Investigating the Association of Vitamin B_{12} and Folate with Neuropsychiatric Diseases with Special Reference to Schizophrenia: Integrated evidence syntheses and policy evaluation

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Acknowledgements

If I were to plot a trajectory of human growth, I would draw a non-linear, stepwise function where a plateau meets a milestone and enters a new height before another plateau ensues, achieves critical mass and reaches new ground, and so on and so forth. Some plateaus stretch long, others barely visible; some milestones are gloriously high, others almost negligible. But at the end of the entire process, the output is fundamentally different from the initial input.

My PhD journey somewhat resembled this trajectory. There were plateaus that seemed endless – many moments of self-doubt, distractions, and fatigue; and there were breakthroughs that caught me off guard and taught me the pure joy of scholarship. Over and over again, this process brought me face-to-face with myself: what I wanted to, could, and could not do. With this, I not only grew as a researcher, but as a human being.

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I lift up my eyes to the hills, where does my help come from?
My help comes from the Lord, the Maker of heaven and earth. (Psalm 121:1)

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Overall Abstract

Background

For their integral roles in DNA/ RNA synthesis, homocysteine metabolism, and numerous methylation reactions, folate and vitamin B_{12} are hypothesized to be associated with the risk of neuropsychiatric diseases. However, compared to other health outcomes, these vitamins have been less studied in the context of schizophrenia.

Objectives

We set out to (1) identify health effects of vitamin B_{12}, (2) investigate an association between folate and vitamin B_{12} and schizophrenia, (3) examine a causal nature of the association, and (4) assess the impact of relevant public health policies on schizophrenia.

Methods

Umbrella reviews were conducted to address the objectives (1) and (2). For objective (3), we conducted a systematic review and meta-analysis of genetic association studies examining the relationship between gene polymorphisms involved in folate metabolism and schizophrenia. For objective (4), we evaluated the impact of folic acid fortification on changes in schizophrenia rates over the past 30 years in 194 jurisdictions.

Results

We found a suggestive level of evidence on the relationship between vitamin B_{12} status and neurological outcomes. For schizophrenia, higher plasma/serum folate concentrations or the variant *MTHFR* 677TT genotype were each associated with decreased and increased risk, respectively. Our meta-analysis further identified significant roles of the *MTHFR* C677T and A1298C polymorphisms at an aggregate level. Mandatory folic acid fortification and the duration of fortification policies were independently associated with declines in the prevalence rates of schizophrenia in individuals aged 15-39 years.

Conclusion

The current evidence suggests that the folate and vitamin B_{12} inadequacy is associated with the risk of schizophrenia and that this relationship may be causal. Mandatory folic acid fortification may be a beneficial strategy for lowering prevalence of schizophrenia among individuals at ages of typical onset. More research on combined or interactive effects of these vitamins or relevant genotypes will advance our current knowledge.

Keywords: folate, vitamin B_{12}, neuropsychiatric disease, schizophrenia, fortification, public health policy

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List of Abbreviations

5-MTHF	5- Methyltetrahydrofolate
BDNF	Brain derived neurotrophic factor
BH4	Tetrahydrobiopterin
CBS	Cystathionine beta synthase
CNV	Copy number variant
COMT	Catechol-o-methyltransferase
DHFR	Dihydrofolate reductase
DSM	Diagnostic and Statistical Manual of Mental Disorders
EWAS	Epigenome wide association studies
FEP	First episode psychosis
FKBP5	FK506 binding protein
FOLH1	Folate hydrolase 1
GBD	Global Burden of Disease studies
GFDx	Global Fortification Data Exchange
GINA	WHO Global Database on the Implementation of Nutrition Action
GWAS	Genome wide association studies
HoloTC	Holotranscobalamin
ICD	International Classification of Diseases
MMA	Methylmalonic acid
MR	Mendelian randomization
MS	Methionine synthase
MTHFD1	Methylenetetrahydrofolate dehydrogenase-1
MTHFR	Methylenetetrahydrofolate reductase
MTR	Methionine synthase
MTRR	Methionine synthase reductase
NTD	Neural tube defect
PANSS	Positive and Negative Syndrome Scale
RDoC	Research domain criteria
SAM	S-adenosyl methionine
SDI	Sociodemographic index
SNP	Single nucleotide polymorphism
WHO	World Health Organization

Chapter 1: Introduction

1.1 Neuropsychiatric Disorders

1.1.1 Overview

Neuropsychiatric disorders broadly refer to "*disorders of affect, cognition, and behavior that arise from overt disorder in cerebral function or from indirect effects of extracerebral disease*"[1]. Neuropsychiatry as a discipline marks a convergence in the previous century of two fields of medicine that had been distinctly separated for a long time: neurology, which studies biological and structural aspects of the brain, and psychiatry, which focuses on mental, emotional, behavioral illnesses[2]. This integration was largely motivated by clinicians in the segmented fields facing a challenge of connecting functions of the brain with emotional and behavioral expressions[2] or encountering individuals simultaneously exhibiting both neurological (i.e., motor) and psychiatric symptoms (i.e., cognitive)[3]. Shared clinical symptoms include cognitive impairments[4,5] and behavioral symptoms or mood dysregulation[6–8].

Development of neuropsychiatry as an integrated discipline was accelerated by recent advances in neuroimaging technologies and understanding of neurotransmitters, molecular biology, and genetics[2]. Some neurological and psychiatric disorders are understood to have shared neuronal pathways involving neurotransmitters[9,10]. Dopaminergic system has been associated with Parkinson's disease, Huntington's disease, and schizophrenia[11]; GABAergic system is reported to be involved in the development of epilepsy, autism disorder, and schizophrenia[11]; and serotonin has been linked to migraine[12], depression, and anxiety[13]. Recent research also reports on shared genetic markers between neurological and psychiatric disorders: *L3MBTL2, CACNB2, SLC9B1* have been associated with migraine, depression, and schizophrenia[14], and *CLCN3, SLC39A8, NT5C2, RERE, ZDHHC2* with schizophrenia and Parkinson's disease[15].

Understanding the complexity and connectedness of neurological and psychiatric disorders is important for epidemiological investigation of risk factors and providing

interdisciplinary care, particularly for severe and chronic conditions such as schizophrenia.

1.1.2 Psychosis

1.1.2.1 Current framework of definitions

Psychosis is a clinical syndrome characterized by core symptomatic features, such as delusions, hallucinations, and disordered thinking[16], with its group of typical symptoms[16,17] often overlapping[18–21]. For example, schizophrenia, which is largely characterized by psychosis[22], is considered a disorder with symptom clusters, i.e., positive, negative, and cognitive symptoms[23]. Positive symptoms of psychosis include delusions, hallucinations; negative symptoms include amotivation, social withdrawal; and cognitive symptoms include deficits in memory, executive function, and mental speed[19,23]. Over half of individuals with bipolar disorder also experience psychotic symptoms in their lifetime[24,25], such as Schneiderian symptoms (i.e., delusions of thought withdrawal or thought broadcast, hallucinations)[20].

Due in part to its complexity, variability in trajectory, and unclear etiology[23,26–28], psychosis is not defined in the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM): only psychotic features are described in DSM-5.[16] The most recent versions of ICD and DSM – ICD-11 (2019)[29] and DSM-5 (2013)[17] list multiple disorders that include psychosis across different categories. For example, DSM-5 lists 13 disorder classes related to psychosis and schizophrenia as well as two mood disorder classes (bipolar disorder and major depressive disorder) with subtypes of accompanying psychotic features[16,17] (see Appendix 1-A). Further, some neurological conditions such as Alzheimer's disease, diffuse Lewy body disease, epilepsy, and Fahr disease are also reported to be associated with psychosis[22].

The ICD and DSM are established and commonly-used frameworks for classifying disorders for clinical diagnosis and management based on presenting symptoms or self-reported experiences[30,31] rather than on precise understanding of etiology or biological

mechanisms[31]. As such, these frameworks are intended to define and categorize conditions as distinct, highly specific, and mutually exclusive disorders in hierarchical branches[31].

While there are similarities between the two classification systems, enhanced by recent harmonization efforts[30], DSM-5 and ICD-11 have differences in their diagnostic criteria (Appendix 1-A). In schizophrenia, for example, the minimum duration of symptoms required is one month in ICD-11 as opposed to six months in DSM-5[30]. The ICD approach is intended to enable coding of earlier detection and treatment[32]. Instead, the DSM-5 includes schizophreniform disorder, which has symptoms lasting less than six months and may include schizophrenia-like disorders. The two systems also differ in their approach to patient's experience of influence or passivity (actions or feelings being imposed by an external entity) as a distinct symptom from delusion[30]. Furthermore, whereas ICD-11 uses six domains of symptoms (positive symptoms, negative symptoms, depressive mood symptoms, manic mood symptoms, psychomotor symptoms, and cognitive symptoms) and a 4-point scale (none, mild, moderate, severe), DSM-5 uses eight domains (hallucinations, delusions, disorganized speech, negative symptoms, impaired cognition, abnormal psychomotor behavior, depression, and mania) and a 5-point scale (none, equivocal, mild, moderate, severe)[30].

The differences between the two classifications are more substantial in the diagnosis of schizoaffective disorder. ICD-11 requires the criteria for schizophrenia to be met in addition to the criteria for a depressive manic or mixed episode (moderate or severe) lasting for one or more months. More importantly, ICD-11 requires onsets of psychotic and mood symptoms to be concurrent or almost concurrent[30]. DSM-5, on the other hand, requires an uninterrupted period of concurrent presentation of major depressive or manic episode along with schizophrenia; at least a two-week period of delusions or hallucinations in the absence of major depressive or manic episode at any point during illness; and major depressive or manic episode for the majority of the lifetime illness duration[30]. These differences and overlap between schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder with psychotic features, and major depressive disorder with psychotic features may result in different diagnoses of cases

dependent on the timing of clinical consultation, timing and duration of certain symptoms, and the classification system used.

Under the existing diagnostic classification systems, distinction is made between affective psychosis (psychosis with mood disturbances as seen in bipolar disorder with psychotic features, major depression with psychotic features, and schizoaffective disorder) and non-affective psychosis (psychosis without mood episodes as seen in schizophrenia and schizophreniform disorder)[33]. Since the early 2000s, a dimensional, spectrum-based approach to evaluating psychosis has emerged[21,34,35]. In this approach, it is proposed that prototypic forms of affective and non-affective psychoses would be located at each extreme of a continuum[36]; or extend from bipolar disorder to schizoaffective disorder to schizophrenia ("schizo-bipolar scale")[21,37]. Indeed, a majority of patients with psychosis display mixed forms[20,34,38] and there exists substantial variability within diagnoses and overlaps between diagnoses[18–21].

1.1.2.2 Research Domain (RDoC) approach

The ICD and DSM classifications are based on symptoms rather than etiology[31]. They do not include consideration of how brain circuits and mechanisms – and potentially genes and epigenetic modifications – are implicated in multiple mental disorders. In an effort to develop an integrated understanding of interactions between neurobiological and environmental factors across multiple neuropsychiatric disorders, the US National Institute of Mental Health (NIMH) initiated a Research Domain (RDoC) project in 2009[39]. RDoC framework is described as a "five-by-seven matrix"[31], where five functional domains (negative valence, positive valence, cognitive systems, systems for social process, and arousal/ modulatory systems), each consisting of five or six constructs, are examined across seven units of analysis (genes, molecules, cells, circuits, physiology, behavior, and self-reports) (Appendix 1-B). The RDoC initiative is more oriented towards promoting research into etiology of a spectrum of neuropsychiatric disorders than facilitating clinical decisions[31,40].

With regard to schizophrenia, several studies have used the RDoC approach to examine the mechanisms behind hallucination[41], auditory hallucination and inhibitory control [42], psychomotor disturbance[43], and working memory[44]. As more research is conducted in the future using the RDoC framework, more light is expected to be shed on the etiology and mechanism of many mental disorders with shared symptoms and features. This, in turn, may stimulate research not only on pharmacological treatment options but on modifiable risk factors for broader public health interventions, which have largely been absent for severe neuropsychiatric disorders such as schizophrenia.

1.1.3 Schizophrenia

1.1.3.1 Overview

Schizophrenia is a complex, severe neuropsychiatric disorder with a lifetime prevalence of approximately 1%[45 46]. Typical onset occurs in adolescence or early adulthood[23,28,47]. Patients with schizophrenia have 15 years shorter average lifespan compared to the general population[23,47] due to high rates of clinically important comorbidities, such as type 2 diabetes, obesity, cardiovascular diseases[48,49] and suicide in the early phase of illness[48,50]. The lifetime risk of suicide among individuals with schizophrenia is reported to be 15-25 times higher than that in the general population[51]. Not surprisingly, schizophrenia is one of the top 20 leading contributors to years lived with disability[52].

The World Health Organization estimated that globally there were 24 million people (3.3 per 1000) living with schizophrenia in 2019[53], an increase from 20.9 million estimated in 2016[47]. The overall societal cost (direct and indirect healthcare costs and productivity losses) was estimated at CAD 6.9 billion in Canada[51], GBP 6.1 billion (CAD 10.7 billion) in the UK[54], and USD 62.7 billion (CAD 86 billion) in the US[55]. Per-patient annual cost varies substantially by country, ranging from USD 94,587 in Norway to USD 5,818 in Thailand[56]. It should be noted, however, that most data on the prevalence and disease burden of schizophrenia are available from high income countries[57] and thus the published estimates may not be representative for middle- or low-income countries.

Although pharmacological treatments are widely available, their efficacy appears to be limited in treating negative symptoms[58–61] or preventing long-term functional disabilities[58,62,63]. Antipsychotics, the most common pharmacological treatment, also cause disturbing side effects[58,60], resulting in discontinuation and consequent relapse. Many patients with schizophrenia experience a cycle of remissions and relapses[64], with 30-80% of patients on antipsychotic medications reported to relapse early in their treatment[58,60].

1.1.3.2 Endophenotypes of schizophrenia

Schizophrenia is a heterogeneous condition with a wide range of cognitive and behavioral symptoms variably manifesting over the course of the illness. In an effort to better understand the neurobiological underpinning of schizophrenia other than genetic variants, "endophenotypes" have been developed in 2003[65] and substantial research have been undertaken. Endophenotypes are quantitative biological markers that are associated with schizophrenia, heritable, present irrespective of the illness phase, and present in unaffected relatives of patients at a higher degree compared to the general population[66]. Because endophenotypes are a measure of underlying brain functions rather than observed symptoms, they are considered more stable markers of schizophrenia[67] compared to now discontinued subtyping of schizophrenia (i.e., paranoid, hebephrenic, undifferentiated, residual, and catatonic as per the DSM-4).

Identification of endophenotypes in schizophrenia is evolving. As of present, several endophenotypes of schizophrenia have been identified in the cognitive and neurophysiological domains; specifically, deficits in attention, working memory, verbal declarative memory, pre-pulse inhibition, oculomotor anti-saccade, and mismatch negativity[66,67].

1.1.3.3 Genetic risk factors for schizophrenia

Experimental, observational, and genetic research has identified multiple risk factors associated with schizophrenia[23,28,68]; however, many of these are yet to be replicated. Schizophrenia has been reported to have high heritability[18,23,68–70], with twin and family

studies reporting heritability ranging from 64 to 81%[71,72]. Several genome-wide association studies (GWAS) have identified weak (OR 1.1-1.5) associations with common variants (single nucleotide polymorphisms: SNPs). These variants include SNPs of the gene encoding the D2 dopamine receptor (*DRD2*); SNPs in genes involved in glutamatergic neurotransmission and synaptic plasticity (*GRIN2A, SRR, GRIA1*); and SNPs in genes encoding voltage-gated calcium channel subunits (*CACNA1C, CACNB2, CACNA1I*) [73,74]. Other genes that are potentially involved in development of schizophrenia include *BDNF* Val66Met (associated with reduction in grey matter volume)[75] and *COMT* Val/Met (involved in dopamine regulation)[76].

Notably, a GWAS from the Schizophrenia Working Group of the Psychiatric Genomics Consortium[77] including a total of 36,989 schizophrenia cases and 113,075 controls (49 ancestry matched, non-overlapping case-control samples and 3 family-based samples) identified 108 loci with genome-wide significance. However, only 12 of the index associations could be credibly explained by a known expression quantitative trait locus (eQTL)[77]. The identification of many candidate variants of small effect associated with non-communicable disorders has led to a widespread interest in the development of polygenic risk scores, which calculate the number of risk alleles of an individual, weighted by allele-specific odds ratios, as tools for investigating gene-gene and gene-environment interactions, and risk prediction[23]. In short, the genetic variants identified in GWAS over the years in association with schizophrenia account for only a small proportion of the heritability estimated from twin and family studies. For example, the heritability estimates for schizophrenia from twin and family studies and GWAS are 64-81% and 22%, respectively[78].

In addition, copy number variant (CNV) analyses have identified some rare variants, e.g., 1:11 translocation (interrupting *DISC1* (Disrupted in Schizophrenia 1)) and the 22q11 deletion (deletion in the chromosome 22q11 region)[23,28,68], which are potentially related to schizophrenia. There is an emerging view that compared to the common alleles of small effect, CNVs and rare variants may have a larger role in schizophrenia[79–83].

Further, with genome wide association studies[49,68,84] failing to identify specific causal genes for schizophrenia[69,85–87] and early segregation studies of schizophrenia failing to support Mendelian models of transmission[88,89], some suggest a neurodevelopmental model[18,90] in psychosis, in which environmental factors play a substantial role in onset and severity of the disorder.

1.1.3.4 Environmental risk factors for schizophrenia

Environmental factors are reported to account for approximately 15-40% of the risk for schizophrenia[71]. Non-genetic risk factors have been less investigated compared to genetic risk factors[91]. The available evidence suggests the involvement of factors such as maternal infection during pregnancy, obstetric complications, season of birth, childhood adversity, cannabis use, urban living[92], first- and second-generation migration[93,94], and stress[70]. Also, a combination of these factors may affect individual's risks differently across their lifespan, independent of or in combination (interaction) with the underlying genetic factors. A recent twin study investigating interactions between genetic and environmental risk factors (childhood adversity, substance use, low birthweight) and their relative importance showed that environmental factors may play a greater role than genetic factors in the etiology of psychotic experience[69]. A recent review of genetic and environmental risk factors of schizophrenia reported a paucity of evidence on gene-environment interactions in schizophrenia (Appendix 1-C)[91].

Geographically, urban dwelling has been reported to be correlated with an increased risk for schizophrenia[92] or psychotic symptoms[95] and this relationship may be potentially mediated by economic stress, social fragmentation, and various pollutants[96,97]. Some authors further suggest that individuals with underlying genetic susceptibility to schizophrenia tend to live in dense or deprived neighborhoods[98–100]. Research from Sweden, France, and Canada has shown that risks from migration may be related to discrimination, social isolation, and low socioeconomic positions[101,102], with the highest risk attributed to migrants from Africa to Western countries[103–105].

Childhood adversity includes economic deprivation, abuse and neglect, and other stressful life events such as parental loss or police involvement[91]. Exposure to adversity in childhood has been reported to be associated with the severity of psychotic symptoms[106,107]. Evidence suggestive of interaction between childhood trauma and *BDNF*[108–110], *COMT* [111], and *FKBP5*[112,113] gene variants, which are potentially implicated in schizophrenia, has been reported (see 1.1.4.3).

Cannabis use appears to be associated with development of schizophrenia[114] or psychotic symptoms[115] as well as higher relapse rates in patients with psychosis[116]. Mendelian randomization studies[117,118] and longitudinal studies[119] reported a potentially causal role of cannabis in schizophrenia risk.

Overall, schizophrenia appears to be a heterogeneous disorder with a complex web of genetic and environmental risk factors[85,86]. Furthermore, risk factors, both genetic and environmental, appear to change with time from the fetal stage to early adulthood[23]. For example, disruptions in synaptic pruning and aberrant synaptic network organization in adolescence have been reported to be related to cognitive and negative symptoms, while subcortical dopamine dysregulation in early adulthood may be related to the onset of positive symptoms[23].

1.2 Nutrition and Neuropsychiatric Diseases

1.2.1 Overview

Nutrition is an important modifiable risk factor for several neuropsychiatric diseases. Nutritional interventions have been considered in research on etiology and as potential modifiers of other therapeutic agents[120]. Nutrition may be broadly implicated in development of neuropsychiatric diseases by impacting the energy metabolism of neurons and glia cells[121]; lack of nutrition and consequent energy supplied to the brain tissues may impair production of neurotransmitters and synaptic remodeling[122]. A systematic review conducted by Aucoin et al.[26] reported a positive correlation between risk of psychosis (more broadly defined than schizophrenia) and a multitude of nutritional

factors, including higher intake of refined carbohydrates and total fat; lower intake of omega-3 and omega-6 fatty acids, vegetables, and fruits. Lower intake of vitamins and minerals have also been identified as potential contributing factors, particularly folate, vitamin B_{12}, vitamin B_6, vitamin C, zinc, and selenium[26]. Low serum concentration of folate was also associated with increased risk of depression, cognitive impairment, and Alzheimer's disease[123].

Individuals with schizophrenia typically have low quality diet and poor metabolic health[124,125], partly due to the metabolic dysfunction and weight gain induced by antipsychotic medications[124]. Some evidence suggests a potential role of food allergy/ sensitivity, which is more prevalent among individuals with schizophrenia compared to healthy controls[26,126,127], in nutritional deficit or poor diet associated with the disorder. Studies have also reported a high level of inflammation and oxidative stress among individuals with schizophrenia[128], which may be linked to nutrition[129].

Overall, the current literature examining the role of nutrition in schizophrenia is limited due to high levels of heterogeneity in study designs, study populations, confounding effects (i.e., sociodemographic factors, comorbidities, interactions among multiple nutrients, interactions with medications), small sample sizes, and short follow-up periods.

1.2.2. Folate and vitamin B_{12}

Folate and vitamin B_{12} are water-soluble B vitamins found in food sources such as leafy green vegetables, nuts, citrus fruits, liver, eggs (folate)[130], and meat, fish, poultry, and dairy products (vitamin B_{12})[131]. Both vitamins play a critical role as cofactors in one-carbon metabolism, in which methyl groups are transferred across multiple, inter-related metabolic pathways required for syntheses of DNA, RNA, amino acids, phospholipids, and for numerous methylation processes[132,133]. Inadequate status of folate or vitamin B_{12} has been associated with multiple health outcomes, most notably neural tube defects (folate)[134,135] and megaloblastic anemia (vitamin B_{12})[136].

Recommended dietary intake of folate and vitamin B_{12} varies by country[137]. Generally, adequate intake levels, as determined by the Institute of Medicine, for folate and vitamin

B_{12} are 400 μg/d and 2.4 μg/d, respectively, for adults aged 19 years or older. The levels are 500-600 μg/d and 2.6-2.8 μg/d, for folate and vitamin B_{12} respectively, for pregnant or lactating women[138].

1.2.3 Folate, vitamin B_{12} and schizophrenia: phenotypic evidence

Evidence on the relationship of folate, vitamin B_{12} with the onset and symptoms of schizophrenia has been growing[139–143] (Table 1-1). Folate concentrations were reported to be lower in individuals with schizophrenia compared to healthy controls[141,144,145] and high folate concentrations have been reported to be associated with a reduced risk of schizophrenia[146,147]. Serum folate concentrations were also lower among schizophrenia patients with deficit syndrome compared to those without deficit syndrome[148] (defined as schizophrenia cases presenting ≥ 2 primary negative symptoms for the preceding 12 months including during clinical stability[149]). Folate inadequacy was also observed among individuals experiencing first-episode psychosis[129].

A few randomized controlled trials studies also reported potentially beneficial effects of folate and vitamin B_{12} on alleviating or managing symptoms. Folic acid supplementation with or without vitamin B_{12} appeared to mitigate symptoms in patients with schizophrenia[87,150] and l-methylfolate showed mitigating effects on negative symptoms[151]. Increasing folate levels appeared to be effective in mitigating negative symptoms[152]. B vitamins supplementation (pooled effects of folate, vitamin B_6, and vitamin B_{12}) has also been reported to reduce total psychotic symptoms in patients with schizophrenia[153].

The relationship between homocysteine and schizophrenia symptoms appears to be consistent. Hyperhomocysteinemia was observed in individuals with schizophrenia in many studies[154–158] and increased plasma homocysteine was reported as a risk factor for schizophrenia[159,160]. In addition, elevated concentrations of prenatal (during third trimester) homocysteine was also reported to be associated with two-fold higher risk of schizophrenia in the offspring[161].

