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van Zonneveld, Sophie M.; Haarman, Bartholomeus C. M.; van den Oever, Ellen J.; Nuninga, Jasper O.; Sommer, Iris E. C.

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REVIEW

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Unhealthy diet in schizophrenia spectrum disorders

Sophie M. van Zonneveld[a], *Bartholomeus C.M. Haarman*[b], *Ellen J. van den Oever*[a], *Jasper O. Nuninga*[a], *and Iris E.C. Sommer*[a]

Purpose of review
The high mortality and prevalence of metabolic syndrome in patients with schizophrenia spectrum disorders (SSD) is maintained by poor diet. This narrative review summarizes recent literature to provide a reflection of current eating habits, dietary preferences, and nutritional status of SSD patients. Elucidating these factors provides new insights for potential lifestyle treatment strategies for SSD.

Recent findings
Only 10.7% of the SSD patients had a healthy dietary pattern, against 23% of the general population. The dietic component of the Keeping the Body in Mind Xtend lifestyle program increased diet quality with 10% for young people with first-episode psychosis, compared to baseline, which was predominantly driven by increased vegetable variety and amounts.

Summary
Recent findings render poor dietary habits as potential targets for treatment of SSD patients. Further studies into anti-inflammatory diets and associations with gut–brain biomarkers are warranted. When proven, structured and supervised diet interventions may help SSD patients escape from this entrapment, as only supplementing nutrients or providing dietary advice lacks the impact to significantly reduce the risk of chronic physical illnesses.

Keywords
dietary pattern, inflammation, nutrient deficiency, schizophrenia spectrum disorders

INTRODUCTION

Schizophrenia spectrum disorders (SSD) represent a cluster of severe mental illnesses, where experiencing psychotic symptoms are the most prominent feature, with a lifetime prevalence of 3% worldwide [1]. The development is suggested to be multifactorial, involving genetic, biological, and social factors. One of these factors, potentially contributing to SSD pathology, is a subtle pro-inflammatory status, as reflected in increased serum levels of c-reactive protein (CRP) and pro-inflammatory cytokines, which is a rather consistent finding in the literature [2–5]. This pro-inflammatory status has been reported in drug-naive patients and is most pronounced in those with high body mass index. Many food components, such as omega-3 fatty acids, components from leafy vegetables and carotene, are direct ligands for immune cells in the gut and have a lowering effect on the immune status, where as other food components, such as saturated fat, have a pro-inflammatory effect on gut-dwelling immune cells [6▪,7].

Historically, there were already researchers who believed that certain diets could treat SSD and that diets may be used instead of medication. In 1966, an association between gluten sensitivity and schizophrenia was described by Dohan [8]. He stated that wheat intake during World War II was associated with rates of hospitalization for schizophrenia in women in five different countries. Almost 15 years later, wheat intake was correlated with schizophrenia prevalence ($r = 0.53$, $P = 0.01$) across 18 countries [9]. It was claimed that eliminating gluten from a patients' diet would treat schizophrenia.

[a]Department of Biomedical Sciences of Cells and Systems and [b]Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence to Sophie M. van Zonneveld, M.Sc., University of Groningen, University Medical Center Groningen, Cognitive Neurosci-ence Center, Antonius Deusinglaan 2, 9713 AW Groningen, The Netherlands. Tel: +31 50 361 6432;
e-mail: s.m.van.zonneveld@umcg.nl

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KEY POINTS

- It is difficult for SSD patients to improve their eating habits due to severe psychiatric symptoms including amotivation, cognitive problems, and low income.
- Poor dietary quality is a serious problem for patients with SSD, with multifaceted negative consequences, including metabolic syndrome that contributes to an increased morbidity and early mortality, thus affecting the quality of life.
- Anti-inflammatory dietary intervention programs, that are structured and supervised, may be necessary to help SSD patients escape from this entrapment.

