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Vitamin Supplementation in the Treatment of Schizophrenia

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Abstract

In this article we review the current literature addressing the treatment of schizophrenia with vitamin supplementation. We first describe the important roles that vitamins play in normal metabolism, then review the evidence pertaining to vitamin deficiency and supplementation in patients with schizophrenia. We then describe mounting evidence suggesting that vitamin supplementation, in particular with folic acid, vitamin B12 and vitamin D, may be important in treatment within certain subgroups of patients. We highlight the need for larger, randomized controlled trials, and recommend further studies examining the incidence of schizophrenia in countries with poor prenatal care and malnutrition, as well as in countries that have adopted mandatory folic acid fortification of grain products.

1) Introduction

Schizophrenia is a devastating and usually chronic illness associated withfunctional disability in social, cognitive, and emotional realms. It is characterized by positive symptoms (hallucinations, delusions), negative symptoms (emotional blunting, apathy), as well as cognitive impairment. While positive symptoms often respond to antipsychotic medication, negative symptoms and cognitive deficits do not. There is an urgent need forpharmacologic treatment beyond current antipsychotic medications to address these residual symptoms, which contribute substantially to functional impairment [1, 2]. Numerous investigators have associated schizophrenia with vitamin deficiencies, either after the illness has been diagnosed or during prenatal development[3-13].Vitamin supplementation could provide therapeutic benefits through separate mechanisms of action than our current medication regimens, which focus largely on monoamine and histamine signaling.

Vitamins are organic compounds that are generallysupplied in the diet; many are unable to be synthesized in adequate amounts by the human body. Vitamins are classified as water-

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soluble and fat-soluble. Most of the nine water-soluble vitaminsact as coenzymes in metabolic processes; only one (vitamin K) of the fourfat-soluble vitamins has a coenzyme role. Fat-soluble vitamins are absorbed and stored within the liver and adipose tissue[14]. To prevent a variety of medical illnesses caused by vitamin deficiencies, the Food and Drug Administration has issued specific recommendations for daily vitamin intake [15](see Table 1). Of note, patients with schizophrenia often take in a high caloric diet that is high in saturated fats with poor fruit and fiber intake[16].

In this article we review the literature addressing both vitamin deficiency and treatment in patients with schizophrenia. Data for this review were obtained from PubMed searches performed through February 2014 (see Table 2). Keyword searches included “vitamin supplementation schizophrenia” and “vitamin schizophrenia clinical trial.” Additionally a search was performed for each individual vitamin combined with “schizophrenia” (e.g. “vitamin A schizophrenia”). Additional articles were obtained through references listed in the initial article list generated. We included only articles that involved measurement of vitamin levels in cohorts of schizophrenia or human clinical trials addressing the treatment of the primary symptoms of schizophrenia (i.e. not for medication side effect treatment). We did not include individual case reports, The search was limited to articles published in English.

2) Brief Historical Perspective

While this review focuses primarily on thecurrent body of literature, it is worth putting it into some historical context. One of the earliest investigators to examine vitamin treatment for schizophrenia was Canadian psychiatrist Abraham Hoffer, who began his work in the 1950s and was a proponent of “orthomolecular psychiatry,”which included treating with high doses of vitamins and nutrients. He argued that standard treatment of schizophrenia plus treatment with vitamin B3 “doubled recovery rates of acute and subacute cases” [17], since vitamin B3 reduced the production of adrenochrome (an oxidized derivative of adrenaline that is neurotoxic) [18]. Hiscontemporary, Thomas Ban, argued against vitamin treatment for schizophrenia, citing no replicable evidence from placebo-controlled trials to support vitamin supplementation [19]. Thus, the benefits of vitamin treatment in schizophrenia have long been debated, and as discussed below, no clear-cut answer has yet emerged, although there has been progresstowards a more clear answer.