Another domain of evidence suggesting potential involvement of folate in the onset and severity of schizophrenia is the role of genetic polymorphisms related to folate metabolism. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that catalyzes the reduction of 5,10- methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is then used for formation of tetrahydrofolate and conversion of homocysteine to methionine[132,162] and is encoded by the *MTHFR* gene. Homozygosity for the common *MTHFR* C677T variant codes for a thermolabile enzyme with impaired function[163], resulting in lower folate concentrations in serum and red blood cells[132]. The *MTHFR* 677TT genotype is associated with approximately 25% higher homocysteine concentrations compared with 677CC genotype[159]. The potential causal role of homocysteine in schizophrenia risk was reported by a Mendelian randomization study[160]. The SzGene (SchizophreniaGene) database, a catalogue of genetic association studies relating to schizophrenia, identified *MTHFR* C677T polymorphism as one of the 24 genetic variants with a nominally significant effect on the risk for schizophrenia as of 2008[164]. The *MTHFR* 677TT genotype appears to be associated with the severity of negative symptoms[159,165] and executive function deficit in patients with schizophrenia[165], as it has been shown to moderate the effect of folic acid and vitamin B_{12} supplementation in patients with schizophrenia[87,166]. Indeed, *MTHFR* 677TT was found to be associated with a higher occurrence of schizophrenia[159]. Other genetic variants implicated in the risk or severity of schizophrenia are A1298C variant in the *MTHFR* gene[163] and 484 C>T variant in the *FOLH1* gene[87]. A meta-analysis of genetic associations between *MTHFR* C677T polymorphism and schizophrenia in individuals of Japanese ancestry[167] also reported a relationship between *MTHFR* genotype and the risk of schizophrenia.

Meanwhile, some studies have reported inconsistent associations between schizophrenia and *MTHFR* genotype. In a case-control study of patients with schizophrenia and healthy controls, Garcia-Miss et al. reported that while low concentrations of red blood cell folate and high concentrations of homocysteine were found in schizophrenia cases, *MTHFR* C677T variant was not a risk factor for the disorder[168]. This result was supported by another case-control study[169], in which despite the low concentrations of vitamin B_{12} and high concentrations of homocysteine in schizophrenia cases compared to controls, there

was no significant difference in the genotypic distribution and allelic frequencies of *MTHFR* C677T polymorphism between the two groups. While these two studies are limited by small sample sizes (n=213, 68, respectively), the authors suggested a potential role of ethnicity (Mexican) in the effect of the *MTHFR* C677T polymorphism[168]. Lack of association between *MTHFR* C677T polymorphism and risk of schizophrenia has been observed in studies with Spanish[170] and Scandinavian[171] samples.

1.2.4 Folate, vitamin B_{12} and schizophrenia: potential epigenetic links

Epigenetics refers to regulatory processes that govern the transcription of DNA sequence into RNA[172]. Epigenetic changes directly affect the expression of a gene without changing the underlying DNA sequence[173] through key mechanisms of DNA methylation, histone modification, chromatin remodeling and RNA regulation by non-coding RNAs[85,172]. As these modifications are triggered by non-genetic factors, epigenetic variation is widely considered to be an interface between genotype, environment, and phenotype[86]. An epigenetic biomarker is considered to be any mark of altered epigenetic mechanism that is measured in the body fluids or tissues defining or predicting a disease or response to exposures or interventions[59].

Due to the polygenic nature of schizophrenia and the likely large role of gene-environmental interactions in their etiology, epigenetics has emerged as a promising field in schizophrenia[174]. In addition, the fact that genome stability and integrity, which is largely controlled by DNA methylation, is highly correlated with many neuropsychiatric disorders[85] and that genes associated with schizophrenia co-localize with genome regions that are more susceptible to mutation[85] also point to the potential value of epigenetic approaches to identifying risk factors for schizophrenia.

Epigenetic modifications are lifelong evolving plastic mechanisms[175]. Combination of environmental and genetic factors modulate brain development[139]. Aberrant patterns of DNA methylation, histone modification, and miRNA have been identified in association with an elevated risk of schizophrenia[70,85]. Research has identified some common

patterns of epigenetic modifications among schizophrenia cases and animal models including hypermethylation of the *RELN* promoter[176,177], altered promoter methylation of protocadherin genes (*Pcdha11, Pcdha9, Pcdhga5*)[85], dysregulation and/or downregulation of miR-132[178,179], miR-195[180], and miR-137[77]. Further, increased methylation of *SOX10*[181], *GABRB2*[182,183], *FKBP5*[59,184], and *BDNF* promoter[70,185–187] and reduced methylation of *COMT*[182,188,189] have been reported to be associated with schizophrenia. The disorder is reported to be associated with more mutation-susceptible genomic regions[85], and factors such as childhood adversity[18,69], substance use[18,69], life events and nutrition[18] are reported to play a role in the epigenetic processes.

It has been suggested that the role of folate and vitamin B_{12} in the epigenetic changes underlying susceptibility to psychosis may be through their effects on the S-adenosyl methionine (SAM) enzyme, a critical factor in the transmethylation pathway and in turn, brain development[190]. For example, SAM enables numerous methylation reactions in the central nervous system, such as synthesis of neurotransmitter and membrane phospholipid and methylation of myelin[132]. Deficiency in SAM and disruption in the transmethylation pathway has been linked with delays in brain development and severe neuropsychiatric diseases[191].

1.2.5 Folate, vitamin B_{12}-dependent epigenetic modifications in schizophrenia

There is limited and conflicting evidence on direct correlation between folate and vitamin B_{12} concentrations and epigenetic marks. One systematic review reported that folic acid supplementation increased global DNA methylation significantly in colorectal mucosal samples, but not in blood samples of adults[192]. In another analysis of older adults, long-term supplementation with both folic acid and vitamin B_{12} was correlated with more DNA methylation changes in leukocytes compared to placebo controls and these patterns were mostly related to developmental processes and carcinogenesis[193]. Maternal folate concentration during pregnancy was also found to be significantly associated with 443 differentially methylated positions (DMPs) in newborns[194], most of which are known to be related to congenital defects and neurodevelopment.

However, these findings were only partly replicated in a recent large-scale epigenome-wide association analysis (5,841 individuals from 10 cohorts)[195], in which the authors found mostly null associations between folate and vitamin B_{12} dietary intake and methylation levels (higher intake associated with hypomethylation). 6 DMPs were identified to be associated with folate intake in this study; however, only one was associated with gene expression levels[195]. In summary, to date, epigenome-wide association studies have not found folate and vitamin B_{12}-associated epigenetic markers that are known to be directly implicated in schizophrenia.

A few points are important in considering possible epigenetic mechanisms in the onset and trajectory of schizophrenia. First, epigenetic patterns, in general, are cell- and tissue-specific[172,175,196–198] – they vary by cell and/or tissue and modifications are altered by advancing age and environmental stimuli[70,199–201]. Thus, caution is needed when interpreting results of epigenetic information collected from blood or buccal cells to other tissue types[172]. Bakulski et al.[202] point out concerns and challenges in extrapolating results of the blood-based epigenetics particularly in the study of neuropsychiatric disorders, which primarily involve the brain. Indeed, while brain tissues might in theory be an ideal gold standard for neuropsychiatric research, the value of epigenetic investigation of brain tissue may be limited by the fact that the brain is a heterogenous organ comprising neurons and glia, with different regions responsible for different functions[203]. Knowledge of which tissue to sample at what time is limited. Furthermore, post-mortem sampling of brain tissues blurs the temporal sequence between epigenetic marks and disease development. The epigenetic patterns identified in the post-mortem tissues may have been caused by the disease[202]. Tissue-based epigenetic research in neuropsychiatry is still scarce and more cross-tissue research is required[202].

Second, DNA methylation is a dynamic process, responsive to variations in the environment[175,196,204–206]. Some evidence of active demethylation challenges the conventional notion that methylation marks stay stable throughout the life course[175]. Combined with the current knowledge of epigenetic changes across the lifespan[132,162], research in epigenetics should take into account critical life stages when pooling data.

Third, schizophrenia is a heterogeneous disorder[59]. While the severity of positive or negative symptoms and cognitive deficits vary substantially by patient[23], the methods used to detecting and measuring psychotic symptoms are also heterogenous[59]. Comorbidities, medication use, and ancestry may further confound research findings[59,207,208].

1.2.6 Potential Mechanisms of Action

The potential pathways linking folate, vitamin B_{12} and schizophrenia are illustrated in Figure 1-1. Much of the available literature examining the role of folate and vitamin B_{12} in the epigenetic mechanisms in the context of schizophrenia generally describe the involvement of the vitamins in one-carbon metabolism, the significance of SAM as a methyl donor, and the toxicity of homocysteine[139,172,209,210]. B-group vitamins, particularly folate, riboflavin (B_2), pyridoxine (B_6), and cobalamin (B_{12}), play a critical role as substrates and cofactors in one-carbon metabolism, which enables the synthesis of DNA and RNA[132,162,211] and modulate DNA methylation[212,213]. In one-carbon metabolism, folate and B_{12} work in tandem to synthesize methionine, and in turn SAM, a universal methyl donor involved in over a hundred methylation reactions and neural functions[132,139,162,192]. Folate and B_{12} also work together in re-methylation of homocysteine, a well-established risk factor with neurotoxic[214–216] and vasculotoxic[217] effects.

Under the "homocysteine hypothesis[218]", elevated homocysteine levels cause vascular disease of the brain and/or neurotransmitter alterations which cause psychiatric disorders. High levels of homocysteine are toxic to neuronal cells[219,220] and have been reported to be associated with the loss of neural plasticity and neurodegenerative disorders[221], as well as schizophrenia[154,159,222,223]. The brain is potentially vulnerable to high concentrations of homocysteine because it lacks betaine re-methylation and transulfuration pathways for its elimination[214]. In schizophrenia, a suboptimal function of the MTHFR enzyme, which re-methylates homocysteine into methionine, has been suggested as one of the causal factors[139]. The *MTHFR* C677T genotypes are key genetic determinants of homocysteine

concentrations in plasma[224–226]. Impaired folate metabolism and consequent accumulation of homocysteine have been observed among individuals homozygous for the variant[224].

Folate and vitamin B_{12} are required for the generation of SAM, an intermediate metabolite involved in numerous methylation reactions including those forming neurotransmitters. Thus, inadequacy of these vitamins may impair functioning of the central nervous system and mood through impaired production of monoamine neurotransmitter[216,227]; imbalances in cytokines and growth factors[228]; and brain atrophy[229].

There may also be a link between low folate status and the known environmental risk factors for schizophrenia. For example, winter births, urban living, childhood adversity, and low socioeconomic position are likely related to low quality diet and/or lack of fresh nutrients[209].

1.3 Policy Landscape

Various policy interventions have been considered[230] for translating evidence of benefits of micronutrients such as vitamin B_{12} and folate into public health actions: fortification, supplementation, and primary care interventions, among others. Primary interventions include publication of national or international guidelines[137] on optimal intake of folate or vitamin B_{12} for population groups and legislating food fortification with folic acid. Secondary interventions include public health education targeting subgroups of individuals who are at risk of folate or vitamin B_{12} deficiency or who require higher levels of these vitamins (i.e., women of reproductive age, pregnant or lactating women, children and adolescents, and older adults) or coverage of these supplements under the national health insurance for the at-risk population groups. Tertiary interventions may consist of routine measurement of blood folate or vitamin B_{12} concentrations among patients with known risk factors for deficiency (e.g., alcohol use disorder, malabsorptive disorders).

Mandatory fortification is regarded as the most cost-effective and sustainable upstream intervention for addressing micronutrient deficiencies and their consequent harms[231], as it does not require large-scale public campaigns or behavior change of the target population. Voluntary fortification, in which food manufacturers are encouraged to add micronutrients to their products, is reported to be less effective compared to mandatory fortification[232]. Voluntary supplementation policies appears to depend, to a large extent, on health literacy, access, cost, and compliance of consumers and food manufacturers[233–235].

Policy actions to optimize folate intake in the population have centered around introducing national mandatory fortification programs. As of 2020, 57 countries have introduced folic acid fortification[232], with Canada and the US starting mandatory programs in 1998[236] and the European Union issuing regulations on voluntary folic acid fortification in its member states in 2006[237]. Most of the fortification programs target wheat flour, corn, rice, cereal grains, and dairy products[232]. For example, Canada fortifies wheat and enriched pasta with folic acid; the US wheat, maize, and rice; and Brazil fortifies maize and wheat[238].

Population interventions to prevent vitamin B_{12} inadequacy have not been as straightforward, due in large parts to uncertainties surrounding the optimal dose of vitamin B_{12} considering different intake requirements of individuals with different clinical characteristics (i.e., absence of intrinsic factor, atrophic gastritis) and variable subclinical health effect reported from vitamin B_{12} deficiency[239]. Discussion continues about the optimal food vehicle[239,240], advanced technologies of fortification[240,241], and dose[239] of potential vitamin B_{12} fortification.

Recent reviews examining the impact of folic acid fortification[230,232,236] over the past three decades reported that mandatory fortification has been effective, albeit in varying degrees depending on geography and population characteristics, in reducing the prevalence at birth of neural tube defects (NTD) and it may have impacts on the frequencies of congenital heart defects, cardiovascular diseases in adults and certain types

of cancer. For example, a large-scale meta-analysis of eight population-based studies from five countries including Canada reported a 46% reduction in risk of NTD comparing pre- and post-fortification[242]; prevalence of NTD in the US decreased by 35% since fortification[243]; and countries with mandatory folic acid fortification were reported to have lower prevalence of spina bifida (subtype of NTD) compared to those without the fortification[244].

The impact of voluntary fortification appears to be small. In Ireland, where liberal, voluntary fortification of folic acid and vitamin B_{12} is allowed, consumption of fortified foods or supplements contributed to higher blood concentrations of the vitamins in adults (aged ≥ 18 years), but not to a sufficient extent to prevent NTD[245]. Among older Irish adults, folate and vitamin B_{12} status was predominantly low despite the voluntary fortification[246]. A cohort of children and adolescents in Australia also showed an increase in serum concentrations of folate against the backdrop of voluntary folic acid fortification, but not to an optimal level[247].

We note that studies that assess the effectiveness of fortification policies generally lack rigor – these studies are largely observational, ecological, or retrospective in study designs[232,236] and lack adjustment for potentially important confounders, such as other public policies, socioeconomic environment, population structure, and food security[232]. Challenges are also compounded by variations in fortification dosages in different countries[232] or on the use of precise biomarkers, particularly for vitamin B_{12}[236].

Furthermore, a preliminary search has not yielded any results assessing the impact of various policy interventions on neuropsychiatric disorders. The absence of policy evaluation in this aspect may be attributed to lack of consensus on etiology of many neuropsychiatric disorders[16,22] as well as to the complexity and heterogeneity of psychiatric disorders.

1.4 Gaps in Knowledge

A preliminary review of the current literature has revealed several areas where further evidence is needed. First, the current evidence on the relationship between folate and vitamin B_{12} and the risk for schizophrenia is limited to certain exposure or outcome types and settings (i.e., folate and vitamin B_{12} as adjunctive therapy to antipsychotic treatment, first-episode psychosis, or case-control studies examining serum concentrations of folate and vitamin B_{12} in cases compared to controls). There has not been evidence synthesis that examined independent effects of folate or vitamin B_{12}, assessing different sources and measures of exposure (dietary intake, supplementation, biomarker) in relation to the risk of schizophrenia. Moreover, many of the previous studies did not adjust for potential confounders, such as age, sex/gender, ethnicity, migration status, socioeconomic status, and comorbidities (with other psychiatric disorders).

Second, the current evidence on the role of environmental factors in etiology and/or severity of schizophrenia is predominantly based on observational studies and have not included epigenetic markers that have been identified to be correlated to the disorder. Furthermore, many of these studies did not stratify by subtype (i.e., ethnicity, type of childhood adversity, years since migration, socioeconomic status, components of urbanicity (density, pollutants, deprivation, etc.), amount and duration of cannabis use). A recent narrative review by Robinson et al.[91] provides a broad overview of the current evidence on various environmental risk factors of schizophrenia but was not focused on folate or vitamin B_{12}. However, it can be complemented by a systematic evidence synthesis with delineation by subtypes of the environmental risks examined.

Third, evidence is scarce in mapping epigenetic markers associated with folate and vitamin B_{12} concentrations and schizophrenia. With more epigenome-wide association studies (EWAS) uncovering folate and vitamin B_{12}-associated epigenetic biomarkers and more robust assays being developed, the current understanding of the pathway from folate and vitamin B_{12} status to development of schizophrenia is likely to improve. In addition, the substantial role of environmental factors (which varies over time) and the high level of heterogeneity among individuals with schizophrenia should be taken into

consideration in the etiology of the disorder. A comprehensive integration of the EWAS findings thus far, mapped against the known environmental risk factors for schizophrenia, particularly those with high levels of epidemiological evidence, may be valuable in advancing the research in this field.

Fourth, there is absence of data on the impact of mandatory folic acid fortification on prevalence or disease burden of schizophrenia in countries that have implemented such programs. A recent review[232] indicated that of the 57 countries with mandatory fortification, only 12 have data on the program's effectiveness on any health outcome. Most of the studies that assessed the impact of fortification focused primarily on NTD, other birth defects, cancers, and cardiovascular outcomes. Moreover, these studies were limited in terms of assessing the policy impact in population subgroups that have been identified to have higher likelihood of low folate and vitamin B_{12} concentrations (i.e., those with *MTHFR* polymorphisms, vegans, older age groups, individuals using folate-reducing medications, etc.).

More broadly, no attempt has been made to date to systematically identify various types of public health policies involving folate and vitamin B_{12} intakes and their effectiveness in achieving health outcomes. There is insufficient data on the impact, if any, of policies other than mandatory fortification implemented at the national/federal level. For example, voluntary folic acid fortification of corn masa flour has been approved by the US FDA to address the higher prevalence of NTD among the Hispanic population[248]; voluntary folic acid fortification has been in place in the UK since 1987 for cereals and spreads[249]; and folic acid has been added to cereal products extensively in a voluntary setting in Ireland for almost 20 years[250]. Yet, the impact of these programs on various health outcomes has not been systematically assessed.

1.5 Development of Research Questions

To address these gaps, we developed a set of research questions designed to investigate the relationship between folate and vitamin B_{12} and schizophrenia in such a way to

provide both comprehensive and focused understanding of the current knowledge. The importance of taking a comprehensive perspective cannot be overstated in the field of nutritional epidemiology because of large variations in how and when micronutrients are consumed, absorbed, and measured at an individual level; multiple factors that are involved in the metabolism and subsequent biological processes; and time-varying nature of the micronutrient – disease relationship.

Based on our preliminary scan of the literature, in which examinations of the independent health effects of vitamin B_{12} appeared to be substantially less in volume compared to inquiries on the associations of folate with various disorders[123], we first set out to explore and synthesize the available evidence on the association of vitamin B_{12} with health outcomes. Our expectations from this comprehensive endeavor were to gain a better understanding of the most widely-studied diseases in relation to vitamin B_{12} status; to obtain insights on the key limitations of the accumulated research on vitamin B_{12} (i.e., volume of research, methodological rigor); and to identify high-level evidence on the relationship between vitamin B_{12} and neuropsychiatric disorders as a broad category.

Next, we narrowed the focus of our inquiry to schizophrenia: what is the relationship between folate, vitamin B_{12} and schizophrenia? Here, we separated the outcome of interest into three areas: (i) the risk of developing schizophrenia in the general population; (ii) the risk of having high severity of symptoms among individuals diagnosed with schizophrenia; and (iii) the effect on antipsychotic treatment among individuals diagnosed with schizophrenia. The first and the second outcomes were explored in relation to folate and vitamin B_{12} status, while the third outcome was examined in the context of controlled trials using folic acid or vitamin B_{12} supplements as an adjunctive therapy.

To address the first two inquiries, we used an umbrella review methodology, which allows for an exposure-wide approach to synthesizing evidence across multiple types of studies and thus providing a bird's-eye view of the totality of syntheses in a given field.[251–254] An umbrella review may also be particularly useful to inform policymakers

and clinicians who require a comprehensive summary of insights arising from various types of research amid a rapid growth in systematic reviews and meta-analyses that address often narrower topics or specific subgroups of individuals.

Our subsequent inquiry was whether the relationship of folate and vitamin B_{12} with schizophrenia was causal. We were informed by the literature on the role of several genetic variants in determining folate concentrations in individuals and consequently contributing to susceptibility to certain health conditions. Such pathways may be utilized as a framework for an instrumental variable analysis, which addresses measured and unmeasured confounding effects and helps identify a causal link between an exposure and an outcome. We sought to synthesize studies that used genetic variants that are involved in the folate and vitamin B_{12} metabolism as instrumental variables to explore the causal nature of the association of interest.

Finally, we shifted gears to identify public health policies that have been introduced to address inadequate status of folate and vitamin B_{12} in the population and to assess their impact on schizophrenia. Our comprehensive literature search yielded no results, other than food fortification with folic acid, in the form of formalized, public health interventions targeting the general population. We designed an ecological study utilizing publicly available data on folic acid fortification policies and the prevalence and incidence of schizophrenia across different countries.

One important gap in knowledge that we identified prior to the dissertation was a potential epigenetic link involving folate and vitamin B_{12} status, other environmental risk factors, and schizophrenia. Research in EWAS is growing rapidly in volume and rigor. From our comprehensive exploration of the literature, it became evident to us that an integrated mapping of epigenetic markers of key environmental risk factors of schizophrenia would be best undertaken outside the bounds of this dissertation and in collaboration with a larger team of experts.

1.6 Organization of Dissertation Chapters

The above research questions were addressed in the subsequent chapters of this dissertation as listed below and visualized in Figure 1-2:

Chapter 2: Q1- What are the health effects of vitamin B_{12} status?

Chapter 3: Q2 - Is there an association between folate, vitamin B_{12} and schizophrenia?

a) Do folate and vitamin B_{12} concentrations predict the risk of schizophrenia in the general population?
b) Do folate and vitamin B_{12} concentrations predict severity among individuals diagnosed with schizophrenia?
c) Does folate and vitamin B_{12} supplementation augment the effects of antipsychotic treatment among individuals diagnosed with schizophrenia?

Chapter 4: Q3 - Is the relationship between folate, vitamin B_{12} status and schizophrenia causal?

Chapter 5: Q4 - What type of public health policies have been implemented in relation to folate and vitamin B_{12} and what are their impact on schizophrenia?