As of yet, antipsychotic drugs are the mainstay treatment for psychotic episodes and are also often prescribed as maintenance treatment. Antipsychotics, however, frequently lead to side-effects like increased appetite and body weight, such that the medication intervenes with the energy balance system: directly by acting on hypothalamic and reward areas of the brain and/or indirectly through changes of the gut microbiota composition [10–12]. Alterations in gut microbiota composition and microbial metabolites affect brain functioning via the so called 'gut-brain axis' (GBA) [11]. The GBA defines bidirectional communication pathways between the gut and brain, involving the autonomic nervous system, immune system, endocrine, and enteric nervous system. Dysregulation of the GBA was previously described in this journal by Genedi *et al.* and a detailed description is beyond the scope of this review [13].

Another important factor contributing to poor eating habits is the negative symptoms, such as apathy and lack of energy [14]. These symptoms prevent many people with SSD from activities as groceries shopping and preparing a home-cooked meal. SSD patients have relatively low incomes. In Western countries, unhealthy food products are easily available and tend to be much cheaper than healthyones, which facilitates the purchase of unhealthy food products by low-income groups [15].

This combination of antipsychotic-stimulated overeating, negative symptoms, and poverty generate a drive to eat high-calorie and low-nutrient food, leading to vitamin deficiencies, obesity, and associated somatic comorbidity. Obesity is highly prevalent in SSD: 58.5% of the SSD patients are obese, compared to 27% in the general population [16]. Severe overweight is associated with metabolic syndrome, which is the precursor of physical diseases like type 2 diabetes and cardiovascular diseases (CVD) that have a significant effect on quality of life and mortality [17]. Mainly due to these physical comorbidities, patients with SSD have a 15–20years lower life-expectancy than that of the general population [18].

To advance our understanding of dietary habits and preferences in SSD, the current narrative review focuses on the latest scientific developments with respect to eating habits, dietary preferences and nutritional status contributing to dietary quality in SSD. Furthermore, this review sheds light on evidence for efficacy and feasibility of dietary interventions and strategies that may alleviate the consequences of SSD.

EATING HABITS AND DIETARY PATTERN OF SCHIZOPHRENIA SPECTRUM DISORDER PATIENTS

Nowadays, it is commonly known that a healthy and varied diet is essential to function properly and to enjoy a healthy life. A healthy dietary pattern consists of a right balance of both macro- and micronutrients. Macronutrients (i.e., fats, carbohydrates (starches and sugars) and proteins) provide energy and build tissue, micronutrients (i.e, vitamins and minerals) have supportive functions in the body and ensure general health. Nutritional intake is influenced by nutritional habits: the way we eat, how often, and what we eat. Recent studies investigating eating habits and dietary patterns of SSD patients are discussed below.

Eating habits including the number and type of meals consumed during the day, snacking between meals, the energy value, and nutritional intake of schizophrenia patients ($n = 85$) compared to healthy control ($n = 70$) was investigated in a Polish study [19] (see Table 1). Dietary pattern appeared to be sex-specific; interestingly, women with schizophrenia consumed three more meals a day and snacked more frequently as compared to health women, where as in men with schizophrenia an opposite tendency was observed – their diets were characterized by over 400 kcal/day lower energy intake and a lower intake of nutrients compared to healthy men [19]. Moreover, women with schizophrenia showed significantly higher energy intake of dinner meal compared to female healthy controls (364.4 ± 154.4 kcal vs. 247.8 ± 172.5 kcal, respectively) and were especially high in saturated fats and carbohydrates [19]. This sex-specific difference maybe explained by the notion that women with mental disorders claim lower self-control while consuming sweet snacks [20]. However, more research is needed to further investigate the sex-specific differences.

