

Review Article



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Nutritional Factors Affecting Mental Health

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ABSTRACT

Dietary intake and nutritional status of individuals are important factors affecting mental health and the development of psychiatric disorders. Majority of scientific evidence relating to mental health focuses on depression, cognitive function, and dementia, and limited evidence is available about other psychiatric disorders including schizophrenia. As life span of human being is increasing, the more the prevalence of mental disorders is, the more attention rises. Lists of suggested nutritional components that may be beneficial for mental health are omega-3 fatty acids, phospholipids, cholesterol, niacin, folate, vitamin B6, and vitamin B12. Saturated fat and simple sugar are considered detrimental to cognitive function. Evidence on the effect of cholesterol is conflicting; however, in general, blood cholesterol levels are negatively associated with the risk of depression. Collectively, the aims of this review are to introduce known nutritional factors for mental health, and to discuss recent issues of the nutritional impact on cognitive function and healthy brain aging.

Keywords: Cognitive function; Dementia; Depression; Healthy brain aging; Mental health

INTRODUCTION

Mental well-being is a core component of optimal health, and is a status that individuals can manage stress from daily living and make positive achievements pursuing public interest and contribution to the community [1]. Maintaining individual's mental health is important to improve personal life values, to reduce medical cost and other social expenses to deal with mental disorders, and to enhance national competitiveness.

Mental disorders, which are the same as psychiatric disorders, are clusters of syndromes which disturb an individual's cognition, emotion regulation or behavior [2]. Common mental disorders include bipolar disorders (manic disorder, depression, and manic-depression), dementia, schizophrenia, and panic disorder [2]. Several factors affecting the development of mental disorders include genetic factors, stress, diet, physical inactivity, drugs, and other environmental factors [3-5]. Among these factors, dietary factors may aggravate or ameliorate symptoms and the progression of the disorders although those are not major etiologies. Nutritional factors having beneficial effect on mental health are polyunsaturated fatty acids (PUFAs), especially omega-3 FAs, phospholipids, cholesterol, niacin, folate,

vitamin B6, vitamin B12, and vitamin D [6-9]. Conversely, saturated fat and simple sugar can be hazardous for brain health, increasing the risk for mental illnesses as well as other metabolic disorders including diabetes and cardiovascular diseases (CVD) [4]. The effects of nutritional factors on mental health have been investigated for a long time; however, strong evidence has not reported as enough to suggest specific nutritional strategy as a preventive means except omega-3 FAs. Previous intervention studies often reported contrasting results, and meta-analysis on those reports showed weak or no association between specific nutrients and indices of mental function [10-12]. Limitations in conducting nutrition-mental health study are as follows: 1) it has difficulties in subject recruit, collection of precise and reliable data from subjects on memory-based questionnaires, identification of the cause-effect relationship, and acquirement of compliance on intervention, 2) due to its heterogeneity, responses to intervention are complex and various, and 3) the study requires involvement of highly trained experts.

In this review, we will introduce known nutritional factors affecting mental health, and discuss recent issues of the nutritional impact on cognitive function and healthy brain aging.

NUTRITIONAL FACTORS AFFECTING MENTAL HEALTH

Nutritional factors relating to mental health have a common aspect in that those factors are associated with the risk of CVD [13]. Omega-3 FAs are famous for cardio-protective effects [14-16]. Folate, vitamin B6 and B12 are parts of homocysteine metabolism, and deficiencies of these nutrients result in increased blood levels of homocysteine, which aggravate mental health [9,17-19]. Niacin is an effective modulator to increase high-density lipoprotein cholesterol and to improve lipidomic profiles [20,21], and vitamin D is associated with the risks of CVD and metabolic syndrome [22,23]. These nutrients are beneficial for mental health. Conversely, excess intake of saturated fat and sugar, which are risk factors for CVD, is detrimental to brain function [4,24]. In addition, recent studies add a promising evidence that specific dietary patterns including Mediterranean diet can be applied as effective strategies to prevent mental disorders [25].