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1.8 Figures and Tables

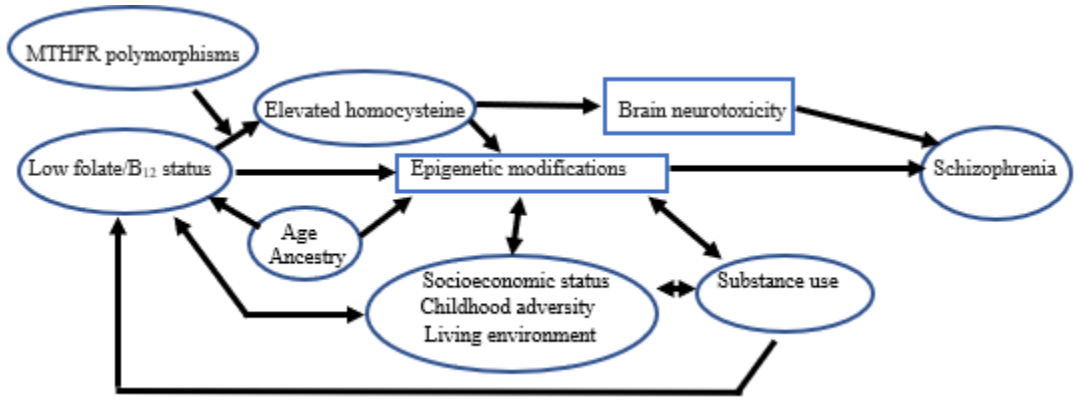

Figure 1-1. Potential mechanism of association between folate and vitamin B12 status and schizophrenia

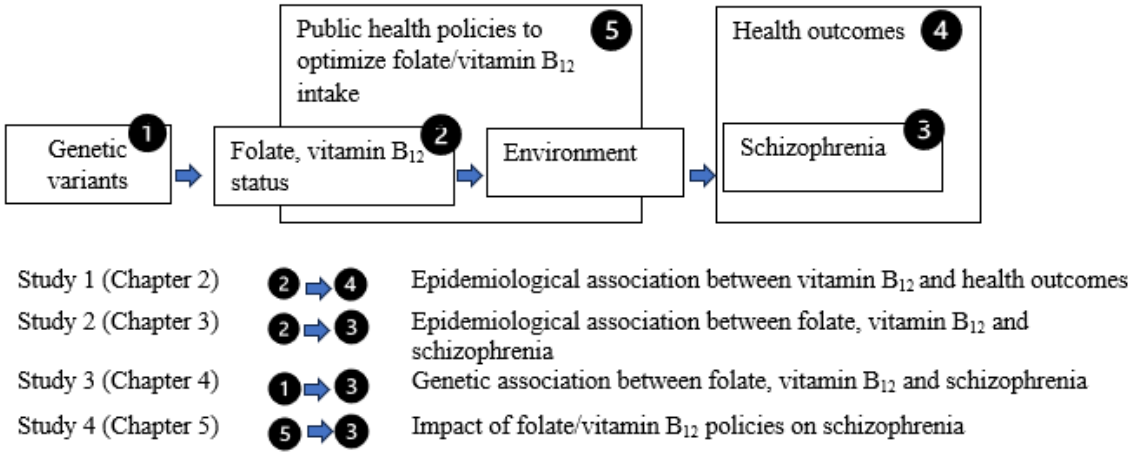

Figure 1-2. Visual illustration of the organization of the research questions

Table 1-1. Summary of systematic reviews and/or meta-analyses on the association between folate, B_{12} and onset and treatment of schizophrenia (from preliminary search)

First Author (Year)	Title	Type of study	Exposure	Outcome	Findings
Onset					
Lewis (2005)	A meta-analysis of the *MTHFR* C677T polymorphism and schizophrenia risk	MA (all studies) 1,119 cases (TT genotype) 1,308 controls (CC, CT genotypes)	*MTHFR* C677T polymorphism	Schizophrenia	The MTHFR C677T TT homozygotes had a significantly increased risk of schizophrenia, OR=1.48 (95% CI: 1.18–1.86) compared to the CT and CC genotypes combined
Muntjeweff (2006)	Homocysteine, *MTHFR* and risk of schizophrenia: A meta-analysis	MA (case-control studies) 2,265 cases (TT genotype) 2,721 controls (CC genotype))	*MTHFR* C677T polymorphism	Schizophrenia	The homozygous genotype (TT) of the MTHFR C677T polymorphism was associated with a 36% (95% CI: 7-72) higher risk of schizophrenia compared to the CC genotype.
Wang (2016)	Serum folate levels in schizophrenia: a meta-analysis	MA (observational studies) 1773 cases, 1930 controls	Folate concentrations	Schizophrenia	Lower serum folate was associated with schizophrenia risk (WMD= -1.57, 95%CI: -2.11, -1.02)
Cao (2016)	Vitamin B12 and the risk of schizophrenia: A meta-analysis	MA (observational studies) 1092 cases 1021 controls	Vitamin B_{12} concentrations	Schizophrenia	Vitamin B_{12} levels were lower in schizophrenia patients compared to healthy controls, but without significant difference (SMD= 0.09, p=0.07).
Cao (2016)	Lower folate levels in schizophrenia: A meta-analysis	MA (observational studies) 1463 cases 1276 controls	Folate concentrations	Schizophrenia	Folate levels were significantly lower in schizophrenia patients compared to healthy controls (SMD= -0.57, p<.001).
Yadav (2016)	Role of *MTHFR* C677T gene polymorphism in the susceptibility of schizophrenia: An updated meta-analysis	MA (all studies) 10,069 cases 13,372 controls	*MTHFR* C677T polymorphism	Schizophrenia	*MTHFR* C677T polymorphism was significantly associated with risk of schizophrenia (OR=1.18, 95% CI: 1.10, 1.27). This association was significant in three ethnic subgroups -

					African (OR=2.51, 95% CI: 1.86, 3.40), Asian (OR=1.21, 95% CI: 1.10-1.33), and Caucasian (OR=1.07, 95% CI: 1.01-1.14)
Firth (2018)	Nutritional deficiencies and clinical correlates in first-episode psychosis: A systematic review and meta-analysis	SR+MA Folate: 827 samples B_{12}: 620 samples	Folate, B_{12} concentrations	First episode psychosis	Blood levels of folate were significantly lower in first episode psychosis cases compared to healthy controls, but no significant difference in vitamin B_{12} levels.
Treatment					
Firth (2017)	The effects of vitamins and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis	SR+MA (RCTs)	B6, B9, B12 plus antipsychotic treatment	Total symptoms, subscale symptoms	B vitamins (B6, B9, B12) significantly improved total symptoms in schizophrenic patients ((g = 0.51, 95% CI: 0.01, 1.01). Their effects were not significant in improving any domain-specific symptoms.
Sakuma (2018)	Folic acid/ methylfolate for the treatment of psychopathology in schizophrenia: A systematic review and meta-analysis	SR+MA	Folic acid group + antipsychotic treatment	Total symptoms, subscale symptoms	Folic acid group supplementation significantly improved negative symptoms compared to placebo (SMD=-0.25, 95% CI: -0.49, -0.01).

1.9 Appendices

Appendix 1-A. List of disorder classes in ICD-11 and DSM-5 that include psychosis

ICD-11	DSM-5
Schizophrenia and other psychotic disorders	Schizophrenia spectrum and other primary psychotic disorders
Schizotypal disorder	Schizotypal personality disorder
Delusional disorder	Delusional disorder
Acute and transient psychotic disorder	Brief psychotic disorder
-	Schizophreniform disorder
Schizophrenia	Schizophrenia
Schizoaffective disorder	Schizoaffective disorder
-	Substance/ medication-induced psychotic disorder
-	Catatonia associated with another mental disorder
-	Catatonic disorder due to another medical condition
-	Unspecified catatonia
Other specific schizophrenia and other primary psychotic disorders	Other specified schizophrenia spectrum and other psychotic disorders
Schizophrenia and other primary psychotic disorders, unspecified	Unspecified schizophrenia spectrum and other psychotic disorders

Appendix 1-B. RDoC framework - matrix of domains and environment [31]

		Environment						
Domains	Negative valence	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports
	Positive valence							
	Cognitive systems							
	Systems for social process							
	Arousal/ modulatory systems							
		Neurodevelopment						

Negative valence: systems that enable response to aversive stimuli (e.g., threats, loss, aggression due to frustration); Positive valence: systems that mediate reward-related activity (e.g., approach motivation, reward responsiveness); Cognitive systems: e.g., attention, perception, memory; Social processes: e.g., affiliation and attachment, facial expressions and other social communication, and perception of self and others; Arousal/ modulatory systems: e.g., circadian rhythms, sleep-wakefulness, and brain-stem activation and arousal systems

Appendix 1-C. List of environmental risk factors for psychosis, strength of evidence, and their potential interaction with genetic factors[91]

Environmental exposure	Strength of evidence*	Genes potentially involved in GxE interactions	Findings on GxE interactions
Obstetric complications	High	*AKT1*	Inconclusive
Maternal infections	Moderate	*GRIN2B* (with HSV2) *CTNNA3* (with CMV)	Inconclusive
Season of birth	Moderate	*DRD4, HLA-DR1*	No interaction
Migration	High	Not known	-
Urbanicity	High	Not known	-
Childhood adversity	Moderate	*BDNF, COMT*	Inconclusive
Cannabis use	Moderate	Not known	-

* Low: very few studies with no consistent findings; Moderate: supported by some studies (may be small samples and mixed results); High: replicated results, consistent findings, large studies conducted; GxE: Gene x Environment

Chapter 2: Health effects of vitamin B12: An umbrella review of systematic reviews and meta-analyses of randomized trials and observational studies

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In Context

We noted scarcity in the integrated evidence of the effects of vitamin B_{12} at a population level. This chapter describes our endeavor to comprehensively synthesize all available high-level evidence (systematic reviews and meta-analyses) on vitamin B_{12} and health outcomes using an umbrella review methodology.

Journal submission

- Submitted to *The American Journal of Nutrition* (December 2023), *Advances in Nutrition* (January 2024), *European Journal of Nutrition* (August, 2024), *Scientific Reports* (October 2024)
- Authors: Samantha Yoo, Azita Montazeri, Derrick Bennett, Peizhan Chen, Susan Duthie,…, Helen McNulty, Monique Potvin Kent, Julian Little.
- Author contributions: JL led the study. JL, AM conceptualized the project and developed the research plan. LS developed the search strategies and executed the search in four English databases. PC and HW employed the same search strategies in two Chinese databases. SY and AM screened articles, extracted data, conducted assessment of methodological quality of the included syntheses, and synthesized the evidence. NJ assisted with data extraction. SY and AM drafted the manuscript. All authors (SY, AM, DB, PC, SD, NJ, AK, JSL, AJM, HM, HMcN, FM, PM, PM, RM, RP, MPK, MR, MS, LS, AS, ET, HW, CY, AY, JL) met regularly to discuss aspects of the review and progress of the project. AJM, ET, FM, DB, PM, HMcN provided critical input for development of the manuscript. All authors read and approved the final version of the manuscript.

2.1 Abstract

Background: Clinical vitamin B_{12} deficiency causes certain hematological, neurological, and gastrointestinal conditions. There is interest in identifying broader health effects associated with vitamin B_{12} intake and status at the population level in the context of ageing populations, an increasing prevalence of veganism, and use of drugs that impair vitamin B_{12}.

Objective: To synthesize the evidence examining population-level health effects of vitamin B_{12} by triangulating evidence from multiple measures of vitamin B_{12} exposures across multiple study designs.

Methods: An umbrella review of systematic reviews or meta-analyses was conducted with a search in Medline, Cochrane Library, EMBASE, CINHAL, Wanfang, and CNKI. Methodological quality was assessed using the AMSTAR-2. Screening, data extraction, and appraisal of the included articles were performed in duplicate.

Results: The search retrieved 5,033 articles, from which 66 articles (30 systematic reviews and 36 meta-analyses) were included. These syntheses reported 56 unique health outcomes across 12 categories. Most of the health outcome associations had few supporting syntheses, with each synthesis integrating a small number of primary studies. The majority of the meta-analyses of observational studies consisted entirely or predominantly of retrospective studies. Methodological quality of the retrieved articles was generally low or medium. None of the evidence on any vitamin B_{12} exposure and health outcomes was of convincing or highly suggestive level of certainty. Eleven associations with cancer, cardiovascular, neurological, and psychiatric disorders were considered suggestive level of evidence; however, these should be interpreted with caution due to high heterogeneity.

Conclusion: None of the existing evidence on the relationship of vitamin B_{12} exposures with health outcomes was of convincing or highly suggestive level of certainty. The associations of vitamin B12 with eleven health outcomes were of suggestive level (four

statistically significant and seven not significant). The evidence included in our synthesis had considerable heterogeneity and uncertainty. Studies with clearly defined exposure measures and populations are needed to gain a better understanding of the role of vitamin B_{12} in population health.

2.2 Introduction

Harmful effects of vitamin B_{12} deficiency are well established. Vitamin B_{12} deficiency causes megaloblastic anemia[1] which, if left untreated, can lead to neurodegeneration[2,3]. Vitamin B_{12} deficiency, through demyelination, also adversely affects neurodevelopment among infants[4] and contributes to neuropathy. Vitamin B_{12}, together with folate and other vitamin co-factors, is required for the synthesis of DNA, RNA, and methionine. Metabolically, vitamin B_{12} deficiency can result in what is referred to as a "methyl trap", where a biologically inactive form of folate accumulates, resulting in a functional folate deficiency[5]. A wide spectrum of other health outcomes have been associated with vitamin B_{12} inadequacy[6].

Because of concerns about the aging population worldwide, and the increasing uptake of veganism and recommended move towards plant-based diets, along with the prevalent use of drugs that inhibit the absorption of vitamin B_{12}, there is interest in assessing the population-level health effects associated with vitamin B_{12} intake and status[7]. Older individuals are at an increased risk of deficiency[8-10], and use of proton pump inhibitors, metformin or histamine 2 receptor antagonists can impair the absorption of vitamin B_{12}[11-13], particularly in an older population[14].

In addition to the diseases of deficiency, epidemiological studies have reported associations of varying degrees between lower dietary and supplemental intake of vitamin B_{12}, and biomarkers indicative of deficient/ low status in the population and increased risk of congenital malformations[15], adverse pregnancy outcomes[16], cardiovascular diseases[17,18], cancers[19-22], cognitive deficits[23-25], psychiatric disorders[26-29.] However, the evidence concerning the potential health effects of vitamin B_{12} is fragmented, and it is challenging to establish the balance of harms and benefits of low

vitamin intake and status in different populations and settings. This hampers the development of evidence-based public health policies to optimize vitamin B_{12} intake and status in the general population.

We aimed to synthesize the evidence concerning the health effects of vitamin B_{12} by triangulating evidence from multiple measures of vitamin B_{12} exposures across study designs. Through an umbrella review, we sought to integrate the findings of systematic reviews and meta-analyses investigating the associations between vitamin B_{12} intake, supplementation, and status indicators and a range of clinical conditions.

2.3 Methods

The protocol for this review was registered with the PROSPERO database CRD 42021265041. We conducted an umbrella review, also known as a review of reviews, which synthesizes the highest level of evidence across a broad range of exposures or outcomes[30]. Umbrella reviews not only are useful in providing a panoramic view of current knowledge, but are also becoming increasingly relevant in the context of rapidly growing number of systematic reviews and meta-analyses. The methodologies adopted in umbrella reviews are described in detail elsewhere[30,31].

2.3.1 Data sources and search strategy

A comprehensive search strategy was developed and executed in Medline, the Cochrane Library, EMBASE, and CINHAL in October 2021 and in Wanfang and CNKI in October 2023 (see Appendix 2-A 1 for the full search strategy). We searched for systematic reviews or meta-analyses examining an association between vitamin B_{12} exposure (dietary intake, supplementation, or plasma/serum concentration of total vitamin B_{12} or methylmalonic acid (MMA)) and any health outcomes, published in full text in peer-reviewed journals. For the search in Medline, the Cochrane Library, EMBASE and CINHAL, we did not use a language filter in the search strategy to avoid bias[32]; however, in the full-text screening we excluded the reviews for which full texts were unavailable in English due to resource limitations. For the search in Wanfang and CNKI, we included articles published in either English or Chinese.

2.3.2 Eligibility criteria and study selection

Two reviewers (SY, AM) independently screened the studies in duplicate in two stages, first by title and abstract and second in full text. Discrepancies were first resolved through consensus and remaining inconsistencies by a third reviewer (JL). We included systematic reviews with or without meta-analyses, systematic reviews of epidemiological studies (cross-sectional studies, prospective/retrospective cohort studies, case-control studies, nested case-control studies, ecological studies); systematic reviews of randomized or non-randomized controlled trials; meta-analysis of epidemiological studies; or randomized controlled trials. We excluded studies reporting prevalence of vitamin B_{12} deficiencies; reviews or meta-analyses examining the combined effects of vitamin B_{12} and other B-group vitamins or micronutrients; narrative reviews; scoping reviews; case reports or case-series; and animal studies. We also excluded syntheses that identified a single study with the exposure or outcome of interest.

Exposures of interest were vitamin B_{12} intake, supplementation, or status indicator. All forms of vitamin B_{12} measurements (dietary intake measured by food frequency questionnaires or food diaries, supplement intakes of cobalamin or methylcobalamin, and measurement of plasma/serum concentration of total vitamin B_{12} or MMA) were eligible. Reviews that relied on circulating homocysteine as a surrogate measure of B_{12} status, studied intermediate biomarkers of a disease as an outcome, and investigated prevalence of vitamin B_{12} deficiency or vitamin B_{12} supplementation were also excluded. Health outcomes with clear definitions and/or diagnostic criteria were included: reviews reporting on endpoints without a clinical definition or with unclear clinical relevance (e.g., subfertility, gut microbiota, reduction of arsenic toxicity) were excluded. No restrictions were made on the study population.

2.3.3 Data extraction and synthesis

Data were extracted in duplicate by at least two independent investigators (SY, AM, NJ) using a standardized and piloted extraction template (Appendix 2-B). From all included studies, we extracted the PubMed ID, URL, first author, journal, year of publication,

years searched, countries represented, study population, sex and age (mean or range of mean and standard deviation) of the study population, total sample size, type of vitamin B_{12} measure, outcome, critical appraisal tools, and authors' conclusions. From the meta-analyses, we abstracted the number of cases and controls, dose and duration of supplement use if available, type of meta-analysis model used, measure of effect with corresponding confidence intervals or p-values, measures of heterogeneity, and measures of small study effects. Disagreements were resolved by discussion and consensus.
We grouped the studies into 11 health outcome categories: cancer, cardiovascular, cognitive, pregnancy-related, congenital, other fetal/perinatal, metabolic, skeletal, infectious diseases, neurological, psychiatric, and other outcomes.

All systematic reviews were descriptively analyzed by type of health outcome. For outcomes, for which multiple systematic reviews or meta-analyses were identified, we compared the study characteristics and findings, i.e., direction and magnitude of the association and statistical significance. When concordant, we selected the evidence with the larger sample size. When discordant, we reported the evidence of the study with the larger sample size for each direction. For each outcome, we examined the reported effects of vitamin B_{12} by exposure type and quantity, as applicable.

2.3.4 Appraisal

The syntheses were qualitatively assessed by two independent reviewers (SY, AM) using AMSTAR-2[33]. The assessment scale consists of 16 items and has been updated from the original version to accommodate reviews of observational studies[33]. We did not generate an overall quality score for each article as per the authors' guidance; rather, we grouped the items into six domains to gain a better understanding of quality by domain. The domains are as follows: review planning and documentation (Q1-Q3), robust execution of the review (Q4-Q7), availability of sufficient description of the included studies (Q8), risk of bias assessment and investigation of heterogeneity among the primary studies (Q9, Q10, Q13, Q14), robust statistical approach to quantitative analysis (Q11, Q12, Q15), and disclosure of conflict of interest of the review authors (Q16).

We also assessed the strength of evidence in each exposure – outcome pair using a set of predefined criteria widely used in previous umbrella reviews[34]. The evidence was assessed as "convincing", "highly suggestive", "suggestive", or "weak" based on its statistical significance, sample size, findings of the largest study included, level of heterogeneity, and presence of small study effects (Appendix 2-C). We further assessed credibility of the evidence indicating lack of association based on the criteria of sample size, heterogeneity, and small study effects.

2.4 Results

2.4.1 Overview of included studies

A total of 5,033 articles were retrieved from the search. After two-stage screening, 66 articles (30 systematic reviews without meta-analysis and 36 meta-analyses) that investigated the association between vitamin B_{12} and health outcomes were included in the final analysis (Figure 2-1). Of the 36 meta-analyses, 32 pooled results from observational studies only and 23 of these relied entirely or predominantly on case-control studies or cross-sectional studies (Table 2-1). The 66 syntheses reported on 56 unique health outcomes across 12 categories (8 cancer outcomes, 14 cardiovascular outcomes, 10 cognitive outcomes, 1 congenital anomaly outcome, 2 perinatal outcomes, 3 pregnancy-related outcomes, 1 autoimmune outcome, 3 skeletal outcomes, 5 neurological outcomes, 4 psychiatric outcomes, 1 anemia outcome, and 4 other outcomes). We did not identify any studies reporting independent effects of B_{12} on infectious diseases or metabolic disorders. Of the 56 unique health outcomes, 27 outcomes (48%) from 33 studies reported evidence synthesized from ≥ 5 primary studies. Counting unique pairs of specific vitamin B_{12} exposure measure and health outcome in specific subpopulations, we identified 85 associations in total (Table 2-1).

Three types of vitamin B_{12} exposure were identified among the retrieved articles: status indicators (plasma, serum, or CSF concentrations of total B_{12}), supplementation (intramuscular, oral, or intravenous routes), and dietary intake (food frequency questionnaires or diet histories). MMA was not identified as an exposure among the articles. Of the total 115 measurements of B_{12} exposures assessed in analyses in which ≥

2 primary studies were included, biomarkers accounted for 55% (63 measurements), followed by supplementation (26%, 30 measurements) and dietary intake (19%, 22 measurements). One measurement combined dietary intake and supplementation use. Study characteristics of the 66 syntheses are presented in Table 2-1.

While we report the summary estimates for each health outcome from the syntheses selected for each non-overlapping association in the following sections, we discuss the direction and magnitude of the associations in all other syntheses, if any, that investigated the same association. Distribution of the overall evidence across the health outcomes is presented in Figure 2-2. Summary of the quantitative evidence is provided in Table 2-2 and visually illustrated in Figure 2-3.

2.4.2 Assessment of methodological quality

Methodological quality of the included syntheses, as assessed using the AMSTAR-2 tool, varied substantially across items. We grouped the items into five domains: review planning and documentation, execution of search, screening, and extraction, descriptive analysis, risk of bias and heterogeneity assessment, and methodologies of meta-analysis.

We did not find any article that had predominantly positive (yes/ partial yes) ratings across all domains. Twenty-nine articles (43.9%) had predominantly positive ratings in review planning and documentation; 17 articles (25.8%) in robust execution of search, screening, and extraction; none in risk of bias and heterogeneity assessment; and 13 articles (39.4%) in robust statistical approach to meta-analysis.

In the domains of review planning and execution, three items – justification for restriction of eligible study designs (Q3), comprehensiveness of the search strategy (Q4), and disclosure of excluded articles with reasons (Q7) – had highest proportions of negative ratings (56.1% - 95.5%).

A risk of bias assessment was not conducted or not reported in 36 articles (54.5%, Q9) and its result was not accounted for in sensitivity analysis or discussion in 60 articles

(90.9%, Q13). For both systematic reviews and meta-analyses, heterogeneity was not discussed or investigated in 51 articles (77.3%, Q14). None of the included syntheses reported on the sources of funding of their component studies (Q10).

In the domain of quantitative analysis, 25 articles (69.4%) did not provide justification for combining effect estimates or addressed adjustment of confounders (Q11). Thirty-one articles (86.1%) did not conduct any sensitivity analysis to account for the impact of high risk of bias studies (Q12). Detailed assessment of the included syntheses is provided in Appendix 2-D.

2.4.3 Cancer outcomes

We identified 9 syntheses examining 15 non-overlapping associations between vitamin B_{12} and cancer outcomes. All articles were meta-analyses of prospective and retrospective observational studies. The type of cancer outcomes examined were breast (n=1), colorectal (n=3), esophageal (n=1), pancreatic (n=1), and renal cell (n=2) cancers. The vitamin exposure was measured predominantly as dietary intake (7 associations) or plasma/serum concentrations (9 associations). Supplementation levels were measured in two associations. The total sample size ranged from 246 to 321,038 participants.

2.4.3.1 Breast cancer

One meta-analysis[35] investigated the relationship between dietary intake and serum concentration of vitamin B_{12}, separately, and the risk of breast cancer. The reported estimates were $RR_{high\ vs\ low}$= 0.88 (0.77, 1.00) for the dietary exposure (14 component studies, 15,783 cases) and $RR_{high\ vs\ low}$= 0.73 (0.44, 1.22) for the serum concentration (4 component studies, 1803 cases). The authors pooled prospective cohorts and case-control studies together for estimates of dietary exposures. The pooled studies showed high levels of heterogeneity (I^2=68.9% among dietary intake studies and I^2=72.5% among biomarker studies). There was no evidence of small study effects for both associations (P_{Egger}=0.12 for dietary intake studies, P_{Egger}=0.18 for biomarker studies).

2.4.3.2 Colorectal cancer

Three meta-analyses[36-38] examined the relationship between dietary intake, supplementation, and plasma/ serum concentrations of vitamin B_{12} and colorectal cancer. Across the three syntheses, sample size ranged from 7,797 to 219,083 participants for dietary intake, 1,732 to 1,938 for blood biomarkers, and 321,038 for supplementation. The pooled estimates of the association with colorectal cancer were $RR_{high\ vs\ low}$ =0.94 (0.83, 1.07) for dietary intake and RR= 0.91 (0.86, 0.98) for dietary intake in a dose-response manner for every 4.5 ug/d increment[38] (11 component studies, 8,042 cases); SMD= -0.99 (-1.74, -0.25) for blood concentration[37] (7 component studies, 774 cases); and $RR_{high\ vs\ low}$= 1.10 (0.92, 1.32) for supplementation[36] (6 prospective cohort studies, 3,554 cases). The level of heterogeneity (I^2) ranged from 22.90% to 98.70%. Small study effects were measured for dietary studies only (I^2=62%)[38].