3) Vitamins

i. B Vitamins

B vitamins play an essential role in cellular metabolism, including transmethylation and oxidation/reduction reactions. Low blood levels of B vitamins are a relatively consistent finding in patients with schizophrenia. Ina cross-sectional study, Kemperman and colleagues reported lower levels of serum vitamin B12 in 61 Dutch patients with schizophrenia when compared to healthy controls; no difference was found in folate and vitamin B6 levels between the groups [3]. In an earlier cross-sectional study, alsoina Dutch population, Muntjeweff and colleaguesdemonstrated lower plasma folate levels in 35 schizophrenia patients compared to controlsafter adjusting for homocysteine levels, and an increased risk

of schizophrenia with decreasing plasma folate levels; they found no difference in vitamin B6 and vitamin B12 levels [4]. In another cross-sectional study among Greek inpatients, there was no difference in plasma folate and B12 levels between patients and controls [20]. However, among medicationnaïve first-episode outpatients with psychosis in India (with diagnosis of schizophrenia, schizoaffective disorder or schizophreniform after 6 months follow-up), Kale et alshowed lower plasma folate and B12 levels in patients versus controls[5], suggesting an effect independent of antipsychotic medication treatment. Goff and associates[6]also reported low folate levels in a cohort of 91 schizophrenia outpatients, and found a significant inverse relationship between folate level and negative symptom severity among non-smoking patients; further work in this group has specifically related a common, low-functioning variant in MTHFR, a key enzyme in the folate metabolic pathway, to risk for negative symptoms[21], related cognitive impairment[22], and reduced prefrontal activation during executive function[23, 24]. The same variant in MTHFR, known as 667C>T (rs1801133), has also been associated with increased schizophrenia risk in a large meta-analysis[25], although at this time it has yet to emerge as a significant risk factor in genome-wide studies.

Several recent B vitamin supplementation strategiesshow promise in schizophrenia. In a small double blind placebo-control study, Godfrey et al., showed symptom and social recovery in 17 schizophrenia patients with baseline low folate levels who received daily methylfolate supplementation (15 mg/day) for six months[26] in addition to standard pharmacologic treatment. In a more recent crossover study, Levine and colleagues demonstrated symptom improvement in 42 schizophrenic patients with elevated homocysteine levels, supplemented with folic acid(2 mg/day), vitamin B6 (25 mg/day) and vitamin B12 (400 mcg/day) [27] in addition to regular antipsychotic treatment. However, it is not evident from this study whether elevated homocysteine levels are required for the symptomatic benefits of treatment with folic acid, since all of the patients had hyperhomocysteinemia. In a small study of 28 patients on a stable dose of antipsychotic medication, Hill and colleagues found no difference in symptom response among patients who received folic acid (2 mg/day) versus placebo (both groups improved); however, among patients with at least one copy of the low functioning variant in the MTHFR gene (677T), negative symptoms improved more in the active treatment group than in the placebo group at trend level (p=.06)[28]. In one of the largest randomized multicenter control trials examining vitamin supplementation, Roffman et al. randomly assigned 140 patients with schizophrenia on a stable antipsychotic dose to either treatment for 16 weeks with folic acid (2 mg/day) and vitamin B12 (400 mcg/day) or placebo[29]. The folate+B12 group showed significant improvement in negative symptom severity, but only when genotype was considered. Specifically, treatment response was strongly influenced by a genetic variant in FOLH1 (rs202676), which facilitates the translocation of dietary folates across the intestinal lumen. While transport of supplemental (synthetic) folic acid does not require FOLH1, patients with the low-functioning variant had lower levels of blood folate (i.e., reflecting pre-trial dietary folate intake) at baseline. This may account for the diminished response to supplementation in this subset of patients, as it may have taken longer to achieve a therapeutic CNS folate level, and sustained folate exposure was necessary to achieve negative symptom reduction.

An important limitation of the cross-sectional studies described above is that nutrient deficiency may reflect a downstream consequence of symptoms (e.g., impaired motivation to eat a healthy diet), rather than a primary cause of pathophysiology. However, somewhat stronger evidence – albeit still correlational – comes from longitudinal studies of populations exposed to famine during neurodevelopment. Although its age of onset is not usually until the second or third decade of life, schizophrenia is widely posited to reflect a delayed consequence of altered neurodevelopment[30]. Local incidence of schizophrenia transiently doubled two decadesafterthe Dutch Hunger Winter of 1944-1945[31]and the Chinese famine in the late 1950s[32]. Among the birth cohort conceived while exposed to the peak of the Dutch famine, there was also an increase in neural tube defects[31]. Given that neural tube defects are strongly associated with prenatal folate deficiency[33], a parsimonious explanation for both diagnoses would be a perturbation in the folate metabolic pathway.