Omega-3 FAs

Omega-3 FAs have been extensively studied with regard to the brain health. Omega-3 FAs' action on brain is mainly as a structural and functional component of membrane phospholipids in brain and retina [26-28]. Alpha-linolenic acid, a plant-based omega-3 FA, is found in flaxseed oil and soybean oil, and main dietary source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is fish oil. These omega-3 FAs are potent activators of transcription factors and inflammatory modulators [29,30]. Anti-inflammatory activities of omega-3 FAs are often related to the suppression of excess extents of pro-inflammatory actions of omega-6 FAs [29].

Among several mental disorders, prevalence of dementia is evidently increasing as the portion of aged population is growing. In subjects with dementia at stage 1a (age-associated memory impairment) and 1b (mild cognitive impairment), low blood levels of omega-3 FAs were observed [31]. As dementia progresses to stage 2 (early dementia) and stage 3 (dementia with behavioral symptoms), mild and moderate protein-energy malnutrition (PEM) often develops, which requires oral nutritional supplements with protein and energy supplementation rather than omega-3 FAs intervention [31]. In case of severe dementia

Table 1. Double blind, randomized, placebo-controlled trials involving omega-3 fatty acids (FAs) supplementation and major mental disorders

Ref. No.	Study design	Daily amounts of omega-3 FAs	Main findings
[32]	33 mild AD patients, omega-3 FAs (n = 18) and placebo (n = 15) for 6 mon	2.3 g (0.6 g EPA + 1.7 g DHA)	Reduce CSF levels of AD biomarkers
[33]	295 mild to moderate AD patients, DHA (n = 171) and placebo (n = 124) for 18 mon	2 g DHA	No effect on cognitive function
[34]	46 depressed women aged 66–95 years, omega-3 FAs (n = 22) and placebo (n = 24) for 8 wk	2.5 g (1.67 g EPA + 0.83 g DHA)	Ameliorate depressive symptoms and improve quality of life
[35]	36 pregnant/depressive women, omega-3 FAs (n = 18) and placebo (n = 18) for 8 wk	3.4 g (2.2 g EPA + 1.2 g DHA)	Lower depressive symptom ratings on the EPDS and BDI
[36]	60 schizophrenia patients, omega-3 FAs (n = 30) and placebo (n = 30) for 8 wk	1.0 g	Reduce PANSS score, general psychopathologic and total scores
[37]	71 first-episode schizophrenia patients aged 16-35 yr, 26 wk	2.2 g (1.32 g EPA + 0.88 g DHA)	Reduce the intensity of symptoms and improve the level of functioning

AD, alzheimer's disease; BDI, beck depression inventory; CSF, cerebrospinal fluid; EPDS, edinburgh postnatal depression scale; PANSS, positive and negative syndrome scale.

Table 2. Altered phospholipids in subjects with Alzheimer's disease (AD)

Ref. No.	Study design	Sample type	Altered phospholipids
[41]	Healthy control (n = 73), amnesic MCI/AD (n = 46), and converter (n = 28) aged 70 yr and older	Plasma	LysoPC a C18:2, PC aa C36:6, PC aa C38:0, PC aa C38:6, PC aa C40:1, PC aa C40:2, PC aa C40:6, and PC ae C40:6 were depleted in the plasma of the converter subjects
[43]	Healthy control (n = 46), MCI (n = 143), and AD (n = 47)	Serum	PC (18:0/20:4), PC (16:0/18:2), and PC (0-18:0/18:2) were decreased in AD
[44]	Healthy control (n = 17) and AD (n = 19)	Serum	PC (16:1/16:1), PC (16:1/16:0), PC (16:0/16:0), PC (16:1/18:3), PC (16:0/18:3), PC (16:0/18:2), PC (16:0/18:1), PC (16:0/18:0), PC (18:2/18:2), PC (18:2/18:1), PC (18:1/18:1), and PC (18:0/18:0) were increased in AD, while PC (16:0/20:5), PC (18:2/20:5), PC (16:0/22:6), PC (16:0/22:5), PC (18:1/20:4), PC (18:1/20:3), PC (18:0/20:3), and PC (18:0/22:6) were decreased in AD

MCI, mild cognitive impairment; PC, phosphatidylcholine; PC aa, diacyl form; PC ae, acyl-alkyl form.

