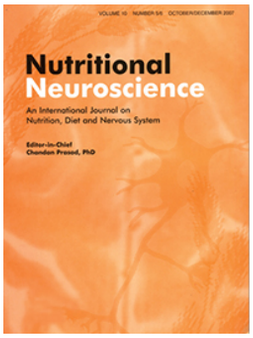

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REVIEW

Nutrition and bipolar disorder: a systematic review

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ABSTRACT

Introduction: Individuals with bipolar disorder (BD) have higher rates of unhealthy lifestyles and risk for medical comorbidities Research currently suggests that dietary factors may play a role in the development of depression and anxiety. Therefore, nutritional approaches are potential strategies for the treatment of BD. The aim of this review is to summarize the available evidence on nutrition and BD. Materials and Methods: The paper was developed based on PRISMA 2020 guidelines. The search was conducted in Sep-2021 using PubMed and Cochrane Library, augmented by manually checked references lists. The search found 986 studies, of which 47 were included, combined with 13 from reference lists, totaling 60 studies. Results: There were 33 observational trials, of which 15 focused on fatty acids, 9 on micronutrients, 5 on specific foods, 4 on macro and micronutrients. The 27 interventional studies mainly focused on fatty acids, micronutrients and N-acetylcysteine (NAC). Discussion: Dietary intake or supplementation of unsaturated fatty acids, mainly Omega-3 seems to be associated with improved BD symptoms, along with seafood, folic acid and zinc. Studies found variable, mainly non-significant impacts of creatine, carnitine, vitamin D, inositol or NAC supplementation on BD. There are promising results associated with Coenzyme Q10 (Coq10) and probiotics. Taken together, these preliminary findings suggest that dietetic approaches might be included as part of BD treatment. Also considering the high risk of metabolic disorders in individuals with BD, they should be encouraged to choose healthy dietary lifestyles, including daily intake of fruits, vegetables, seafood and whole grains.

KEYWORDS

Nutritional psychiatry; bipolar disorder; mood; diet; treatment; mental health; neuroscience; psychiatry

Introduction

Nutritional psychiatry is a rapidly expanding field of study, which has recently benefited from the advances of neurosciences, epidemiological research on risk factors as well as the renewed interest in the role of lifestyle in mental health [1]. Extensive observational evidence consistently demonstrates that diet quality is a predictor of depression risk – independent of other factors, such as education and body weight [2]. Moreover, randomized controlled trials in people with even severe major depressive disorder show efficacy and cost-effectiveness in improving depression symptomatology [3–7]. Concordantly, meta-analytic data confirms that dietary change improves depression symptoms in both clinical and non-clinical populations [8]. Considering that poor diet and dysfunctional eating behaviors are modifiable risk factors, it is possible that these will be converted into critical interventions for mental health [3,9,10]. Indeed, new clinical practice guidelines for mood disorders include diet, along with other aspects of lifestyle, as foundational and 'non-negotiable' treatment targets [1,11].

Nutrition in BD is important for two factors. Firstly, individuals with BD have high rates of unhealthy lifestyle habits. Appetite fluctuation and changes in the energy are core features of this illness, often associated with poor nutritional choices [12]. Depression in bipolar disorder, the predominant phase, is often characterized by atypical symptoms including increased appetite. Secondly, there are disproportionally high rates of general medical comorbidities in BD, such as diabetes mellitus, metabolic syndrome, cardiovascular disease, osteoporosis and endocrine dysregulation compared to

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the general population [13]. These rates are driven by both the intrinsic pathophysiology of the illness, which includes systemic factors (e.g. brain and systemic immuno-inflammatory activation [14–16], glucose-insulin abnormalities [13], oxidative stress imbalances [17], mitochondrial dysfunction and premature/accelerated aging [18]), as well as medication side effects and unhealthy lifestyle. Diet, nutritional patterns, and specific nutrients may have an influence on these mechanisms [19]. For instance, the Mediterranean diet has anti-inflammatory properties, Omega-3's can have anti-inflammatory activity and impact neuroplasticity, and calorie control can present antioxidant effects, while excess sugar can impair mitochondrial activity and excess gluten can increase inflammation [20,21].

Individuals with BD seek treatments that are effective, safe and affordable [22]. Several pharmacological and psychological treatments are available, but the symptoms are challenging to resolve, and full remission is often difficult to achieve [23], risking decreased functionality and lower quality of life. Although the field is nascent, nutrition seems a promising treatment target in BD, as observational and interventional studies are beginning to support this notion. The objective of this paper was to systematically review the available evidence on nutrition and BD symptoms, mechanisms, and associated comorbidities.

