [45]. It is notable that Witte's calorie-restricted group improved memory function despite no BDNF increase [46], suggesting that

peripheral BDNF may not reflect all neural benefits of diet, or that other factors compensated for BDNF's role. Additionally, baseline nutritional and health status likely modulates responsiveness. In healthy, normal-weight individuals with adequate BDNF levels, dietary changes might have limited impact (ceiling effect), whereas in metabolically compromised individuals, there might be more room for BDNF modulation. For instance, Irani et al.'s study involved women with food addiction – a group that may have had dysregulated neurotrophic signaling – and found a pronounced BDNF rise with TRF [47]. By contrast, Kessler's trial in healthy adults found no BDNF change with light intermittent fasting, perhaps because their BDNF was well-regulated at baseline [48].

Negative findings in some studies might also stem from the body's counter-regulatory mechanisms. Sustained caloric deprivation (as in continuous CR) can increase cortisol and chronic stress responses that might blunt BDNF production or increase its utilization [49, 50]. The significant BDNF decreases seen in Glud et al.'s very-low-calorie diet group (especially among women) suggest a possible stress-related suppression of BDNF under conditions of rapid weight loss [50]. Severe energy restriction might lower levels of leptin and insulin and raise stress hormones, which could downstream reduce BDNF expression (animal data indicate that chronic stress and hypercortisolemia can suppress BDNF). In Glud's study, gender differences emerged: only women on the diet showed BDNF declines [50], hinting at potential interactions between diet-induced hormonal changes (e.g., estradiol, which can affect BDNF) and energy balance. Meanwhile, the acute postprandial BDNF drops after high-fat/carbohydrate meals (Gravesteijn et al.) point to another mechanism [51]: an immediate influx of nutrients, especially fats and sugars, may transiently reduce BDNF release or detection. This could be due to postprandial inflammatory responses or insulin spikes; high insulin might drive BDNF uptake into tissues or alter cleavage of proBDNF, temporarily reducing circulating levels. These short-term declines recovered within hours, implying they reflect dynamic transport or binding rather than depletion of BDNF per se.

It is also critical to consider methodological factors when interpreting the heterogeneous outcomes. BDNF was measured in serum in several studies, but in plasma or by different assays in others. This distinction is non-trivial: serum BDNF is substantially influenced by platelet degranulation during clotting, whereas plasma BDNF (from anticoagulated blood) is generally lower and thought to reflect more stable circulating levels. A diet or exercise stimulus might mobilize BDNF from platelets or endothelium without truly increasing neural secretion. For example, Gibbons et al. found that light exercise increased serum BDNF modestly via platelet activation, without a corresponding rise in plasma BDNF [52]. If some interventions preferentially affect platelet BDNF release (or platelet count), results could vary based on whether serum or plasma was analyzed. The use of different assay platforms (ELISA vs. electrochemiluminescence) and sampling times (e.g., fasting BDNF in the morning vs. unspecified times) across studies adds further variability. These technical factors might partly explain why some trials observed changes while others did not, even if biological effects were present to a mild degree.

recent evidence suggests that dietary supplementation with probiotics and synbiotics may also positively influence BDNF concentrations. A systematic review and meta-analysis by Foshati et al. demonstrated that pro-/synbiotic supplementation significantly increased BDNF levels in human subjects [53]. This finding highlights the potential role of gut microbiota modulation in supporting brain health. Therefore, diets rich in probiotic and synbiotic foods could serve as a non-pharmacological approach to enhancing BDNF levels. Future studies should investigate the effects of such dietary patterns on BDNF concentrations to provide a more comprehensive understanding of their impact on cognitive and mental health.