Researchers of a larger Danish trial investigated the dietary habits and levels of physical activity in SSD

Table 1. Summary table of diet studies discussed in this narrative review

Authors, year	Country	Sample	Age (years)	Study aim	Results
StefÃnska *et al.*, 2018 [19]	Poland	85 SCZ, 70 HC	18–65	Cross-sectional study to assess nutritional habits including the number and type of meals consumed during the day, snacking between meals, the energy value, and content of chosen nutrients in diets of SCZ patients.	Women with SCZ consumed three more meals a day and snacked more frequently as compared to healthy women. In men with SCZ an opposite tendency was observed - their diets were characterized by lower energy intake and lower intake of nutrients compared to healthy men.
Jakobsen era/., 2018 [21]	Denmark	428 SCZ/SAD with increased waist circumference, 3016 individuals general Danish population	18–75	Observational cross-sectional study to investigate dietary habits and physical activity in overweight SSD and compare results with current recommendations and with result from general Danish population.	The total caloric intake of the SSD patients was similar to that of the Danish general population. The distribution of fat, carbs, and protein (35% of energy from fat, 49% from carbohydrate and 16% from protein) intake matched the Danish Health Authorities' guidelines and was similar to dietary pattern of the Danish general population. The intake of saturated fat, sugar and alcohol exceeded the recommended amounts and the corresponding intake in the general population. Intake of fibers, fruit, vegetables, and fish was insufficient and significantly lower than the general population. Overall estimated quality of the dietary habits of SSD patients was poor. The quality was poorer than in the general population. Only 62% of the SSD patients took part in the preparation of their food. Negative symptoms were found to be strongly linked to poorer nutritional quality and less physical activity.
Costa *et al.*, 2019 [23▪]	Portugal	100 SCZ	Mean age 44.6	A cross-sectional study to (i) assess dietary intake SCZ [comparing inpatient and outpatients; (ii) determine adherence to Mediterranean diet; (iii) explore potential relationships between the Mediterranean diet and lifestyle-related factors.	SCZ patients reported a poor to moderate quality of the dietary intake. They consumed more than twice as much caffeine, compared to the EFSA recommendations. Mean fiber intake was significantly lower than recommended and there was a trend to significantly lower folate intake. Smokers reported poorer diet quality compared to nonsmokers.
Firth *et al*, 2018 [24]	UK	SMI: 262 SCZ, 952 BD, 14.619 MDD 54,010 SMI-free	Mean age 56.5	Population-scale study to examine differences in nutritional intake and diet-associated inflammation between people with SMIs and the general population.	Intake of total energy, carbohydrates, total fat, saturated fat, and protein were highly elevated compared to HC. SCZ patients showed elevated DII scores compared to HC.
Jahrami *et al.*, 2019 [26]	Bahrain	120 SCZ, 120 HC	20–60	Case-control study to examine association between dietary inflammation and SCZ.	The E-DII score was higher in SCZ patients compared to HC.
Niarchou *et al.*, 2020 [28]	UK	335.576 individuals from the UK biobank study	40–69	Genome-wide association study to investigate genetic contribution to dietary intake in individuals from UK Biobank study.	Slight association between SCZ and 'fish and plant eaters'.
Kelly *et al.*, 2019 [47]	USA	16 SCZ/SAD who had elevated AGA IgG {≥ 20 U) but were negative for celiac disease	18–64	Double-blind RCT pilot study to exploring the removal of gluten from the diet in an inpatient setting that focused on a subgroup showing antibodies related to wheat.	The gluten-free group improved on the CGI scale, negative symptoms and on attention as compared to those receiving gluten flour. No differences in positive or global cognitive symptoms were found. The gluten-free group also showed a robust relative improvement in gastrointestinal adverse effects and medium to large improvements in domains of abdominal pain, diarrhoea, constipation and indigestion.
Adamowicz *et al.*, 2020 [48▪▪]	Poland	87 SCZ of which 59 had MetS	19–67	RCT to verify the relationship between the presence of MetS and cognitive function of SCZ patients and to assess the possibility of changing cognitive function by introducing Mediterranean dietary intervention.	SCZ patients with MetS, who followed the dietary intervention, improved on cognitive functioning after three months of dietary intervention, whereas those without the dietary intervention did not.
Teasdale *et al.*, 2019 [50▪▪]	Australia	12 FEP	15–25	Two-year outcomes of the 1 2-week lifestyle pilot intervention that improved dietary intake and prevented antipsychotic-induced weight gain.	Diet quality was higher, and discretionary food intake was 40% lower, at two years compared to baseline. Weight and waist-circumference did not increase.