Materials and methods

The current review was based on the PRISMA 2020 guidelines [24]. To answer the question 'Do specific nutrients or foods affect, or are associated with, BD mechanisms, symptoms and/or associated comorbidities?' we designed a search with the term 'bipolar disorder' and broader terms related to nutrition: diet OR nutrition OR macronutrient OR omega OR 'dietary supplement'. The search was conducted in September 2021 using PubMed and Cochrane Library. References lists were also manually checked for additional references. The inclusion criteria were (I) manuscripts with 10 or more individuals with BD (>18 years old), (II) manuscripts that analyzed (observational) or supplemented (interventional) any nutrient or specific food focusing looking at improvement of BD´s symptoms or comorbidities (as primary or secondary outcomes), (III) manuscripts written in English, (IV) studies published from 2001 to 2021, and (V) interventional studies with a minimum duration of 3 weeks. The exclusion criteria were (I) studies focusing the dietary impact on pharmacotherapy side effects, (II) studies with physical activity and other lifestyle interventions in combination with nutritional interventions, (III) studies that only analyzed alcoholic intake, (IV) manuscripts that included participants with 'mental disorders' without specifying BD, (V) studies that analyzed participants with psychosis without specifying BD, (VI) Studies on pregnant and breastfeeding women, (VII) secondary studies (same sample) that reanalyzed similar outcomes from the primary study.

One reviewer was responsible for the screening, using the website Covidence [25]. After excluding studies that clearly did not meet the inclusion criteria, the remaining articles were screened by full-text reading and assessed for eligibility. The reference list from the included articles and reviews on related topics were then checked for possible additional relevant studies. A table with the extraction data was created with first author, country, design, population studied, intervention, duration, outcomes, main results and statistical power (SUPPLEMENTARY MATERIAL 1). Also, the same reviewer assessed the quality of the studies related to six main biases: selection (randomization), allocation (baseline comparison), detection (blinding), attrition (dropout), false positive report (adequate sample size) and statement of conflict of interest (Table 1).

Results

Search results

The final search yielded 986 studies. After removing duplicates ($N = 60$), studies in other languages and publications prior to 2001 ($N = 97$), titles and abstracts from 829 studies were screened. Studies that did not clearly meet the inclusion criteria and/or met the exclusion criteria were excluded. The remaining 57 studies were analyzed by full text reading, after which 10 were excluded because they did not meet the full inclusion criteria. This led to 47 included studies, which were combined with 13 studies that were obtained from the bibliography from the included studies and reviews found in the search, totaling 60 studies (Figure 1).

Study characteristics

The characteristics and main outcomes of the 60 articles included in this systematic review are presented in SUPPLEMENTARY MATERIAL 1. They were published between 2001 and 2021, and most of the studies were from the United States.

Study design

Most of the studies were observational (55%; $N = 33$), mainly focusing on fatty acids ($N = 15$), followed by

Table 1. Quality assessment of the included studies.

Observational						
Study	Selection bias	Allocation bias	Detection bias	Attrition bias	False positive report bias	Statement of possible conflict of interest
Almeida et al., 2018	n/a	n/a	High	n/a	high	no
Bly et al., 2014	n/a	low	High	High	high	yes
Boerman et al., 2016	n/a	n/a	High	n/a	high	yes
Chang et al., 2017	n/a	medium	High	Medium	high	yes
Cheng et al., 2019	Low	high	High	n/a	high	yes
Chiu et al., 2003	n/a	medium	Low	n/a	high	no
Chowdhury et al., 2017	n/a	high	High	n/a	high	yes
Dickerson et al., 2019	n/a	low	High	n/a	high	yes
Elmslie et al., 2001	n/a	low	High	n/a	high	yes
Evans et al., 2012	n/a	low	High	n/a	high	yes
Evans et al., 2012	n/a	n/a	High	n/a	high	yes
Evans et al., 2014	n/a	high	High	High	high	yes
Evans et al., 2015	n/a	low	High	High	high	no
González-Estecha et al., 2011	n/a	medium	High	n/a	high	yes
Hunjan et al., 2021	n/a	n/a	High	n/a	low	yes
Kendirlioglu et al., 2020	n/a	low	High	High	high	yes
Kilbourne et al., 2007	n/a	low	High	n/a	low	yes
Koga et al., 2019	n/a	medium	Low	n/a	high	yes
Lapid et al., 2013	n/a	n/a	High	n/a	high	yes
Lokjo et al., 2019	n/a	low	High	Medium	high	yes
Luy et al., 2021	n/a	low	High	n/a	high	yes
Maremmani et al., 2011	n/a	high	High	n/a	high	yes
McInnis et al., 2018	n/a	medium	High	Medium	high	yes
McNamara et al., 2010	n/a	high	Low	n/a	high	yes
Noaghiul & Hibbeln, 2003	n/a	high	High	High	high	no
Noguchi et al., 2013	n/a	medium	High	n/a	high	no
Pomponi et al., 2012	n/a	high	High	n/a	high	yes
Pradeep et al., 2014	n/a	high	High	n/a	high	yes
Sagduyu et al., 2005	n/a	n/a	High	High	high	no
Saunders et al., 2015	n/a	medium	High	n/a	high	yes
Scola et al., 2018	n/a	high	High	n/a	high	yes
Siwek et al., 2017	n/a	medium	High	n/a	high	no
Voggt, et al., 2015	n/a	low	High	Medium	high	yes
Interventional						
Study	Selection bias	Allocation bias	Detection bias	Attrition bias	False positive report bias	Statement of possible conflict of interest
Behzadi et al., 2009	low	low	Low	Medium	low	no
Bauer et al., 2019	low	low	Low	Low	high	yes
Berk et al., 2008	low	low	Low	Low	low	low
Berk et al., 2012	low	medium	Low	Medium	high	yes
Berk et al., 2019	low	medium	Low	Low	high	yes
Brennan et al., 2013	low	medium	Low	Medium	low	yes
Ciappolino et al., 2020	low	low	Low	High	high	yes
Dickerson et al., 2018	low	low	Low	Low	high	no
Elmslie et al., 2006	low	medium	Low	Low	low	yes
Frangou et al., 2007	low	high	High	High	high	yes
Hirashima et al., 2004	low	medium	Low	High	high	no
Kaplan et al., 2001	n/a	high	n/a	Low	high	no
Keck et al., 2006	low	medium	Low	Low	high	no
Marsh et al., 2017	low	medium	Low	Medium	high	yes
McNamara et al., 2015	low	medium	Low	High	high	yes
Mcphilemy et al., 2020	low	medium	Low	Low	low	no
Mehrpooya et al., 2018	low	medium	Low	Medium	low	yes
Murphy et al., 2012	low	high	Low	Medium	low	yes
Nierenberg et al., 2006	low	medium	High	High	high	no
Nierenberg et al., 2017	n/a	medium	n/a	Medium	high	no
Osher et al., 2005	n/a	high	n/a	Medium	high	no
Porcu et al., 2018	low	medium	low	Low	high	yes
Reininghaus et al., 2018	high	medium	high	Medium	low	yes
Russo, 2010	low	high	high	High	high	yes
Shahrbabaki et al., 2020	low	medium	low	High	low	yes
Shakeri et al., 2016	low	low	low	Low	low	low
Toniolo et al., 2018	low	medium	low	Low	high	yes