While a more thorough discussion of the mechanisms by which prenatal folate deficiency contribute to the development of schizophrenia is outside of the scope of this article, we emphasize three ideas proposed by Brown and Susser[34] who elaborate that folate deficiency: 1)interferes with DNA synthesis and repair, leading to an increase in de novo mutations; 2) interferes with DNA methylation and gene expression; and 3)limits the conversion of homocysteine to methionine, resulting in a buildup of homocysteine in the developing brain. Further, investigators in the Prenatal Determinants of Schizophrenia (PDS) study analyzed banked sera from a US cohort of mothers during pregnancy, finding that elevated third trimester homocysteine (which is inversely related to folate) was associated with a twofold increase in schizophrenia risk in offspring[35]. However, Brown and Susser also point out that elevated homocysteine levels may contribute to the development of schizophrenia through other mechanisms (dysfunction of NMDA receptor, placental vasculopathy leading to fetal hypoxia) than by disruption in folate metabolism[34].

ii. Vitamin D

Vitamin D is a critical regulator of calcium metabolism, and also plays roles in gene expression and immune function. Vitamin D deficiency has been implicated by several schizophrenia investigators, although conclusions are limited by small sample size and the lack of comparison to healthy individuals. Within a cross-sectional study of 102 psychiatric inpatients in New Zealand, of 19 patients who had severe vitamin D deficiency, 13 had schizophrenia (34% vs. 9.4% other psychiatric diagnoses)[7]. Vitamin D deficiency and associated psychosis has been noted in dark-skinned immigrant populations. In a retrospective chart review of 18first generation immigrants from Africa and Haitiwith acute psychosis, all patients had vitamin D levels in the insufficient range[36]; however many of the clinical descriptions of the episodes were not consistent with a schizophrenia diagnosis, and only seven of these patients went on to be diagnosed with schizophrenia. Similarly, in a cross-sectional study of Norwegian patients, vitamin D deficiency was present in 80% of the psychotic immigrant population with dark complexions. Among native-born Norwegians with psychosis, 43% had vitamin D deficiency and had lower serum vitamin D levels compared to reference sample [8]. In a cross-sectional study of 35 adolescent inpatients, 33.7% patients were vitamin D deficient; of those deficient 40% exhibited psychotic features

compared to 16% of patients who were not vitamin D deficient[9]. In a case-control study, Crews et. al found significantly lower levels of serum vitamin D among 69 first-episode psychosis inpatients compared to matched healthy controls[10] (OR of being vitamin D deficient was 2.99 in patients relative to controls). In another small study of first-episode patients, more severe negative symptoms and cognitive impairment were correlated with lower vitamin D levels. These patients had not received more than a total of four months of antipsychotic treatment[37]. Finally, in a recent meta-analysis, BelvederiMurri et al. found that patients with psychotic disorders (mainly schizophrenia) had consistently lower vitamin D levels compared to healthy controls[11]. The authors examined 7 studies overall for a total of 523 patients and 7545 controls. Of note there was heterogeneity of effect size, and most studies were case-control or cross-sectional. As with all observational studies, we emphasize that the results have to be taken with caution, given there may be many potential confounding variables that are present in patients with schizophrenia and also affect vitamin D levels such as insufficient nutrient intake or little sunlight exposure.

Vitamin D deficiency early in life may also contribute to schizophrenia risk. McGrath et al. examined a Danish cohort of over 400 patients with schizophrenia and carefully matched controls in which neonatal dried blood spots had been collected[38]. Among individuals in the lowest quintiles of neonatal vitamin D there was a two-fold elevated risk of schizophrenia compared to those in higher quintiles. Interestingly, those neonates with the highest vitamin D levels also had an increased risk of schizophrenia. In a birth cohort of over 2000 people in the UK, Sullivan et al. did not find an association between maternal vitamin D levels and risk of psychotic illness at age 18[39]. However, it is likely that some individuals at this age have not yet experienced onset of the illness; it will be important to follow the cohort over the subsequent years.