One of these studies[37] also reported on a combined risk of colorectal cancer and adenoma polyp (dietary intake SMD= -0.06 (-0.17, 0.05), 17 studies, 6,514 cases; biomarker SMD= -0.55 (-0.77, -0.33), 17 studies, 6,514 cases). Another of these studies[38] reported an association of total intake (combination of dietary intake and supplementation) with colorectal cancer risk ($RR_{high\ vs\ low}$=0.87 (0.78, 0.97), 6 studies, 4,345 cases).

2.4.3.3 Esophageal cancer

One meta-analysis[39] reported on the esophageal cancer risk associated with dietary intake. Ten prospective and retrospective studies (495,508 participants and 3,161 cases) were pooled and resulted in a significant association between dietary intake of vitamin B_{12} and a risk of esophageal cancer ($OR_{high\ vs\ low}$=1.30 (1.05, 1.62)). There was large heterogeneity among the included studies (I^2=73.5%) and Egger test was $p<0.05$.

2.4.3.4 Pancreatic cancer

We identified one meta-analysis examining dietary and blood levels of vitamin B_{12}, separately, and their associations with pancreatic cancer[40]. For both measures, case-control studies and prospective cohorts were pooled in a single meta-analysis. Risk estimates were comparable between the two exposure measures: $RR_{high\ vs\ low}$=0.97 (0.78, 1.16) for dietary intake (6 component studies, 1,598 cases) and $RR_{high\ vs\ low}$=1.17 (0.64,

1.70) for blood levels (3 component studies, 1,032 cases). Heterogeneity among the primary studies was small to moderate (I^2=9.10% for dietary intake and I^2=37.2% for biomarker).

2.4.3.5 Renal cell cancer

Two meta-analyses[41,42] reported on the relationships of dietary intake, supplementation, and blood levels of vitamin B_{12} with renal cell cancer. The component studies in both syntheses were few in number (2-3) with varying designs. The pooled estimates were $RR_{high\ vs\ low}$= 0.73 (0.51, 1.06) for biomarker (3 component studies, 1,578 cases), $RR_{high\ vs\ low}$= 1.14 (0.86, 1.49) for dietary intake (2 component studies, 780 cases), and $RR_{high\ vs\ low}$= 1.24 (0.90, 1.70) for supplementation (sample size not reported). Small heterogeneity (I^2= 1.4-1.5%) was reported for dietary and biomarker studies.

2.4.4 Cardiovascular outcomes

Seven evidence syntheses (5 meta-analyses and 2 systematic reviews) investigated 15 non-overlapping associations between vitamin B_{12} measures and cardiovascular outcomes. Four of the five meta-analyses were conducted on observational studies (two consisted entirely of prospective cohorts, one entirely of case-control studies, and one not reported). Total sample size ranged from 622 to 294,478 across the syntheses. Supplementation was studied in 7 associations, plasma/serum concentrations in 6 associations, and dietary intake in 2 associations. Six outcomes were analyzed as subgroups of major cardiovascular events; however, information on the included studies was not available. All but one of the associations were investigated in single synthesis: only the relationship between dietary vitamin B_{12} and risk of stroke was studied in one meta-analysis and one systematic review of comparable sample sizes and the authors reached similar conclusions. Below, we present 9 associations that were reported with adequate details.

2.4.4.1 Major cardiovascular event

One meta-analysis[43] of randomized clinical trials examining supplement intake of vitamin B_{12} in a general population (17 studies, 294,478 participants) reported a non-significant

association ($RR_{high\ vs\ low=}$ 0.99 (0.95, 1.02)) with major cardiovascular events (I^2= 37%). Small study effects were not reported. Dosage and duration of the supplementation were not reported.

2.4.4.2 Stroke

The association of dietary vitamin B_{12} intake with the risk of stroke was non-significant ($RR_{high\ vs\ low}$=1.02 (0.93, 1.12)) in one meta-analysis of prospective cohorts[44] (130,965 participants, 5,590 cases). A dose-response relationship between 3 ug/d increase in the dietary intake and risk of stroke was also non-significant (RR=1.01 (0.93, 1.12)). Heterogeneity was low (I^2=0%) and small study effects were not significant (P_{Egger}= 0.68). Another systematic review[45] examining four studies on dietary intake concluded that the association was uncertain.

2.4.4.3 Coronary heart disease

Five prospective studies (103,272 participants, 1,251 cases) were pooled in a meta-analysis[46] investigating the relationship between dietary intake and coronary heart disease. The summary estimate ($RR_{high\ vs\ low}$=0.97 (0.70, 1.25), I^2=53.6%) and dose-response effect per 3 ug/d increment (RR=0.97 (0.80, 1.14)) were not significant.

2.4.4.4 Abdominal aortic aneurysm

A meta-analysis of four case-control studies[47] (1,326 participants, 667 cases) reported a non-significant association between circulating levels of vitamin B_{12} and abdominal aortic aneurysm (SMD= -0.34 (-0.55, 0.13)). There was large heterogeneity (I^2=95.0%). Small study effects were not reported.

2.4.4.5 Venous thrombosis

One meta-analysis[48] of prospective and retrospective studies (13 studies, 4,346 participants, 2,038 case) investigated the association between plasma levels of total vitamin B_{12} and venous thrombosis and its three subtypes (following sections). The standardized mean difference between cases and controls was not significant (SMD= -

0.34 (-0.55, 0.13)). Heterogeneity was large (I^2= 91.0%) and small study effect was reported as non-significant.

2.4.4.6 Deep vein thrombosis/ Pulmonary thromboembolism

Deep vein thrombosis and pulmonary thromboembolism was examined as a combined outcome from 6 studies (2,834 participants, 1,351 cases). The summary risk estimate was SMD= -0.24 (-0.53, 0.06) with large heterogeneity (I^2= 92%).

2.4.4.7 Cerebral venous thrombosis

Two studies (622 participants, 226 cases) were pooled for cerebral venous thrombosis and produced a non-significant risk estimate of SMD= -0.45 (-1.02, 0.35). Heterogeneity was large (I^2=90%) and small study effects were not significant.

2.4.4.8 Retinal vein occlusion

The pooled risk estimate for retinal vein occlusion was SMD= -0.45 (-1.24, 0.35) based on three studies (752 participants, 398 cases). Large heterogeneity was reported (I^2= 91%).

2.4.5 Cognitive outcomes

We identified 23 syntheses (8 meta-analyses and 15 systematic reviews) that examined the relationship between vitamin B_{12} exposure and cognitive outcomes. Dementia, including Alzheimer's disease (AD) and vascular dementia, Parkinson disease, and mild cognitive impairment were investigated in 14 articles, while cognitive function and its sub-domains were examined in 15 articles. Plasma/serum concentrations was the most commonly used measure (18 articles), followed by supplementation (8 articles) and dietary intake (6 articles). Four meta-analyses examined the association between biomarkers and AD among retrospective studies with sample sizes varying from 300 to 5,048 individuals. Three meta-analyses each investigated the relationship between vitamin B_{12} biomarkers/ dietary intake and Parkinson's disease (prospective cohorts of 141,346 participants and retrospective studies of 1,659 participants) and various domains of cognitive function (prospective cohorts of 1,579 – 5,252 sample size). One meta-

analysis reported on RCTs investigating the relationship between vitamin B_{12} supplementation and cognitive function. Six systematic reviews synthesized RCTs that examined the association between vitamin B_{12} supplementation and various domains of cognitive function; these reviews included 2-5 component studies with total sample size ranging from 210 to 396 individuals. Here, we report total 23 non-overlapping associations between different measures of vitamin B_{12} exposure and unique outcomes.

2.4.5.1 Alzheimer's disease

Five meta-analyses and eight systematic reviews synthesized the relationship between biomarkers (11 articles), dietary intake (2 articles) of vitamin B_{12} and AD. For biomarkers, a meta-analysis of 33 retrospective studies[49] (5,048 participants) reported a significantly lower levels of plasma total vitamin B_{12} (pooled mean difference (MD= -47.88 (-70.75, -25.01)) among individuals diagnosed with AD compared to controls. Cerebrospinal fluid concentration of vitamin B_{12} was also significantly lower (SMD= -0.50 ($p<0.012$)) among individuals with AD compared to controls in another meta-analysis of four case-control studies[50] (300 participants). The role of dietary intake was assessed in one meta-analysis[51] of three prospective cohorts (5,254 participants), which reported a non-significant relationship ($RR_{high\ vs\ low}$=0.99 (0.99, 1.00)). Heterogeneity was high (I^2=87%) for plasma concentration and low (I^2=0%) for dietary intake. Small study effects were not reported in any of these syntheses.

Eight systematic reviews[52-59] narratively synthesized the association between blood concentrations and risk of AD. The number of component studies ranged from 2 to 8 across the reviews. All but two reviews included case-control or cross-sectional studies and the findings were mixed with respect to the direction and magnitude of the association. Two of these narrative reviews[52,59] also examined the association of dietary intake and AD with few subsets of component studies and reported no association.

2.4.5.2 Parkinson's disease

One meta-analysis examined the relationship between dietary intake and plasma levels of vitamin B_{12}, separately, with Parkinson's disease[60]. Significant association was reported

for blood levels (SMD= -0.38 (-0.51, -0.25), 10 case-control studies, 1,659 participants) but not for dietary intake ($OR_{high\ vs\ low}$=1.05 (0.76, 1.35), 2 prospective cohorts and 1 case-control study). Heterogeneity measured was low (I^2=23.4% among biomarker studies, I^2=0% among dietary studies). Small study effects were not reported.

2.4.5.3 Dementia

One meta-analysis[51] and two systematic reviews[57,58] examined dementia outcome. All three syntheses used plasma/serum concentrations of vitamin B_{12}. The meta-analysis pooled 4 prospective cohorts, which followed 2,630 older adults for 2.4-4.5 years and reported no significant association with incidence of dementia ($RR_{high\ vs\ low}$=1.00 (0.98, 1.02)). The heterogeneity among the component studies was low (I^2=9.1%). Similarly, two narrative syntheses reported inconclusive findings from cohorts and cross-sectional studies. The included studies were heterogeneous in terms of the selected biomarkers of vitamin B_{12} status (e.g., cobalamin, methylmalonic acid, holo-transcobalamin), and duration of follow-up.

2.4.5.4 Vascular dementia

One systematic review[56] synthesized two cross-sectional studies (153 participants) and reported significantly low serum levels of vitamin B_{12} among individuals with vascular dementia compared to controls, each patient group reporting a mean of 230.17 ± 7.26 pg/mL ($p<0.001$) and 280.6 ± 20.86 pg/mL ($p<0.001$), respectively.

2.4.5.5 Mild cognitive impairment

One systematic review[61] narratively synthesized five studies (one cross-sectional, one cohort, and three randomized controlled trials) and reported conflicting findings: while observational studies indicated a potential correlation between vitamin B_{12} deficiency and onset of mild cognitive impairment, randomized controlled trials did not support a positive effect of vitamin B_{12} supplementation on cognitive function.

2.4.5.6 Vascular cognitive impairment

One meta-analysis of mixed observational studies[62] reported a mean difference of -130.44 (-225.46, -35.41) in serum concentrations of vitamin B_{12} between individuals with vascular cognitive impairment and healthy controls. The authors reported that heterogeneity was low and small study effects were not significant.

2.4.5.7 Global cognition

Global cognition or cognitive function in general in the context of vitamin B_{12} status was reported by two meta-analyses and nine systematic reviews. Biomarkers were measured in 7 articles, supplementation in 5 articles, and dietary intake in 1 article. The relationship between serum/plasma concentrations and global cognitive decline was quantitatively summarized from four prospective cohort studies (1,579 participants) and no association was identified[51]. Six systematic reviews of observational studies presented inconclusive evidence with high levels of heterogeneity in the study populations (baseline vitamin B_{12} status, baseline cognition), vitamin B_{12} status measurements, cognitive test instruments, and lengths of follow-up.

The effect of vitamin B_{12} supplement use was assessed in another meta-analysis[63] of three randomized controlled trials (442 participants). The vitamin was provided at 100 mcg/d for 4 – 117.5 weeks across the included trials and no association was detected (SMD=0.02 (-0.17, 0.21)). Four systematic reviews of randomized controlled trials also did not show significant effect of the supplement use on cognitive function. The authors noted wide variations in the dose, duration, and route of supplementation.

2.4.5.8 Cognitive speed/ Executive function/ Memory

Two meta-analyses[51,63] reported on sub-domains of cognition. Vitamin B_{12} supplementation (1000 mcg/d for 4 – 117.5 weeks) had no significant effect on cognitive speed (SMD= -0.10 (-0.23, 0.04)), executive function (SMD= 0.09 (-0.09, 0.28)) or memory (SMD= 0.04 (-0.19, 0.26))[62]. Heterogeneity was low across the trials pooled for all sub-domains (I^2= 0% - 9.7%) and no small study effects were detected. The second meta-analysis examined the relationship between plasma/ serum concentration and

memory from four prospective cohorts and also reported no association (β=0.01 (-0.01, 0.03)). Heterogeneity was low (I^2= 0%).

2.4.5.9 Cognition among children

We found three systematic reviews examining the association between maternal dietary intake, maternal plasma concentration, child's dietary intake, and child's plasma/serum levels of vitamin B_{12} and cognitive function of the offspring. One of these reviews was limited to the Indian population. The component studies on maternal exposures (3-4 studies on maternal biomarker, 3-4 studies on maternal diet) largely overlapped across the three reviews and findings were inconsistent. Various types of cognitive tests were used across the component studies. A systematic review from India also reported inconsistent results from two randomized controlled trials on the effect maternal use of vitamin B_{12} supplement on cognitive, language, and motor skills of the offspring at 9 and 30 months[64]. Syntheses on child's vitamin B_{12} exposure were heterogeneous in terms of cognitive test scales (e.g., mental processing index, intelligence quotient, memory, gross motor skills, neurocognitive development, and school performance) and presented mixed findings.

2.4.6 Congenital anomalies

2.4.6.1 Neural tube defects

One meta-analysis[65] and one systematic review in an Indian population[64] investigated the relationship between maternal blood concentration of vitamin B_{12} and neural tube defects in the offspring. The quantitative synthesis (9 case-control studies, 2,133 participants, 567 cases) reported a summary effect of $OR_{low\ vs\ high}$=2.41 (1.90, 3.06). The authors reported a moderate level of heterogeneity (I^2=47%) and possible small study effects. The narrative synthesis, limited to two primary studies conducted in India, produced similar findings that low concentration of maternal total vitamin B_{12} or transcobalamin were associated with higher risk for neural tube defects.

2.4.7 Other fetal or perinatal outcomes

One systematic review[64] of randomized controlled trials and observational studies of varying designs conducted in India reported on two perinatal outcomes associated with maternal vitamin B_{12} status.

2.4.7.1 Birthweight/ Birth size

Across four studies (695 participants), low vitamin B_{12} levels in maternal blood or cord blood was associated with lower birth weight (< 2500 grams) or intrauterine growth retardation (birthweight below the 10^{th} centile for gestational age at delivery).

2.4.7.2 Insulin resistance in the offspring

Two studies (1,354 participants) produced different findings with regard to the relationship between maternal vitamin B_{12} status and insulin resistance in offspring at 6 and 9 years.

2.4.8 Pregnancy related outcomes

We identified two meta-analyses of observational studies[66,67] and two systematic reviews[64,68] reporting on the association between vitamin B_{12} biomarker and three pregnancy-related outcomes: pre-eclampsia, early pregnancy loss, and post-partum depression. Post-partum depression was examined qualitatively only.

2.4.8.1 Pre-eclampsia

A meta-analysis of 21 case-control studies[66] (3,211 participants) reported a significant association of WMD= -15.24 (-27.52, -2.95) of lower maternal blood levels of vitamin B_{12} and risk of preeclampsia. A systematic review of three case-control studies conducted in India[64] (1,025 participants) also reported an inverse relationship between vitamin B_{12} biomarker and risk of pre-eclampsia.

2.4.8.2 Early pregnancy loss

Low plasma levels of vitamin B_{12} were significantly associated with high risk of early pregnancy loss (SMD=0.61, (0.30, 0.92)), pooled from two case-control studies involving 100 cases[67]. Heterogeneity was small (I^2=8.12%).

2.4.8.3 Post-partum depression

The relationship of vitamin B_{12} concentration with post-partum depression was examined in two studies in one systematic review[68] (1,029 participants). One of these studies reported a significant finding, while the other did not.

2.4.9 Autoimmune disorders

2.4.9.1 Atopic dermatitis

One meta-analysis[69] (86 participants) and one systematic review[70] (71 participants) reported on the effect of vitamin B_{12} supplement use on treatment of atopic dermatitis. The two articles each synthesized two randomized controlled trials of comparable sample size, with one trial overlapping between them. The supplementation was 0.7% topical administered 2-3 times per week for 4-8 weeks across the component trials. The summary effect showed significant improvement in the symptoms score (MD=-3.19 (-4.27, -2.10)). Heterogeneity was low (I^2=0%).

2.4.10 Skeletal outcomes

One meta-analysis[71] and one systematic review[72] reported on the relationship between different measures of vitamin B_{12} and three skeletal outcomes among older adults: bone mineral density, fracture risk, and osteoporosis/ bone loss. All of the six associations investigated were non-overlapping. The sample size ranged from 649 to 70,327 participants across the associations. Blood concentration was measured in six associations and dietary intake in two associations. Quantitative synthesis was available only for bone mineral density among postmenopausal women[71].

2.4.10.1 Bone mineral density in postmenopausal women

The relationship between serum concentration of vitamin B_{12} and bone mineral density among postmenopausal women was meta-analyzed from six case-control studies (288 cases) and significant mean differences were reported (MD=11.22 (3.06, 19.38))[71]. The authors reported small heterogeneity (I^2=17%). Small study effects were not reported.

2.4.10.2 Bone mineral density in older adults

A systematic review[72] synthesized two prospective cohort studies (7,173 participants) measuring dietary intake and 10 cross-sectional and cohort studies (4,903 participants) measuring biomarkers among older adults. The authors reported no significant association from the two dietary intake studies and conflicting findings from the ten articles measuring biomarkers.

2.4.10.3 Fracture risk in older adults

The systematic review of bone mineral density[71] synthesized evidence from three cohort studies of fracture risk (70,327 participants) and reported no significant association between dietary intake of vitamin B_{12} and risk of fracture. Biomarkers were used in two of the cohort studies (5,768 participants) and reported directions of association were different.

2.4.10.4 Osteoporosis/ Bone loss in older adults

The same review[72] synthesized four cross-sectional and cohort studies (4,022 participants) investigating the relationship between blood levels of vitamin B_{12} and risk of bone loss or osteoporosis. Conflicting results were reported from the studies.

2.4.11 Neurological outcomes

We identified two meta-analyses[73,74] and four systematic-reviews[75-78] reporting on the relationship between vitamin B_{12} (supplementation or biomarker) and five neurological outcomes: peripheral neuropathy, diabetic peripheral neuropathy, multiple sclerosis, post-herpetic neuralgia, and neurologic function (among older adults). Total seven associations were synthesized. Peripheral neuropathy, diabetic peripheral neuropathy, and multiple sclerosis outcomes were synthesized quantitatively. Total sample size ranged from 207 to 12,371 participants.

2.4.11.1 Peripheral neuropathy

Lowered plasma concentration of vitamin B_{12} was significantly associated with peripheral neuropathy ($OR_{low\ vs\ high}$=1.51 (1.23, 1.84)) based on 32 cross-sectional and case-control

studies (12,371 participants and 2,948 cases)[74]. Heterogeneity among the included studies was moderate (I^2=43.3%) and small study effects were reported as not significant. The authors reported a subgroup analysis of randomized controlled trials of the vitamin supplementation (4 studies, 446 participants), which produced smaller effect size in the same direction ($OR_{low\ vs\ high}$=1.36 (0.66, 2.79), I^2=28.9%). The supplementation used was heterogeneous, ranging from 0.75 to 2.0 mg/d of methylcobalamin for 28-168 days alone or in combination with other nutrients or medications.

2.4.11.2 Diabetic neuropathy

One meta-analysis of 13 randomized controlled trials[79] pooled the effects of adjunctive methylcobalamin supplementation on treatment of diabetic neuropathy in two comparative settings: routine treatment and other B vitamins. The authors reported significant treatment effects in both settings: $OR_{=}$11.47 (4.05, 32.54) compared to routine treatment and OR=12.19 (9.20, 16.14) compared to other B vitamins. Levels of heterogeneity were low to moderate (I^2=55.8% for treatment vs routine; I^2=0% for treatment vs other B-vitamins) and small study effects were not significant for the B-vitamin comparison analysis. Another systematic review[76] investigated the same association from three interventional studies (352 participants). Each of the trials used different modes of supplementation (intramuscular, oral, intravenous) and different comparators (oral nortriptyline, oral epalrestat). The findings were inconsistent.

2.4.11.3 Multiple sclerosis

One meta-analysis of case-control studies[73] reported a significant difference in serum concentration of vitamin B_{12} among individuals with versus without multiple sclerosis (SMD= -0.24 (-0.42, -0.06), 8 component studies, 414 cases). Heterogeneity was low (I^2=29.3%). One systematic review[75] reported inconsistent findings from four small-scale studies (total 207 participants) examining the relationship between serum concentrations of vitamin B_{12} and multiple sclerosis.

2.4.11.4 Post-herpetic neuralgia

Three randomized controlled trials (total 268 participants) were narratively synthesized[76] to examine the effects of subcutaneous/ transcutaneous cobalamin on relief of neuropathic pain compared to placebo. The trials showed significant benefits in reducing intensity of pain.

2.4.11.5 Neurologic function among older adults

One systematic review[78] synthesized a total of 12 longitudinal and cross-sectional studies examining the relationship between vitamin B_{12} biomarkers and various measures of neurological function and neuropathy symptoms. The authors reported the findings separately for generally healthy older adults (8 studies, 4,535 participants) and for older adults with clinically or biochemically defined vitamin B_{12} deficiency (4 studies, 1,134 participants). The risk estimates from the included studies were heterogeneous in effect size and direction of association.

2.4.12 Psychiatric outcomes

We identified seven syntheses (one meta-analysis[80] and six systematic reviews[81-86]) examining psychiatric conditions. The outcomes investigated were schizophrenia, depression, psychiatric symptoms in older adults with depression, and autism spectrum disorder. Only schizophrenia and depression in the general population were synthesized quantitatively. The sample size ranged from 87 to 21,837 participants across the syntheses. Of the five associations investigated, one was examined by three studies and these reviews included overlapping original studies.

2.4.12.1 Schizophrenia

A meta-analysis of 13 case-control studies[80] (2,113 participants) reported a non-significant relationship between serum concentration of vitamin B_{12} and schizophrenia (SMD=0.09 (-0.03, 0.2)). The authors reported moderate level of heterogeneity (I^2=40%) and no small study effects (P_{Egger}=0.58).

2.4.12.2 Depression

A meta-analysis of 12 observational studies (11 cross-sectional, 1 prospective cohort) examined the relationship between dietary intake of vitamin B_{12} and risk of depression among adults[81]. Compared to the lowest category of intake, the highest category had a summary effect of $RR_{high\ vs\ low}$=0.86 (0.75, 0.99) across the studies. The authors also reported subgroup analyses by sex: $RR_{high\ vs\ low}$=0.94 (0.77, 1.15) for males and $RR_{high\ vs\ low}$=0.79 (0.65, 0.97) for females. Levels of heterogeneity were low to medium (I^2=31.3% for overall effect, I^2=47.5% for males, and I^2=3.1% for females).

2.4.12.3 Depression among older adults

One systematic review identified four cross-sectional studies focusing on depression among adults aged 60 years or older[82]. Plasma/serum concentrations of vitamin B_{12} were not significantly lower among participants with depression in all of these studies; however, one study suggested potential effect modification by sex.

2.4.12.4 Psychiatric symptoms in older adults with depression

Two retrospective studies were presented in one systematic review[83] discussing the relationship between the vitamin biomarkers and cognitive symptoms among older adults with depression or other neuropsychiatric conditions. Outcome measures included memory loss, cognitive function, behavioral disturbance, and sensorimotor dysfunctions and were significantly associations with lower concentrations of vitamin B_{12}.