different micronutrients ($N = 9$), specific foods ($N = 5$), and macro and/or micronutrients ($N = 4$). The remaining studies were interventional studies (45%; $N = 27$), involving administration of a variety of nutrients: fatty acids, combined or specific micronutrients and other interventions.

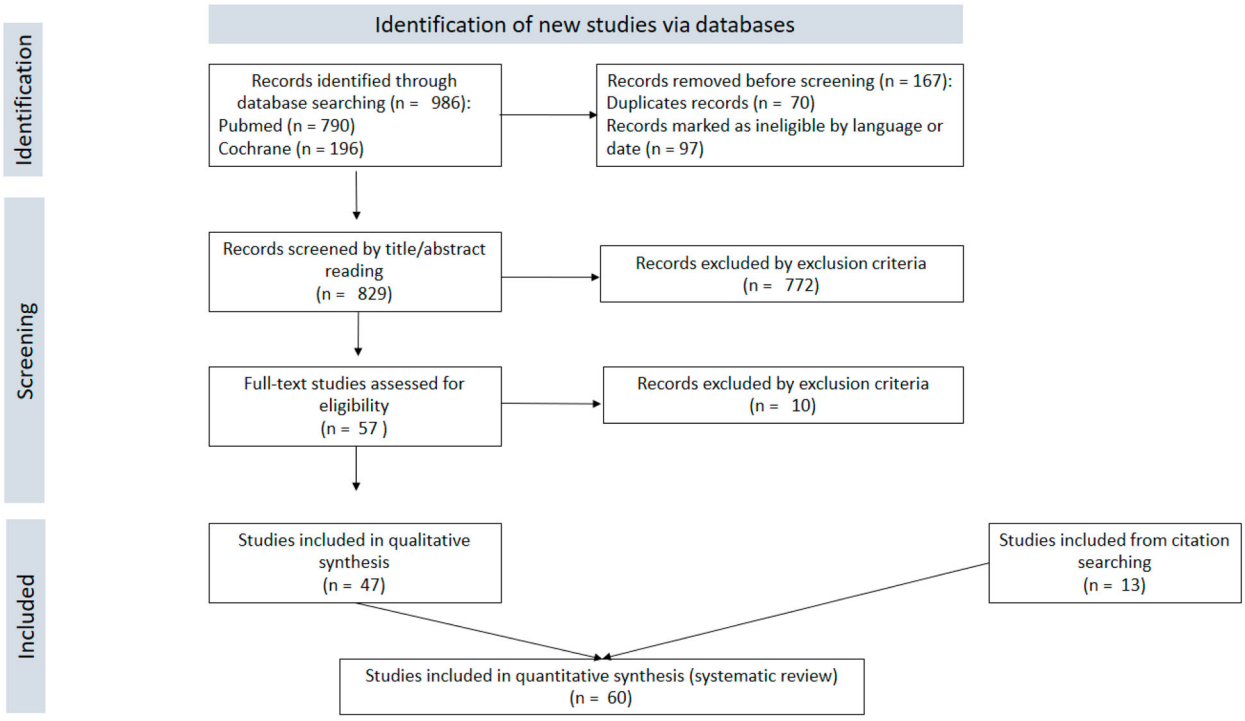

Figure 1. Flow diagram of the systematic review included articles, based on PRISMA.