Intervention studies have had mixed results. In a Finnish birth cohort of over 9000 people, vitamin D supplementation with at least 2000 IU/day in males in the first year of life reduced the risk of schizophrenia by 77% (RR .23) compared to those receiving less than 2000 IU/day; these findings did not hold true in females[40]. The authors hypothesize that early vitamin D supplementation is crucial for pro-differentiating signals in the developing brain, and potentially also for normal brain recovery after insult. In the study of immigrant population discussed above[36], Dealberto provided daily vitamin D supplementation of 1000 IU/dayin addition to ongoing antipsychotic treatment, and concluded there were no changes in psychiatric symptoms after vitamin supplementation.

iii. VitaminsC and E

Vitamins C and E are antioxidants that protect against cellular damage due to inflammation or highly reactive oxygen-containing molecules. In a small cross-sectional study among 20 inpatients with schizophrenia and 15 controls, patients had lower fasting vitamin C levels and lower urinary vitamin C excretion after 1.0 g oral vitamin C load[12].The investigators then examined plasma vitamin C levels in a separate group of schizophrenia patients (n=15) vs controls after vitamin C supplementation (70 mg/day for four weeks in addition to antipsychotic treatment); the plasma vitamin C levels were similar in both groups, but urinary excretion was lower among patient sample, suggesting an impairment in vitamin C

metabolism. In another small study among 14 inpatients with schizophrenia in India, plasma vitamin E and C levels were significantly lower when compared to control subjects[13].

One study reported a decrease in the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome Scale (PANSS) scores among patients on antipsychotic treatment after supplementation with vitamin C, vitamin E, and omega-3 fatty acids[41]; however given the combination treatment it is difficult to conclude what effects are due to vitamin supplementation alone. A randomized placebo-control study by Bentsen et al.[42] also supplemented vitamin C (364 mg/day) and vitamin E (1000 mg/day) to patients with schizophrenia on antipsychotic medication; among those patients with low red blood cell polyunsaturated fatty acids (PUFAs), the vitamin supplementation actuallyimpaired recovery from acute psychosis compared to placebo. The authors hypothesize that vitamin E at a high enough dose can act as a pro-oxidant if there is inadequate antioxidant activity, thus increasing oxidative stress; it could also inhibit the beneficial γ- and δ tocopherols.They posit that vitamin C may counteract some detrimental effects of vitamin E. Beauclair et al. performed an 8-week open label trial of progressively increasing doses of vitamin C (max dose 8 g/day) among 13 patients with residual symptoms of schizophrenia despite antipsychotic treatment[43]. Ten of the thirteen patients showed improvement on CGI scores and plasma vitamin C levels increased over the eight weeks of treatment. The authors report that most of the symptomatic improvement occurred in the positive symptom domain. Notably, there was no control group in this study, and the weekly study visits with medical staff may also contribute to improvement in psychotic symptoms.

In a prospective double-blind placebo-controlled study of forty outpatients in India, Dakhale et al.[44]examined vitamin C supplementation (500 mg/day) for eight weeks in patients with schizophrenia taking second generation antipsychotics. The authors found that in the vitamin C group, there was a reduction in serum malondiahldehyde (MDA)levels (a measure of antioxidants), an increase in plasma ascorbic acid levels, and a decrease in BPRS scores. Of note, similar trends were also present in the placebo group. When the two groups were compared, the vitamin C group had a significantly greater decrease in MDA and BPRS scores and significant increase in ascorbic acid levels. It is a not clear whether there is some interaction between second generation antipsychotic medications and vitamin C, or if vitamin C acts through another mechanism. The authors propose that vitamin C may inhibit peroxidation of phospholipids and act as a free radical scavenger. While the overall study is well designed, the results must be taken cautiously given the small number of patients.

iv. Vitamin A

Vitamin A is converted to retinoic acid, which plays critical role in neuronal differentiation and migration; a disruption in the process could contribute to the underlying pathophysiology of schizophrenia. In the PDS study (detailed above)[35], investigators found that low maternal vitamin A levels during the second trimester of pregnancy are associated with a three-fold increase in schizophrenia spectrum disorders; no association was found during the third trimester (analysis not done on first trimester samples)[45]. The study finding is consistent with the hypothesis that prenatal vitamin deficiency plays a role in the development of schizophrenia. Further, the finding of elevated homocysteine levels

(associated with low folate levels) in this cohort was present only in the third trimester, suggesting specific vitamin levelsare crucial at different stages of development for the prevention of schizophrenia.

4.) Conclusions and Future Directions

Vitamin supplementation, particularly with folic acid, vitamin B12 and vitamin D, may play an important role in the treatment of schizophrenia within certain subgroups. In those patients who are vitamin D deficient (darker skin, living at latitude with less sunlight)supplementation with vitamin D may be protective among those vulnerable to psychosis.. Among those patients with specific genetic variants in the folate metabolic pathway, supplementation with both folate and vitamin B12 can be beneficial, especially in improving negative symptoms. While there is less compelling evidence for treatment with other vitamins, and even some evidence to the contrary, further studies are necessary to make treatment decisions.

