Diet and Psychosis: A Scoping Review

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Keywords

Dietary constituents · Nutritional guidelines · Mental health · Schizophrenia spectrum disorders

Abstract

Introduction: Schizophrenia spectrum disorders (SSD) represent a cluster of severe mental illnesses. Diet has been identified as a modifiable risk factor and opportunity for intervention in many physical illnesses and more recently in mental illnesses such as unipolar depression; however, no dietary guidelines exist for patients with SSD. **Objective:** This review sought to systematically scope the existing literature in order to identify nutritional interventions for the prevention or treatment of mental health symptoms in SSD as well as gaps and opportunities for further research. **Methods:** This review followed established methodological approaches for scoping reviews including an extensive a priori search strategy and duplicate screening. Because of the large volume of results, an online program (Abstrackr) was used for screening and tagging. Data were extracted based on the dietary constituents and analyzed. **Results:** Of 55,330 results identified by the search, 822 studies met the criteria for inclusion. Observational evidence shows a connection between the presence of psychotic disorders and poorer quality di-

etary patterns, higher intake of refined carbohydrates and total fat, and lower intake or levels of fibre, ω -3 and ω -6 fatty acids, vegetables, fruit, and certain vitamins and minerals (vitamin B₁₂ and B₆, folate, vitamin C, zinc, and selenium). Evidence illustrates a role of food allergy and sensitivity as well as microbiome composition and specific phytonutrients (such as L-theanine, sulforaphane, and resveratrol). Experimental studies have demonstrated benefit using healthy diet patterns and specific vitamins and minerals (vitamin B₁₂ and B₆, folate, and zinc) and amino acids (serine, lysine, glycine, and tryptophan). **Discussion:** Overall, these findings were consistent with many other bodies of knowledge about healthy dietary patterns. Many limitations exist related to the design of the individual studies and the ability to extrapolate the results of studies using dietary supplements to dietary interventions (food). Dietary recommendations are presented as well as recommendations for further research including more prospective observational studies and intervention studies that modify diet constituents or entire dietary patterns with statistical power to detect mental health outcomes.

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Introduction

Schizophrenia spectrum disorders (SSD) represent a cluster of severe mental illnesses with a lifetime prevalence of 0.7% [1]. The aetiology of schizophrenia remains to be fully elucidated though it is understood that this group of disorders results from a combination of genetic, biological, and social factors.

Symptoms of SSD include positive symptoms such as delusions and hallucinations, as well as negative and cognitive symptoms. Typically, the first episode of psychosis is preceded by a prodromal or clinical high-risk state where the individual experiences attenuated or brief psychotic symptoms, as well as other symptoms such as social withdrawal, depression, and a decline in social or occupational functioning. While recovery rates from the first episode of illness are high, over 80% of individuals will relapse [2]. Relapses vary in their duration, intensity, and frequency, and they are often precipitated by factors such as stress, substance use, medication non-adherence, social adversity, and medical factors. Approximately 50% of individuals will experience episodic as opposed to continuous disability [2]. Conventional treatment of schizophrenia includes a combination of medical and psychosocial interventions.

In addition to the impact on emotional well-being, functioning, and quality of life, patients suffering from psychotic disorders are at dramatically elevated risk of medical comorbidities, which have a significant impact on mortality and morbidity. As a result, the life-expectancy of patients with schizophrenia has been estimated to be 8–20 years shorter than in the general population [3, 4]. A recent Canadian study evaluated causes of death in individuals with SSD compared to the general population living in the developed world. This group found that circulatory conditions are the number 1 cause of death in individuals with SSD whereas the general population is most likely to die as a result of cancer/neoplasm [3]. Many factors account for this difference and the increased risk of mortality such as low socioeconomic status, tobacco use, poor diet, and physical inactivity that compound any genetic predisposition and metabolic complications caused by anti-psychotic medication [5–9]. While it is known that nutritional factors can influence the course of medical and metabolic illness in schizophrenia, uptake of such interventions is low. The field of nutritional psychiatry is beginning to uncover how food choice impacts mental health in SSD; thus, nutritional interventions have the potential to improve both mental and physical health in this vulnerable popu-

lation [10]. Currently, limited nutritional treatment guidelines exist for mental health in general [11], and none exists for SSD specifically.

The field of nutritional psychiatry research is relatively new although, at present, it has accumulated a robust collection of observational studies, preclinical studies demonstrative of mechanisms by which nutritional factors can impact neurological, cognitive, and emotional health, as well as a small number of intervention studies. The evidence is most robust in the area of unipolar depression. A 2017 meta-analysis found that a healthier dietary pattern was associated with a decreased risk of depression, and a “Western diet” was associated with an increased risk of depression [12]. While reverse causality has been suggested, prospective studies have also demonstrated an increased risk of depression related to poorer diet patterns over the long term [13]. Recently, 2 single-blind randomized controlled trials (RCTs) of individuals with major depressive disorder found that an adjunctive dietary intervention reduced depressive symptoms compared with placebo [14, 15]. In 1 trial, the number needed to treat for remission was 4 [15]. Additionally, there is an increasing amount of research demonstrating that other forms of lifestyle-based interventions, such as exercise, have been shown to be highly effective adjunctive treatments in SSD [16, 17].

Clinicians often accurately cite obstacles and challenges in implementing a dietary intervention in patients with psychosis. These include cognitive barriers, motivational difficulties, cultural acceptance, and social determinants of health, as well as psychotic symptoms themselves [18]. However, intervention studies have been undertaken which have demonstrated the feasibility and acceptability of dietary interventions in this population. One study in first episode psychosis (FEP) patients showed an increase in vegetable intake as well as a reduction in discretionary food intake and calories [4]. Another reported that a Mediterranean diet (MD)-based intervention resulted in improvements in diet quality associated with a reduced risk of cardiovascular disease in individuals with severe mental illness [19]. These studies were designed to assess diet in relation to metabolic and physical health outcomes. Unfortunately, intervention studies that assess the effect of diet on symptoms of psychotic disorders are fewer in number. This apparent lack of evidence prompted the undertaking of the present review with the following primary objective: to conduct a scoping review of the existing literature on nutritional interventions to improve mental health in SSD individuals.

Methods

Scoping reviews are conducted to identify and describe key concepts, and types and sources of evidence when the topic at hand is either complex or being reviewed for the first time [20]. Because of the broad, diverse, and poorly developed nature of the literature relating to psychosis and nutrition, we have adopted Arskey and O'Malley's [20] 5-stage framework for conducting a scoping review. These stages include: identifying the research question, identifying relevant results, selecting studies, charting data, and reporting results. Our research question is as follows. What is the current evidence base for nutritional interventions for primary prevention, secondary prevention, or treatment of mental health symptoms in individuals suffering from or at risk for SSD? What are potential opportunities and gaps for further study within this emerging area?

Identifying Relevant Studies

An a priori search strategy was developed and then refined and tested through an iterative process by an experienced medical information specialist in consultation with the review team. Using the OVID platform, we searched Embase and Embase Classic on January 6, 2017, and Ovid MEDLINE® including In-Process and Other Non-Indexed Citations and Epub ahead of print on December 12, 2016.

Strategies utilized a combination of controlled vocabulary (e.g., "Psychotic Disorders" or "Nutritional Physiological Phenomena"), and keywords (e.g., "nutrition," "diets," or "vegan"). Vocabulary and syntax were adjusted across databases. There were no language, date, or methodology restrictions, but opinion pieces and reviews were removed from the results. Specific details regarding the strategies appear in online supplementary Appendix 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000493399). Searches were repeated on April 15, 2018, for the years 2017 and 2018 only. Our updated search was modified based on our refined list of dietary constituents that was developed and refined throughout the initial screening process (online suppl. Appendix 1), for instance, search terms found not to be relevant by the study authors such as "alcohol," "citric acid," and "glutathione." Additional relevant results were identified through forward and backward tracking of key search results, grey literature search, and leveraging existing networks and conferences. Duplicates were removed.