(E)JDII, (Energy-density) Dietary Inflammatory Index; AGA IgG, antigliadin antibodies of the immunoglobulin G type; CGI, Clinical Global Impression; EFSA, European Food Safety Authority; FEP, first-episode psychosis; HC, healthy control; MDD, major depressive disorders; MetS, metabolic syndrome; RCT, randomized controlled trial; SAD, schizophrenia affective disorders; SCZ, schizophrenia; SMI, severe mental illness; SSD, schizophrenia spectrum disorders; UK, United Kingdom; the USA, United States of America.

patients ($n = 428$) with overweight (defined as an increased waist circumference of >88 cm for women or > 102 cm for men) [21]. They assessed positive and negative symptoms, cognition, and global functioning. The total caloric intake of the SSD patients was similar to that of the Danish general population. The distribution of fat, carbs, and protein (35% of energy from fat, 49% from carbohydrate, and 16% from protein) intake matched the Danish Health Authorities' guidelines and was similar to the dietary pattern of the Danish general population. However, the intake of saturated fat, sugar, and alcohol exceeded the recommended amounts and the corresponding intake in the general population. Also, the intake of fibres, fruit, vegetables, and fish was insufficient and significantly lower than the general population. Based on the dietary quality score, the overall estimated quality of the dietary habits of SSD patients was poor, only 10.7% of the SSD patients had healthy dietary patterns against 23% of the general population. Furthermore, the quality was poorer than in the general population. Importantly, only 62% of the SSD patients took part in the preparation of their food, even though the definition 'home cooked' was quite broad (e.g., a self-made sandwich). Unfortunately, the authors did not find corresponding figures to compare with the general population. Negative symptoms were found to be strongly linked to poorer nutritional quality and less physical activity.

In a critical letter to the editor, it was stated that the study used suboptimal nutrition assessment methods, which could explain the lack of differences in fat, carbs, and protein intake between schizophrenia patients and the Danish general population [22]. Due to the large day-to-day and seasonal fluctuation in what people consume, the results of a single-time point 24-h diet recall are inadequate for measuring inter-individual (or inter-group) differences. Furthermore, it was stressed that 24h-recall should be carried out by trained interviewers, such as dieticians, to ensure minimizing commonly recognized biases such as misreporting and forgetting foods.

A more comprehensive approach to evaluate dietary intake of 100 schizophrenia patients was done in a cross-sectional study from a Portuguese population [23▪]. Dietary intake was assessed using asemi-quantitative food frequency questionnaire of the previous 12 months. Diet quality was determined by adherence to the Mediterranean diet. This dietary pattern is characterized by a high intake of fruits, legumes, vegetables, whole-grains, olive oil, nuts, and seeds, moderate consumption of fish, low to moderate consumption of dairy products, and low intake of red and processed meats. Schizophrenia patients reported a poor to moderate quality of the dietary intake. They consumed more than twice as much caffeine, compared to the European Food Safety Authority recommendations (400 mg/day). Furthermore, mean fiber intake was significantly lower than recommended (21.6 ± 6.6 vs. 25 g/day) and there was a trend to significantly lower folate intake (310.0 ± 105.0 vs. 330 μg/day).

Conversely, in another population-scale study, no difference was found in dietary fiber intake of the schizophrenia group ($n = 262$) compared to the general UK population ($n = 54.010$) [24]. However, intake of total energy, carbohydrates, total fat, saturated fat, and protein were highly elevated compared to healthy control participants. They also explored the inflammatory potential of the diet using the dietary inflammatory index (DII). The DII was developed to estimate the inflammation potential of the diet [25]. Schizophrenia patients showed elevated DII scores compared to controls. Unfortunately, the exact DII scores were not demonstrated in the article. According to the authors, not only excessive caloric, carbohydrate, and fat intake increases inflammation, but also the simultaneously increased adipose tissue, which enhances chronic, systemic inflammation. They therefore suggest that more attention should be given to anti-inflammatory nutrients.