A number of questions remain. For example, should it be common practice to supplement patients' antipsychotic medications with a cocktail of vitamins? For how long should treatment be continued? There is a clear need for larger, randomized control trials examining vitamin treatment, in particular in relation to dosing, genotype, and specific types of symptoms (e.g. negative symptoms or cognitive symptoms), and in combination with specific antipsychotic medications. It would also be informative to examine the incidence of schizophrenia in underdeveloped countries with poor prenatal care and malnutrition; blood samples and prenatal serum could help determine levels of deficiency, and ideally response to supplementation. Further, it may be valuable to examine patterns of schizophrenia incidence and severity in countries that have recently adopted mandatory folic acid fortification of grain products. Finally, while vitamins generally are generally considered safe and well tolerated, several investigators have linked high doses of vitamin intake to cancer risk[46] although this has been disputed in other meta-analyses[47]. Additionally, it must be noted that there is always the possibility of a publication bias given the lack of negative studies published. Although recent studies demonstrate promise for vitamin supplementation in schizophrenia, as with all interventions, patients and their providers will ultimately need to consider both the risk and benefit sides of the equation prior to initiating treatment.

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Key Points

- Patients with schizophrenia have lower serum concentrations of certain vitamins compared to healthy individuals.
- Vitamin supplementation may play arole in the treatment of schizophrenia within certain subgroups of patients.
- Further studies, including larger, randomized control trials are needed to fully elucidate the role of vitamin supplementation in the treatment of schizophrenia.

Table 1

Vitamins

Vitamin	Source	Function	Deficiencies	Daily recommended values (based on 2000 calorie diet)
Water Soluble				
Thiamine (Vitamin B1)	Cereals, bread, grains, legumes, seeds	Coenzyme in formation/ degradation of a-ketols and oxidative decarboxylation of a keto acids	Beriberi; Wernicke-Korsakoff syndrome	1.5 mg
Riboflavin (Vitamin B2)	Dairy, cereals, legumes	Coenzyme in oxidation/reduction reactions	Dermatitis, cheilosis, glossitis	1.7 mg
Niacin (Vitamin B3)	Meats, cereals, whole grains	Coenzyme in oxidation/reduction reactions	Pellagra	20 mg
Pyridoxine (Vitamin B6)	Chicken, fish, pork, eggs, starchy vegetables	Acts as coenzyme for amino acid reactions	Microcytic anemia, dermatitis with cheilosis and glossitis	2 mg
Folate (Vitamin B9)	Liver, leafy vegetables; fortified grain products	Key in one-carbon metabolism	Megaloblastic anemia; neural tube defects	400 μg
Cobalamin (Vitamin B12)	Animal products (meat, dairy)	Key for remethylation of homocysteine to methionine; isomerization to form succinyl coA; DNA synthesis	Megaloblastic anemia; pernicious anemia; neuropsychiatric symptoms	6 μg
Ascorbic Acid (Vitamin C)	Citrus fruits, potatoes, spinach	Reducing agent in hydroxylation reactions; antioxidant	Scurvy (defective collagen)	60 mg
Biotin	Liver, egg yolk	Coenzyme in carboxylation reactions	Rare	300 μg
Pantothenic Acid	Eggs, liver, yeast	Part of CoA, transferring acyl groups	Unknown	10 mg
Fat Soluble				
Vitamin A	Liver, dairy, kidney, green vegetables	Regulates RNA synthesis; need for visual cycle, reproduction (spermatogenesis), growth, differentiation of epithelial cells	Xerophtalmia (dryness of conjunctiva, cornea →blindness); infertility; growth abnormality	5,000 IU*
Vitamin D	Fish, liver, egg yolk, fortified milk	Regulates gene expression; regulates calcium/phosphorus	Rickets/Osteomalacia (bone demineralization in children/adults)	400 IU
Vitamin E	Vegetable oils, liver, eggs	Antioxidant	Mostly in premature infants; RBC membrane fragility	30 IU
Vitamin K	Greens, egg yolk, liver	Coenzyme in post-translational modification of clotting factors	Rare (hypoprothrombinemia); supplemented in newborns	80 μg