Study Selection

Title and abstract screening was completed using Abstrackr, an online open-source program that facilitates rapid screening decisions and concurrent tagging of results [21]. Studies were assessed for eligibility according to the following criteria:

- Inclusion Criteria
 - Studies of participants with psychotic disorders or symptoms or pre-clinical studies of models of psychotic disorders or symptoms that report on a mental health-related outcome.
 - Studies assessing or modifying participant diet; this includes whole diet, or use of a food, supplement, or natural health product that provides an active constituent naturally occurring in the general North American diet.
- Exclusion Criteria
 - Studies assessing or administering herbal medicines (apart from those used for culinary purposes in the general North American diet) or other constituents not typically found in

significant quantities in the human diet (i.e., St. John's Wort, GABA, or S-adenosylmethionine).

- Studies of endogenously produced dietary components (i.e., cholesterol, vitamin D, or non-essential amino acids) without reference to dietary intake or supplementation.
- Studies with outcomes related to the impact on medication side effects or physical health outcomes only (i.e., tardive dyskinesia or weight gain).
- Studies of vitamin B₁ (thiamine) were excluded due to the large volume of studies and the previously established link between thiamine deficiency and psychosis (Wernicke-Korsakoff syndrome).
- Review articles, opinion papers, letters, and systematic reviews.
- Non-English language papers unless an English abstract with sufficient information for data extraction was available.

Duplicate screening was completed by a team of 4 reviewers, which included both primary investigators and 2 research assistant volunteers providing independent assessment of each study identified. We engaged the artificial intelligence function of Abstrackr to rank-order abstracts based on the likelihood of relevance [22]. Screening was completed so that all studies with a probability of at least 0.4 of relevance were screened manually. This process ensures that the inherent inaccuracy of machine learning of Abstrackr (~4.2% of studies are incorrectly identified for exclusion) would be buttressed by duplicate screening by a member of our research team [22]. Concurrently, tags related to dietary constituents, methodology, population, and mechanism were applied to the studies selected for inclusion based on title and abstract review. Discrepancies between reviewers were resolved by consensus between the study primary investigators (M.A. and L.L.).

Charting the Data

A data extraction template was created and piloted among study authors for each broad study design category: pre-clinical, observational, and experimental. It was refined and finalized based on data extracted from a sample of studies. Data were extracted from abstracts or full texts as appropriate.

Collating, Summarizing, and Reporting Results

Data were analyzed and presented primarily according to dietary constituents. When possible, the scope of the current literature for a given section was displayed in one or more charts to provide the reader with an overall impression of the available information, gaps, broad study methodology, and directionality of findings. In order to concisely display directionality of findings, studies reporting improvement in at least one outcome of interest (such as positive, negative or cognitive symptoms, anxiety, depression, or quality of life) were categorized as "decreasing psychopathology," even if other outcomes assessed reported no effect. Studies reporting worsening in at least one outcome of interest were categorized as "increasing psychopathology." No studies reported both an increase and decrease in psychopathology outcomes. Additionally, to allow for concise display, studies that reported an association between worsening symptoms with higher levels of a nutrient and improved symptoms with lower levels of a nutrient were combined, and all tables were oriented to display the effects of a higher intake of the dietary constituent of interest. A narrative summary of each section highlighted themes, trends, promising areas, and gaps for each broad study type to accompany the charts. In addition, authors emphasized any reported adverse effects of a

Fig. 1. PRISMA flow chart. AI, artificial intelligence.

given dietary constituent and potential biological mechanisms underpinning the association between dietary constituents and mental health outcomes in individuals with psychosis. Given the heterogeneity of the literature, a flexible and iterative approach was taken by both principal investigators to summarize and present the literature in a meaningful and relevant way.

Results

Our initial search revealed 73,063 results, which was reduced to 52,634 after de-duplication. Using Abstrackr to facilitate screening allowed study authors to manually screen just under 50% of results (26,053), relying on the artificial intelligence feature of the program to screen the remaining articles. The current project would not have been feasible without the support of this technology. An additional 438 articles were excluded at the data extraction phase resulting in 718 relevant articles that underwent data extraction via full-text or abstract review (Fig. 1; PRISMA flow diagram).

The updated search resulted in 1,135 results in OVID MEDLINE and 2,691 in Embase and Embase Classic with a total of 2,696 following conservative automatic de-duplication using EndNote X7. The same double screening process resulted in 112 abstracts identified as potentially relevant, 1,886 abstracts excluded manually, and 698 abstracts excluded by the artificial intelligence feature.

Manual de-duplication was conducted during the data extraction phase. Thirty abstracts were excluded at the data extraction phase resulting in an additional 82 articles. An additional 22 articles were identified through backward tracking of identified articles during the data extraction phase.

Distribution of Studies

Figures 2–4 display the distribution of the articles included with respect to year of publication, methodology, and geographic location, respectively (please see online supplementary File 1 for a full list of studies included). It is evident that the field of nutritional psychiatry has recently gained interest and an expanding volume of literature with nearly half of the included studies published in the last 8 years and two-thirds in the last 2 decades. Earlier studies were largely related to vitamins, minerals, amino acids, and food sensitivities. Most recent areas of study include dietary patterns, dietary macronutrients, microbiome, and phytochemicals. The geographic location is reported for all studies assessing or involving human participants as traditional diets vary by region.

Dietary Patterns

Primarily motivated by the concerns of obesity and physical comorbidity in schizophrenia, many studies have assessed the overall diet of patients with psychosis,

Fig. 2. Distribution of articles by year of publication.

Fig. 3. Distribution of articles by study methodology.

Fig. 4. Distribution of articles by geographic location.

Table 1. Specific foods associated with psychosis in cross-sectional studies

Higher intake associated with psychosis		Lower intake associated with psychosis	
food	<i>n</i>	food	<i>n</i>
Full-fat cream	1	Milk	3
Milk and dairy	1	Fish (including 1 meta-analysis)	5
Fish	1	Red meat	1
Red meat	1	Potato	1
Olive oil	1	Nuts	1
Reduced-calorie butter/margarine	1	Pulses	1
		Chicken	1

n, number of studies.

and many intervention studies have aimed to help their patients improve their diet (Fig. 5).

The observational studies show a clear trend. Eight studies show an overall poorer quality diet or higher intake of unhealthy foods, and 5 show higher intake of convenience foods. Patients with psychosis are more likely to skip breakfast and eat evening snacks [23], eat quickly [24], avoid hard foods [25], and lack structure in their meals [26]. Two studies reported that a healthier diet was associated with less psychopathology. One study of 200 participants reported a higher incidence of psychosis among patients eating a vegetarian diet; these patients were also more likely to be deficient in vitamin B₁₂ [27]. One study that lacked a comparison group reported an “adequate diet” in 73% of patients [28].

The association between total caloric intake and psychosis was unclear. Nine cross-sectional studies found that patients consumed fewer calories or found an association between fasting or malnutrition and worse psychopathology. Eleven cross-sectional studies reported that patients consumed higher calories; 2 showed no association. One case series (*n* = 35) reported that fasting had a beneficial effect while 1 case series reported on 10 cases of FEP following rapid self-induced weight loss.

Some cross-sectional studies reported different levels of intake of individual foods between SSD and healthy populations. These are listed in Table 1.

Additionally, 3 individual foods have been studied through animal studies with Black seed (*Nigella sativa*)

Fig. 5. Studies assessing dietary patterns. Dec, decreased psychopathology or decreased risk/incidence of SSD; Inc, increased psychopathology or increased risk/incidence of SSD; Equ, equivocal/no association.

conferring benefit to positive symptoms [29, 30] and fenel and pear juice improving both positive and negative symptoms [31, 32]. Two animal studies showed connection between soft diet and worsened biological markers of psychosis and positive symptoms.

Twenty-two experimental studies assessed the impact of dietary programs in patients with psychosis. An additional 2 protocols lacking results were located. The interventions consisted of diet and nutrition education programs advocating for an overall healthier diet. Many contained components of cooking classes, budgeting, and grocery shopping. Some contained additional components related to a healthy lifestyle such as exercise (19 of 22 studies), smoking cessation, and psychosocial interventions such as cognitive behavioural therapy or motivational interviewing. In 6 of these studies, mental health symptoms or quality of life were the primary outcome; in contrast, the remaining studies were designed to detect changes in cardiovascular risk factors, weight, or metabolic parameters. The completed studies ranged from 10 to 770 participants (mean 160 ± 196) with durations spanning 4–120 weeks (mean 32 ± 32 weeks). Eleven of the completed studies used a control group, 7 employed randomization, and 2 reported the use of blinding. Overall, 17 of 22 studies reported at least 1 positive mental health outcome.