Regarding the outcomes of the 60 included studies, most of them investigated differences in nutritional factors between individuals with BD and healthy controls, or the association of symptoms severity in BD (62%; $N = 45$). Secondary outcomes that were investigated included nutrients, blood levels ($N = 18$), food intake ($N = 8$), anthropometrics ($N = 2$), and biological outcomes ($N = 6$) such as neuroimaging, heart rate variability, microbiome, genetics, exercise and smoking habits.

Main nutritional factors

Fatty acids

Fatty acids are long-chain hydrocarbons that can be classified as saturated (single bond among carbons) or unsaturated (double bonds among carbons). Some fatty acids are produced by the body, but the ones considered essential must be consumed through diet, such as polyunsaturated linoleic and α- linoleic acids, which are called Omega-3 and Omega-6, respectively [24].

Observational Studies. Fifteen studies evaluated fatty acid blood levels ($N = 11$) or fatty acid intake ($N = 4$) in individuals with BD. Overall, these studies support the association between fatty acids metabolism and BD. Individuals with BD exhibited lower blood levels of Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) which are related to low intake of these fatty acids [26–31] higher levels of inflammation [32] and a higher ratio of omega 6: Omega-3 (Arachidonic acid (AA):EPA + DHA) compared to healthy controls [31,33,34].

Regarding linoleic acid (LA), four studies concluded that higher LA plasma and intake levels were associated with better BD outcomes, including amelioration of depressive symptoms [35–38]. One study did not find significant results regarding Omega-3 [39].

Another cohort study of 1111 subjects reported that BD subjects usually consumed less polyunsaturated fat (PUFA), and more saturated fat [38]. Regarding clinical outcomes, three studies verified that individuals with higher blood levels of EPA, AA, LA and Alpha-lipoic acid (ALA) were associated with improved extraversion, neuroticism, agreeableness (NEO Personality) and fewer suicide attempts [35,38,40].

In terms of biological outcomes, the high Omega 6/Omega 3 ratio in the diet found in individuals with BD was associated with higher peripheral levels of inflammatory mediators [31]. LA seems to have a similar association, with a negative correlation between LA plasma levels and severity of inflammation in BD [36–38,40]. In addition, lower levels of dietary PUFA were related to the presence of gut microbiome dysbiosis [38]. However, the microbiome is influenced by a myriad of factors, including psychiatric medications [38].

Interventional Studies. Overall, interventional studies support a small effect-size for Omega-3 supplementation in BD in secondary biological outcomes, but which was not translated into meaningful

symptomatic improvement. For example, two interventional studies found a potential benefit of Omega-3 supplementation in BD. One was a small 4-week trial with BD individuals (intervention $N = 12$; placebo group $N = 9$) compared to healthy controls ($N = 12$), where the intervention group received 2 g or 10 g of Omega-3. Both doses caused a significant increase in neuronal membrane fluidity – brain water proton transverse relaxation time. However, there was no difference between groups in Hamilton Depression Rating Scale (HDRS) or Young Mania Rating Scale (YMRS) [41]. Likewise, an open-label trial of 1.5–2 g of EPA per day for 6 months was conducted in 10 subjects with BD. Although only 5 subjects completed the study, they had a decrease in depression symptoms [42]. Four other studies used Omega-3 supplements given for 8, 12 or 16 weeks, which were compared to placebo or healthy controls, with doses varying from 1 to 6 grams. There was no significant improvement in HRDS scores after 2 g of EPA supplementation [43]. There were no significant differences between groups for scores on the YMRS, Inventory for Depressive Symptomatology, Global Assessment of Functioning and Montgomery-Åsberg Depression Rating Scale (MADRS) after 6 g of EPA or 4 g of fish oil [44,45]. Regarding mania severity (YMRS), there was a significant improvement in the group that received 1 g of Omega-3 compared to placebo [47].

In a 52-week trial, comparing lithium and quetiapine, there was no significant association between YMRS or HDRS and fatty acid variations in either treatment group [46]. In another study, there was a lack of improvement in the Brief Assessment of Cognition in Affective Disorder after 12 weeks of supplementation of 1250 mg of Omega-3, compared to placebo [48]. However, the healthy controls had higher plasma levels of Omega-3 at baseline [48]. Lastly, a 52-week study which evaluated Omega-3 supplementation (1 g of EPA + 1 g of DHA), concluded that there were no statistical benefits compared to placebo regarding number of relapses (occurrence of a mood episode), hospitalization, medication and depressive symptoms [49]. Even though there was a slight improvement in mania symptoms in the intervention group, the authors noted that it was not clinically meaningful [49].