In line with this, the association between dietary inflammation, measured with the DII, and schizophrenia, was examined in another Middle Eastern study, investigating 120 schizophrenia patients and 120 age- and sex-matched healthy controls [26]. The energy adjusted DII score was higher in schizophrenia patients compared to healthy controls (1.99 ± 1.39 vs. 1.60 ± 1.38, respectively), indicating that schizophrenia patients indeed consume a more pro-inflammatory diet, with less anti-inflammatory compounds, than the general Middle eastern population, which in itself is more Mediterranean and less pro-inflammatory than the average Western diet [27].

Currently, there is increasing attention to nutrigenetics: personal dietary advice based on DNA. The genetic contribution to dietary intake was investigated in a large sample ($n = 335.576$) of individuals from the UK biobank study [28]. Based on a principal component analysis applied to a generic dietary questionnaire, responses generated two diet components: (1) meat-related diet, (2) fish and plant-related diet. With these two components, the authors were able to make a very rough prediction from the genes as to whether you genetically tend to be a 'eat eater'or a 'ish and plant eater' Surprisingly, in contrast to what they expected, schizophrenia patients were slightly associated with 'fish and plant eaters'. According to the authors, an explanation could be that schizophrenia patients have the genetic tendency to be fish and

plant eaters, but due to various external factors such as lack of energy and motivation, low economic status or drug treatment tend to use a more meat-related diet. However, more research is needed to replicate this finding in other populations.

Eating habits influenced by antipsychotic medication

In general, the perception is that high prevalence rates of obesity, metabolic syndrome, and type 2 diabetes in patients with SSD are partly the consequence of poor lifestyle characteristics and pharmacological treatments. Specifically, second-generation antipsychotics are associated with an increase in appetite and food intake that can contribute to weight gain.

However, a recent meta-analysis, investigated appetite regulating hormones in 1792 first-episode psychosis (FEP) and 1364 controls [29]. FEP patients showed higher insulin levels compared to controls ($g = 0.34$, 95% CI: 0.19–0.49, $P < 0.001$), even in the antipsychotic-naïve patients ($g = 0.39$, 95% CI: 0.12–0.66, $P = 0.005$). Moreover, they found decreased levels of leptin, a satietyhormone released from adipose tissue, even in antipsychotic-naïve FEP patients ($g = -0.62$, 95% CI: −1.11 to 0.12, $P = 0.015$). Thus, the authors concluded that impaired appetite regulation, in terms of elevated insulin levels and decreased leptin levels, occur in early psychosis, before antipsychotic treatment.

In contrast, a scoping review by Stogios *et al.* supports the notion that antipsychotic treatment can lead to disturbed eating patterns in patients, which may contribute to antipsychotic-induced weight gain [30▪]. Based on evidence from food surveys and self-report questionnaires to assess changes in food intake of psychotic patients, they found increased appetite and craving for fatty food, as well as increased caloric intake and snacking after starting antipsychotic medication, which may be associated with increased disinhibition to hunger. Increased disinhibition defines the likelihood to overeat when exposed to palatable food or stress. According to data from the neuroimaging studies reviewed by the authors, no differences were found in brain processing of food in antipsychotic-naive first compared to healthy controls. Persistent anti-psychotic exposure may lead to decreased activity in satiety areas and increased activity in reward anticipation areas [30▪].

NUTRITIONAL AND SOMATIC CONSEQUENCES OF UNHEALTHY EATING BEHAVIOR

The above-mentioned studies show that unhealthy eating behavior, whether or not affected by antipsychotics, influences the level of macronutrient intake of SSD patients.