Fig. 6. Studies assessing dietary carbohydrates and fibre. Dec, decreased psychopathology or decreased risk/incidence of SSD; Inc, increased psychopathology or increased risk/incidence of SSD; Equ, equivocal/no association; Carb, carbohydrate.

Fig. 7. Studies assessing fat and essential fatty acid intake and essential fatty acid levels. Dec, decreased psychopathology or decreased risk/incidence of SSD; Inc, increased psychopathology or increased risk/incidence of SSD; Equ, equivocal/no association; EFA, essential fatty acids; PUFA, polyunsaturated fatty acids.

		Total Fat Intake	Saturated Fat Intake	Omega-3		Omega-6		EFA/PUFA	
				Intake	Levels	Intake	Levels	Intake	Levels
Pre-clinical	Dec	1		14					
	Equ								
	Inc	2		1					
Observational	Dec	2	1	5	34	1	19	1	3
	Equ	1			9		3		4
	Inc	10	3	6		2	10		2
Case Reports	Dec				3		1		
	Equ								
	Inc	1							
Experimental	Dec				13				
	Equ				14				
	Inc				1				

One meta-analysis has been completed in this area, assessing the impact of lifestyle programs on depression in patients with psychotic disorders [33]. While it found a benefit, this analysis included studies and patient populations beyond the scope of the present review (ex. exercise and psychosocial component only; patients with “serious mental illness”).

Carbohydrates and Fibre

Observational evidence has found an association between the consumption of higher-glycaemic-index foods and increasing odds of anxiety and depression. Serum glucose levels are known to effect cognition, mood, and anxiety in healthy and diabetic populations as demonstrated in a small number of observational and experimental studies [34]. As a result, there is interest in a possible role of dietary carbohydrate intake in the pathogenesis of mental illnesses.

The 13 observational studies assessing total dietary carbohydrates showed mixed results with 4 reporting a higher intake in SSD, 2 reporting a lower intake in SSD, and 7 reporting no association. Of the 10 studies which assessed refined sugar, breakfast cereals, and sweetened drinks, all found an association between higher intake and psychosis. Observational studies assessing fibre intake also showed a fairly consistent trend with 9 finding a lower intake in SSD patients and 2 finding a higher intake (Fig. 6).

There is research in the use of low carbohydrate diets in the treatment of psychotic disorders. Four case reports present cases of patients eating low-carbohydrate diets. Two described the precipitation of psychotic episodes (1 in a patient with a previous history) while the other 2 reports describe 3 patients with chronic schizophrenia whose psychopathology improved significantly while following a ketogenic diet. Two animal studies that implemented ketogenic diets reported improvements in positive, negative, cognitive, and biological outcomes, and 1 open label experimental study using the ketogenic diet in 10 patients for 2 weeks reported significant improvement in symptoms. In both the case reports and the intervention trial, authors note that a return to the previous diet caused a rapid relapse in symptoms.

Fats

Seventeen observational studies have examined total and saturated fat intake in patients with schizophrenia compared to a control group. Results are mixed, though more studies found an association between increased consumption of total fat or saturated fat and schizophrenia (Fig. 7). Regarding intake of essential fatty acids (EFA), including ω -3 and ω -6 series, a clearer trend emerges. In collating findings from studies that compared consumption of ω -3 and ω -6 fatty acids in patients with SSD relative to a healthy control group, we see that 5 studies reported that individuals with SSD are more

likely to consume a diet that is lower in ω -3 fatty acids, and 2 studies reported that individuals with SSD are more likely to consume a diet that is higher in ω -6 fatty acids. One case-control study reported lower levels of ω -6 consumption in patients with schizophrenia compared to controls. Furthermore, 1 study compared intake of ω -3 and ω -6 fatty acids in 146 community-dwelling participants with schizophrenia to national averages in the USA. They found there was no significant difference [35]. On the contrary, a large prospective cohort study ($n = 33,623$) reported that decreased consumption of ω -3, docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and eicosapentaenoic acid (EPA), and ω -6, arachidonic acid (AA) and linoleic acid (LA), was associated with psychosis spectrum symptoms in women [36].

Numerous ($n = 72$) studies have either assessed tissue levels of EFA in individuals with SSD relative to a control group, or they have measured the association between symptoms of psychosis and EFA including: EPA, DHA, α -LA (ALA), LA, and γ -LA (GLA). EFA levels are measured in a variety of tissue samples, including blood (RBC membranes, serum, and phospholipids), and post-mortem brain. In Figure 7, we have charted the number of studies that showed an association between elevated levels of EFA (either ω -3, ω -6, or undifferentiated EFA/polyunsaturated fatty acid, PUFA) and psychopathology or risk/incidence of SSD. Two meta-analyses of EFA levels in RBC membranes in patients with schizophrenia versus a control group have been published. In summary, medication-naïve individuals with SSD were found to have decreased levels of DHA, DPA, and AA relative to controls. Individuals taking atypical anti-psychotics were found to have reduced levels of DHA, individuals taking typical anti-psychotics were noted to have reduced levels of DHA, DPA, AA, LA, and GLA, and those taking any anti-psychotics were found to be associated with reduced levels of DPA, DHA, and LA [37, 38].

Case reports provide anecdotal evidence that manipulating EFA intake, status, or stores may contribute to clinical improvement in patients with SSD. Three case reports of ω -3 interventions showed benefit in patients with schizophrenia, in addition to 1 case report of evening primrose oil (contains primarily GLA and LA) [39], and 1 case series of a low-fat diet. Clinical trials ($n = 28$) have focused on assessing the efficacy and safety of ω -3 fatty acids with sample sizes ranging from $n = 9$ to $n = 320$ and treatment duration from 6 to 104 weeks. As shown in Figure 7, findings have been heterogeneous with 13 positive trials, 14 equivocal (including 3 study protocols), and 1 negative. Reported adverse effects include: mild nausea,

diarrhoea, indigestion, irritable bowel syndrome, and upper respiratory tract infection. In many clinical trials ($n = 11/28$), no adverse effects and gastrointestinal symptoms could be ameliorated by taking ω -3 supplements with food.

Deas et al. [40] attempted to conduct a meta-analysis of RCTs of ω -3 interventions to prevent transition to psychosis in a clinical high-risk population. Due to limited available data at the time, they simply reported on findings of 2 positive trials. Three additional meta-analyses have been conducted along the spectrum of schizophrenic illness, 2 included any ω -3 interventions, 1 only EPA. All 3 found that the effect of ω -3s was insignificant on symptoms of chronic schizophrenia though it may be beneficial for its prevention or at the early stages of the illness [41–43].

Pre-clinical studies support the efficacy of ω -3-enriched diets to attenuate behaviours induced by animal models of schizophrenia. In addition, 1 study found that oleanolic acid (found in olive oil) attenuated psychotic-like symptoms in mice [44].

Protein

Dietary protein provides a source of amino acids, which play critical building block roles in the synthesis of a range of neurotransmitters. While some observational studies have looked at dietary protein intake, a larger body of studies has explored the relative amounts of the tissue levels of different amino acids and interventions using amino acid supplements (Fig. 8).

Three studies revealed a lower intake of protein in patients with psychosis, while 2 showed a higher intake, and in 5 there was no association. One found an association between higher protein intake and lower symptom severity, and 1 case report suggested a benefit from a higher intake of protein and additional amino acids. The effects of increased dietary protein may be mediated by the supply of essential amino acids or by decreasing the relative amount of dietary carbohydrates or saturated fatty acids, which have postulated mechanisms for harmful effects as discussed in other sections.

Of the observational studies examining levels of individual essential amino acids, many displayed a mixture of positive and negative results with a few exceptions. The following amino acids were not included in Figure 8 because 2 or fewer studies existed for each: alanine, arginine, tyrosine, and cysteine-rich whey protein.