Micronutrients

Observational Studies. Selected micronutrients were analyzed in blood and hair samples. One study analyzed micronutrient blood levels of 60 individuals with BD and 60 healthy controls. They verified that vitamins A, E, C, zinc levels were inversely proportional to oxidative stress (concentration of serum malondialdehyde), which was higher in BD subjects. Similar, serum selenium, sodium, potassium and calcium were significantly lower in those with BD [50]. Likewise, hair samples of 26 BD individuals showed lower levels of manganese, iron, nickel, zinc and selenium compared to healthy control groups [51]. On the other hand, hair copper concentration was higher in BD subjects. These results are in line with a multinational analysis showing that manganese, calcium and iron levels were lower in more than 20k BD individuals, while copper levels were higher [52]. Compared to more than 3000 individuals with schizophrenia or major depression, 1901 BD individuals presented higher plasma levels of folate and vitamin B12 – but all of these groups presented levels within the normal range [53].

Despite two observational studies that did not find statistical significance regarding copper concentration and BD episodes or symptoms [54,55]. One of these studies concluded that blood lead and cadmium, which are common persistent heavy metal pollutants linked to mood disorders [56], were higher in 25 BD subjects compared to healthy control groups [54]. Regarding serum vitamin D, a study verified that 118 individuals with BD have lower levels than the general population, but it cannot be inferred that vitamin D protects from psychiatric disorders [57]. Similarly, a study analyzed 11 geriatric BD subjects and did not find significant impact of serum vitamin D on BD symptoms [58].

Interventional Studies. Supplementation of 3 mg of folic acid added to valproate for 3 weeks lead to improvement in manic symptoms, mainly language, thought disorder, irritability and disruptive-aggressive behavior, when compared to placebo in 88 BD type I patients divided into two groups [59]. Likewise, 10 BD subjects, in a 6-week open-label trial, the daily administration 15 mg of methylfolate was associated with decreased depressive symptoms, but no change in mania [60]. An 8-week trial with 35 BD subjects of an antioxidant supplement composed of vitamins C, E, B6, Magnesium, Manganese and Zinc decreased the severity of BD symptoms and increased the levels of Hepatocyte Growth Factor, which is probably associated with lower inflammation [61]. Finally, the results of an open-label trial with a multi-nutrient supplement (24 chelated minerals and vitamins + inositol + grape seed + choline) found lower Brief Psychiatric Rating Scale (BPRS), HDRS and YMRS after 6 months [62]. Supplementation of vitamin D in a 12-week randomized-controlled trial with 25 BD subjects (5000 UI of vitamin D3 or placebo) did not significantly impact BD symptoms [63].

N-Acetyl-Cysteine: interventional studies

There are five randomized-controlled trials comparing the effects of N-acetylcysteine (NAC) on BD symptoms and inflammation parameters. These 5 studies had more than 50 BD participants with durations of 12–32 weeks [64–68]. The first trial was published in 2008 and divided participants into 2 g of NAC per day or placebo. There was a significant improvement in MADRS, BDRS and CGI scores in the treatment group. Even though manic symptoms also improved, there was not a significant difference among groups [64]. The second study aimed to investigate the maintenance efficacy of adjunctive NAC in bipolar depression. All the participants received NAC for 8 weeks and, after that, were randomized to continue with NAC or placebo. Participants had an overall decrease in symptoms in the open label phase, but there were no significant results from the randomized part of the study (placebo or NAC) [65]. The third aimed to examine the effects of NAC or a 'mitochondrial cocktail' of NAC together with other nutrients (carnitine, Coq10, alpha-lipoic acid, magnesium, vitamins C, D, E and B complex) that might enhance mitochondrial biogenesis in bipolar depression, when compared to placebo. The only scale that the combined intervention (NAC + other nutrients) had a greater significant reduction was the MADRS [66].

Another study randomly assigned participants to receive one of the treatments: 1 g of aspirin, 1 g of NAC, combined aspirin and NAC at same doses or placebo. There was no significant difference among groups regarding symptoms severity or inflammatory mediators levels, but a significant greater response of treatment of NAC combined with aspirin than the other groups [68]. Lastly, the use of 1,8 g of NAC caused a significant reduction in depressive and anxiety symptoms on those with high levels of reactive C-reactive Protein (>3 mg / L). Besides, the supplementation was able to improve reactive C-reactive Protein levels when compared to placebo [67]. Meta-analyses of NAC for bipolar disorder suggest improvement in depressive symptoms with moderate effect sizes [69].