When compared with animal and epidemiological evidence, our findings show partial alignment. While animal studies consistently demonstrate that energy restriction and ketosis enhance brain BDNF [40, 54, 55], human trials yielded more variable outcomes. Intermittent fasting and ketogenic diets increased BDNF in some studies, supporting ketone-related mechanisms, but effects were neither universal nor immediate. The influence of exercise appears stronger than diet al.one, suggesting that combined interventions may yield greater BDNF benefits. Observational studies also report complex associations between BDNF, obesity, mood, and cognition, highlighting the multifactorial nature of BDNF regulation [56, 57]. Notably, external evidence suggests that BDNF improvements may mediate better mental health outcomes during dietary interventions. Overall, our findings mirror broader scientific uncertainty and reinforce the idea that the impact of diet on BDNF is moderated by factors such as metabolic status, ketosis, intervention duration, and concurrent exercise, warranting further mechanistic research.

The findings of this systematic review suggest that specific dietary interventions, particularly intermittent fasting and ketogenic diets, may hold promise as non-pharmacological strategies to enhance BDNF levels, potentially supporting neuroplasticity, cognitive function, and mental health in adults. Given the role of BDNF in neurodegenerative diseases, mood disorders, and metabolic health, incorporating such dietary strategies could

complement existing interventions aimed at promoting brain health. However, given the inconsistency across studies and variability in individual responses, clinicians should exercise caution and personalize dietary recommendations based on individual needs, health status, and risk profiles. Further high-quality clinical trials are warranted before firm dietary guidelines targeting BDNF modulation can be established.

The present systematic review has several strengths, including the exclusive inclusion of clinical trials (mostly randomized), use of controlled or well-defined dietary interventions, and exploration of diverse dietary patterns, enhancing causal inference and generalizability. However, significant heterogeneity in intervention types, participant characteristics, and study durations introduced variability that complicated direct comparisons. Many studies had small sample sizes, limiting statistical power to detect modest BDNF changes, particularly given the biomarker's high intra-individual variability. Furthermore, while blood BDNF was consistently measured, its relationship with central nervous system BDNF remains uncertain, raising questions about clinical relevance. The review also acknowledges risks of bias inherent to dietary trials, such as lack of blinding and publication bias. Despite these limitations, the identified patterns suggest that diets supporting metabolic and cognitive health may help maintain or elevate BDNF levels, although more robust and long-term studies are needed.

Future research should target populations with initially low BDNF levels, such as individuals with depression, cognitive decline, or specific genetic polymorphisms, to better capture diet-induced changes. Factorial trials combining diet and exercise interventions are needed to explore potential synergistic effects on BDNF. Mechanistic studies incorporating biomarkers like ketone bodies, cytokines, and gut microbiota profiles, as well as neuroimaging assessments, would enhance understanding of underlying pathways. Standardization of BDNF measurement protocols—regarding sample type, timing, and functional assays—is critical to improve comparability across studies. Finally, longer-term and follow-up studies are necessary to determine the durability of diet-induced BDNF changes and their implications for long-term brain health.

In conclusion, this systematic review highlights that dietary interventions can influence BDNF levels in adults, but the effects are not uniform and depend on the nature and context of the diet. Intermittent fasting and ketogenic diets show the most promise in increasing BDNF, aligning with mechanistic expectations from animal studies and metabolic physiology. However, many common dietary approaches yield no significant change, and some extreme diets may even lower BDNF, underscoring a need for caution. The inconsistencies and gaps in the current evidence underscore that we are only beginning to understand the diet–BDNF relationship.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40795-025-01174-3.

Supplementary Material 1

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Author contributions
Conceptualization, M.S., A.N., and M.M.N; methodology, M.M.N., and P.R.; writing—original draft preparation, M.M.N., A.S., and A.D.; writing—review and editing, M.M.N., and G.R. All authors have read and agreed to the published version of the manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article and its supplementary information files. No additional datasets were generated or used.

Declarations

Ethics declaration
Not applicable. This study is a systematic review and did not involve the collection of new human or animal data.

Consent to publish
Not applicable.

Conflict of interest
The authors declare no conflict of interest.

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