*IU = International units

Table 2

Vitamin studies in schizophrenia

Publication	Study Design	Sample Characteristics	Measurement/ Intervention	Key Findings	Comments
B vitamins					
Kepmerman et al., 2006 [3]	Cross-sectional	61 Dutch schizophrenia patients identified by chart review, compared to age and sex matched data from Dutch National Food Consumption Survey	Measured serum vitamin B6, folate and B12 and essential fatty acids; 3 pts with hyperhomocysteinemia were given B vitamin supplementation	Patients had lower vitamin B12 levels and higher homocysteine levels compared to controls; no differences in folate and B6 in patients compared to controls	Small sample size, did not address vitamin levels in relation to symptoms, no strict exclusion criteria
Muntjeweff et al., 2003 [4]	Cross-sectional	35 Dutch outpatients with schizophrenia, 104 controls	Measured plasma and red blood cell (RBC) folate levels and plasma vitamin B6, B12, homocysteine levels	Patients had 1) lower plasma and higher RBC folate levels after adjusting for homocysteine; 2) there was increased risk of schizophrenia with decreasing plasma folate. No difference between groups in serum vitamin B6 and B12 levels	Small sample size, homogenous population
Haidemenos et al., 2007 [20]	Cross-sectional	97 Greek inpatients with schizophrenia, 103 controls	Measured plasma folate, B12, homocysteine levels	No difference in folate and B12 levels between groups; patients had elevated homocysteine levels	Did not address potential confounding factors, control group not age and sex matched
Kale et al., 2010 [5]	Cross-sectional, subjects compared to healthy controls	31 medication naïve first-episode outpatients with psychosis in India, 48 healthy controls	Measured plasma folate, B12, homocysteine, and cortisol levels	Lower plasma folate and B12 levels in patients vs. controls, (effect is independent of treatment with antipsychotics); association with psychiatric symptoms	Small sample size
Goff et al., 2004 [6]	Cross-sectional	91 schizophrenia outpatients, compared to representative sample from Framingham Offspring Study	Measured serum folate, B12, homocysteine levels, measured clinical symptoms	Lower folate levels in schizophrenia patients compared to controls, inverse relationship between folate level and negative symptom severity	Inverse correlation between negative symptom severity and folate levels was significant in nonsmokers but not smokers (smoking may lower folate levels and conceal the relationship)
Roffman et al., 2008 [21]	Cross-sectional	200 outpatients with schizophrenia	Obtained MTHFR genotype, previously	Serum folate levels did not differ between genotype;	Suggest lower serum folate levels among

Publication	Study Design	Sample Characteristics	Measurement/ Intervention	Key Findings	Comments
			measured serum folate and homocysteine levels from 85 of the patients	an increase in the low functioning MTHFR (677T) load conferred risk for negative symptoms	T/T carriers worsen negative symptoms, although small sample size
Roffman et al., 2008 [22]	Cross-sectional	185 outpatients with schizophrenia	Obtained MTHFR and COMT genotype, measured neurocognitive performance	Patients homozygous for hyperfunctional COMT allele and carrying a low functioning MTHFR allele showed increase in perseverative errors	Population overlapped with Roffman et al. 2008a study
Roffman et al., 2008[23]	Cross-sectional	79 outpatients with schizophrenia, 75 matched healthy controls	Obtained MTHFR and COMT genotype, subjects performed cognitive task associated with DLPFC activation while undergoing fMRI	Low functioning MTHFR variant was associated with decreased working memory load dependent activation DLPFC; MTHFR genotype effects stronger in patients than controls	Mult-site cohort with different scanners
Roffman et al., 2011 [24]	Cross-sectional	31 outpatients with schizophrenia, 25 matched healthy controls	MTHFR genotype, subjects performed antisaccade task while undergoing fMRI	Low functioning MTHFR genotype influenced error-related activation in dorsal anterior cingulate cortex (dACC) in both patients and controls	Amount of dACC activation is predicted by allele load
Godfrey et al., 1990 [26]	Double blind placebo-controlled	123 patients with major depression or schizophrenia, matched healthy controls	Daily 15 mg methylfolate supplementation for 6 months	Symptom and social recovery in 17 schizophrenia patients with low folate levels treated with methlyfolate	Small sample number, all patients had low folate levels at baseline
Levine et al., 2006 [27]	Double blind placebo-controlled crossover	42 inpatients with schizophrenia and elevated plasma homocysteine completed study	Daily administration of 2 mg folate, 25 mg pyridoxine, 400 micrograms for 3 months, then cross over to placebo or vice versa; clinical rating scales performed	Symptom improvement and neuropsychological testing improvement in active treatment group	All patients had elevated homocysteine and lower serum folate at baseline
Hill et al., 2011 [28]	Double blind placebo-controlled	28 outpatients with schizophrenia	Daily administration of folate 1 mg for 3 months, MTHFR genotype obtained, assessed psychopathology, global functioning, quality of life at 4,8,12 weeks; measured serum and RBC folate, serum B12	No effect of folate supplementation on symptom response; subjects with at least one copy of the lower functioning MTHFR allele had more negative symptom improvement in the treatment group vs placebo group at trend level	Small sample size (low power), only one patient was homozygous and for T allele; patients were not folate deficient