Specific foods: observational studies

Five observational studies investigated the effect of specific food intakes in BD. First, a cross-national study analyzed seafood intake from 11 countries and explored the relationship with a BD diagnosis. Greater seafood consumption was associated with lower prevalence rates of BD ($r<-0.60$) [70]. Similarly, a Japanese study analyzed the consumption of 56 foods and 9 dishes. In 75 BD individuals, greater consumption of fish and vegetables was significantly associated with improved physical and psychiatric symptoms [71].

One study with 273 participants compared diet patterns in BD subjects and healthy controls. The group of BD individuals presented lower Mediterranean diet score and lower intake of healthy carbohydrates compared to health controls, besides the patient group had regular consumption of meat, potato and refined grains [72]. On the other hand, a cross sectional study analyzed juice, fruits and vegetable intake, as well as meal habits of 6710 participants, including individuals with BD, schizophrenia and healthy controls. They found no significant differences among groups, but BD individuals were more likely to eat alone and eat only one meal per day [73]. Another cross-sectional study with 562 BD and major depression reported that BD individuals consumed more coffee (13.3 vs 10.3 units per week) than those without BD, but there was no significant difference regarding chocolate intake [74]. Similarly, a study of 69 elderly men found no significant differences regarding meat, fish, salt and skimmed milk intake between BD participants and healthy controls [75]. Lastly, a UK Biobank study analyzed self-reported dietary habits of more than 163k individuals with different psychiatric disorders. Regarding the intake of the 20k individuals with BD, they did not find any statistical significance on polygenic propensity for this specific disorder associated with dietary behavior. Their findings suggest it is necessary to have further research related to biological and environmental factors that influence dietary habits and psychiatric disorders [76].

Macronutrients

Two observational studies with more than 500 participants, including BD patients and healthy control groups, analyzed diet using 24-hour dietary recall. Although one study suggested that participants with BD consumed fewer calories, carbohydrates and fat in general, they also had higher rates of metabolic syndrome and altered blood biomarkers than healthy controls [77]. In contrast, another study verified that BD individuals had a higher intake of total daily sucrose, carbohydrates, fluid intake and intake of sweetened drinks compared with healthy controls [77].

Two studies evaluated blood tests and dietary recall of participants. One analyzed 66 participants with mania, showing that individuals with BD consumed more fiber (19.9 g vs 16.1 g) and less trans-fat (0,9 g vs 2,4 g), compared to a schizophrenia group. A higher consumption of protein was positively associated with improved memory, language and BPRS [79]. The second study suggested that 54 BD participants had a significantly lower intake of EPA, DHA and AA, as well as selenium, than healthy controls [80].

Other interventional studies

An 8-week trial evaluated the supplementation of 200 mg of CoQ10 or placebo. Compared to baseline, the 69 participants from both groups showed decreased MADRS scores, but the group with CoQ10 had a larger significant decrease [81].

Three recent studies explored the potential of probiotics in BD symptoms. Compared to placebo, a combination of *Lactobacillus GG* and *Bifidobacterium lactis* for 83 BD subjects for 24 weeks seemed to protect against rehospitalization and led to fewer days in the hospital but did not significantly impact BD symptoms [82]. Similarly, compared to placebo, a 4 bacterial strain probiotic for 8 weeks did not improve mania or depressive symptoms in either group of 25 BD participants [83]. Also, 27 individuals with BD who took a probiotic composed of 9 bacterial strains showed a difference on the LEIDS-r rumination score, but not other LEIDS-r scores, other clinical scales (HAMD, BDI-II, AS, WHO-QOL) or inflammatory markers [84].

Two randomized controlled trials that investigated carnitine supplementation (78 participants: 500 mg/per day for 12 weeks; 40 participants: 15 mg/kg per day for 16 weeks) found no significant differences compared to the placebo group for BD symptoms or weight loss [85,86]. Similarly, a study that compared 6 g creatine supplementation to placebo for 6 weeks for bipolar depression found no significant reduction in MADRS scores, in 35 individuals with BD from either groups [87]. Likewise, a randomized-controlled trial of 66 BD participants treated with lamotrigine, risperidone or inositol for 16 weeks showed no benefit of inositol compared to these other options, with lamotrigine demonstrating the best therapeutic effects [88].

Quality assessment

As it can be seen in Table 1, the studies included in this review had a variety of limitations. Regarding the 33 observational studies, no causality can be inferred from them overall. Besides, most of the studies had some allocation bias ($N = 21$), as they presented the comparison of baseline characteristics from participants, but the groups were not significantly different ($p > 0.05$). Only two of the studies mentioned whether staff were blinded to participant status [27,31]. Also, only one study calculated an adequate sample size [76], which means that most of the studies included presented a high risk of false positive report bias. Regarding attrition bias, the same study was the only one study that cited intention to treat related to dropouts [76].