(stage 4), enteral nutrition or parenteral nutrition is recommended to subjects with severe PEM [31]. Omega-3 FAs (1.0–3.4 g) intervention improved symptoms of Alzheimer's disease (AD), depression and schizophrenia as shown in **Table 1** [32–39]. Mechanisms underlying beneficial effects of omega-3 FAs' on symptoms of mental disorders are regulations of integrity and fluidity of membrane, neurite growth, neurotransmitters, endothelium, neuronal survival, neurodegeneration, transcription, and inflammation [40]. Although further investigations are needed to identify the ideal dose of omega-3 FAs and the ratio of EPA and DHA, in general, 1 g daily intake of EPA and DHA is recommended to maintain brain health.

Phospholipids and cholesterol

Phospholipid is a principal component to maintain integrity and functionality of neuronal membrane, and is recently suggested as a blood biomarker for mental health. Altered plasma phospholipids were observed in patients with mild cognitive impairment (MCI) and AD [41,42]. Metabolome analyses enabled to screen phospholipid profiles and to identify altered levels in response to specific conditions in a comprehensive way [43,44]. Ether phospholipids, phosphatidylcholines, sphingomyelins and sterols were low in AD patients, and three metabolites [2,4-dihydroxybutanoic acid, unidentified carboxylic acid, and phosphatidylcholine {PC (16:0/16:0)}] were identified as signature markers for the possible progression of MCI to AD [43]. Examples of altered phospholipids in subjects with AD are listed in **Table 2** [41,43–45].

Cholesterol also constitutes neuronal membrane to be responsible for fluidity, and acts as a signaling modulator for gene transcription, which is involved in nutrients metabolism and inflammation. In a large Korean Cancer Prevention Study cohort (n = 1,329,525), risk of depression was related to low levels of serum cholesterol concentration, suggesting the

possible needs of cholesterol-raising regimen in subjects with depression [46]. However, a dietary intervention in increasing blood cholesterol has not been tried because the cholesterol-raising regimen such as high intakes of saturated fat, trans-fat, cholesterol, and total calories can cause increased the risk of other metabolic diseases (e.g. obesity, diabetes, and CVD).

Vitamin B: niacin, folate, vitamin B6, and vitamin B12

Vitamin B is involved in energy metabolism as forms of cofactors, nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). In a NAD-FAD-dependent and – independent ways, the B vitamins, especially niacin, folate, vitamin B6, and vitamin B12 affect mental health. Famous hypothesis for mental disorders is ‘homocysteine hypothesis’ that excess homocysteine causes the development of psychiatric symptoms. Particularly, folate, vitamin B6, and vitamin B12 are involved in homocysteine metabolism, and low levels of the B vitamins and high levels of homocysteine were observed in subjects with MCI, dementia, and depression [9,17-19,47,48]. Suggested mechanisms underlying homocysteine action on brain function are impairments in cerebral vasculature and function of neurotransmitters, and increases in neurotoxicity and oxidative stress [40,49,50]. Niacin’s action on brain function is less studied compared with other vitamin B nutrients. A case-study reported that a subject with pellagra, a disease from niacin deficiency, showed psychiatric disorders, mainly behavioral deterioration and dementia, which were recovered by niacin intervention [51]. Recent studies on dietary intervention of niacin, especially nicotinamide riboside (NR), suggested that NR exerts neuroprotective effects, and restores cognitive decline by the regulation of beta-secretase 1 degradation and expressions of mitochondrial metabolism-related genes (aconitase, citrate synthase, glucose phosphate isomerase 1, phosphoglycerate kinase, and pyruvate dehydrogenase kinase) relating to the action of proliferator-activated receptor- γ coactivator 1 α [52,53]. So far, vitamin B nutrients intervention relating to brain function showed equivocal results regarding their efficacy on cognitive function [54-59].