Publication	Study Design	Sample Characteristics	Measurement/ Intervention	Key Findings	Comments
Roffman et al., 2013 [29]	Parallel-group, double blind placebo-controlled	140 outpatients with schizophrenia, randomly assigned to group	Treatment group received folate 2 mg/day plus vitamin B12 400 mcg day for 16 weeks, measured serum folate, B12, homocysteine, RBC folate, clinical rating scales performed, genotype obtained for genes regulating folate metabolism	Folate+B12 group had improvement in negative symptom severity vs. control when genotype considered (low functioning FOLH1 variant had strongest effect)	Negative symptom improvement was significant but small
Vitamin D					
Menkes et al., 2012 [7]	Cross-sectional	102 psychiatric inpatients in New Zealand	Measured serum vitamin D levels	13 of 19 patients with severe vitamin D deficiency had schizophrenia	Small sample size, patients of Maori background were over-represented
Dealberto et al., 2013 [36]	Retrospective chart review followed by intervention	18 first generation immigrants from Africa and Haiti who were inpatients and psychotic	Measured serum vitamin D levels, then supplemented with 1000 IU/day	All patients had vitamin D levels in insufficient range	Small sample number, very specific population, not all carried schizophrenia diagnosis, no matched control group, unclear duration of vitamin D supplementation
Berg et al., 2010 [8]	Cross-sectional	67 immigrants living in Norway and 66 Norwegians – both groups had diagnosis of psychotic disorder; within group comparison and comparison to sample from population-based health study	Examined serum vitamin D levels	Vitamin D deficiency present in 80% of psychotic immigrant group with dark complexions; 43% of Norwegians with psychosis had vitamin D deficiency and lower serum vitamin D than Norwegians in reference group	
Gracious et al., 2012 [9]	Cross-sectional	35 adolescent inpatients	Measured serum vitamin D (25-hydroxyvitamin D)	33.7 % patients were vitamin D deficient; of those 40% displayed psychotic symptoms vs. 16% who were not vitamin D deficient	Adolescent population
Crews et al., 2013 [10]	Case-control	69 inpatients with first-episode psychosis, matched healthy controls	Measured serum vitamin D (25-hydroxyvitamin D)	Vitamin D levels significantly lower in psychotic patients (36%) compared to controls (16%)	Not all patients with confirmed diagnosis of schizophrenia
Graham et al., 2014 [37]	Cross-sectional	20 first episode schizophrenia outpatients, 20 healthy controls	Measured serum vitamin D levels, clinical symptom evaluation	Association between vitamin D insufficiency and more severe	Small sample size