Considering the 27 interventional studies, many studies were open label, underpowered and uncontrolled, seriously limiting capacity to interpret or extrapolate the results. There was also a majority of these interventional, that were blinded and randomized controlled trials ($N = 21$). Like the observational studies, most presented some allocation bias ($N = 20$), as the groups were not significantly different at baseline ($p > 0.05$). Only a few studies ($N = 11$) had low attrition bias, as they referred to dropouts and included an intention-to-treat analysis [44,45,49,64–68,84,85]. Even a smaller number ($N = 9$) calculated sample size [47,49,59,64,81,83–86], therefore most studies risked a high false positive report bias. Therefore, these primary results should be considered as hypothesis generators to be confirmed in larger and multi-centric randomized control trials.

Discussion

Overall, this analysis of nutritional factors examined a relatively small list of nutrients and none has yet examined or conducted a trial of whole diet patterns. The results from most observational studies included here show that fatty acids blood levels are usually low in individuals with BD, compared with healthy controls, which are probably related to low intake [27–31,33,38]. Still, some studies verified positive associations between increased intake and better BD outcomes [31,35–38,40], such as improvement in depressive symptoms and personality scores, as well as less suicide attempts and inflammation. However, this epidemiological evidence did not translate into clear clinical benefits of Omega-3 supplementation as an adjunctive treatment for BD. This can be seen as most of the interventional studies did not find significant results on BD outcomes after fatty acid supplementation. Overall, the use of 1 g up to 10 g of DHA and/or EPA or fish oil did not impact symptoms 'scores (HDRS, YMRS, MADRS, Inventory for Depressive Symptomatology, Global Assessment of Functioning, Brief Assessment of Cognition in Affective Disorder), relapses or hospitalization [41,43–45,47–49].

An important point related to fatty acids intake is the ratio of Omega-6 / Omega-3 unsaturated fatty acids. This ratio is increased by the Western diet and is associated with obesity, inflammation and cardiovascular disease [89,90]. People with lower ratios may have a decreased risk of mood disorders [91]. It is however unclear if this ratio is the mediator of this association or simply a marker of a Western diet pattern. LA is the main source of increased Omega-6 in diet and is one of the essential fatty acids. Studies included in this review suggest that increased LA intake or blood levels were associated with protection against BD [36–38,40]. BD individuals can have altered linoleic acid

metabolism, due to dietary habits and medication, which might impact these results [36–38,80,92]. Reviews and guidelines have suggested that Omega-6 / Omega-3 ratio could be improved by increasing Omega-3 intake [89], by supplements or consumption of wild fish and oils, flaxseed and its oil, walnuts and chia seeds [93]. This is in line with studies included in this review suggesting that regular seafood, fish and Mediterranean diet seems to be a protection factor for BD development and prognosis [70–72], because these foods and associated dietary patterns are the main source of Omega-3 [94]. Moreover, blood nutrient levels can be reduced secondary to stress, illness, and the inflammatory response [95,96]. Given the common observation of increased inflammation in those with mood disorders [97], nutrient deficiencies can be a result of the disorder itself. Similarly, acute illness results in an increased rate of fatty acid oxidation, which can affect PUFA levels in people with mood disorders [98]. Nutritional epidemiology is methodologically complex, with multiple issues including substantial measurement error in the estimation of dietary intakes, heterogeneity in the way dietary intakes are considered or categorized, the high level of covariance between diet, socio-economic factors and other health behaviors such as physical activity, the possibility for both reverse causality and residual confounding, and the challenges of blinding dietary interventions [3]. However, extensive previous epidemiological research yields consistent evidence of prospective associations between many and varied measures of diet quality and incident mental health conditions regardless of a wide range of potentially confounding variables, such as employment, educational attainment and physical activity [99]. Moreover, examining the intake of individual nutrients or food groups rather than whole of diet is probably a flawed approach, given the complexity of diet and the dense interactions between foods and their constituents, while supplementation of individual nutrients is not equivalent to dietary consumption [100] and should likely be considered a separate construct. Indeed, extant research offers limited support for dietary supplementation in psychiatry [101], while emerging data from randomized controlled trials targeting 'whole of diet' are yielding more consistently promising results [5,6,101,102]. An exception to this may be the antioxidant NAC, where the evidence seems to be promising. This is supported by a meta-analysis, that concluded that NAC effects on bipolar depression are superior to placebo, but more clinical trials are necessary, especially those with a longer duration [69].

One additional potential intervention is CoQ10, a compound synthesized by the mitochondrial membrane. It has been studied as an adjunctive treatment for multiple sclerosis and migraines. It is also a promising research option for BD, due to its role in bioenergetics and antioxidant activity [81,103]. Also, probiotics, prebiotics and symbiotics might have a positive impact on BD due to the probable imbalance in the gut microbiota of individuals affected by affective disorders like BD [104], but definitive studies are necessary. Patients with diverse psychiatric disorders present lower blood levels of carnitine [105] and creatine [106], but this has not been specifically verified in BD.