2.4.12.5 Autism spectrum disorder among children

Three systematic reviews[84-86] synthesized small-scale trials of supplementing vitamin B_{12} among children with autism spectrum disorder. All three reviews included the same two randomized controlled trials of subcutaneous methylcobalamin (64.5 ug/kg every 3 days for 6 weeks, 75 ug/kg every 3 days for 8 weeks) and one review examined an additional cohort study (25-30 ug/kg per day for 6-25 months). Positive changes in core symptoms were reported.

2.4.13 Anemia outcome

2.14.13.1 Megaloblastic anemia

One meta-analysis of 17 case-control studies[87] (625 cases) reported a significant association between serum concentrations of vitamin B_{12} and the risk of megaloblastic anemia (SMD= -2.54 (-3.39, -1.69) among Chinese population. Heterogeneity was high among the component studies (I^2=97.3%). Small study effects were not reported.

2.4.14 Other outcomes

2.4.14.1 Retinal vascular occlusive disease

One meta-analysis[88] of four case-control studies (287 cases) reported a non-significant relationship (SMD= -0.06 (p=0.48)) between serum concentration of vitamin B_{12} and the risk of retinal vascular occlusive disease. Heterogeneity or small study effects were not reported.

2.4.14.2 Normal tension glaucoma

Two case-control studies (90 cases) were quantitatively synthesized[89] and significant relationship was reported between serum vitamin B_{12} levels and the risk of normal tension glaucoma (WMD=5.81 (3.53, 15.14)). Heterogeneity was high (I^2=89%).

2.4.14.3 Phenylketonuria

One meta-analysis[90] pooled six observational studies (307 cases) and reported a non-significant association between vitamin B_{12} biomarkers and phenylketonuria (SMD=0.19 (-0.91, 1.29)). Heterogeneity was high (I^2=94%).

2.4.14.4 Helminth infection

One systematic review[91] examined five cross-sectional and case-control studies (1,391 participants) and reported inconsistent findings on blood concentrations of vitamin B_{12} between individuals infected with helminths compared to controls.

2.4.14.5 Leprosy

Two cross-sectional studies (total 1,225 participants) were narratively synthesized[91]. The component studies found higher concentration of serum vitamin B_{12} in the lepromatous

group compared to other clinical groups and among late-disease patients compared to early-disease patients.

2.4.15 Credibility Assessment

Of the 85 associations examined in the syntheses, none met our pre-defined criteria for convincing or highly suggestive level of credibility. Most of the syntheses were not sufficiently powered to detect relationships with high levels of credibility (>1,000 cases or > 20,000 participants for continuous outcomes). Level of heterogeneity among the component studies was moderate to high for a large proportion of the syntheses (see Appendix 2-C for the full list of credibility assessment). Four significant associations and seven non-significant associations met the criteria for suggestive level of credibility (Table 2-2).

Higher total intake of vitamin B_{12} was inversely associated with colorectal cancer risk (RR=0.87 (0.78, 0.97), compared to lower total intake, among 262,404 participants (4,345 cases)[38]. A large number of the sample were from prospective cohort studies. Heterogeneity was low (I^2=22.9%) and the authors reported no evidence of small study effect (P_{Egger}=0.62).

In the opposite direction of association, higher dietary intake of vitamin B_{12}, compared to lower intake, was also associated with increased risk of esophageal cancer (OR=1.30 (1.05, 1.62)) among 992,269 participants (3,332 cases), recruited mostly from prospective cohort studies. The authors reported high level of heterogeneity among the included studies (I^2=73.5%) but no evidence of small study effects (P_{Egger}>0.05)[39].

Lower serum concentrations of vitamin B_{12} was associated with the presence of peripheral neuropathy (OR=1.51 (1.23, 1.84)) among 12,371 participants (2,948 cases). All of the component studies were retrospective in nature. The authors reported moderate level of heterogeneity (I^2=43.3%) and no evidence of small study effects[74].

Highest versus lowest levels of dietary intake of vitamin B_{12} were associated with lower risk of depression (RR=0.86 (0.75, 0.99)) pooled from 21,837 participants (3,172 cases)[81]. Most (93.8%) of the participants were from cross-sectional studies. The outcome measure used across the component studies also varied. The authors reported I^2=31.30% and P_{Egger}=0.48.

Meanwhile, the following associations were reported as non-significant based on large-scale meta-analyses with >1,000 cases: vitamin B_{12} supplement use – colorectal cancer (RR=1.10 (0.92, 1.32), 321,038 participants and 3,554 cases from 6 prospective cohorts); dietary intake - pancreatic cancer (RR=0.97 (0.78, 1.16), 1,598 cases from predominantly retrospective studies); biomarker – pancreatic cancer (RR=0.73 (0.51, 1.06), 1,032 cases from 3 prospective cohorts); dietary intake – renal cell cancer (RR=1.14 (0.87, 1.49), 127,826 participants and 1,578 cases from predominantly retrospective studies); supplement use – major cardiovascular events (RR=0.99 (0.95, 1.02), 294,478 participants and 156,663 cases from 17 randomized controlled trials); dietary intake – coronary heart disease (RR=0.97 (0.70, 1.25), 103,272 participants and 1,251 cases from 5 prospective cohorts); and dietary intake – stroke (RR=1.02 (0.93, 1.12), 130,965 participants and 5,590 cases from 10 prospective cohorts).

2.5 Discussion

2.5.1 Summary of findings

We have undertaken a comprehensive approach to identify and synthesize the evidence on the relationship between vitamin B_{12} and health outcomes by triangulating evidence from multiple measures of B_{12} exposure and study designs in systematic reviews and meta-analyses. Overall, methodological quality of the syntheses retrieved was low and we did not find strong evidence on any measure of the vitamin for any health outcome.

Most of the identified associations had only a few supporting syntheses with each synthesis integrating a small number of primary studies. Only 18 syntheses (27%) examined vitamin B_{12} as a sole exposure; in the remaining reports, vitamin B_{12} was one of multiple number of exposures investigated. In half of the syntheses, the authors did not

provide quantitative analyses due to the substantial heterogeneity among the studies or small amount of evidence identified. Moreover, the majority of the meta-analyses of observational studies (19 out of 27) consisted entirely or predominantly of case-control or cross-sectional studies, in which temporality of the association could not be ascertained. Even among meta-analyses of prospective cohort studies or randomized controlled trials, large variations in exposure measurement (e.g., quartile or quintile cutoffs, differences in dosage or duration of follow-up) were apparent, adding to the uncertainty of observed associations. In addition, authors tended to conclude in favor of a null effect when pooled estimates suggested a wide confidence interval representing substantial uncertainty.

2.5.2 Evidence of suggestive level of credibility

We examined the four statistically significant associations with a suggestive level of credibility[38,39,74,81] in more detail, including associations between total intake and colorectal cancer; dietary intake and esophageal cancer; dietary intake and depression; and serum concentration and peripheral neuropathy. We noted several concerns: variability in the pooled exposure, i.e., differences in the cut-off threshold for categorizing dietary intake or blood concentration for comparison[38,39,81]; heterogeneity in outcome definitions, i.e., aggregation of different assessment scales[38,81]; and varying levels of confounder adjustment across the primary studies[38,81]. In addition, it was unclear if the authors investigating dietary intake calibrated the values across the countries in which the component studies were conducted. Self-reported dietary intake, typically assessed using food frequency questionnaires or recall methods, is prone to systematic error and bias and dietary references values vary across countries or regions[92]. These heterogeneities require a nuanced understanding of the potential biases inherent in each synthesis.

We note several potential mechanisms that may underlie the association of vitamin B_{12} with cancers and neurological disorders. Vitamin B_{12} is critically involved in one-carbon metabolism, which is required for numerous methylation reactions, biosynthesis of nucleotide, DNA replication and repair, and regulation of gene expression[93-97]. Disruptions in one-carbon metabolism may affect genomic integrity[98], and epigenetic

modifications involving tumor suppressor genes[99]. Vitamin B_{12} also has been associated with higher anti-oxidant and anti-inflammatory capacity[100]. In addition, vitamin B_{12} is a required coenzyme for methylmalonyl CoA mutase, which catalyzes the isomerization of methylmalonyl CoA to succinyl CoA[101,102], leading to oxidation of odd-chain fatty acids and catabolism of ketogenic amino acids. Odd-chain fatty acids are implicated in suppression of cancer cells[103,104] and ketogenic amino acid, which metabolizes into acetyl-CoA, plays an important role in myelin synthesis[105]. Vitamin B_{12} deficiency is known to cause spinal cord lesions and demyelination[106] and plays an important role in regeneration of peripheral nerves[107].

The potential link between vitamin B_{12} and depression may be explained by the vitamin's role in homocysteine metabolism and the synthesis of monoamine neurotransmitters. SAM, a product of homocysteine metabolism dependent on adequate supply of vitamin B_{12}, is important in the turnover of dopamine and serotonin[108-110], while increased level of homocysteine results in activation of N-methyl-D-aspartate glutamate receptors[111], which inhibits methylation reactions in the central nervous system and undermines brain functions[112]. Evidence on the effectiveness of SAM as an adjunctive therapy for depressive disorders is inconclusive with randomized controlled trials showing different directions and magnitudes of effectiveness[113].

2.5.3 Important considerations in the present and future vitamin B_{12} research

Several factors should be accounted for when investigating the potential health effects of vitamins B_{12}. First, robust measurement of vitamin exposure is challenging[114,115]. Multiple biomarkers are used in clinical and research settings, but each has limitations without consensus on the best indicator of status. While it is ideal to use a combination of measures, e.g., total vitamin B_{12}, holoTC, and methylmalonic acid[114], to assess status, this is not commonly performed due to practical and financial limitations associated with performing multiple measures. For example, in the syntheses identified in our study, plasma/serum total vitamin B_{12} was the primary biomarker used.

Second, compared to other B-vitamins, particularly folate, dietary intake of vitamin B_{12} is reported to correlate less with biomarkers likely as a result of the non-linear absorption of the food-bound form. Apart from in clinical B_{12} deficiency arising from loss of intrinsic factor (pernicious anemia)[1,10], malabsorption is associated with older age[1,9,116], use of medications such as proton pump inhibitors[116] or methotrexate[117], metformin, H2-receptor antagonists and underlying comorbid conditions, which may confound the true association of vitamin intake with status, and in turn, with health outcomes. The syntheses retrieved in this study did not report full adjustment for or stratification by known confounders. This might have contributed to the largely small effect sizes or wide confidence intervals reported by the authors.

Third, because vitamin B_{12} works in the context of the folate and methionine cycles, its action and function depends on the status of other related nutrients, i.e., riboflavin, vitamin B_6, and choline, at an individual level. The interactive actions of nutrients in the one-carbon metabolism were not within the scope of our review. A comprehensive investigation examining the health outcomes associated with different combinations of one-carbon nutrients would benefit our understanding in this field.

Fourth, several genetic variants are associated with vitamin B_{12} status, thus moderating the relationship between vitamin B_{12} and health outcomes. For example, a recent review [118] reported 59 single-nucleotide polymorphisms from 19 genes that are associated with vitamin B_{12} status, which may also interact with the environment[119]. While the precise mechanism of genetic effects is yet to be elucidated, there appears to be ethnic differences in the distribution of genetic factors that determine vitamin B_{12} status[118]. A systematic synthesis of evidence examining the associations between vitamin B_{12}-related genetic variants and health outcomes will add contextual understanding of the phenotypic relationships identified in our current analyses.

The last consideration is that the health outcomes associated with vitamin $B_{12,}$ as for other vitamins likely depend to a large extent on baseline status in individuals[120-123]. Often the largest beneficial health effect related to higher vitamin intake is seen in individuals with

low or deficient status with baseline vitamin status predicting disease onset or treatment outcome[121]. Unfortunately, we did not identify syntheses that accounted for baseline vitamin intake or status when measuring the effect of its exposure.

2.5.4 Strengths and limitations

We employed a broad search across four key databases in medicine and healthcare, and we included syntheses examining various study designs, study populations, and exposure/outcome measures. We also included systematic reviews without meta-analyses to capture as much evidence as possible on health outcomes, for which measurements or indices have not been fully standardized for quantitative comparison. In addition, we used standardized methods of piloting and duplication to screen, extract, and assess the retrieved articles.

Nevertheless, we were restricted by the inherent limitations of umbrella review methodology. Umbrella reviews rely on systematic reviews and meta-analyses as analytic units to identify and quantify associations between exposures and outcomes. Thus, only evidence that has already been reported in a systematic review or meta-analysis will be captured in an umbrella review. There are likely many primary studies and health outcomes that have not been included in an existing review. Also, as risk estimates are aggregated across the populations, small effect sizes or equivocal findings in subpopulations may be diluted or missed altogether, particularly in the presence of large heterogeneity among the included studies. We made efforts to mitigate this problem by separately categorizing any population subgroups or subcategories of health outcomes in our analyses, and by identifying syntheses reporting equivocal associations based on sufficiently powered samples. However, we note that an effect on subgroups or subcategories might have been missed if the identified syntheses combined all groups in their pooled analyses. We advise caution when applying the findings of umbrella reviews in developing population health recommendations.

A critical assessment of the influence of approaches used in each synthesis to pool component study data, i.e., differences in definitions between high versus low intake or

status, combination of different outcome measurement tools, pooling heterogeneous population groups, adjustment for potential confounders, etc., was not undertaken at this time as we prioritized identifying associations with suggestive level of evidence at an umbrella level. Possible omission of more recent primary studies yet to be synthesized in systematic reviews or meta-analyses is another limitation of umbrella reviews.

Our criteria for credibility assessment can also be further improved to incorporate important factors such as design of component studies, given the known limitations of observational study designs. We also note that different approaches to classifying the credibility of evidence may result in different findings. A recent review reported that approximately half of the umbrella reviews published as of 2022 assessed certainty of evidence and the methodologies used to assess credibility varies widely in the absence of formal guidance[34].

2.6 Conclusion

We did not identify convincing or highly suggestive level of evidence on an independent association of vitamin B_{12} with any health outcomes at the population level reported in systematic reviews and meta-analyses. Four significant associations with colorectal cancer, esophageal cancer, peripheral neuropathy, and depression were identified to be of suggestive credibility. The evidence identified in our umbrella review was mostly weak, and three out of the four associations of suggestive credibility relied heavily on retrospective studies and reported large heterogeneity. While umbrella reviews by design do not represent all scientific evidence on a topic, they are one method to assess the totality of syntheses available in the evidence. We note that more studies with clearly defined thresholds and populations are needed to gain better understanding of the role of vitamin B_{12} in population health.

2.7 References

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2.8 Figures and Tables

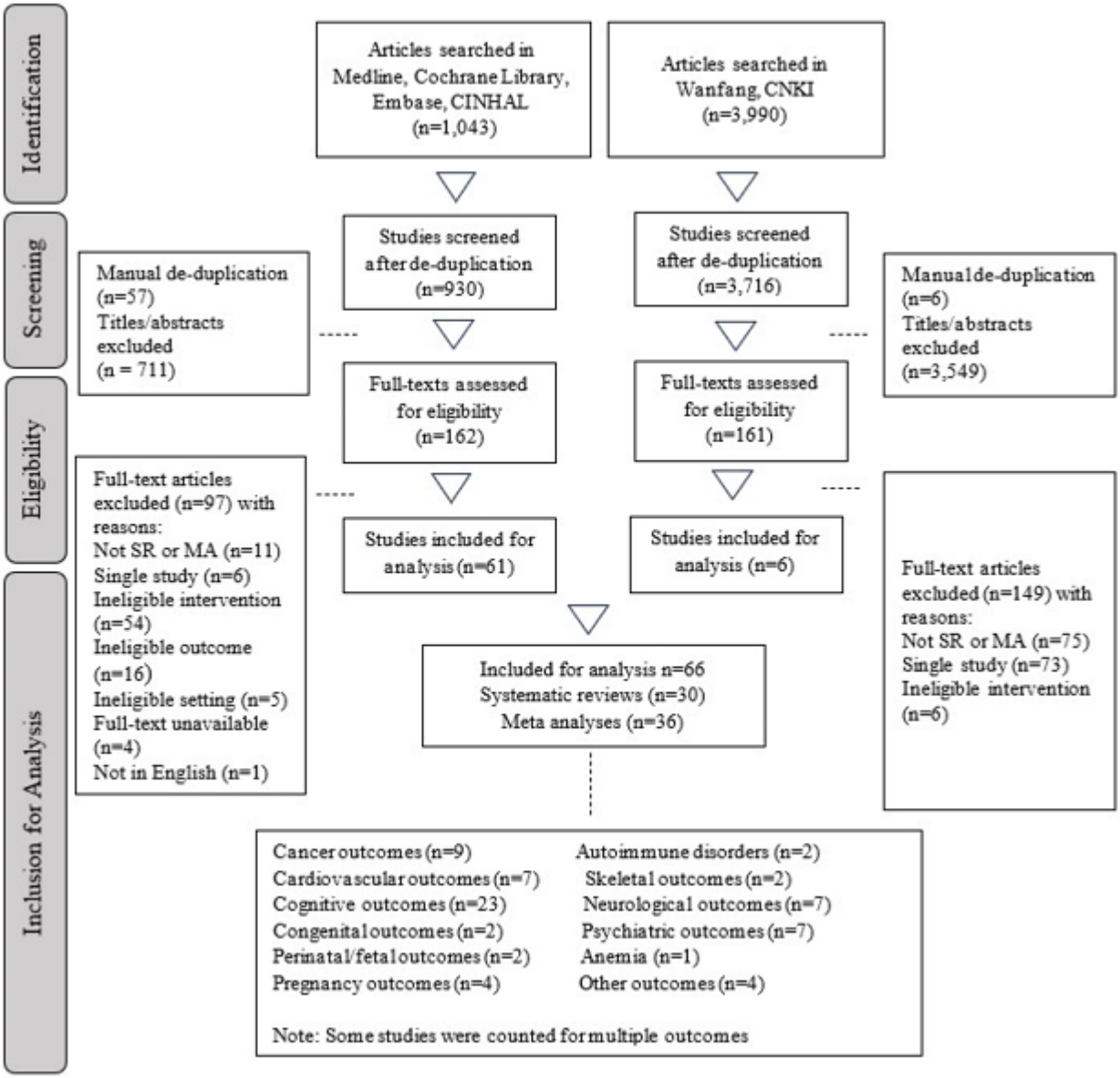

Figure 2-1. PRISMA diagram of the process of selecting syntheses examining the relationship of vitamin B12 and health outcomes

Health Outcome	Meta-analysis	No meta-analysis
Cancer	●●●●●●●●●●●●●●	
Cardiovascular disease	●●●●●●●●●●●●●	●●
Cognitive outcomes	●●●●●●●●●●●●	●●●●●●●●●●●●●●●●
Congenital anomalies	●	●
Perinatal/ fetal outcomes		●●
Pregnancy outcomes	●●	●●
Autoimmune disorders	●	●
Skeletal outcomes	●	●●
Neurological disorders	●●●●●	●●●●
Psychiatric disorders	●●	●●
Anemia	●	
Other outcomes	●●	●●

● represents a meta-analysis of unique exposure-outcome association

Figure 2-2. Distribution of the volume of evidence on health effects of vitamin B_{12} by health outcome

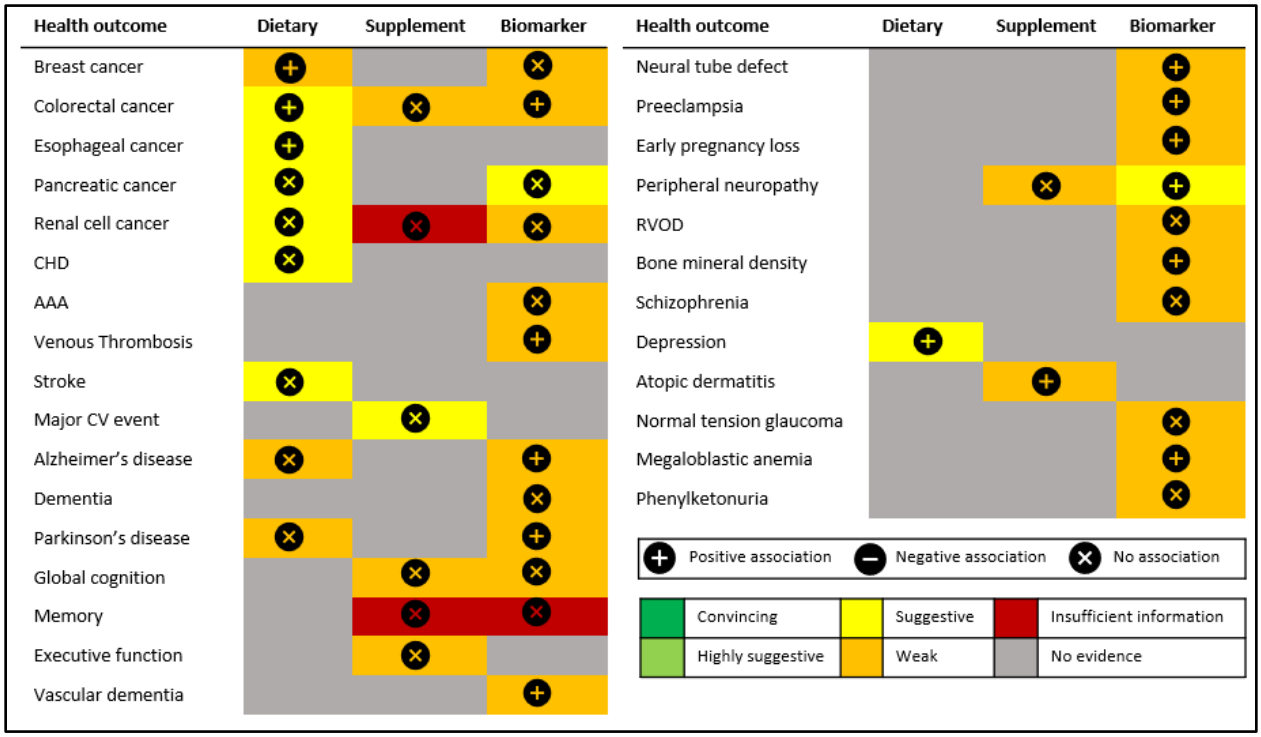

Figure 2-3. Summary of meta-analysis findings of vitamin B_{12} and health outcomes by measure of exposure

Table 2-1. Characteristics of the 66 included syntheses on the association between vitamin B_{12} and health outcomes

Health outcome	B_{12} exposure	Synthesis type	Included datasets (Total sample)	Component study design	First author (Year) ††
Cancer outcomes (8 outcomes, 9 studies, 15 associations)					
Breast cancer	Dietary intake	MA	14 (367,118)	7 prospective cohort (354,349) 7 case-control (12,769)	Wu (2013)[35]
	Biomarker*	MA	4 (3,606)	4 prospective cohort	
Cervical neoplasia	Biomarker	MA	2 (962)	2 nested case-control	Garcia-Closas (2015)[124]
HPV persistence	Biomarker	MA	2 (246)	2 prospective cohort	
Colorectal cancer	Supplement	MA	6 (321,038)	6 prospective cohort	Liu (2015)[36]
Colorectal cancer	Dietary intake	MA	8 (7,797)	8 case-control	Shiao (2018)[125]
		MA	4 (1,998)	4 prospective cohort	
	Biomarker	MA	8 (8,309)	8 prospective cohort	
		MA	6 (1,938)	6 case-control	
Colorectal cancer/AP	Dietary intake	MA	17 (14,864)	5 prospective cohort (2,818) 12 case-control (12,046)	
	Biomarker	MA	20 (11,730)	9 prospective cohort (9,121) 11 case-control (2,609)	
Colorectal cancer	Dietary intake	MA	11 (219,983)	3 prospective cohort (203,276) 8 case-control (16,707)	Sun (2016)[38] ††
	Total intake**	MA	6 (262,404)	3 prospective cohort (258,098) 3 case-control (4,306)	
	Biomarker	MA	4 (1,732)	4 case-control	
Esophageal cancer	Dietary intake	MA	10 (992,269)	8 case-control (10,320) 2 prospective cohort (981,949)	Qiang (2018)[39]
Pancreatic cancer	Dietary intake	MA	6 (NR)	4 case-controls (1,170) 2 prospective cohort (428)	Wei (2020)[40]
	Biomarker	MA	3 (NR)	2 nested case-control (334) 1 prospective cohort (698)	
Renal cell carcinoma	Dietary intake	MA	3 (127,826)	2 cases-control (125,094) 1 prospective cohort (1,827)	Clasen (2020)[41]
	Biomarker	MA	2 (NR)	2 nested case-control	
Renal cell cancer	Biomarker	MA	2 (1,560)	1 nested case-control (448) 1 case-control (1,112)	Mao (2015)[42]