Serum levels of folate and vitamin B12 and their relation to negative and positive symptoms were assessed in a cross-sectional study of 42 schizophrenia patients [31]. Results showed that 41.5% of the patients had a low folate level and 39% of the patients had low vitamin B12 levels compared to normal values. Additionally, folate was significantly correlated with vitamin B12, which is not surprising since folate and vitamin B12 are closely related in the interaction of DNA synthesis [32]. Negative symptoms were assessed by the Scale for the Assessment of Negative Symptoms (affective flattening, anhedonia, attention, and difficulties talking). A significant negative correlation between vitamin B12 and negative symptoms was found. However, no significance was found between serum levels of folic acid and negative symptoms. The authors suggest adding supplements for patients with low folate or vitamin B12. Insufficient folate intake was confirmed in another study done in 62 schizophrenia patients [33]. Conversely, vitamin B12 deficiency was not replicated in this study; the intake of vitamin B12, although lower than controls (2.4 ± 0.7 mcg vs. 3.9 ± 0.6 mcg), was 100% of the norm.

The latter study also showed lower calcium and vitamin D in SSD patients compared to healthy controls [33]. Consequences of low calcium levels are disruptions in cellular pathways, which could lead to an increased chronic disease risk including metabolic syndrome, diabetes type 2, and CVD [34]. A link between vitamin D deficiency and schizophrenia was found in a large-scale case-control study that investigated random blood samples of Danish babies ($n = 2606$) born between 1981 and 2000 [35]. The results showed that vitamin D deficient newborns have a 44% higher risk of being diagnosed with schizophrenia as adults when compared with people of the same age and sex born with regular vitamin D levels. These findings imply that maternal vitamin D deficiency is a risk factor for schizophrenia in the offspring. Lower vitamin D levels were also found in a previous cross-sectional study in 93 schizophrenia patients compared to controls [36]. Intriguingly, vitamin D levels were significantly inversely associated with CRP, an acute-phase protein representing inflammation [36]. Since vitamin D has anti-inflammatory properties, it has been emphasized as adjunctive therapeutic means. An 8week randomized controlled trial (RCT) on vitamin D supplementation in 24 clozapine-treated SSD patients with low vitamin D levels revealed no effects on SSD symptoms [37]. However, another study observed positive correlations between concentrations of the antipsychotic aripiprazole and

vitamin D concentrations in the aripiprazole treated group ($n = 51$), indicating that this antipsychotic may potentially benefit patients through improving their vitamin D status [38].

Although dietary fiber deficiency was not always confirmed [24], in general SSD patients show insufficient fiber intake [21,23▪]. Nutritional fibers - also known as prebiotics – serve as food for gut microbiota species. By bacterial fermentation of dietary fibers, the main metabolites produced in the colon are short-chain fatty acids (SCFAs), which are speculated to play a key role in neuro-immunoendocrine regulation, emphasizing the GBA [39]. Recently, a pilot study in 10 schizophrenia patients and 16 healthy controls showed that the microbiota of schizophrenia patients were characterized by increased abundance of harmful bacterial (Proteo-bacteria) and decreased SCFA-producing bacteria, such as the *Faecalibacterium* and *Lachnospiraceae* genera, affecting neuro-immunoendocrine regulation [40].

Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are one of the two polyunsaturated fatty acids (PUFAs) families and are important for many health effects, including cerebral processes. The other PUFA family is omega-6. Omega-3 and omega-6 PUFA have a complex synergistic and antagonistic relationship and mounting evidence indicate that an optimal ratio of omega-3/omega-6 PUFA is important for cognitive functioning and mental health [41]. Both fatty acids can cross the blood-brain barrier and omega-3 fatty acids are important in influencing cellular an inflammatory signaling like suppressing nuclear transcription factor kappa B (kappa B) and reducing cytokines, such as containing-1 (IL-1), IL-6, and tumor necrosis factor (TNF)-alpha which are all involved in the development of metabolic syndrome [42]. Recently, a review showed that numerous studies have found significant deficits in PUFAs, particularly DHA, in the peripheral blood and brain of SSD patients, associated with negative and positive symptoms [43]. In line with this, a double-blind RCT in 46 patients with recent-onset psychosis showed that omega-3 and omega-6 PUFA are associated with social cognition and uncooperativeness, respectively, at baseline, providing novel evidence for a differential role of omega-3 vs. omega-6 PUFA [44▪]. Based on the knowledge that PUFAs have anti-inflammatory properties, and that in SSD, PUFA insufficiency has been linked to psychotic symptoms and cognitive difficulties, findings have prompted several clinical trials to investigate if dietary omega-3 fatty acid supplementation could improve the course of illness in schizophrenic patients.