Observational studies assessing tryptophan levels were more likely to show decreased levels in patients with psychosis. Two animal studies showed that tryptophan de-

	Dietary Protein	Histidine	Isoleucine	Leucine	Lysine	Methionine	Phenylalanine	Threonine	Tryptophan	Tryptophan Depletion	Valine	Arginine	Glycine	Serine
Pre-clinical	Dec			1	2				1			3	5	16
	Equ													1
	Inc					2				2			2	
Observational	Dec	4	3	3	2	2	2	3	3	16	1	not assessed		
	Equ	5			1	1	1	5	1	12	1			
	Inc	2	1	2	2	1	4	5	1	5	1			
Case Reports	Dec	1				1								
	Equ													
	Inc													
Experimental	Dec				5				6	1			17	7
	Equ								1	2		1	5	6
	Inc					6				4			1	

Fig. 8. Studies assessing dietary protein or individual amino acid intake and levels. Dec, decreased psychopathology or decreased risk/incidence of SSD; Inc, increased psychopathology or increased risk/incidence of SSD; Equ, equivocal/no association.

pletion worsened positive symptoms and that tryptophan supplementation mitigated this effect. In humans, 6 experimental studies using tryptophan supplementation reported a benefit to at least 1 symptom domain (including positive and negative symptoms, cognitive symptoms, and quality of life), and 1 showed no effect. One study reported a worsening of psychopathology in a subset of patients [45] while the remaining did not report adverse events. Four human studies showed worsening psychopathology as a result of depleting levels of tryptophan (or a combination of amino acids including tryptophan), 2 showed no effect, and 1 showed a benefit.

The amino acid lysine was found to improve positive symptoms in 2 animal studies and at least 1 symptom domain in all 5 human studies.

The non-essential amino acids glycine and serine have been studied through experimental trials using supplements. Several pre-clinical and experimental studies using adjunctive glycine have reported a benefit (17 of 23) in a variety of domains; 1 meta-analysis found benefits in positive and depressive symptoms [46], and 1 in positive and total symptoms [47] when analyzing patients taking non-clozapine medications. Sixteen of 17 animal studies using serine found benefit, primarily with respect to cognitive and positive symptoms. Seven of 13 studies using supplemental serine in patients with psychosis have re-

ported a benefit; 1 meta-analysis found significant reductions in negative and cognitive symptoms [46] and another in negative and total symptoms [47].

In contrast, the amino acid methionine was found to be elevated in psychosis populations in 4 of 7 observational studies; 2 animal studies and 6 human experimental studies reported worsening psychopathology with methionine supplementation.

Food Sensitivity and Intolerance

Over the last 4 decades, 18 observational studies (cross-sectional) have measured antibodies to foodstuffs in patients with schizophrenia compared to a reference group (Fig. 9). All of these studies report on antibodies to gluten/wheat, and a meta-analysis of biomarkers of gluten sensitivity in patients with schizophrenia was published in 2014 [48]. This study found that certain biomarkers of gluten sensitivity are elevated in patients with schizophrenia, but that the immune response pattern to gluten is distinct from that seen in coeliac disease. Only 1 observational study of gluten-related antibodies has been published since this meta-analysis. This recent paper by Severance et al. [49] found that anti-TTG6 IgG was elevated in 166 patients with FEP compared to controls. This finding is interesting in that this is the only study that has measured anti-TTG6 IgG in individuals with schizophrenia, and this

Fig. 9. Studies of gluten sensitivity (GS), gluten intake, or gluten-free (GF) diet in schizophrenia.

isoform of TTG (anti-TTG2 IgA is one of the diagnostic markers of coeliac disease) is expressed in brain.

Three epidemiological studies have reported on the association between gluten/wheat intake and the prevalence or incidence of schizophrenia. In 1966, Dohan [50] stated that wheat intake during World War II in Finland, Norway, Sweden, Canada, and the United States was associated with rates of hospitalization for schizophrenia in women. In 1980, Templer and Veleber [51] published that wheat intake was correlated with schizophrenia prevalence ($r = 0.53$, $p = 0.01$) across 18 countries. Lastly, a large epidemiological study found that the rate of schizophrenia was only 2 per 65,000 in the Pacific Islands, at a time when there was very low exposure to grain [52].

Thirteen experimental studies assessing the impact of an elimination diet to target food sensitivity in patients with schizophrenia were published between 1969 and 2013. Twelve of these studies involved a gluten-free diet. The remainder assessed a dairy (casein)-free diet ($n = 1$) or a “cereal-free, milk-free” diet ($n = 5$). Sample sizes ranged from $n = 2$ to $n = 157$. No adverse effects of the dietary interventions were reported although only 4 studies reported specifically on adverse effects. In addition, 8 case reports of a gluten-free therapeutic diet have been reported, including 6 patients with multi-episode schizophrenia and 2 FEP patients. De Santis et al. [53] reported that a GF diet resulted in reversal of left frontal hypoperfusion on SPECT scan, and 6/7 case reports were positive.

Microbiome

Diet has emerged as an accessible target for intervention to modify the gut microbiome (GMB) composition whether by consuming probiotics via fermented foods, prebiotics (“food” to support and stimulate the growth of

beneficial microorganisms), or by avoiding foods that contribute to gut dysbiosis.

Pre-clinical studies have found that administration of probiotics (*Bifidobacterium longum*) to mice attenuated rearing behaviours induced by a dopamine agonist (animal model of schizophrenia) and that prebiotics (B-GOS) given to rats had pro-cognitive effects, and increased levels of *Bifidobacterium* species [54, 55].

Regarding data in humans, 4 studies have assessed and found differences in the oropharynx microbiome composition in patients with SSD versus controls, and 3 studies reported differences in GBM composition. Overall, high-level differences were found between patients and controls at both the phylum and genus levels in the oropharynx and GBM. These differences were associated with particular metabolic pathways, clinical response, levels of intestinal immune activation, and antibodies to gluten [56–58]. One case report demonstrated improvements in constipation and positive symptoms as well as changes in GMB composition with a 1-month adjunctive prebiotic intervention [59]. One placebo-controlled RCT of a probiotic intervention has been conducted in outpatients with schizophrenia. This group did not find an impact of the intervention on the positive and negative syndrome scale score though they did report significant improvement in gastrointestinal symptoms and a reduction in antibodies to *Candida albicans*, a marker of intestinal inflammation, in the intervention group [60, 61].

Vegetables and Fruits

The observational data consisted primarily of cross-sectional studies comparing the consumption of fruits and vegetables by patients with psychosis to control subjects, and the results were highly consistent (Fig. 10). Twenty-two cross-sectional studies reported on the relationship between dietary intake of fruits and vegetables

and the presence of psychosis (average sample size 506, range of 8–1,825). Twenty studies showed an association between a lower intake and the presence of psychosis, and 1 found a relationship between increased intake and decreased psychosis. One showed no association. One case report reported improved symptoms with higher intake of fruit and vegetable juice in combination with vitamins, minerals, and enzymes [62].

One randomized, placebo-controlled experimental study provided 6 months of free fruits and vegetables, with or without instructions and support, to 102 schizophrenia patients. It failed to detect an impact on positive or negative symptoms [63]. The study found a significant increase in fruit and vegetable intake at the end of the intervention based on patient report; however, using the last observation carried forward, there was no difference in the primary outcome, the number of fruit and vegetable servings consumed 12 months after the intervention as reported consumption returned to pre-intervention levels. Interestingly, there was no change in blood levels of folate, vitamins C and E, or carotenoids, which were measured as an additional objective assessment of diet. It is possible that patients were reporting changes in their diet that were not consistent with their actual intake, which raises concerns about compliance and the accuracy of the reported increase in intake. The power calculation of the study was also based on the primary outcome of changes in fruit and vegetable intake. The study reported that participants' diets did not change in terms of intake of oil-rich fish, potatoes, pasta or rice, or whole-grain bread; the vegetables were in addition to their previous diets. It is possible that the mental health effects of increasing vegetable intake may be related to multiple factors in dietary patterns containing more of these foods.