	Supplement	MA	2 (NR)	1 prospective cohort (NR) 1 case-control (2,301)	
Cardiovascular outcomes (14 outcomes, 7 studies, 15 associations)					
Major CV event	Supplement	MA	17 (294,478)	17 RCT	Myung (2013)[43]
CV death	Supplement	MA	9 (NR)	9 RCT	
Angina	Supplement	MA	4 (NR)	4 RCT	
MI	Supplement	MA	14 (NR)	14 RCT	
Non-fatal MI	Supplement	MA	4 (NR)	4 RCT	
Stroke	Supplement	MA	5 (NR)	5 RCT	
TIA	Supplement	MA	2 (NR)	2 RCT	
CHD	Dietary intake	MA	5 (103,272)	5 prospective cohort	Jayedi (2019)[46]
AAA	Biomarker	MA	5 (1,326)	5 case-control	Takagi (2017)[47]
Venous thrombosis	Biomarker	MA	13 (4,380)	NR	Zhou (2012)[48]
DVT/PTE	Biomarker	MA	6 (2,834)	6 case-control	
CVT	Biomarker	MA	2 (622)	NR	
Retinal vein occlusion	Biomarker	MA	3 (752)	NR	
Stroke	Dietary intake	MA	10 (130,965)	10 prospective cohort	Chen (2020)[44]
Stroke	Dietary intake	SR	4 (130,210)	4 prospective cohort	Iacoviello (2018)[45]
CVD	Biomarker	SR	3 (17,472)	2 case-control (1,680) 1 prospective cohort (15,792)	Eikelboom (1999)[126]
Cognitive outcomes (10 outcomes, 23 studies, 23 associations)					
AD	Biomarker	MA	33 (5,048)	30 case-control (4,781) 3 cross-sectional (267)	Lopes da Silva (2014)[49]
AD	Biomarker	MA	14 (1,462)	14 case-control	Xie (2017)[127]††
AD	Biomarker	MA	22 (1,426)	22 case-control	Zhu (2019)[128] ††
AD	CSF***	MA	4 (300)	4 case-control	De Wilde (2017)[50]
AD	Dietary intake	MA	3 (5,254)	3 prospective cohort	Doets (2012)[51] ††
Dementia	Biomarker	MA	4 (2,630)	4 prospective cohort	
Global cognition	Biomarker	MA	4 (1,579)	4 prospective cohort	
Memory	Biomarker	MA	4 (3,460)	4 prospective cohort	
Global cognition	Supplement	MA	3 (442)	RCT	Markun (2021)[63] ††
Cognitive speed	Supplement	MA	3 (1,049)	RCT	
Executive function	Supplement	MA	3 (1,252)	RCT	
Memory	Supplement	MA	3 (NR)	RCT	
Parkinson's disease	Dietary intake	MA	3 (141,963)	2 prospective cohort (141,346) 1 case-control (617)	Shen (2015)[60]

	Biomarker	MA	10 (1,659)	10 case-control	
AD	Biomarker	SR	6 (NR)	6 prospective cohort	Dangour (2010)[52]
	Dietary intake	SR	3 (NR)	3 prospective cohort	
AD	Biomarker	SR	2 (NR)	2 case-control	Athanasopoulos (2016)[53]
AD	Dietary intake	SR	3 (NR)	3 prospective cohort	Shah (2013)[59]
	Biomarker	SR	4 (NR)	1 prospective cohort	
				1 case-control	
				2 cross-sectional	
Cognitive function	Biomarker	SR	2 (NR)	1 prospective cohort	
				1 cross-sectional	
AD	Biomarker	SR	3 (1,052)	2 prospective cohort (780)	Ellinson (2004)[54]
				1 case-control (272)	
Cognitive function	Biomarker	SR	2 (470)	1 prospective cohort (410)	
				1 case-control (60)	
AD	Biomarker	SR	7 (3,413)	2 prospective cohort (1,095)	Raman (2007)[55]
				5 case-control (2,318)	
Cognitive function	Biomarker	SR	8 (2,637)	7 prospective cohort (2,556)	
				1 case-control (81)	
Vascular dementia	Biomarker	SR	2 (153)	2 cross-sectional	Perez (2012)[56]
AD	Biomarker	SR	2 (137)	2 cross-sectional	
Vascular cognitive impairment (China)	Biomarker	MA	7 (671)	NR (reported as observational)	Yang (2014)[62]
MCI	Biomarker	SR	2 (NR)	1 cross-sectional	Etgen (2011)[61]
				1 prospective cohort	
Cognitive function	Supplement	SR	3 (NR)	3 RCT	
Dementia	Biomarker	SR	2 (NR)	1 case-control	Vogel (2009)[57]
				1 cross-sectional	
AD	Biomarker	SR	4 (NR)	3 case-control	
				1 cross-sectional	
Cognitive function	Biomarker	SR	3 (NR)	1 prospective cohort	
				2 cross-sectional	
	Supplement	SR	6 (NR)	6 RCT	
Cognitive function	Dietary intake	SR	3 (4,674)	3 prospective cohort	Barnes (2014)[129]
	Supplement	SR	5 (283)	5 RCT	
	Biomarker	SR	6 (4,228)	6 prospective cohort	
Cognitive function	Supplement	SR	5 (NR)	5 RCT	Jia (2008)[130]

Cognitive function	Biomarker	SR	22 (8,438)	22 prospective cohort	O'Leary (2012)[58]††
AD	Biomarker	SR	8 (3,697)	8 prospective cohort	
Dementia	Biomarker	SR	8 (5,902)	8 prospective cohort	
AD or dementia	Biomarker	SR	3 (266)	3 prospective cohort	
Cognitive function	Supplement	SR	6 (210)	6 RCT	Balk (2007)[131]
Cognition	Maternal diet	SR	4 (NR)	4 prospective cohort	Venkatramanan (2016)[132]††
(Offspring)	Maternal blood†	SR	4 (NR)	4 prospective cohort	
Cognition	Dietary intake	SR	3 (NR)	1 RCT	Venkatramanan (2016)[132]††
(Children)				1 prospective cohort	
				1 cross-sectional	
	Biomarker	SR	5 (NR)	2 cross-sectional	
				2 prospective cohort	
				1 nested case-control	
Cognition	Maternal diet	SR	4 (8,617)	4 prospective cohort	Veena (2016)[133]
(Offspring)	Maternal blood	SR	3 (798)	3 prospective cohort	
Cognition	Maternal blood	SR	3 (767)	3 prospective cohort	Behere (2021)[64]††
(Offspring, India)	Maternal supplement	SR	2 (396)	2 RCT	
Congenital anomalies (1 outcome, 2 studies, 2 associations)					
NTD	Maternal blood	MA	9 (2,133)	9 case-control	Wang (2012)[65]††
NTD (India)	Maternal blood	SR	2 (1,200)	2 case-control	Behere (2021)[64]††
Perinatal/ fetal outcomes (2 outcomes, 1 study, 2 associations)					
Birthweight/size (India)	Maternal blood	SR	4 (695)	4 prospective cohort	Behere (2021)[64]††
Insulin resistance (India)	Maternal blood	SR	2 (1,354)	2 prospective cohort	
Pregnancy related outcomes (3 outcomes, 4 studies, 4 associations)					
Preeclampsia	Biomarker	MA	21 (3,211)	21 case-control	Mardali (2021)[66] ††
Early pregnancy loss	Biomarker	MA	2 (202)	2 case-control	Bala (2021)[67]
Preeclampsia (India)	Biomarker	SR	3 (1,025)	3 case-control	Behere (2021)[64]††
Postpartum depression	Biomarker	SR	2 (1,029)	1 cross-sectional (62)	Trujillo (2018)[68]
				1 prospective cohort (967)	
Autoimmune disorders (1 outcome, 2 studies, 1 association)					
Atopic dermatitis score	Supplement	MA	2 (86)	2 RCT	Zhu (2019)[69]
Atopic dermatitis symptoms	Supplement	SR	2 (71)	2 RCT	Vieira (2016)[70]
Skeletal outcomes (3 outcomes, 2 studies, 6 associations)					
BMD (Postmenopausal)	Biomarker	MA	6 (649)	6 case-control	Zhang (2014)[71]

BMD	Dietary intake	SR	2 (7,173)	2 prospective cohort	Macedo (2017)[72]††
(Older adults)	Biomarker	SR	10 (4,093)	1 prospective cohort (117)	
				9 cross-sectionals (3,976)	
Fracture risk	Dietary intake	SR	3 (70,327)	3 prospective cohort	
(Older adults)	Biomarker	SR	2 (5,768)	2 prospective cohort	
Osteoporosis	Biomarker	SR	4 (4,022)	3 cross-sectional (3,020)	
(Older adults)				1 prospective cohort (1,002)	
Neurological disorders (5 outcomes, 7 studies, 6 associations)					
PN	Biomarker	MA	32 (12,371)	32 case-control/cross-sectional	Stein (2021)[74]
	Supplement	MA	4 (446)	4 RCT	
Multiple sclerosis	Biomarker	MA	9 (807)	9 case-control	Zhu (2010)[73]††
Multiple sclerosis	Biomarker	SR	4 (207)	3 RCT (170)	Bagur (2017)[75]
				1 case-control (37)	
Diabetic PN	Supplement	MA	7 (422)	7 RCT (vs placebo)	Jia (2005)[79]††
	Supplement	MA	13 (575)	13 RCT (vs other B vitamins)	
Diabetic PN pain	Supplement	SR	3 (352)	2 RCT (342)	Julian (2020)[76]††
				1 prospective cohort (10)	
Post-herpetic neuralgia pain	Supplement	SR	3 (268)	3 RCT	
Diabetic PN pain	Supplement	SR	2 (NR)	2 RCT	Khalil (2021)[77]††
Neurologic function	Biomarker	SR	12 (6,529)	10 cross-sectional (5,419)	Miles (2015)[78]††
(Older adults)				2 prospective cohort (1,110)	
Psychiatric disorders (4 outcomes, 7 studies, 5 associations)					
Schizophrenia	Biomarker	MA	13 (2,113)	13 case-control	Cao (2016)[80]††
Depression	Dietary intake	MA	12 (21,837)	10 cross-sectional (20,479)	Wu (2022)[81]
				2 prospective cohort (1,358)	
Depression	Biomarker	SR	4 (2,863)	3 cross-sectional (2,169)	Frazer (2005)[82]
(Older adults)				1 case-control (694)	
Psychiatric symptoms	Biomarker	SR	2 (NR)	2 case-control	Olagunju (2021)[83]
(Older adults with depression)					
ASD	Supplement	SR	2 (87)	2 RCT	Li (2018)[84]
(Children)					
ASD	Supplement	SR	2 (87)	2 RCT	Sathe (2017)[85]
(Children)					
ASD	Supplement	SR	3 (100)	2 RCT	Rossignol (2021)[86]††
(Children)					
Anemia (1 outcome, 1 study, 1 association)					

Megaloblastic anemia (China)	Biomarker	MA	17 (1,921)	17 case-control	Zai (2015)[87]
Other outcomes (4 outcomes, 4 studies, 5 associations)					
Retinal vascular occlusive disease	Biomarker	MA	4 (574)	4 case-control	Cahill (2003)[88]
Normal tension glaucoma	Biomarker	MA	2 (172)	2 case-control	Li (2016)[89]
Phenylketonuria	Biomarker	MA	6 (2,190)	6 case-control	Montoya Parra (2018)[90]
Helminth	Biomarker	SR	4 (1,381)	3 cross-sectional (1,326) 1 case-control (55)	Layden (2018)[91] ††
Leprosy	Biomarker	SR	2 (1,225)	2 cross-sectional	

* plasma/serum concentration of total vitamin B_{12}; ** dietary intake + supplementation; *** cerebrospinal fluid concentration of vitamin B_{12};
† maternal plasma/serum concentration of total vitamin B_{12}; †† vitamin B_{12} was the only exposure measure investigated in the synthesis
AAA: abdominal aortic aneurysm; AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; AP: adenoma polyp; ASD: autism spectrum disorder; BMD: bone mineral density; CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; CVT: cerebral venous thrombosis; DVT: deep vein thrombosis; MA: meta-analysis; MCI: mild cognitive impairment; MI: myocardial infarction; NR: not reported; NTD: neural tube defect; PN: peripheral neuropathy; PTE: pulmonary thromboembolism; RCT: randomized controlled trials; SR: systematic review; TIA: transient ischemic attack

Table 2-2. Findings from the included meta-analyses on vitamin B_{12} and health outcomes and their assessed credibility

Health outcome	B_{12} exposure	# Datasets	#Total (#Case)	Pooled risk (95% CI/ p-value)	I^2 (%)	P_{Egger}	Credibility	Reference
Breast cancer	**Dietary**	**14**	**367,118 (15,783)**	**RR= 0.88 (0.77, 1.00) (p= 0.05)**	**68.90**	**0.12**	**Weak**	Wu (2013)[35]
	Biomarker	4	3,606 (1,803)	RR= 0.73 (0.44, 1.22) (p= 0.23)	72.5	0.18	NS (Weak)	
Cervical neoplasia	Biomarker	NR	448 (186)	NR	NR	NR	-	Garcia-Closas
HPV persistence	Biomarker	NR	215 (129)	NR	NR	NR	-	(2015)[124]
Colorectal cancer	**Supplement**	**6**	**321,038 (3,554)**	**RR= 1.10 (0.92, 1.32)**	**49.10**	**NR**	**NS (Suggestive)**	Liu (2015)[36]
Colorectal cancer	Dietary (CC)	8	7,797 (3,337)	SMD= 0.07 (0.02, 0.11) (p=0.003)	2.40	NR	Weak	Shiao (2018)[125]
	Dietary (PC)	4	1,998 (760)	SMD= -0.02 (-0.11, 0.07) (p=0.66)	26.70	NR	NS (Weak)	
	Biomarker (CC)	**6**	**1,938 (774)**	**SMD= -0.99 (-1.74, -0.25) (p=0.009)**	**97.80**	**NR**	**Weak**	
	Biomarker (PC)	8	8,309 (3,299)	SMD= -0.04 (-0.09, 0.00) (p=0.06)	34.60	NR	NS (Weak)	
Colorectal cancer/AP	Dietary	17	14,864 (6,514)	SMD=-0.06 (-0.17, 0.05) (p=0.31)	91.40	NR	Weak	
	Biomarker	20	11,730 (4,764)	SMD=-0.55 (-0.77, -0.33) (p<0.0001)	96.40	NR	Weak	
Colorectal cancer	**Dietary**	**11**	**264,805 (8,042)**	**RR= 0.94 (0.83, 1.07) (p=0.64)**	**67.00**	**0.27**	**NS (Suggestive)**	Sun (2016)[38]
	Total intake	**6**	**262,404 (4,345)**	**RR= 0.87 (0.78, 0.97) (p=0.01)**	**23.00**	**0.62**	**Suggestive**	
	Biomarker	4	1,732 (685)	RR= 0.93 (0.56, 1.53)	NR	0.45	NS (Weak)	
Esophageal cancer	**Dietary**	**10**	**992,269 (3,332)**	**OR= 1.30 (1.05, 1.62)**	**73.50**	**<0.05**	**Suggestive**	Qiang (2018)[39]
Pancreatic cancer	**Dietary**	**6**	**NR (1,598)**	**RR= 0.97 (0.78, 1.16)**	**9.10**	**0.60**	**NS (Suggestive)**	Wei (2020)[40]
	Biomarker	**3**	**NR (1,032)**	**RR= 1.17 (0.64, 1.70)**	**37.20**	**NR**	**NS (Suggestive)**	
Renal cell carcinoma	**Dietary**	**3**	**127,826 (1,578)**	**RR= 1.14 (0.87, 1.49)**	**1.50**	**NS**	**NS (Suggestive)**	Clasen (2020)[41]
	Biomarker	**2**	**NR (780)**	**RR= 0.73 (0.51, 1.06)**	**1.40**	**NS**	**NS (Weak)**	

Renal cell cancer	Biomarker	NR	NR (NR)	RR= 0.72 (0.52, 1.00) (p=0.05)	NR	NR	-	Mao (2015)[42]
	Supplement	**2**	**NR (NR)**	**RR= 1.24 (0.90, 1.70) (p=0.19)**	**NR**	**NA**	**NS (-)**	
Major CV event	**Supplement**	**17**	**294,478 (156,663)**	**RR=0.99 (0.95, 1.02)**	**37.00**	**NR**	**NS (Suggestive)**	Myung (2013)[43]
CV death	Supplement	9	NR (NR)	RR=0.96 (0.90, 1.03)	27.00	NR	-	
Angina	Supplement	4	NR (NR)	RR=0.93 (0.72, 1.20)	77.00	NR	-	
MI	Supplement	14	NR (NR)	RR=0.99 (0.93, 1.06)	4.00	NR	-	
Non-fatal MI	Supplement	4	NR (NR)	RR=1.03 (0.93, 1.14)	1.00	NR	-	
Stroke	Supplement	5	NR (NR)	RR=0.91 (0.80, 1.03)	8.00	NR	-	
TIA	Supplement	2	NR (NR)	RR=1.12 (0.93, 1.12)	0.00	NR	-	
CHD	**Dietary**	**5**	**103,272 (1,251)**	**RR=0.97 (0.70, 1.25)**	**53.60**	**NR**	**NS (Suggestive)**	Jayedi (2019)[46]
AAA	**Biomarker**	**5**	**1,326 (667)**	**SMD= -0.42 (-1.09, 0.25)**	**95.00**	**NR**	**NS (Weak)**	Takagi (2017)[47]
Venous thrombosis	**Biomarker**	**13**	**4,346 (2,038)**	**SMD= -0.34 (-0.55, -0.13) (p=0.002)**	**91.00**	**NS**	**Weak**	Zhou (2012)[48]
DVT/PTE	**Biomarker**	**6**	**2,834 (1,351)**	**SMD= -0.24 (-0.53, 0.06) (p=0.11)**	**92.00**	**NS**	**NS (Weak)**	
CVT	**Biomarker**	**2**	**622 (226)**	**SMD= -0.45 (-1.02, 0.11) (p=0.11)**	**90.00**	**NS**	**NS (Weak)**	
Retinal vein occlusion	**Biomarker**	**3**	**752 (398)**	**SMD= -0.45 (-1.24, 0.35) (p=0.27)**	**95.00**	**NS**	**NS (Weak)**	
Stroke	**Dietary**	**5**	**130,965 (5,590)**	**RR=1.02 (0.93, 1.12)**	**0.00**	**0.68**	**NS (Suggestive)**	Chen (2020)[44]
AD	**Biomarker**	**33**	**5,048 (2,784)**	**MD= -47.88 (-70.75, -25.01)**	**87.00**	**NR**	**Weak**	Lopes da Silva (2014)[49]
AD	Biomarker	4	300 (92)	SMD= -0.48 (-0.87, -0.09) (p=0.02)	NR	NR	Weak	De Wilde (2017)[50]
AD	Biomarker	14	1,462 (698)	SMD= -0.64 (-0.93, -0.35)	85.00	NS	Weak	Xie (2017)[127]
AD	Biomarker	22	1,426 (733)	MD= -34.30 (-41.86, -26.74)	0.00	NS	Weak	Zhu (2019)[128]
Vascular cognitive impairment	**Biomarker**	**7**	**671 (349)**	**MD= -130.44 (-225.46, -35.41)**	**NR**	**NR**	**Weak**	Yang (2014)[62]
AD	**Dietary**	**3**	**5,254 (431)**	**RR=0.99 (0.00, 1.00)**	**0.00**	**NR**	**NS (Weak)**	Doets (2012)[51]
Dementia	**Biomarker**	**4**	**2,630 (263)**	**RR=1.00 (0.98, 1.02)**	**9.10**	**NR**	**NS (Weak)**	
Global cognition	**Biomarker**	**4**	**1,579 (NR)**	**β=0 (-0.00, 0.01)**	**42.6**	**NR**	**NS (-)**	

Memory	**Biomarker**	**4**	**3,460 (NR)**	**β=0.01 (-0.01, 0.03)**	**0.00**	**NR**	**NS (-)**	
Global cognition	**Supplement**	**3**	**442 (217)**	**SMD=0.02 (-0.17, 0.21)**	**6.30**	**0.66**	**NS (Weak)**	Markun (2021)[63]
Cognitive speed	**Supplement**	**3**	**1,049 (514)**	**SMD=-0.10 (-0.23, 0.04)**	**0.00**	**0.39**	**NS (Weak)**	
Executive function	**Supplement**	**3**	**1,252 (607)**	**SDM=0.09 (-0.09, 0.28)**	**9.70**	**0.37**	**NS (Weak)**	
Memory	**Supplement**	**3**	**NR (NR)**	**SMD=0.04 (-0.19, 0.26)**	**41.70**	**0.32**	**NS (Weak)**	
Parkinson's disease	**Dietary**	**3**	**141,963 (736)**	**OR=1.05 (0.76, 1.35)**	**0.00**	**NR**	**NS (Weak)**	Shen (2015)[60]
	Biomarker	**10**	**1,659 (735)**	**SMD= -0.38 (-0.51, -0.25)**	**23.40**	**NR**	**Weak**	
NTD	**Biomarker**	**9**	**2,133 (567)**	**OR=2.41 (1.90, 3.06) (p<0.00001)**	**47.00**	**Possible**	**Weak**	Wang (2012)[65]
Preeclampsia	**Biomarker**	**21**	**3,211 (1,390)**	**WMD= -15.24 (-27.52, -2.95)**	**97.80**	**0.004**	**Weak**	Mardali (2021)[66]
Early pregnancy loss	**Biomarker**	**2**	**202 (100)**	**SMD= 0.61 (0.30, 0.92)**	**8.12**	**NA**	**Weak**	Bala (2021)[67]
Atopic dermatitis score	**Supplement**	**2**	**86 (43)**	**MD= -3.19 (-4.27, -2.10)**	**0.00**	**NR**	**Weak**	Zhu (2019)[69]
BMD (Postmenopausal)	**Biomarker**	**6**	**649 (288)**	**MD=11.22 (3.06, 19.38) (p=0.01)**	**17.00**	**NR**	**Weak**	Zhang (2014)[71]
PN	**Biomarker**	**32**	**12,371 (2,948)**	**OR=1.51 (1.23, 1.84)**	**43.30**	**NS**	**Suggestive**	Stein (2021)[74]
	Supplement	4	297 (149)	OR=1.36 (0.66, 2.79)	28.90	NR	NS (Weak)	
Diabetic PN	**Supplement (vs routine treatment)**	**7**	**422 (236)**	**OR=11.47 (4.05, 32.54)**	**55.80**	**NR**	**Weak**	Jia (2005)[79]
	Supplement (vs other B vitamins)	**13**	**575 (451)**	**OR=12.19 (9.20, 16.14)**	**0.00**	**NS**	**Weak**	
Multiple sclerosis	**Biomarker**	**8**	**807 (414)**	**SMD= -0.25 (-0.45, -0.04)**	**29.3**	**0.98**	**Weak**	Zhu (2010)[73]
Schizophrenia	**Biomarker**	**13**	**2,113 (1,092)**	**SMD=0.09 (-0.03, 0.22) (p=0.07)**	**40.00**	**NR**	**NS (Weak)**	Cao (2016)[80]
Depression	**Dietary**	**12**	**21,837 (3,172)**	**RR=0.86 (0.75, 0.99)**	**31.30**	**0.48**	**Suggestive**	Wu (2022)[81]
Megaloblastic anemia	**Biomarker**	**17**	**1,921 (625)**	**SMD= -2.54 (-3.39, -1.69)**	**97.30**	**NR**	**Weak**	Zai (2015)[87]
Retinal vascular occlusive disease	**Biomarker**	**4**	**574 (287)**	**SMD= -0.06 (-0.22, 0.10) (p=0.48)**	**NR**	**NR**	**NS (Weak)**	Cahill (2003)[88]
Normal tension glaucoma	**Biomarker**	**2**	**172 (90)**	**WMD= 5.81 (-3.53, 15.14) (p=0.22)**	**89.00**	**NR**	**NS (Weak)**	Li (2016)[89]
Phenylketonuria	**Biomarker**	**6**	**2,190 (307)**	**SMD= 0.19 (-0.91, 1.29) (p=0.67)**	**94.00**	**NR**	**NS (Weak)**	Montoya Parra (2018)[90]