Publication	Study Design	Sample Characteristics	Measurement/ Intervention	Key Findings	Comments
				negative symptoms and cognitive deficits	
Belvederi Murri et al., 2013 [11]	Meta-analysis	7 studies; 523 patients with schizophrenia, 7545 controls	Examined serum vitamin D levels	Patients with psychotic disorders (mostly schizophrenia) had consistently lower levels of serum vitamin D	Heterogeneity of effect size, most were observational studies
McGrath et al., 2010 [38]	Case-control	424 Danish patients with schizophrenia, 424 controls from Danish national health registers and neonatal biobank	Examined vitamin D (25 hydroxyvitamin D3) levels in neontatal dried blood samples	Those in lower 3 quintiles of vitamin D had 2-fold increased risk of schizophrenia; highest quintile also had increased schizophrenia risk	Unclear why hypervitaminosis D is correlated with increased schizophrenia risk
Sullivan et al., 2013 [39]	Prospective cohort	2047 maternal-offspring pairs in UK	Examined maternal serum vitamin D levels and offspring that developed psychosis	No association between maternal vitamin D levels and risk of psychotic illness at age 18	Likely some offspring have not yet experienced onset of psychotic symptoms at age of evaluation (18)
McGrath et al., 2004 [40]	Prospective cohort	Finnish birth cohort of >9000 people	Examined vitamin D supplementation in the first year of life; looked at incidence of schizophrenia and non-psychotic disorders at age 31	Among males, either regular or irregular vitamin D supplementation reduced schizophrenia risk; supplementation with at least 2000IU/day reduced risk by 77%; no reduction in risk among females	Wide confidence intervals; women may have later onset illness (i.e. after age 31)
Brown et. al, 2007 [35]	Nested case-control	Population-based birth cohort; 63 schizophrenia patients and 122 controls	Measured serum homocysteine levels from banked sera from cohort of mothers	Elevated 3rd trimester homocysteine levels (inversely related to folate) associated with twofold increase risk of schizophrenia in offspring	Elevated homocysteine levels can contribute to schizophrenia development through other mechanisms than disruption in folate metabolism
Vitamins C and E					
Suboticanec et al., 1986 [12]	Cross-sectional, then interventional	Group 1: 20 inpatients with schizophrenia, 15 controls Group 2: 15 inpatients with schizophrenia and 15 controls	Examined serum and urinary vitamin C levels; then supplemented with vitamin C (70 mg/day for 4 weeks) in a new group of cases/controls	Patients had lower serum and urinary vitamin C excretion after oral vitamin C load; after supplementation for 4 weeks no difference in vitamin C serum levels between groups, but urinary excretion lower in	Suggest impairment in vitamin C metabolism in patients with schizophrenia

Publication	Study Design	Sample Characteristics	Measurement/ Intervention	Key Findings	Comments
				patients	
D'Souza et al., 2003 [13]	Cross-sectional	14 inpatients with schizophrenia, 18 controls	Measured plasma vitamin E and C levels	Vitamin E and C levels were significantly lower in patients vs controls	Small sample size
Arvindakshan et al., 2003 [41]	Case-control	28 outpatients with schizophrenia, 45 healthy controls	Supplementation with vitamin e and C, omega-3 fatty acids, measured clinical symptoms using scales	Improvement in symptomatology after supplementation	Unclear effects of vitamin supplementation alone due to combination treatment, small sample size
Beauclair et al., 1987 [43]	Open-label trial	13 outpatients with schizophrenia with residual symptoms	Measured plasma vitamin C levels, given increasing doses of vitamin C (1 g – 8 g daily) over 8 weeks	10 of 13 patients showed clinical improvement after supplementation, plasma vitamin C levels increased	No control group, small sample size
Dakhale et al., 2005 [44]	Double-blind placebo-controlled	40 outpatients with schizophrenia in India taking antipsychotic medications	Measured serum vitamin C, malondialdehyde (MDA), supplemented with vitamin C (500 mg/day) for 8 weeks, measured clinical symptoms	At baseline, increased serum MDA and lower vitamin C among patients; after treatment reduction in MDA and increase in vitamin C; decrease in symptoms (all significant changes compared to placebo group)	Potential interaction between second generation antipsychotics and vitamin C
Bentsen et al., 2013 [42]	Randomized double-blind placebo controlled	99 patients with schizophrenia or schizoaffective disorder within four weeks of hospitalization	Treated with omega-3 fatty acid or vitamin E 364 mg/day + vitamin C 1000 mg/day or placebo for 4 months, measured polyunsaturated fatty acids (PUFAs), clinical symptoms measured	Treatment with vitamins C and E impaired course of improvement of psychotic symptoms in patients with low red blood cell PUFAs	Study was done in acute-subacute patients; difficult to generalize to more stabilized patients
Bao et al., 2012 [45]	Nested case-control	Population-based birth cohort (Prenatal Determinants of Schizophrenia study); 55 schizophrenia patients and 106 controls	Measured serum vitamin A levels from banked sera from cohort of mothers	Low 2nd trimester vitamin A levels associated with three fold increase in schizophrenia spectrum illnesses; no association found during 3rd trimester	Analysis not done on first-trimester samples

MTHFR = Methylenetetrahydrofolate reductase, COMT = Catechol-o-methyltranferase, DLPFC = Dorsolateral prefrontal cortex, FOLH1 = Folate hydrolase 1, fMRI = functional magnetic resonance imaging