Phytonutrients

Phytonutrients are chemical compounds produced by plants, which possess biological activity. While they are not defined as essential nutrients, some confer effects on human health [64]. Research has been conducted on a range of phytonutrients with respect to psychosis in the form of human experimental, observational, and pre-clinical studies (Table 2). Due to the heterogeneity of constituents studied, the results are displayed in Table 2 with a description of dietary sources and a summary of the current evidence. The intervention studies using phytonutrients were generally small with 10 to 143 participants. No adverse events were reported. Many human and pre-clinical studies assessed mechanism as a second-

Fig. 10. Studies assessing dietary fruit and vegetable intake. Dec, decreased psychopathology or decreased risk/incidence of SSD; Inc, increased psychopathology or increased risk/incidence of SSD; Equ, equivocal/no association.

ary outcome and found decreases in lipid peroxidation and inflammatory cytokines, and effects on glutamate, dopamine, acetylcholinesterase, and brain-derived neurotrophic factor.

Minerals

Studies related to minerals were primarily observational in nature, looking at tissue levels of various minerals in both SSD and healthy populations (Fig. 11). Not included in the chart were minerals with ≤ 3 cross-sectional studies including boron, cobalt, lithium, molybdenum, sulphur, and vanadium. For many minerals, the results were mixed with studies showing associations between psychosis and both higher and lower levels of the minerals. These included calcium, cobalt, iron, magnesium, molybdenum, phosphorus, potassium, and sodium. Studies finding higher levels of copper in an SSD population were more common as were studies finding lower levels of zinc, selenium, and manganese (Fig. 11). A recent meta-analysis of observational studies found lower serum concentrations of zinc in patients with schizophrenia compared to healthy controls [65].

A small number of experimental studies have been completed. One used 50 mg of zinc in 30 patients and found significant reductions in positive and negative

Table 2. Summary of dietary sources of phytonutrients and research related to psychosis

Phytonutrient	Dietary sources	Supporting research
L-Theanine	Green tea	3 experimental studies found benefit in positive and negative symptoms and sleep
Sulforaphane	Broccoli, cauliflower, cabbage, Brussel sprouts, kale	1 experimental study found improvement in cognition and brain-derived neurotrophic factor; not in positive and negative symptoms 4 animal studies found benefit
Resveratrol	Grapes, blueberries, raspberries	1 study found improved cognition 4 animal studies found benefit
EGCG	Green tea	1 study found no effect on positive and negative symptoms, anxiety, or depression
Quercetin	Onions, berries, kale, grapes, plums	1 study found improvement in positive symptoms in combination with other nutrients 1 case report reported benefit from supplementation
Polyphenols	Green and black tea, red wine, chocolate, olives, olive oil, many fruits, and vegetables	1 study found improved cognition
Curcumin	Turmeric	1 study found increased brain-derived neurotrophic factor but no effect on cognitive symptoms
Caffeine	Coffee, tea	Observational studies showed both improvement and worsening of symptoms with higher intake
Genistein	Soy	1 animal study found benefit
Astaxanthin	Shrimp, salmon, trout, crab, lobster	1 animal study found benefit
Morion	Onion	1 animal study found benefit
Copoletin and rutin	Citrus, tea, buckwheat, asparagus	1 animal study found benefit
Crocins	Saffron	1 animal study found benefit
Phytosterols	Vegetables, seed and nut oils	2 observational studies found an association between lower intake and psychosis
Antioxidants	Various fruits, vegetables, herbs, spices, and legumes	1 observational study found no association with psychosis

symptoms and aggression risk [66]. One using zinc in combination with vitamins C, E, and B₆ demonstrated a reduction in anxiety but not depression or overall psychopathology [67]. One study using chromium supplementation failed to show a benefit. One research group attempted to complete a double-blind RCT of a multivitamin and mineral formula with an open label run-in; however, all of the 19 participants declined randomization. The study compared these results to the results of patients who had declined participation and those waiting to participate, and observed significant reduction in

anti-psychotic medication use as well as positive and negative symptoms at 15 and 24 months, respectively [68].

A small number of case reports reported benefit from zinc supplementation, low levels of magnesium in patients with psychosis and benefit of magnesium supplementation, benefit from molybdenum supplementation, decreased levels of iron and resolution of a first episode with iron supplementation as well as decreased levels of phosphorus. Two animal studies reported a decrease in positive symptoms and anxiety with zinc supplementation.

		Calcium	Chromium	Copper	Iron	Magnesium	Manganese	Phosphorus	Potassium	Selenium	Sodium	Zinc
Pre-clinical	Dec											2
	Equ											
	Inc											
Observational	Dec	8	1	6	11	11	6	2	3	10	2	19
	Equ	9	1	15	5	12	2	2	0	6	1	9
	Inc	7	4	21	7	12	0	3	3	2	4	6
Case Reports	Dec				2	4		1				1
	Equ											
	Inc											
Experimental	Dec											2
	Equ		1									
	Inc											

Fig. 11. Studies assessing mineral intake and levels. Dec, decreased psychopathology or decreased risk/incidence of SSD; Inc, increased psychopathology or increased risk/incidence of SSD; Equ, equivocal/no association.

		B2	B3	B6	B12	Folate	B12 + Folate	Choline	Inositol	A	C	D	E	Comb A, C and/or E
Pre-clinical	Dec					2		2			3			
	Equ													
	Inc													
Observational	Dec		2	9	20	36		7	1	4	14	3		
	Equ	3		2	23	19			2	3	8	1		
	Inc		1		1	2								
Case Reports	Dec	10		4	40	6	4				5			
	Equ					1					1			
	Inc		1			1				1				
Experimental	Dec		3	9		6	5	2			4	1	1	3
	Equ	2	7	1	2	1		1	6		1	1	4	
	Inc													1

Fig. 12. Studies assessing vitamin intake and levels. Dec, decreased psychopathology or decreased risk/incidence of SSD; Inc, increased psychopathology or increased risk/incidence of SSD; Equ, equivocal/no association.

Vitamins

The family of B vitamins has received extensive interest with respect to their role in mental health and particularly in psychotic disorders (Fig. 12). A large number of observational studies show lower folate, B₁₂, B₆, and

choline in patients with psychosis. Many case reports have reported low levels of vitamin B₁₂ in this population as well as improvement in symptoms with supplementation. Vitamins B₅ and B₇ were excluded from the results table having only 1 study each. Studies assessing vitamin

B₁ were excluded from the review due to the previously established connection with neuropsychiatric symptoms such as confusion, inattention, and disorientation [69].

A number of experimental studies using vitamins B₆, B₁₂, and folate have shown benefit, most frequently to total psychopathology, and a recent meta-analysis combined RCTs using adjunctive B₆, folate, and B₁₂ and found a significant improvement in total psychopathology but not in positive or negative symptoms individually [70]. Ten studies of B₆ ranged from 8 to 40 participants and used doses of 30 to 1,200 mg for 1–48 weeks in length. Four were double-blind, randomized, and placebo-controlled studies. Five double-blind, randomized, placebo-controlled studies of B₁₂ and folate in combination ranged from 22 to 140 participants and used B₁₂ doses of 400 µg and 2 mg of folate for 12–16 weeks in length. Studies of folate ranged from 8 to 55 participants and used doses of 0.5–15 mg for 4–12 weeks in length. Six of 8 were randomized, double-blind and placebo-controlled studies.

Regarding the antioxidant vitamins, the majority of observational studies showed lower levels of vitamins C and A and a lower intake of vitamin D. A small number of case reports and experimental studies using vitamin C supplementation have reported benefit. These experimental studies used a wide range of doses in <40 participants for up to 8 weeks. In 4 experimental studies that demonstrated a benefit of vitamin E supplementation in the treatment of anti-psychotic-associated movement disorders, secondary outcomes of psychosis symptoms failed to demonstrate a benefit in most of these studies. One study in which psychopathology was the primary outcome reported improvement. A meta-analysis which combined studies utilizing vitamins A, C, and/or E found no impact on total psychopathology [70].