A randomized placebo-controlled trial was performed to investigate the effects of omega-3 fatty acid supplementation (fish oil containing 720 mg of EPA and 480 mg of DHA per day) on metabolic syndrome in 80 patients with schizophrenia [45]. At baseline, schizophrenia patients showed higher plasma TNF-alpha levels than healthy controls. Compared to baseline, triglycerides and TNF-alpha levels of the patients were significantly decreased after 12 weeks of omega-3 fatty acid supplementation. Furthermore, the previously mentioned double-blind RCT in 24 schizophrenia patients showed that 12-weeks of omega-3 supplementation (fish oil containing EPA 740 mg and DHA 400 mg daily) improved social cognition in patients compared to placebo [44▪]. In accordance with this, another 12-week RCT showed ameliorating effects of omega-3 supplementation (2400 mg of fish oil (Natural Made, USA) as 2 soft gels combined with a total of 720 mg of omega-3 fatty acid, EPA 360 mg and DHA 240 mg) on cognitive dysfunction in 80 schizophrenia patients with metabolic syndrome [46].

Knowing that SSD patients have nutrient deficiencies, and that some nutrient supplementation studies show beneficial effects, raised the question whether the usual dietary intake of these patients require supplementation with vitamins and minerals by default [33]. The authors state that supplementation is only justified in schizophrenia patients who show vitamin deficiencies based on analysis of their food habits. In their opinion, providing supplementation on regular basis is not needed, and they deem it is important to provide schizophrenia patients with appropriate food education that will allow them to choose healthy food products that contain all nutrients needed for proper functioning of the body. Including the central nervous system.

INTERVENTION STUDIES TO IMPROVE DIET IN SCHIZOPHRENIA SPECTRUM DISORDERS

Converging lines of evidence point toward disturbed eating behavior and nutrient deficiencies in SSD as a potent target for therapeutic actions.

A double-blind RCT pilot study of a gluten-free diet was performed in 16 patients with schizophrenia or schizoaffective disorder who had elevated antigliadin antibodies of the immunoglobulin G type (AGA IgG; ≥ 20 U) but were negative for celiac disease [47]. The participants received standardized gluten-free meals and were randomized in a double-blind fashion to receive either a gluten-free shake (containing 10 g of rice flour each day) or a control shake (containing 10 g gluten flour each day). The gluten-free intervention resulted in improvement on the Clinical Global Impression scale (CGI; effect size Cohen $d = -0.75$), negative symptoms (Cohen $d = -0.53$), and attention (Cohen $d = 0.60$), as

compared to the control group receiving gluten. The gluten-free group also showed a robust relative improvement in intestinal complaints. No differences in positive or global cognitive symptoms were found.

Adamowicz *et al.* studied the effects of a dietary intervention, based on the Mediterranean diet, on cognition in 87 patients with schizophrenia and metabolic syndrome [48▪▪]. Patients were in the remission phase of schizophrenia, all using antipsy-chotics for pharmacological treatment. In total, roughly 2/3 of the participants met the criteria for schizophrenia combined with metabolic syndrome, and about half of them were randomly selected for the dietary intervention. The other 1/3, schizophrenia patients without a metabolic syndrome, were used as a control group of comparison. Results showed that schizophrenia patients with metabolic syndrome, who followed the dietary intervention, improved on cognitive functioning after three months of dietary intervention, whereas those without the dietary intervention did not. Significant improvement was found on the Stoop Test time at the 3rd attempt by 3.38 s, on the Trail Making Test time decreased at the 2nd attempt by 16.78 s. Verbal fluency improved (on average 2.10 more animal names and 1.07 more acute subjects). Improvement on working memory was shown by a larger number of digits repeated directly (on average by 0.8 words more) and in total (on average by slightly more than one digit more; $P < 0.05$) [48▪▪].