AAA: abdominal aortic aneurysm; AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; AP: adenoma polyp; ASD: autism spectrum disorder; BMD: bone mineral density; CC: case-control; CHD: coronary heart disease; CV: cardiovascular; CVD: cardiovascular disease; CVT: cerebral venous thrombosis; DVT: deep vein thrombosis; MA: meta-analysis; MCI: mild cognitive impairment; MI: myocardial infarction; NA: not applicable; NR: not reported; NTD: neural tube defect; PC: prospective cohort; PN: peripheral neuropathy; PTE: pulmonary thromboembolism; SR: systematic review; TIA: transient ischemic attack. - : insufficient information to assess credibility

2.9 Appendices

Appendix 2-A. Search strategies

MEDLINE
1. exp Vitamin B 12/ 2. ((vitamin* or vit or co?enzym*) adj2 (b12 or b 12)).tw,kw. 3. (cobalamin* or hydro?cobalamin* or c?anocobalamin* or adenosylcobalamin* or methylcobalamin* or dibencozid* or cobamamid* or cobamid* or eriton or deoxyadenosinecobalamin*).tw,kw. 4. or/1-3 5. diet/ or eating/ or drinking/ 6. ((calorie or calories or caloric or diet* or feed* or food* or macronutrient* or micronutrient* or nutrient* or nutritional) adj2 (intake or intakes)).tw,kw. 7. ingest*.tw,kw. 8. Dietary Supplements/ 9. ((diet* or food or herbal) adj2 supplement*).tw,kw. 10. (neutraceutical* or nutracentical*).tw,kw. 11. Food Preferences/ 12. exp Nutrition Therapy/ 13. Foods, Fortified/ 14. ((fortified or enriched or supplement*) adj2 food*).tw,kw. 15. Nutritional Status/ 16. ((nutrition* or food*) adj2 status*).tw,kw. 17. or/5-16 18. 4 and 17 19. meta-analysis/ or "systematic review"/ 20. Systematic Reviews as Topic/ 21. (systematic adj2 review*).tw,kw. 22. systematic review.pt. 23. (meta analys* or metaanalys*).tw,kw. 24. meta analysis.pt. 25. (((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw. 26. or/19-25 27. 18 and 26
EMBASE

1. cyanocobalamin/
2. ((vitamin* or vit or co?enzym*) adj2 (b12 or b 12)).tw,kw.
3. (cobalamin* or hydro?cobalamin* or c?anocobalamin* or adenosylcobalamin* or methylcobalamin* or dibencozid* or cobamamid* or cobamid* or eriton or deoxyadenosinecobalamin*).tw,kw.
4. 1 or 2 or 3
5. diet/
6. exp food intake/
7. ((calorie or calories or caloric or diet* or feed* or food* or macronutrient* or micronutrient* or nutrient* or nutritional) adj2 (intake or intakes)).tw,kw.
8. ingest*.tw,kw.
9. ingestion/
10. diet supplementation/ or dietary supplement/
11. ((diet* or food or herbal) adj2 supplement*).tw,kw.
12. (neutraceutical* or nutracentical*).tw,kw.
13. food preference/
14. exp diet therapy/
15. fortified food/
16. ((fortified or enriched or supplement*) adj2 food*).tw,kw.
17. nutritional status/
18. ((nutrition* or food*) adj2 status*).tw,kw.
19. or/5-18
20. 4 and 19
21. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
22. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
23. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
24. umbrella review*.ti,ab,kf,kw.
25. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
26. or/21-25
27. 20 and 26

Cochrane Database of Systematic Reviews (CDSR)

1. ((vitamin* or vit or co?enzym*) adj2 (b12 or b 12)).tw,kw.
2. (cobalamin* or hydro?cobalamin* or c?anocobalamin* or adenosylcobalamin* or methylcobalamin* or dibencozid* or cobamamid* or cobamid* or eriton or deoxyadenosinecobalamin*).tw,kw.
3. 1 or 2
4. ((calorie or calories or caloric or diet* or feed* or food* or macronutrient* or micronutrient* or nutrient* or nutritional) adj2 (intake or intakes)).tw,kw.
5. ingest*.tw,kw.
6. ((diet* or food or herbal) adj2 supplement*).tw,kw.
7. (neutraceutical* or nutracentical*).tw,kw.
8. ((fortified or enriched or supplement*) adj2 food*).tw,kw.
9. ((nutrition* or food*) adj2 status*).tw,kw.
10. or/4-9
11. 3 and 10

DARE

1. ((vitamin* or vit or co?enzym*) adj2 (b12 or b 12)).tw,kw.
2. (cobalamin* or hydro?cobalamin* or c?anocobalamin* or adenosylcobalamin* or methylcobalamin* or dibencozid* or cobamamid* or cobamid* or eriton or deoxyadenosinecobalamin*).tw,kw.
3. 1 or 2
4. ((calorie or calories or caloric or diet* or feed* or food* or macronutrient* or micronutrient* or nutrient* or nutritional) adj2 (intake or intakes)).tw,kw.
5. ingest*.tw,kw.
6. ((diet* or food or herbal) adj2 supplement*).tw,kw.
7. (neutraceutical* or nutracentical*).tw,kw.
8. ((fortified or enriched or supplement*) adj2 food*).tw,kw.
9. ((nutrition* or food*) adj2 status*).tw,kw.
10. or/4-9
11. 3 and 10

CINAHL

S19 S4 AND S18
S18 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
S17 ((nutrition* or food*) N2 status*)
S16 ((fortified or enriched or supplement*) N2 food*)
S15 (neutraceutical* or nutracentical*)
S14 ((diet* or food or herbal) N2 supplement)
S13 ingest*
S12 ((calorie or calories or caloric or diet* or feed* or food* or macronutrient* or micronutrient* or nutrient* or nutritional) N2 (intake or intakes))
S11 (MH "Diet Therapy+")
S10 (MH "Food Preferences")
S9 (MH "Nutritional Status")
S8 (MH "Dietary Supplements+") OR (MH "Food, Fortified") OR (MH "Nutrients+")
S7 (MH "Fluid Intake") OR (MH "Food Intake+") OR (MH "Dietary Reference Intakes")
S6 (MH "Eating")
S5 (MH "Diet+")
S4 S1 OR S2 OR S3
S3 (cobalamin* or hydro?cobalamin* or c?anocobalamin* or adenosylcobalamin* or methylcobalamin* or dibencozid* or cobamamid* or cobamid* or eriton or deoxyadenosinecobalamin*)
S2 ((vitamin* or vit or co?enzym*) N2 (b12 or b 12))
S1 (MH "Vitamin B12")

Appendix 2-B. Extraction template

Category	Item	Options
Study information	First author	
	Year of publication	
	Journal	
	PubMed ID	
	Title	
	URL	
	Type of synthesis	SR | MA
	Type of included studies	
	Years searched	
	Number of studies included	
	Quality assessment of included studies	
	Protocol registration	
	Use of reporting guidelines	
Study population	Inclusion and exclusion criteria	
	Countries included	
	Total number of participants	
	Sex (n, %)	
	Age (mean (SD), median (IQR)	
Exposure	Measure of exposure	Dietary | Supplement | Biomarker
	Dietary intake – method	
	Supplement – dose, duration	
	Biomarker – type	Serum | Plasma | MMA | other (specify)
	Definition of exposure	
	Time of exposure	
Outcome	Health outcome	
	Measure of outcome	
Meta-analysis	Number of studies included in meta-analysis	
	Model used	
	Total number of participants	
	Total number of cases	
	Total number of controls	
	Measure of effect	
	Reported summary effect (95% CI, p-value)	
	Heterogeneity (I^2, p-value)	
	Small study effects (P_{Egger}, p-value)	
Comment		

Appendix 2-C. Credibility assessment criteria

Grading	Associations
Convincing	- Statistical significance of $p<10^{-6}$ - Pooled >1,000 cases (or >20,000 participants for continuous outcomes) - Largest component study reports a statistically significant result ($p<0.05$) and has a prediction interval that excludes the null - Do not have large heterogeneity ($I^2<50\%$) - No evidence of small study effects ($p>0.10$) or of excess significance bias ($p>0.10$)
Highly suggestive	- Statistical significance of $p>10^{-6}$ - Pooled >1,000 cases (or >20,000 participants for continuous outcomes) - Largest component study reports a statistically significant result ($p<0.05$)
Suggestive	- Statistical significance of $p<0.01$ - Pooled >1,000 cases (or >20,000 participants for continuous outcomes)
Weak	- Statistical significance of $p<0.05$
Not significant	- Statistical significance of $p\geq 0.05$

Appendix 2-D. AMSTAR-2 assessment of the 66 included syntheses

Synthesis	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q13	Q14	Q11	Q12	Q15	Q16
	Review planning			Search, screening, extraction				Description	RoB & heterogeneity				MA method			CoI
Wu[35]	Y	N	N	PY	Y	Y	N	PY	N	N	Y	N	N	Y	Y	Y
Garcia-Closas[124]	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Liu[36]	Y	N	N	PY	Y	Y	N	PY	N	N	N	N	N	N	Y	Y
Shiao[125]	Y	PY	N	PY	Y	N	N	PY	N	N	N	N	N	N	N	Y
Sun[38]	Y	PY	N	PY	Y	Y	N	PY	N	N	Y	N	N	Y	Y	N
Qiang[39]	Y	PY	N	PY	Y	Y	N	PY	N	N	Y	N	N	Y	Y	Y
Wei[40]	Y	PY	N	PY	Y	Y	N	PY	N	N	N	N	N	N	Y	Y
Clasen[41]	Y	PY	N	PY	Y	Y	N	PY	N	N	N	N	N	N	Y	Y
Mao[42]	Y	PY	N	PY	Y	Y	N	PY	N	N	Y	N	N	Y	Y	N
Eikelboom[126]	N	N	Y	N	N	N	N	PY	N	N	N	N	-	-	-	N
Myung[43]	N	N	N	PY	Y	N	N	Y	PY	N	N	N	N	N	Y	Y
Jayedi[46]	Y	Y	N	N	Y	Y	N	PY	Y	N	N	Y	N	N	Y	Y
Takagi[47]	Y	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	N
Zhou[48]	Y	PY	N	PY	Y	N	N	PY	PY	N	N	N	Y	N	Y	Y
Chen[44]	Y	PY	N	PY	Y	Y	N	Y	Y	N	N	Y	Y	N	Y	Y
Iacoviello[45]	N	N	N	N	N	N	N	N	Y	N	N	N	-	-	-	Y
Yang[62]	N	PY	N	N	N	N	N	N	Y	N	N	Y	Y	N	N	N
Athanasopoulos[53]	N	N	N	N	Y	N	N	N	N	N	N	N	-	-	-	N
Dangour[52]	Y	PY	Y	PY	N	N	N	Y	N	N	N	N	-	-	-	N
Lopes da Silva[49]	Y	PY	N	Y	N	N	N	N	N	N	N	N	N	N	Y	Y
Xie[127]	Y	PY	N	PY	Y	Y	N	N	Y	N	N	N	Y	N	N	N
Zhu[128]	N	N	N	N	N	N	N	N	Y	N	N	N	Y	N	Y	N
Shah[59]	N	N	Y	N	N	N	N	N	N	N	N	N	-	-	-	N
de Wilde[50]	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Etgen[61]	Y	N	N	N	N	N	N	N	N	N	N	N	-	-	-	Y
Vogel[57]	N	N	N	N	N	N	N	N	N	N	N	N	-	-	-	N

Perez[56]	N	N	N	N	N	N	N	Y	N	N	N	N	-	-	-	N
Shen[60]	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y
Barnes[129]	Y	N	N	N	N	N	N	N	N	N	N	N	-	-	-	Y
Jia[130]	Y	PY	N	PY	N	N	N	Y	N	N	N	Y	N	N	N	Y
Raman[55]	Y	PY	N	N	N	Y	N	N	N	N	N	Y	-	-	-	N
Balk[131]	Y	PY	N	N	N	N	N	N	Y	N	N	N	-	-	-	Y
Markun[63]	Y	Y	N	Y	Y	N	Y	PY	Y	N	N	Y	Y	Y	Y	Y
Venkatramanan[132]	Y	N	N	PY	Y	Y	N	Y	PY	N	N	N	-	-	-	Y
Ellinson[54]	Y	N	N	N	N	N	N	PY	N	N	N	N	-	-	-	N
O'Leary[58]	Y	PY	N	N	N	Y	N	N	Y	N	N	N	-	-	-	Y
Doets[51]	Y	PY	N	PY	Y	Y	N	PY	PY	N	N	Y	N	N	N	Y
Wang[65]	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
Behere[64]	N	PY	N	PY	Y	Y	N	PY	PY	N	N	N	-	-	-	Y
Veena[133]	Y	PY	N	N	N	Y	N	PY	PY	N	N	N	-	-	-	Y
Bala[66]	N	N	N	PY	N	Y	N	N	N	N	N	N	N	N	Y	Y
Mardali[66]	Y	PY	N	PY	N	Y	N	PY	Y	N	N	Y	Y	N	Y	Y
Trujillo[68]	Y	Y	N	PY	Y	Y	Y	PY	Y	N	N	N	-	-	-	Y
Vieira[70]	N	N	N	N	Y	Y	N	PY	N	N	N	N	-	-	-	Y
Zhu[69]	Y	Y	N	PY	Y	Y	N	PY	Y	N	N	Y	N	N	N	Y
Marcedo[72]	Y	PY	N	N	Y	Y	N	N	N	N	N	N	-	-	-	N
Zhang[71]	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N	Y	Y
Bagur[75]	N	N	N	N	Y	Y	N	N	N	N	N	N	-	-	-	N
Stein[74]	Y	Y	N	N	Y	N	N	PY	Y	N	N	N	N	N	Y	Y
Jia[79]	Y	PY	N	PY	Y	Y	N	PY	PY	N	N	Y	Y	N	Y	N
Zhu[73]	Y	N	N	PY	Y	Y	N	PY	PY	N	N	Y	Y	N	Y	N
Julian[76]	N	PY	N	N	Y	N	N	N	Y	N	N	N	-	-	-	Y
Khalil[77]	Y	PY	N	Y	Y	Y	Y	N	Y	N	N	Y	-	-	-	Y
Miles[78]	Y	PY	N	N	Y	Y	N	N	Y	N	Y	N	-	-	-	Y
Cao[80]	N	PY	N	N	N	N	N	PY	Y	N	N	Y	N	N	Y	Y
Wu[81]	Y	PY	N	N	Y	N	N	PY	Y	N	N	Y	Y	N	Y	Y

Frazer[82]	Y	N	N	N	N	N	N	N	N	N	N	N	-	-	-	Y
Olagunju[83]	N	PY	N	N	Y	Y	N	PY	N	N	N	N	-	-	-	Y
Li[84]	N	PY	N	N	N	N	N	PY	PY	N	N	N	-	-	-	Y
Sathe[85]	Y	PY	N	N	Y	N	N	N	Y	N	N	N	-	-	-	Y
Rossignol	N	PY	N	PY	N	Y	N	PY	PY	N	N	N	-	-	-	Y
Zai[87]	Y	N	N	N	N	N	N	N	Y	N	N	Y	Y	N	Y	N
Cahill[88]	N	N	N	N	N	N	N	N	N	N	N	N	-	-	-	N
Li[89]	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N
Montoya Parra[90]	N	N	N	PY	N	N	N	N	N	N	N	N	N	N	N	Y
Layden[91]	Y	N	N	N	N	N	N	N	N	N	N	N	-	-	-	Y

Q1. Did the research questions and inclusion criteria for the review include the components of PICO

Q2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol

Q3. Did the review authors explain their selection of the study designs for inclusion in the review

Q4. Did the review authors use a comprehensive literature search strategy

Q5. Did the review authors perform study selection in duplicate

Q6. Did the review authors perform data extraction in duplicate

Q7. Did the review authors provide a list of excluded studies and justify the exclusions

Q8. Did the review authors describe the included studies in adequate detail

Q9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review

Q10. Did the review authors report on the sources of funding for the studies included in the review

Q11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results

Q12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis

Q13. Did the review authors account for risk of bias in individual studies when interpreting/ discussing the results of the review

Q14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review

Q15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review

Q16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review

- : not applicable (meta-analysis was not conducted)

CoI: conflict of interest; MA: meta-analysis; N: no; PY: partial yes; RoB: risk of bias; Y: yes

Chapter 3: Associations of vitamin B_{12} and folate status with schizophrenia onset and treatment outcome: Integrated synthesis of the evidence using umbrella reviews

In Context

In our previous umbrella review (chapter 2), we identified a suggestive level of evidence on the association of vitamin B_{12} with neurological (neuropathy) and psychiatric (depression) conditions. Although several limitations were noted, e.g., potential variability in exposure and outcome definitions and lack of adjustment for potential confounders, this finding was encouraging with regard to the possible involvement of vitamin B_{12} in neuropsychiatric health outcomes.

In this chapter, we specified the outcome of interest to schizophrenia in relation to the status of folate and vitamin B_{12}. We conducted an integrated synthesis of systematic reviews and meta-analyses investigating a relationship between measures of folate or vitamin B_{12} status and schizophrenia onset or symptom severity.

Journal Submission

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- Authors: Samantha Yoo, Azita Montazeri, Helen McNulty, Monique Potvin Kent, Julian Little
- Author contributions: SY, HMcN, MPK, JL conceptualized the study. SY adapted the search strategies from Research 1 and executed the search. SY and AM screened articles, extracted data, and conducted methodological quality assessment of all included articles. SY synthesized the evidence and drafted the manuscript. AM, HMcN, MPK, and JL provided critical input in development of the manuscript. All authors read and approved the final version of the manuscript.

3.1 Abstract

Background: Accumulating evidence indicates that deficiencies of folate or vitamin B_{12} may be linked with the onset and progression of schizophrenia, but the evidence is fragmented. Relationships between vitamin B_{12} and folate and schizophrenia are biologically plausible given the essential role of these B vitamins in one-carbon metabolism, which is required for DNA and RNA biosynthesis and methylation reactions. In these umbrella reviews, we sought to integrate epidemiological evidence on this topic, considering different measures of vitamin intake or status.

Method: MEDLINE, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews were searched for systematic reviews with or without meta-analyses that examined exposure to vitamin B_{12} or folate from dietary intake and use of supplements, blood concentration or genotypes (replicated as associated with blood concentration) in relation to schizophrenia onset or progression. Effect sizes were estimated using random-effects models. For associations with nominal statistical significance, excess significance and prediction interval were additionally calculated. The methodological quality of all included systematic reviews was assessed using AMSTAR-2 and we rated overall credibility of the final evidence using predefined criteria.

Results: Sixteen evidence syntheses were identified reporting a total of 25 associations. Overall, the methodological quality of these systematic reviews assessed using AMSTAR-2 was weak to moderate. Of these, 12 articles were meta-analyses examining folate or vitamin B_{12} status and the risk of schizophrenia and 4 articles (one systematic review with, and three without, meta-analysis) examined the effect of using folic acid supplements with or without B_{12} on improving schizophrenia symptoms. Three associations were deemed to be "suggestive": an inverse association between plasma/serum folate concentration and the risk of schizophrenia (OR= 0.57 (0.47, 0.70), $p<0.001$, $I^2=82.8\%$ ($p<0.001$)); an overall positive relationship between the variant *MTHFR* 677TT (compared to the 677CC) genotype and the risk of schizophrenia (OR=1.31 (1.20, 1.64), $p<0.001$, $I^2=61\%$ ($p<0.001$)), and more strongly so in a subgroup

of studies conducted in Asia (OR=1.50 (1.23, 1.84), p<0.001, I^2=61% (p<0.01)). There was evidence of small study effects for the genetic studies (P_{Egger}>0.10).

Conclusion: There appeared to be convergence of the findings that higher plasma/serum folate concentrations or the variant *MTHFR* 677TT genotype were each associated with decreased and increased risk, respectively, for schizophrenia. The current evidence on the effect of vitamin B_{12} or folic acid supplements as an adjunctive treatment for schizophrenia symptoms was not sufficient to draw conclusions. Further research should investigate measures of folate status at different lifecycle stages or under different conditions, e.g., maternal folate status during pregnancy, childhood/adolescents, or use of drugs known to interfere with folate metabolism.

3.2 Introduction

Schizophrenia is a complex neuropsychiatric disorder with a lifetime prevalence of 1%[1,2]. It is largely characterized by psychosis[3] with symptom clusters, namely positive symptoms, (delusions, hallucinations), negative symptoms (amotivation, social withdrawal), and cognitive deficits[4]. Its etiology appears to involve both genetic and environmental risk factors[4-7].

A putative link between schizophrenia and folate dates back to the 1960s, with studies identifying higher concentrations of homocysteine (a functional marker of vitamin B_{12} or folate deficiency) among individuals with schizophrenia[8] and reporting symptom-alleviating effects of methionine administration[9-11]. Later studies reported significantly lower blood concentrations of vitamin B_{12} or folate among patients with schizophrenia or first-episode psychosis compared to healthy controls[12-18]. These findings are partially supported by investigations of the effects of severe prenatal food shortages that occurred during the Dutch Hunger Winter (1944-1945; also known as the Dutch Famine)[19,20] and the Chinese famine (1959-1961)[21,22], in which associations between maternal malnutrition and schizophrenia in the offspring were observed. A few randomized controlled trials have investigated the effect of folic acid with or without vitamin B_{12} as

an adjunctive therapy for treatment of schizophrenia[23-27]. In general, the authors reported positive effects of these vitamins in alleviating negative and overall symptoms[23,25,27].

Further evidence for a possible role of folate in the etiology of schizophrenia comes from the *Schizophrenia Gene* database, which identified the methylenetetrahydrofolate reductase (*MTHFR*) C677T polymorphism as one of 24 genetic variants with nominal significance for schizophrenia risk[28]. The *MTHFR* C677T polymorphism involves a C >T substitution at base pair 677 of the gene encoding the folate-metabolizing MTHFR enzyme[9,29]. Individuals with the homozygous variant *MTHFR* 677TT genotype, compared to the CC genotype, are reported to have 30-35% reduced enzyme activity[30-32,] and reduced blood folate concentrations[33]. Therefore, the *MTHFR* genotype is considered as a proxy for blood folate status in some studies. The *MTHFR* genotype also appears to be associated with the severity of negative symptoms[9,34] and cognitive deficit[34] in schizophrenia.

Several umbrella reviews have been undertaken in the recent years to synthesize evidence on overall health effects of folate[35]; risk factors for major mental disorders[36] or schizophrenia[37], or the effect of nutrient supplements in treatment of mental disorders[38]. However, all of these reviews restricted their scope to meta-analyses and two were further restricted to peripheral (plasma/serum) biomarkers[36,37]. Evidence on the role of folate and vitamin B_{12} in development or treatment of schizophrenia was unavailable[35] or drawn from 1-2 studies only[36-38]. We aimed to address these limitations in the available evidence by providing a more integrated synthesis of the existing evidence on the association between folate or vitamin B_{12} status and schizophrenia onset and progression across multiple measures of vitamin use or status.

3.3 Methods

The protocol for these reviews was registered with the PROSPERO database CRD 42023410859. We conducted umbrella reviews of systematic reviews with or without meta-analyses examining the relationship between folate or vitamin B_{12} and

schizophrenia. The search strategy and eligibility criteria were developed based on the PICOS framework as detailed in the subsequent sections.

The study population was either general population when related to the risk of developing schizophrenia or individuals diagnosed with schizophrenia when related to progression or severity of the illness. No restriction was placed on age, sex, gender, severity of schizophrenia symptoms, or settings (inpatient, outpatient, community). Animal studies or studies using postmortem samples were excluded.

3.3.1 Eligibility

With regard to exposure, all types of folate or vitamin B_{12} intake or status, i.e., dietary intake, supplement use, or blood concentrations were considered. Studies that examined dietary intake were eligible only if the intake amount was quantified or if clear cut-offs for quantile or quartile were provided. *MTHFR* genotypes that are known to be associated with low blood folate concentrations[30,39] were also considered as a proxy for exposure. Studies that examined supplementation or biomarkers were eligible if dose or measurement was provided separately for each vitamin. Studies investigating combined effects of all B vitamins or folate and vitamin B_{12} with other nutrients were eligible for potential subgroup analyses; however, those examining the effect of multivitamins or broad-spectrum micronutrient formulas were excluded.