Perinatal Exposure

A small body of evidence has explored the impact of perinatal exposure to different dietary constituents and the risk of psychosis in the offspring. The exposure of interest is highly heterogeneous; however, a small number of factors have received more attention. Five animal studies and 3 experimental studies used choline or phosphatidylcholine interventions pre- and/or postnatally, and reported benefit to positive and cognitive symptoms in susceptible animals and improved sensory gating in human infants with elevated genetic risk. Eight observational studies connected psychosis risk with maternal malnutrition or famine, and 4 with maternal iron deficiency. A smaller number of studies reported connection with maternal obesity, vitamin deficiency, maternal immune re-

actions against food constituents, decreased levels of copper and manganese, high levels of maternal serum DHA, and low maternal folate.

Safety

Overall, the majority of studies reported that the interventions were safe or did not report on safety. A small number of studies reported adverse events, but these were exclusively in the studies assessing high doses of individual nutrients such as vitamin B₃ (300–3,000 mg/day), folate (2 studies only at a dose of 1 mg/day and 0.3–1 mg/kg/day, 6 studies did not report or reported no adverse events), and choline (2 g/day). Reported adverse effects for ω-3 fatty acids include: mild nausea, diarrhoea, indigestion, irritable bowel syndrome, and upper respiratory tract infection. Many clinical trials ($n = 11/28$) reported an absence of adverse effects with some suggesting that gastrointestinal symptoms could be ameliorated by taking ω-3 supplements with food.

Discussion

Our results revealed a number of constituents and mechanisms potentially relevant to the development and progression of psychosis (Fig. 13).

Dietary Pattern

Overall, significant evidence exists that dietary patterns are associated with psychosis and that therapeutic intervention can impact psychopathology. There is a need for more randomized, controlled, and blinded intervention studies powered to detect changes in mental health rather than metabolic outcomes. There is also an opportunity for greater clarity with respect to the dietary recommendations provided.

Carbohydrates and Fibre

While the relationship between psychosis and total dietary carbohydrates is unclear, there appears to be an association with higher intake of refined carbohydrates in observational studies. None of the studies included assessed the mechanism by which dietary carbohydrates might be affecting psychosis symptoms; however, some have been proposed. Higher glycaemic index foods may cause reactive hypoglycaemia which includes a number of neuropsychiatric symptoms when induced in a laboratory setting [34].

The ketogenic diet is a high-fat, low-carbohydrate diet that has been used since the 1920s as a therapy for paediatric epilepsy. The diet results in the use of ketone bodies,

Fig. 13. Summary of mechanisms linking food and psychosis.

rather than glucose, as the fuel source for the brain. Abnormalities in glucose tolerance and insulin resistance as well as mitochondrial dysfunction and energy metabolism disturbances have all been associated with the pathogenesis of psychosis and could be potential mechanisms for this diet to exert an effect [71].

With respect to dietary fibre, increased intake lowers the glycaemic index of food [72]; as such, fibre may also exert an effect by way of decreasing reactive hypoglycaemia. Preliminary evidence exists suggesting that fibre may affect mental health by way of modifying the GBM. Indigestible dietary carbohydrates provide a food source for gut bacteria and affect the relative levels of different species with MD and leafy green vegetables contributing to more beneficial species [73]. The relevance of GBM composition to mental health in SSD will be discussed later in this review.

Fats

The recommended amount and type of dietary fat to consume is a controversial area in the field of nutrition science at the present time. For example, in recent years, we have seen a shift away from emphasizing the importance of a low-fat (and therefore often high-carbohydrate) diet towards including healthier fats in the diet [11, 74]. In parallel to this, industrialization has brought a dramatic change in the relative amount of ω -3 and ω -6 fatty acids consumed as part of the standard North American diet, in part due to the ubiquitous consumption of processed seed oils, which are relatively high in ω -6 PUFAs. An imbalance of ω -6 to ω -3 fatty acids impacts antagonistic biological pathways that can lead to an overproduction of inflammatory cytokines [75].

Several potential mechanisms have been proposed to explain the potential efficacy of EFA in SSD. It has been suggested that individuals with SSD may have abnormal-

ities in EFA metabolism leading to abnormal levels [76] and that treatment with anti-psychotic medications can lead to normalization of EFA levels [77]. The balance of EFA can impact levels of inflammation [41] and oxidative stress [78], and alter serotonin responsivity and dopamine neurotransmission [79, 80]. EFAs have demonstrated neuroprotective effects [81].

Within the scope of nutritional interventions for psychosis, much attention has been paid to the role of EFAs. Treatment or prevention of psychosis and related symptoms with EFAs represents a safe adjunctive intervention with strong biological plausibility, particularly in the symptom domains of cognitive and negative symptoms, where treatment options are much more limited. That being said, several important gaps remain to be clarified by subsequent research studies. For instance, given the abundance of studies that have measured tissue levels of EFA in individuals with SSD, an analysis by stage of illness is warranted. In addition, further exploration of ω -6 to ω -3 ratios in patients with SSD versus controls is necessary, given the opposing impact of these types of fatty acids on inflammation. Perhaps most striking is the potential confounder of dietary intake of ω -3 and ω -6 fatty acids in experimental studies of EFA supplements in individuals with schizophrenia. Future studies should either be conducted in individuals with more homogenous dietary intake or include dietary questionnaires in order to statistically account for differences in diet. Alternatively, whole-diet interventions impacting intake of fats or EFA in individuals with SSD powered to detect changes in mental health outcomes are necessary.

Protein

Overall, there is a lack of prospective and experimental research into the effects of dietary protein, which warrants further study. Some observational evidence sug-

gests a possible association between levels of amino acids and psychopathology. However, it is noted that a lack of a clearly defined deficiency status limits the interpretation of these results. Studies measuring tryptophan levels were more likely to show an association between lower levels and psychopathology; pre-clinical and experimental studies reported benefit. Tryptophan is the precursor for serotonin synthesis, and animal and human studies have shown that manipulation of tryptophan intake can affect brain levels of serotonin resulting in relapse of depression in patients and susceptible healthy subjects [82]. Second-generation anti-psychotic medications are known to modulate serotonergic neurotransmission.

Additionally, the amino acids lysine, glycine, and serine have shown benefit in patients with psychosis when used in a supplemental form in experimental studies. Glycine and serine can modulate NMDA receptors and are hypothesized to exert an effect as a result of the glutamatergic NMDA receptor hypofunction theory of schizophrenia [46].

Observational and experimental studies have reported an association between the amino acid methionine and harm. The mechanism by which methionine is involved in mental health appears to be related to methylation and its role in the 1-carbon metabolism, a complex pathway that relies on adequate levels of vitamins B₆ and B₁₂ and the active form of folic acid [83]. Disruptions in this pathway due to vitamin deficiency or mutations to the MTHFR gene may increase levels of homocysteine, which is known to be neurotoxic, as well as impacting the synthesis of glutathione [84]. One study included in this review stated that although they did not assess dietary intake, they hypothesize that the elevated CSF methionine seen in patients with psychosis is related to metabolism rather than excess intake [84].

Clinicians may consider encouraging patients to include adequate amounts of protein in their diet to ensure the provision of essential amino acids, which cannot be synthesized endogenously if consumed in inadequate quantities. Due to the larger body of evidence and proposed mechanism, emphasis may be placed on strong sources of tryptophan, lysine, serine, and glycine. Because dietary sources of many amino acids overlap significantly, there may be limited opportunity to modify these levels selectively through dietary intervention as in the supplement studies.

Food Sensitivity and Intolerance

An association between gluten sensitivity and schizophrenia was described by Dohan [50] in 1966. More re-

cently, mechanisms linking gluten sensitivity and schizophrenia have been hypothesized supported by findings that patients with schizophrenia show elevated levels of gastrointestinal inflammation, systemic markers of inflammation, and immune dysregulation, and evidence of altered gut permeability. The composition of the GBM has been implicated in the relationship between food sensitivities and schizophrenia, in part due to its crucial role in the gut-brain axis and immune system regulation. The interested reader is directed to the following review articles for further discussion of these mechanisms [85, 86].