From the studies that analysed micronutrients, folic acid and zinc seems to be associated with BD, thought to be due to inadequate dietary intake [50,52,54,59–61]. Folic acid might have led to benefits in 2 interventional studies [59,60]. This might be due to the low levels of folate in BD individuals [107], and this deficiency is associated with higher levels of homocysteine in patients compared to controls, which might be toxic to the dopamine system [107,108]. Low folic acid may be a consequence of low intake of high-quality foods. Zinc is also often deficient in clinical populations, due to dietary insufficiency or pharmacological effects in its metabolism [109]. As this mineral has important roles as a neural messenger and modulator it has been used as an adjunctive treatment for major depression [110]. For BD, zinc might help improve depressive symptoms [111]. Also, imbalance of the zinc / copper ratio may contribute to symptoms [112]. It is unclear if copper has a negative impact on BD [51,52], but there may be a higher intake of copper proportional to zinc, which may potentially have negative consequence in terms of cellular stress, inflammation and hormonal responses [113]. Some studies of multivitamins and minerals suggested benefits in BD [50,62]. As is the case with most of the studies in this area, these pilot findings have methodological limitations that remain open to confirmation by methodologically definitive studies. However, as noted above, nutrient levels can be a function of illness and studies have reported lower levels of folate in depressed patients in the absence of differences in appetite and weight [114,115], while duration and severity of illness are inversely associated with serum folate levels [114,116]. Similarly, zinc levels may be reduced secondary to the immune response in major depressive disorder [117], while increases in serum zinc have been observed coincident with the resolution of depressive episodes in the absence of supplementation [118].

Preliminary studies suggest that a balanced diet rich in micronutrients may be a protective factor for BD [71,72]. There are data showing that BD participants consume less than recommended amounts of fruits

and vegetables [73], a factor associated with poorer mental health [119]. Similarly, BD participants usually consume more sugar and refined carbohydrates [78], which is associated with depression and anxiety [120,121]. A secondary analysis of data from a clinical trial [65] showed an interaction between better diet quality with improved symptoms in people receiving a nutraceutical combination with N acetylcysteine [121]. Moreover, a review showed that a healthier dietary pattern, such as the Mediterranean diet, seems protective for BD outcomes [72]. It is likely that inadequate dietary habits aggravate BD outcomes and that BD itself and its treatment contribute to poor diet habits [122,123]. This has been shown in participants diagnosed with other disorders, such as major depression. The best example is 'SMILES trial' in which participants were randomized in diet intervention or control for 12 weeks. The intervention was composed of seven individual nutritional consulting sessions with dietitians, who focused on a balanced diet, such as Mediterranean diet compared to a social support control condition. The group that received dietary support presented a significant greater improvement in MADRS scores that correlated closely with the degree of dietary change [102]. Importantly, diet might be part of a cost-effective treatment, when recommendations are based on natural foods – such as fruits, vegetables, whole grains and other unprocessed foods [11].

It is also important to highlight that BD individuals are predisposed to medical comorbidities and have a greater risk of premature mortality [77]. Therefore, dietary and other related lifestyle interventions should a part of the treatment plan to manage these comorbidities. However, more detailed studies are essential to understand the best approach for this varied population [124].

The results of this review should be interpreted at light of some limitations. Only studies in English were screened, which can lead to a bias as relevant studies might be excluded if they were written in another language. More importantly, there is inter-individual variability in the pathophysiology of BD, which is difficult to capture in studies with modest sample sizes. Most of the studies were preliminary in nature, of variable methodological quality and there is a clear lack of definitive studies. Considering supplementary dietary interventions, the evidence is still limited, and some supplements might even do harm – like vitamin A, garlic extract and green tea, affecting bone, coagulation and liver functioning, respectively [125,126]. In the future, special diets, such as ketogenic and Mediterranean, may be an alternative to adjunctive treatment, but the studies are still nascent. Few findings have been convincingly replicated, which makes it hard to draw conclusions for clinical practice. Besides, studies with other nutritional factors, such as citrulline, l-arginine, and nitric oxide [126,127], were not selected by the systematic search methodology. For this reason, it was not possible to include these papers in the present review.

Taken together, the findings of this systematic review suggests that dietary modification and possibly some supplements might be helpful in the treatment of BD. There is equivocal data to support the use of Omega-3 in BD symptoms and recent trials have been disappointing. In general, healthy dietary choices, such as regular consumption of fruits, vegetables and whole grains might provide therapeutic benefits in BD subjects as suggested by studies undertaken in MDD, but this needs verification from randomized controlled trials. Due to lack of relevant studies, there was no evidence in favor or against the use of creatine, carnitine, vitamin D, inositol. Lastly, interventions that correct dysbiosis and increase antioxidant activity seem promising to BD, such as the use of CoQ10, NAC andprobiotics. Definitive studies are necessary to establish specific nutritional interventions that might be effective as adjunctive treatment for BD.

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