Antioxidants

The brain is vulnerable to oxidative stress because it has lipid-rich area especially in neuronal membrane and is metabolically active. Tight balance between oxidative stress and antioxidant system is required to maintain the structural integrity and optimal functions of brain [60]. Vitamins A, C, and E are major non-enzymatic antioxidants in foods, and there are emerging evidences that these antioxidant vitamins are protective against cognitive decline and mental disorders including anxiety disorders, attention-deficit/hyperactivity disorder, autism, bipolar disorder, depression, schizophrenia, and substance abuse [6,61-63]. Low blood levels of antioxidant vitamins are observed in subject with various mental disorders. Perinatal retinol deficiency shown as low levels of serum retinol concentrations is significantly associated with the increased risk (more than threefold) of schizophrenia and other schizophrenia spectrum disorders in the Prenatal Determinants of Schizophrenia study [64]. Subjects with high tertile of vitamins C and E intakes have lower risk of AD than subjects with lower intake tertiles of these antioxidant vitamins in the Rotterdam Study [65]. Especially, amyloid-beta deposition in brain relating to increased oxidative stress is one of the major causes of AD [66], and low levels of vitamins C and E in blood and/or cerebrospinal fluid were observed in AD patients [67,68]. Vitamin E intervention reduces amyloid-beta deposition, reactive oxygen species as well as nitric oxide synthesis, and prevents against cognitive impairment and the progression to AD [69]. Recently, a new approach to identify underlying mechanisms of neurodegenerative disorders and to investigate the intervention efficacy to improve the symptoms of mental disorders has applied. Application of redox proteomics approach enables to identify disease stage-specific modifications in oxidative stress-related

molecules and to demonstrate a cluster of changes in protein oxidative modification by the specific nutritional intervention [70]. In general, existing intervention studies show beneficial effects of antioxidants on improving general symptoms of mental disorders, and the optimal combinations and the recommended duration of antioxidant vitamin intake need to be investigated.

Saturated fat and sugar

Because many factors affecting mental health are overlapped as those for CVD [13], dietary saturated fat and Western-style diet may impair cognitive function [71-73], and subjects with high BMI have low scores of a 37-item version of the Mini-Mental State Examination [74]. High levels of blood sugar due to excess sugar intake or uncontrolled blood sugar are main manifestations of diabetes. Recent findings consistently reported the positive association between diabetes and dementia [75,76], and diabetes induces AD in animal models [77,78]. Also, higher blood glucose and HbA1c concentrations were associated with reduced memory capacity and structural changes in hippocampus in cohort of healthy, older, nondiabetic individuals without dementia [79]. Intervention studies should focus on the development of practical dietary guidelines for each mental disorder and the identification of effective ways to compromise the negative effects of these saturated fat and simple sugars on mental disorders. Identifying the optimal dietary patterns such as Mediterranean diet is one of promising ways to find the effective dietary guidelines [25].

CONCLUSION

As the world is aging rapidly, attention on aging-related mental disorders has increased. Increased R & D planning and investment relating to these illnesses aim to reduce medical cost burden and to improve mental health as well as quality of life. Based on current evidence, nutritional factors are important for mental well-being. Especially, eating balanced meals on a regular basis and consuming nutrients for mental health including omega-3 FAs, antioxidants, niacin, folate, vitamin B6, and vitamin B12 at recommended dietary intake levels are suggested. Development of dietary guideline that is specific to each type and stage of mental disorder, and the identification of nutritional biomarkers on cognitive functions are suggested to study in the future. Because mental disorders are heterogeneous in symptoms and etiologies, well-designed diet intervention study on large cohorts is guaranteed to identify effective nutritional strategy.

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