Teasdale *et al.* investigated a 12-week Keeping the Body in Mind (KBIM) lifestyle intervention as a possible treatment in young people with FEP [49]. During the KBIM intervention, weekly individual dietetic consultations, group groceries shopping tours, assisted cooking sessions, and sport groups were offered as part of a broader lifestyle program. The lifestyle intervention showed beneficial effects compared to standard care for youth with FEP; for example, dietary intake was improved with 47% reduction in discretionary food intake – defined as foods and drinks not necessary to provide the nutrients the human body's needs – and about 25% less daily energy and salt intakes. Moreover, anti-psychotic-induced weight-gain was attenuated in the intervention group [49]. The investigators hypothesized that these improvements would maintain with an extended lifestyle program (KBIM Xtend); individualized consultations, cooking groups, and exercise components remained available to the participants, but with less intensive follow-up [50▪▪]. The mean number of contacts with the dietitian over the two years was 24.3; 9.2 in the initial 3-months and 15.1 in the KBIM Xtend program. Indeed, after two years, the dietic component of the KBIM Xtend lifestyle program increased the diet quality of the patients ($n = 12$) by 2.3 points, compared to baseline. This improvement was predominantly driven by increased vegetable variety and amount. Furthermore, discretionary food intake was 40% lower (340kcal/day) compared to baseline. Interestingly, antipsychotic-induced weight-gain was still absent when simultaneously combined with interventions like physical activity and prescribing of best-practice antipsychotics that metabolic side-effect take into account. However, replication studies including long-term follow-up are warranted.

CONCLUSION

The present review outlines recent developments in the elucidation of the factors contributing poor eating behavior in SSD patients. SSD patients consume more high-caloric, low-nutrient meals and snack more often compared to the general population. Specific foods and dietary patterns having anti-or pro-inflammatory potentials can, among other factors, influence the inflammatory state. Given the role of diet in modulating inflammatory markers, excessive caloric intake, and increased consumption of pro-inflammatory food components such as calorie-dense, nutrient-sparse meals may contribute to the pathologic course of SSD. Poor dietary quality may lead to the development of obesity and metabolic syndrome. Additionally, poor diet causes nutrient deficiency and seems to affect the gut microbiome, which is aggravated by antipsychotic drugs.

Nutrient supplements may help to alleviate the symptoms of nutrient deficiency, as well as several SSD symptoms. However, supplementation alone will not diminish metabolic syndrome or the high death rate that comes with it. Thus, the management of dietary factors is important for SSD patients. It is remarkable that in the few dietary intervention studies, beneficial somatic effects were investigated and demonstrated, but mental health effects were not investigated. Since this adverse loop may result in far-reaching effects on quantity and quality of life, including daily functioning, future studies should focus on both somatic and mental effects and interventions to help patients escape to a healthier life. These studies will increase knowledge to better understand the effects of diet on SSD, and/or whether the disorder itself leads to such a diet. These studies should include biomarkers of inflammation, intestinal permeability, and gut microbiome, aiding in the understanding of the role of specific diets in SSD. Factors like caffeine, nicotine, alcohol, and other drugs – surely having an effect on the diet - should also be taken into account.

Healthy diets need to be tasty, inexpensive, and easy to prepare. Therefore, we recommend a multidisciplinary approach to tackle this problem, like the KBIM intervention of Teasdale *et al.* More help is needed, to enable dieticians to coach, to arrange cooking classes, and/or to provide food boxes at home. This requires financial support from the government and health insurance companies.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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This review summarizes the reported effects of nutritional components and their metabolites on the immune system through manipulation of specific (pharmacological) receptors. Nutritional components, such as vitamins, fibers, and unsaturated fatty acids are able to resolve inflammation, whereas saturated fatty acids tend to exhibit proinflammatory effects.

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