In summary, gluten-free diets represent a potential safe adjunctive therapeutic strategy for a subset of patients with schizophrenia. Further experimental studies are needed, and none has been conducted in the last 5 years. Given the challenges with monitoring compliance, perhaps a clinical trial in an inpatient setting could be considered. Furthermore, the feasibility of this kind of treatment would be improved if it were possible to identify patients who would be more likely to benefit from a GF diet based on biomarkers. As such, clarification of which biomarkers of gluten sensitivity to measure clinically is needed. Subsequent studies could consider including measurement of anti-TTG6 IgG, the isoform of TTG expressed in brain, or anti-gliadin IgG based on the current literature. Studies assessing other food sensitivities or intolerances in patients with schizophrenia with the exception of dairy and gluten are lacking.

Microbiome

The impact of the GMB composition on health and disease is a rapidly growing area of research. We are beginning to understand that the GMB composition is a major factor influencing key bodily systems such as immune functioning, metabolic health, mental health, and the gut-brain axis.

Preliminary findings suggest that individuals with SSD may show differences in microbiome composition, and that this may represent a potential target for therapeutic intervention. Diet is of particular interest here in that it is one of the modifiable determinants of microbiome composition (i.e., dietary prebiotics, probiotics, and avoidance of foods that contribute to dysbiosis). Further research is needed to clarify the specific differences in microbiome composition between patients with SSD versus healthy controls. These types of studies could lead to the development of a biomarker to identify patients who would specifically benefit from microbiome-directed interventions. Further research is also needed to inform dose and strain of probiotic, dose and type of pre-

biotic, and type of dietary intervention required for efficacy. In addition, no controlled studies of a prebiotic or synbiotic (combined prebiotic and probiotic) intervention have been conducted in individuals with schizophrenia.

Vegetables and Fruit

A significant body of observational data shows a lower intake of vegetables and fruits in patients with psychosis. However, experimental data are lacking with only 1 study published. There are several proposed mechanisms by which fruits and vegetables may have a positive impact on mental health. These are related to the provision of constituents such as fibre, vitamins, minerals, and phytonutrients, which are discussed in other sections of this review.

In addition to possibly being relevant in psychosis pathogenesis, vegetable intake is known to affect many of the medical comorbidities common in patients with SSD. Meta-analyses have associated higher intakes of vegetables with reduced cardiovascular risk [87], reduced all-cause mortality [88], and reduced risk of type 2 diabetes [89]. Despite these results, more experimental research into the mental health effects of dietary fruit and vegetable intake is warranted.

The studies assessing vegetables and fruits should also be interpreted in conjunction with the studies assessing dietary patterns. While the values of certain dietary constituents have included controversy and differing opinions, the beneficial role of fruits and vegetables is highly consistent, and the studies reporting or manipulating diet quality, which largely showed associations with less disease or improvement in disease progression, emphasized fruit and vegetable intake.

There is a need for more prospective studies and experimental studies, which evaluate or manipulate intake of vegetables and fruits.

Phytonutrients

Although preliminary, the majority of these studies assessing phytonutrients in animal models or clinical populations reported positive outcomes, lack of adverse events, and plausible mechanisms of action; however, small sample size and limited scope of phytonutrients that have been studied to date limit generalizability. Further intervention studies, especially in humans, appear to be warranted.

Because these nutrients are obtained from fruits and vegetables, these data provide a further rationale for inclusion of fruits and vegetables in the diet. Clinicians and patients may consider emphasizing sources of phytonu-

trients with the most evidence to support their utility. These include: green tea, broccoli, onions, and berries.

Minerals

Overall, the studies on the relationship between minerals and psychosis are few in number and limited in quality. The vast majority were of cross-sectional design, and, given the poor diet known to be consumed by patients with psychosis, it is unclear if mineral deficiencies preceded the disorder or were a result of it. Prospective studies would be beneficial in differentiating these two possibilities.

None of the studies included in this review assessed the mechanism by which minerals may be affecting mental health; however, several have been studied. Zinc plays a role in a vast range of cellular functions, including signal transduction, gene expression, and apoptosis [65]. It is concentrated in the limbic system of the brain in glutamatergic zinc-enriched neurons and is known to modulate NMDA receptor activity as an antagonist as well as interacting with GABA and serotonin receptors. Schizophrenia has been linked to variants in a number of zinc transporters. Selenium functions as a cofactor for the reduction in antioxidant enzymes such as glutathione [90]; the role of oxidative stress in psychosis is mounting [91]. This review excluded studies related to Wilson disease (WD), an autosomal recessive condition related to impaired copper metabolism resulting in accumulation of copper in the brain and other organs – psychosis is a well-established symptom [92]. Patients with WD display changes on electroencephalogram and hypoperfusion on SPECT scan, and it has been proposed that serum copper affects dopamine activity through several copper-dependent enzymes involved in synthesis and degradation. Cuprizone, a copper chelator which is known to cause white-matter abnormalities, is used to induce a schizophrenia-like syndrome in animal models for research [92]. It is known that copper and zinc levels in the body are related. While one study reported decreased absorption and increased excretion of zinc with a high-copper diet, it is well established that prolonged intake of high levels of zinc (50 mg/day) decreases copper absorption and depletes body levels [90]. Taken together, zinc/copper homeostasis may be of relevance to psychosis pathogenesis and warrant further research.

The mineral with the most evidence to suggest a beneficial role in the prevention or management of psychosis is zinc. Further research in the form of clinical trials appears to be warranted. Clinicians may consider emphasizing foods that provide a good source of dietary zinc.

Vitamins

There is observational and experimental evidence suggesting a possible protective role of vitamin B₆, B₁₂, and folate in psychosis. As highlighted previously, B₁₂, B₆, and folate play a role in the 1-carbon metabolism cycle, affecting levels of neurotoxic homocysteine [83]. Each of these vitamins also plays a role in neurotransmitter synthesis and affects oxidative stress levels [93, 94].

As oxidative stress is an established concern in the pathogenesis of psychosis, this mechanism has been proposed for the potential relevance of vitamin A, C, and E adequacy or supplementation.

Because vitamins are found in fruits and vegetables, nuts, and seeds, these results may provide a further rationale for the inclusion of these diet components; however, the relevance of these studies to diet is potentially limited by the very large doses used in these studies. The recent meta-analysis found that studies using higher doses of B vitamins were more likely to show benefit than those using lower doses.

Perinatal Studies

Perinatal studies have highlighted maternal dietary choline, iron, and overall nutritional adequacy as relevant in the primary prevention of psychotic disorders. While the primary objective of this review is to identify dietary strategies to implement in patients with or at high risk of psychosis, knowledge about the importance of adequate choline intake and avoidance of maternal iron deficiency and malnutrition is potentially relevant from a population health perspective.

Context of Findings within the Current Literature

Although heterogeneity exists among the studies reported in this review, there are many common themes as well as consistency with established information about healthy eating patterns and traditional diets. For example, MD has an extensive body of research to support its use in preventing and treating a range of health concerns including cardiovascular disease and cognitive health [95] as well as, more recently, major depressive disorder [15]. Many of the foods that were highlighted in this review as having potential beneficial effects in the prevention or treatment of psychosis are present in abundance in the MD. This dietary pattern is abundant in vegetables, fruits, fish, and seafood (sources of ω -3 fatty acids), legumes, and nuts (source of prebiotic fibre), yogurt (dietary source of probiotics), and healthy fats such as olive oil. Many of the constituents that have been proposed as beneficial, including fibre, vitamins, minerals, phytonutrients, and

ω -3 fatty acids, are present in these healthy foods, and higher body levels of these constituents may be markers for intake. Conversely, foods limited in the MD include processed foods, sweets, and refined grains, all of which were associated with harm in the present review. The MD is but one example of a traditional, whole-food dietary pattern that has received much research attention.

It is worth acknowledging that the perception of what constitutes a “healthy diet” has changed significantly over the past several decades. This may be of relevance in interpreting studies that evaluated entire dietary patterns and assessed them as “healthy” or “unhealthy.” For example, the American Dietary Guidelines removed cholesterol as a nutrient of concern in 2015 due to lack of evidence that dietary cholesterol impacts serum cholesterol levels [96]. Additionally, perception about total dietary fat, saturated fat, and total dietary carbohydrates has all changed [74]. This limits the generalizability of observational studies and experimental studies assessing or implementing “healthy diets” and necessitates a thorough assessment of individual constituents such as macro- and micro-nutrients. Many of the intervention studies that implemented a whole-diet approach were unclear about the nutrition education that was provided or the recommendation given, simply stating that they advocated for improved nutrition. This is a limitation in interpreting these studies.

Strengths

This scoping review has a number of strengths. It involved a highly extensive search strategy and screening of a very large volume of abstracts in order to capture the full breadth and depth of literature in this field. It was completed by an interdisciplinary team of clinicians/researchers offering unique and complementary expertise and perspectives.

Limitations

One limitation of this review is the very large scope. Because of the very large volume of studies included it was not feasible to analyze each with a high level of detail, and the results obtained may include over-simplifications and a lack of attention to the unique characteristics of individual studies. The interpretation of the results is also limited by a number of characteristics of the studies included in the review.

Study Design

Many of the studies included were observational in design with the vast majority being cross-sectional studies.

This limits the ability to draw conclusions about causality and the directionality of the association between inadequate nutrition and psychosis. Due to a multitude of factors, it is likely that this association is complex and bidirectional. While the number of prospective studies obtained in this review was very limited, prospective studies in unipolar depression have shown that poor dietary choices precede the increased risk of developing this mental disorder [13].

Also, many studies that contribute to our mechanistic understanding have utilized animal models. Given the differences between animal and human diets and the limitations of the animals for psychosis, these data may be limited in their applicability to humans with SSD. Further research should focus on human studies.

Studies included in this review assessed patients in both early and chronic stages of psychotic illnesses and were analyzed collectively. These different stages may be unique in their responsiveness to nutritional interventions [97, 98].

Many of the intervention studies assessed were designed to assess metabolic outcomes and assessed mental health symptoms or quality of life as secondary outcomes. There is a need for more whole-diet interventions powered to detect changes in mental health outcomes.

Perhaps most striking is the potential confounder of heterogeneity in dietary intake among study participants both between and within groups. For instance, many experimental studies of ω -3 fatty acid supplements fail to consider dietary intake of both ω -3 and ω -6 fatty acids. Because of the antagonistic effects on inflammation possessed by these 2 fatty acids, the relative proportion is of importance, and a very high intake of dietary ω -6 in some or all study participants could have a significant impact on study outcomes [75]. Failing to account for dietary intake could result in within-group differences large enough to obscure the impact of the intervention under study. Future studies should either be conducted in individuals with more homogenous dietary intake or include dietary questionnaires in order to statistically account for differences in diet.

Measurement Error

Although a small number of studies looked at CSF or brain levels, the vast majority of observational studies assessing vitamins, minerals, and amino acids assessed serum or plasma levels which may be less relevant. For example, only 1% of the body's magnesium is present in the blood; as such, there are concerns about the utility of blood levels in assessing magnesium sufficiency [99]. It has been suggested that assessment of RBC magnesium is

more useful, but only a minority of studies included in this review used this measurement. Zinc also lacks an accepted, reliable measurement to assess individual zinc sufficiency making the assessment of suboptimal zinc challenging [90]. The different tissue sources used to measure levels of vitamins, minerals, fatty acids, and amino acids may account for some of the variability in results.

Additionally, many of the observational studies relied on patient report to assess intake quantities and frequencies, with some using only one 24-h recall. A recent editorial highlighted a number of issues related to the use of this type of assessment in diet/psychosis research [100, 101]. As a result of daily and seasonal variation in diet, a single-time-point 24-h diet recall is unsuitable for capturing interindividual and intergroup differences. A second issue raised is that of misreporting, particularly underreporting in the overweight and obese population and among those with severe mental illness affected by cognitive, memory, and motivational difficulties. Lastly, there are limitations related to using existing general population data as a comparison as opposed to recruiting matched healthy controls. Even minor differences in the methodology used for assessing diet intake could have significant effects.

Extrapolating from Studies of Dietary Supplements

Another limitation of this review is the applicability of some of the experimental studies, which used vitamin, mineral, phytochemical, fatty acid, and amino acid interventions in the form of dietary supplements. Some used doses of nutrients that can be feasibly obtained in the diet including sulforaphane (30 mg), zinc (50 mg), folate (0.5 mg), vitamin C (500 mg), and vitamin B₁₂ (400 μ g). In contrast, some of the intervention studies using vitamins used very high doses that cannot be achieved through dietary modification such as L-theanine, curcumin, vitamin B₃, and vitamin B₆. Because this distinction is unclear, we chose to include all intervention studies regardless of dose while acknowledging this as a limitation.

Feasibility of Dietary Interventions in Individuals with SSD

Throughout this review, it has been acknowledged that modifying the diet of individuals with psychotic disorders requires consideration of a number of barriers related largely to symptoms and socio-economic status [18]. It is important to note that many of the experimental studies which showed positive outcomes in psychopathology employed a multimodal approach, including educational and practical skill components, self-care, and wellness

Table 3. Summary of evidence-informed dietary recommendations for individuals with psychotic disorders

Dietary factors to decrease	Sources	Dietary factors to increase	Sources	Dietary patterns to consider	Notes
Refined carbohydrates	Refined sugar, sugar-sweetened beverages, confectioneries, sweets, and refined grain products (cereals, bread, pasta)	Fruits and vegetables	Especially broccoli, onions, berries, grapes	Traditional, whole-foods or healthy dietary pattern	i.e., Mediterranean diet
Convenience food	Processed and packaged food, premade food, restaurant food	High-fibre foods	Vegetables, fruit, whole grains, bran cereals, legumes, nuts, and seeds	Gluten-free diet	Consider a therapeutic trial
		Sources of ω -3 fatty acids	Fish, seafood	Ketogenic diet	Consider a therapeutic trial
		Sources of vitamin B ₁₂	Meat, seafood, eggs, soy		
		Sources of folate	Edamame, spinach, okra, artichokes, asparagus, broccoli, Brussel sprouts, lettuce, avocado, enriched wheat products, lentils, beans, organ meat		
		Sources of vitamin B ₆	Meat, fish, organ meat, enriched cereals, soy products, nuts, lentils		
		Sources of zinc	Oysters, wheat germ, liver, pumpkin seeds, baked beans, soy products, beef, pork		
		Adequate dietary protein	Meat, fish, legumes, soy, nuts and seeds, whole grains, eggs		
		Protein sources that are high in glycine, lysine, serine, tryptophan	Glycine: meat sources of collagen (bone broth, animal skin, pork rinds), gelatin powder Lysine: eggs, soy, fish, beef Serine: eggs, soy, fish, milk, seeds Tryptophan: eggs, seeds, soy, cheese, beef		
		Sources of vitamin C	Various fruits and vegetables		

components, motivational enhancement strategies, and planning and budgeting skills. Mental health teams supporting individuals with SSD are often well equipped to address these barriers by harnessing an interdisciplinary team to support behavioural changes such as taking medication, decreasing substance use, and other self-care and instrumental activities. Unfortunately, dietitians, naturopaths, and other nutrition-informed professionals are often not included in these teams and may be inaccessible for patients to consult with privately due to financial barriers. Inclusion of these nutrition-focused professions within the interdisciplinary team may be an opportunity to improve efficacy and feasibility of dietary interventions in this complex population [102].

Future Directions

Implications for Clinical Practice

While the evidence obtained in this review is preliminary in nature, it is largely consistent with general dietary recommendations as well as recommendations known to be therapeutic in treating the comorbidities found in this population. The evidence suggests that these dietary approaches are of very low risk, are of low cost [103], and have at least some compelling potential for benefit. As such, the following recommendations are put forward in Table 3.

Need for Further Research

Overall, there is a need for more observational studies, which are prospective in nature and able to distinguish factors which play a causal role in the development of psychosis from those that result from the poor diet choices made by this population. Future research studies need to be attentive to ontological issues in nutrition research [104], as well as address a lack of clarity of associations between intake, biomarker, and nutritional status. This will help to further clarify macro- and micro-nutrients which are harmful or protective to guide additional research.

Constituents that are particularly lacking in experimental data include carbohydrates, fibre, microbiome, vegetables, and protein. More importantly, there is a significant need for intervention studies, which modify in-

take of dietary constituents or entire dietary patterns with statistical power to detect changes in mental health outcomes.

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