Eligible comparators were healthy controls or individuals without schizophrenia diagnosis in evidence related to the risk of schizophrenia and standard antipsychotic use in evidence related to the treatment effect of the vitamins.

The outcome was onset of schizophrenia/ first-episode psychosis (FEP) or progression of symptoms or treatment outcomes of schizophrenia. We limited the outcome to primary diagnosis of schizophrenia/ FEP. Diagnoses of schizophrenia and related conditions under either the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM) were considered eligible. Schizoaffective disorder, other mood disorders with psychotic features (i.e., major depressive disorder

with psychotic features), and psychoses induced by other conditions or related medications were excluded to minimize heterogeneity. For evidence examining the effect of folate or vitamin B_{12} on treatment of schizophrenia, any scales of general, positive, or negative symptoms and any measurement of cognitive functions were eligible.

Case reports, case series, and commentaries were excluded. No other restriction was placed on study design. Language restriction was not imposed on the search strategy in order to avoid bias[40].

3.3.2 Data sources and search strategy

We searched four electronic databases: PubMed/MEDLINE, Embase, PsycINFO, and Cochrane Database of Systematic Reviews from inception to March 21, 2023. The search strategies were developed with the help of librarians using keywords and Medical Subject Heading (MeSH) related to folate, vitamin B_{12}, dietary intake, supplementation, plasma/serum concentrations, and schizophrenia. The search was limited to human studies. No restrictions were placed on the year of publication. The full search strategy for MEDLINE is available in Appendix 3-A. Reference lists of the included evidence syntheses were manually searched to identify other eligible articles.

3.3.3 Screening

All search results were imported to the Covidence platform for systematic review[41] and Zotero reference management software[42]. All articles underwent two-stage screening – title and abstract-based, followed by full-text based screening – as per the predefined inclusion and exclusion criteria. Both stages of screening were conducted by two independent reviewers. All discrepancies between the two reviewers were resolved by discussion.

3.3.4 Extraction

Two reviewers independently extracted data from the final list of included evidence syntheses using a predefined and piloted data extraction template. All discrepancies were resolved by discussion. Key information extracted include the following: (1) basic study

information (first author, title, year of publication, country of study, conflict of interest, source of funding); 2) study design (type of review, inclusion and exclusion criteria, sample size, number of events, if applicable); 3) study population (age, sex, gender (if available), comorbidities, other psychiatric disorders, socioeconomic status); 4) exposure (vitamin type, measurement method, baseline measurement, follow-up duration, dose & duration, if applicable, combination with other nutrients or drugs, if available); 5) outcome (diagnosis, age at diagnosis, time since diagnosis, severity, treatment if available) and 6) quantitative information (meta-analysis model, pooled estimates, 95% confidence interval, heterogeneity, publication bias).

3.3.5 Quality assessment

We assessed all included systematic reviews for their methodological quality using AMSTAR-2[43]. Two reviewers independently performed the assessment and discrepancies were resolved by discussion. The tool consists of 16 items across the domains of search methodology, risk of bias assessment of primary studies, meta-analysis methodology, and interpretation of findings.

3.3.6 Evidence synthesis

All selected articles were categorized into two outcome groups: those examining the link between folate or vitamin B_{12} and the risk of schizophrenia and others examining the effect of the vitamins on various treatment effects among individuals with schizophrenia. For each outcome group, the evidence was categorized by vitamin – folate alone, vitamin B_{12} alone, combination of folate and vitamin B_{12} - and again by type of measurement – dietary intake, supplementation, and blood concentration.

For each exposure-outcome category, we prioritized meta-analyses over systematic reviews without meta-analyses. Systematic reviews without quantitative analyses were reported separately but compared with findings from quantitative analyses in direction and magnitude. In the event of ≥ 2 evidence syntheses in any exposure-outcome category, we selected one using multiple criteria including the largest sample size, the latest publication year, and the highest methodological quality. In the absence of quantitative

analysis in any category, we summarized the narrative syntheses including descriptive analyses. Any subgroup analyses, if available, were presented alongside overall pooled effects for each category.

For all meta-analyses identified, we estimated the effect size and its 95% confidence interval using a random effects model. For the syntheses that reported findings as a standardized mean difference (SMD), we converted the metric into an odds ratio (OR) for comparability across the evidence, if raw data from the primary studies were provided in the article. We also calculated 95% prediction intervals using a random-effects model to investigate the dispersion of effect sizes[44]. Small study effects were assessed using Egger's test of asymmetry (significance threshold $p<0.10$)[45] and the test of excess significance (significance threshold $p<0.10$)[46]. The test of excess significance pertains specifically to meta-analyses and measures if the number of statistically significant findings are in excess considering their power. The method for excess significance test is described in detail in previous umbrella reviews[36,47].

The evidence syntheses were finally assessed for credibility based on the predefined criteria (Appendix 2-C) consisting of sample size, statistical significance, heterogeneity levels, and publication bias. The evidence was classified into four credibility classes: convincing, highly suggestive, suggestive, and weak.

All statistical analyses were conducted using Metafor in R software[48] and SAS version 9.4[49].

3.4 Results

3.4.1 Overview

We retrieved 98 evidence syntheses from our search, of which 29 were duplicates (Figure 3-1). Thirty-four articles were excluded based on titles and abstracts, followed by 19 after full-text reviews. We did not find any articles published in non-English languages. Thus, we identified a total of 16 evidence syntheses reporting 25 associations from the final screening (Table 3-1).

Twelve articles were meta-analyses reporting pooled effects of folate or vitamin B_{12} status on the risk of schizophrenia; one was a meta-analysis on the treatment effect of folic acid on schizophrenia symptoms; and three were narrative syntheses of the effect of folic acid with or without vitamin B_{12} on various schizophrenia symptom scores. We did not find articles examining the role of dietary intake of folate or vitamin B_{12} in onset or treatment of schizophrenia.

In terms of the reported outcomes, 12 articles reported on the risk of schizophrenia and four on the treatment of schizophrenia symptoms, with each outcome group pooling data entirely from biomarkers and supplementation, respectively. Among the 12 evidence syntheses that reported on folate or vitamin B_{12} biomarkers, four examined plasma/serum concentrations and eight investigated the presence of *MTHFR* genotypes known to determine low folate status.

All the four evidence syntheses investigating folate or vitamin B_{12} status pooled data entirely from case-control or cross-sectional component studies, with pooled sample sizes ranging from 620 to 23,441 individuals. The authors used blood concentrations of folate or vitamin B_{12} as continuous variables and reported mean differences between individuals with and without schizophrenia or first-episode psychosis. All the eight syntheses of the relationship between *MTHFR* genotypes and schizophrenia pooled data from case-control studies and reported odds ratios of schizophrenia risk by genotype.

From the four articles that synthesized the effect of folic acid or vitamin B_{12} on treatment of schizophrenia, seven associations were reported (folic acid alone (n=4), joint effects of folic acid and vitamin B_{12} (n=3)). All four articles pooled data entirely of randomized controlled trials ranging in total sample sizes from 49 to 925 participants. Only one article reported a meta-analysis using mean difference in symptoms scores between intervention and comparator groups.

Finally, one evidence synthesis narratively reviewed a moderating effect of *MTHFR* and other genotypes on the treatment effects of folic acid or vitamin $B_{12,}$ based on six randomized controlled trials.

3.4.2 Quality assessment

We assessed all the included evidence syntheses on methodological quality using AMSTAR-2 (Appendix 3-B). Overall, the articles were rated to be weak to moderate quality. Only two out of 14 meta-analyses examining biomarkers (plasma/serum concentrations or presence of MTHFR polymorphisms) conducted a risk of bias assessment of their included studies. Descriptive information (e.g., sociodemographic data, severity or duration of illness, time of sampling, etc.) was not provided in majority of the analyses. Clear description of the research question, eligibility criteria, and robust search methodology was another domain found to be weak across the articles. All meta-analyses tested publication bias and six conducted meta-regression to investigate sources of heterogeneity. Quality of the included articles was considered when we selected the evidence for each exposure-outcome category.

3.4.3 Folate biomarkers and risk of schizophrenia

Two meta-analyses[50,51] examined the differences of plasma/serum concentration of folate between schizophrenia cases and healthy controls. The two evidence syntheses were published in the same year and had mostly overlapping studies. While findings from the two meta-analyses are in the same direction and similar magnitude, we report the analysis of Cao et al.[44] because it was assessed to have higher methodological quality and to have a more recent and extensive search strategy.

The meta-analysis synthesized 20 case-control studies comparing plasma/serum folate concentrations between schizophrenia cases (n=1,463) and healthy controls (n=1,276). The 20 study samples came from Asia (n=11), Europe (n=6), Africa (n=2), and America (n=1) with the mean ages ranging from 22.1 (5.0) years to 40.4 (10.5) years. Sample size of the component studies ranged from 38 to 468 participants and the number of cases ranged from 18 to 234.

Overall pooled effects of plasma/serum folate using random-effects model was significantly different between the two groups (OR= 0.57 (0.47, 0.70), p<0.001). The 95% prediction interval included the null (0.26, 1.28). Small study effects were not significant (P_{Egger}=0.44) and the test of excess significance was not significant (χ^2=0.29, p=0.71). There was marked heterogeneity between the included studies (I^2=82.8% (p<0.001)).

The pattern of association was consistent across subgroup analyses by age group (<30 years vs ≥ 30 years), year of publication (before 2010 vs after 2010), biomarker measurement methods, or by whether FEP was included in the case group (yes vs no). However, the pooled effects were different across geography, with studies conducted in Asia reporting a statistically significant inverse association (OR=0.49 (0.39, 0.61), p<0.001), while studies in Europe, Africa, and America did not show significant associations (OR_{Europe} = 0.79 (0.43, 1.43), OR_{Africa} = 0.43 (0.12, 1.57), $OR_{America}$ = 0.85 (0.61, 1.19)) (Figure 3-2). Heterogeneity was high in all subgroups except America (a single study) (I^2_{Asia} = 76.7% (p<0.01), I^2_{Europe} = 69.05% (p<0.01), I^2_{Africa} = 93.79% (p<0.01). For the Asia subgroup, the 95% prediction interval was statistically significant (0.25, 0.96) and there was no evidence of small study effects (p=0.33) or excess significance (p=0.87).

3.4.4 Vitamin B_{12} biomarkers and risk of schizophrenia

Only one meta-analysis was identified[52], which pooled 13 case-control studies comparing blood vitamin B_{12} concentration between schizophrenia cases (n=1,092) and healthy controls (n=1,021). The 13 datasets were predominantly from Asia (n=6) and Europe (n=5), with a mean age ranging from 22.0 to 40.4 years across the samples. The component studies had sample sizes ranging from 38 to 468 participants and cases ranging from 35 to 234.

Overall, plasma/serum vitamin B_{12} concentration was not significantly different between the two groups (OR=1.10 (0.83, 1.47), p=0.067). Subgroup analyses by geography or

ethnicity were not reported. There was moderate heterogeneity between studies (I^2=40% (p=0.07)) and no evidence of small study effects (P_{Egger}=0.583).

3.4.5 Folate-related genotypes and risk of schizophrenia

We identified a total of 11 meta-analyses from seven publications examining the association between *MTHFR* variants and the risk of schizophrenia, of which six examined *MTHFR* C677T[9,24,25,27,48] and five *MTHFR* A1298C[29-32,53]. All of the primary case-control studies included in these meta-analyses were included in the most recent systematic reviews for each polymorphism[53,54], which were also rated to have higher methodological quality compared with the older meta-analyses.

3.4.5.1 *MTHFR* C677T

The most recent analysis, by Yadav et al.[54], pooled the largest number of original studies (n=38) and provided the most extensive subgroup analyses by genetic model. The meta-analysis included total 23,441 participants and 10,069 cases. Meta-analysis of homozygotes (*MTHFR* 677 TT vs CC) included 13,047 participants and 5,559 cases.

Across all ethnicities (3 African samples, 17 Asian samples, and 18 "Caucasian" samples), the meta-analysis showed a significant association between homozygosity for the *MTHFR* C677T variant (TT) and the risk of schizophrenia compared to homozygosity for the common variant (CC) ($OR_{TT\ vs\ CC}$ = 1.40 (1.20, 1.64), p<0.001). The prediction interval included the null (0.71, 2.80). There was moderate heterogeneity (I^2= 61% (p<0.001)) and the result of the Egger test for small study effects was significant (P_{Egger}=0.09).

No component study had ≥ 1,000 cases. The included original samples ranged from 41 to 1,081 in sample size and from 21 to 619 in the number of cases. Sixteen out of 38 studies reported nominal significance at α=0.05. A further test of excess significance suggested potential reporting bias (χ^2=16.44, p < .0001).

Subgroup analysis for Asian ethnicity (cases n=3,092, controls n=3,892) showed a higher magnitude of association compared to the overall effects (OR $_{TT\ vs\ CC}$ = 1.50 (1.23, 1.84), p<0.001) (Figure 3-3). There was moderate heterogeneity (I^2= 60.9% (p<0.001)) and potential small study effects were detected (P_{Egger}=0.02). Further analyses of the prediction interval included the null (0.81, 2.80) and the test of excess significance was significant (χ^2=6.78, p=0.005).

Analysis of the "Caucasian"[1] samples (cases n=2,311, controls n=3,379) did not show significant association (OR $_{TT\ vs\ CC}$ = 1.16 (0.94, 1.44), p=0.14) with moderate heterogeneity between the studies (I^2=51% (p<0.01)) and no evidence of small study effect (P_{Egger}=0.72). The prediction interval included the null (0.61, 2.24); however, the test of excess significance suggested potential reporting bias (χ^2=9.38, p=0.001).

In the analysis of the three African samples (in aggregate, cases n=156, controls n=217) there was a statistically significant association (OR $_{TT\ vs\ CC}$ = 5.39 (2.70, 10.75), p<0.001)).

3.4.5.2 *MTHFR* A1298C

Five meta-analyses examined the effect of *MTHFR* A1298C genotypes[29-32,53]. The most recent publication[53] pooled the largest number of studies including all of the component studies included the previous evidence syntheses.

A total of 19 case-control studies (cases n=9,537, controls n=4,049) was included in the meta-analysis (7 Asian samples and 12 "Caucasian" samples). For overall association between homozygosity for the *MTHFR* A1298C variant (CC) and the risk of schizophrenia compared to homozygosity for the common variant (AA), 18 studies were used (cases n=2,531, controls n=3,443). Total sample size varied across the component

[1] *Caucasian* is in quotes because it is an outdated terminology of political and administrative origin to describe "white" individuals and encompasses heterogenous ethnic groups (see Bhopal et al.(1998), Flanagin et al. (2021), Marinez et al. (2022) in Section 6.8 Bibliography). Used by the authors of included articles.

studies, ranging from 48 to 804 participants, and the number of cases from 25 to 255 participants.

The overall effect was statistically significant but small in size (OR $_{CC\ vs\ AA}$ = 1.20 (1.03, 1.39), p=0.02). There was moderate heterogeneity (I^2= 37.0% (p=0.06)) with no evidence of small study effect (P_{Egger}=0.11). Prediction interval included the null (0.76, 2.12). We did not find evidence of excess significance bias (χ^2=1.30, p=0.13).

Both Asian (cases n=1,212, controls n=1,304) and "Caucasian" (cases n=1,319, controls n=2,139) subgroup analyses showed similarly small effect sizes. For Asians, the effect of *MTHFR* 1298CC genotype on schizophrenia compared to the *MTHFR* 1298AA genotype was reported as OR $_{CC\ vs\ AA}$ = 1.34 ((0.93, 1.93), p=0.11). Heterogeneity was modest (I^2=36.99% (p=0.06)), small study effect was not significant (P_{Egger}=0.18); and prediction interval was wide (0.69,2.64). Excess significance bias was not significant (χ^2=0.26, p=0.30). For "Caucasians", the association was OR $_{CC\ vs\ AA}$ = 1.24 (0.96, 1.62), p=0.10. Heterogeneity was moderate (I^2=36.46% (p=0.15)), small study effect was not significant (P_{Egger}=0.43); and the prediction interval crossed the null (0.71, 2.18). We found no evidence of excess significance bias (χ^2=1.09, p=0.15) (Figure 3-3).

3.4.6 Folate and vitamin B_{12} biomarkers and the risk of first-episode psychosis

We identified one evidence synthesis[55] that meta-analyzed six studies of folate and four studies of vitamin B_{12}, comparing blood concentrations of these vitamins between individuals with FEP and healthy controls. First-episode psychosis was broadly defined to include individuals receiving early interventions for psychosis and those within the first three years of antipsychotic treatment for schizophrenia or non-affective psychosis[55].

For folate, the six studies were conducted in China, India, Poland, Spain, and Turkey and the total sample size was 827 participants and total cases 421 participants. The authors reported significant differences in plasma/serum/erythrocyte folate concentrations using Hedge's g (g= -0.624 (-1.18, -0.07), I^2=92.4%) between FEP and healthy controls. For vitamin B_{12}, the four studies in India, Poland, Spain, and Turkey (313 FEP cases and 307

healthy controls) did not show significant differences (g= -0.059 (-0.22, 0.10), p=0.47, I^2=0%) between the two groups.

The authors further provided a narrative synthesis of the relationship between the vitamin concentrations and different symptoms measured with PANSS (Positive and Negative Symptom Scale)[56] across the studies. Serum folate was reported to be negatively correlated with total symptoms[18] (n=76); with negative symptoms[18,57] (n=196); and with general symptoms[58] (n=39). For vitamin B_{12}, two studies using the same sample[58,59] (n=174) found that higher serum concentration of vitamin B_{12} correlated with lower negative symptom scores, while one study[60] (n=79) reported a weak inverse correlation between plasma concentration of vitamin B_{12} and positive symptoms.

3.4.7 Folate and vitamin B_{12} supplementation and treatment of schizophrenia

We identified one meta-analysis[61] and three systematic reviews without quantitative analyses[62-64] that investigated the effects of folic acid used as an adjunctive therapy to the antipsychotic treatment on improvement of symptoms among individuals with schizophrenia. All of the component studies examined in the four syntheses were randomized controlled trials published between 1990 and 2017. The meta-analysis encompassed all component trials included in the systematic reviews and two additional unpublished trials retrieved from clinical trial registries.

The meta-analysis also pooled trials (n=3) whose participants had diagnoses other than schizophrenia (i.e., major depressive disorder and schizoaffective disorder) and trials (n=3) offering B vitamins in a combination regimen. With regard to investigating independent effects of folic acid or vitamin B_{12} in treatment of schizophrenia, we identified three trials (two published[25,26] and one unpublished[65]) investigating a relationship of folic acid and changes in total and negative symptoms. Results of these trials were not separately meta-analyzed; thus, we narratively summarize their findings in the following sections. We did not find trials examining independent effects of vitamin B_{12} on treatment of schizophrenia symptoms.

The symptom scores were treated as a continuous variable. Changes from the mean baseline score were calculated and compared between intervention and control groups using standardized mean difference. Because this reported metric contained information on the direction of change (symptom improvement or deterioration), we did not transform it into odds ratios.

3.4.7.1 Folic acid in treatment of total and negative symptoms

Participants in the three trials were comparable in terms of diagnosis (schizophrenia according to DSM-4), age (18-70 years), stability of symptoms (measured as PANSS-T ≥ 60 or SANS global assessment ≥ 3), and active administration of antipsychotic medications for ≥ 6 weeks. All the three trials, two of which were conducted in the USA and one across UK, Italy, and Finland, had a relatively small sample size, ranging from 26 to 55 participants, and their durations were 12 weeks. Two[25,65] of the three trials used observed case analysis (i.e., only including individuals who completed the trial) and one[25] reported intention-to-treat analysis. The authors conducted a subgroup analysis and did not find any significant difference between the groups using the different analyses.

Administration of folic acid at 2mg/d for 12 weeks did not show a statistically significant difference compared to placebo (no adjunctive therapy) in terms of changes in total symptoms (SMD=0.20 (-0.54, 0.94)) or negative symptoms (SMD= 0.14 (-0.60, 0.89)) on SANS[26]. A dose of 500 mg/d folic acid for 12 weeks also did not result in significant difference in symptom scores (SMD= -0.21 (-1.06, 0.65)) for total symptoms; SMD= -0.28 (-1.14, 0.58) for negative symptoms)[65]. Similarly, 15 mg/d of l-methylfolate for 12 weeks did not produce a statistically significant difference compared to placebo in improving total symptom scores (SMD= -0.35 (-0.88, 0.19)) or negative symptom scores (SMD= -0.36 (-0.89, 0.18)) on PANSS[25].

3.4.7.2 Folic acid combined with other B vitamins in treatment of total and negative symptoms

We identified two trials[23,24] from the meta-analysis that examined the joint effects of B vitamins. In a trial conducted in Israel with individuals with ≥ 1 year of continuous illness

and homocysteine concentration > 15 μmol/L, a regimen of 2 mg/d folic acid, 0.4 mg/d vitamin B_{12}, and 25 mg/d vitamin B_6 did not show a significantly different effect, compared to placebo, in improving total symptoms (SMD= -0.45 (-1.06, 0.16)) or negative symptoms (SMD= -0.32 (-0.93, 0.29))[23]. The sample size was not reported. Another trial from the USA (n=140) offering 2 mg/d folic acid and 0.4 mg/d vitamin B_{12} to individuals aged 18-68 years with stable symptoms reported similar changes in scores between the intervention and placebo groups for total symptoms (SMD= 0.01 (-0.34, 0.37)) and negative symptoms (SMD= -0.27 (-0.63, 0.09))[24].

3.4.8 Moderating role of genotypes in the treatment effect of folic acid and/or vitamin B_{12}

One systematic review[64] reported on six trials, in which individuals with schizophrenia were given folic acid with or without vitamin B_{12} or placebo and the treatment response was stratified by genotype. The *MTHFR* C677T genotypes were the most studied (6 trials, n=414), followed by *COMT* G675A (4 trials, n=351) and *FOLH1* C484T and *MTR* G1298A (each 3 trials, n=316). *MTR* A2576G genotypes were studied in one trial (n=140). These studies were conducted in the USA (4 studies), Finland (1 study), and Australia (1 study). The sample sizes varied between 31 and 139. The supplementation offered was folic acid alone (4 studies) or folic acid with other B vitamins (2 studies). The folic acid regimen offered varied between 0.5 – 5 mg/d for 3-24 weeks. Findings were inconclusive for all genetic polymorphisms examined.

3.4.9 Credibility assessment

We did not find any association meeting the credibility criteria of "convincing" or "highly suggestive" (Table 3-2). Two associations were assessed to be suggestive: the association between plasma/serum folate and risk of schizophrenia (overall and in Asia) and the association between *MTHFR* 677TT genotype and risk of schizophrenia compared to *MTHFR* 677CC genotype (overall and among Asian ethnicity). These studies included > 1,000 cases in the analyses with the largest component studies having p-values < 0.05; however, the pooled p-values did not meet the threshold of $p<10^{-6}$.

Further, the evidence on the peripheral blood markers of folate status comprised entirely of retrospective studies and thus is susceptible to selection and information biases. The evidence on the *MTHFR* genotypes also had potential small study effects and excess significance bias.

3.5 Discussion

3.5.1 Summary of findings

We systematically synthesized current evidence on the relationship between folate or vitamin B_{12} and schizophrenia onset and treatment outcome. Our syntheses found that plasma/serum concentration of folate, but not vitamin B_{12}, was significantly lower among individuals diagnosed with schizophrenia compared to healthy controls. This finding was consistent only in the subgroup of Asians. The association with the folate biomarker was in agreement with the evidence around folate deficiency predicted by the presence of the variant *MTHFR* 677TT genotype. We found a significant, positive pooled association of the *MTHFR* 677TT genotype with increased risk of schizophrenia compared to the 677CC genotype. This finding was consistent in direction across the ethnicity subgroups, although the results did not reach statistical significance threshold in all subgroups. The variant *MTHFR* 1298CC genotype showed a smaller but significant overall effect on the schizophrenia risk; however, the effect diminished in the ethnicity subgroups. The effect of supplementing folic acid with or without vitamin B_{12} on management of schizophrenia symptoms was weak and statistically not significant; however, the evidence was underpowered to detect meaningful effect.

While we did not identify any evidence around dietary intake of folate or vitamin B_{12}, it is well established that blood concentrations are more valid and reliable measures of folate or vitamin B_{12} exposures compared to dietary intake. The lack of evidence around dietary exposures in the context of schizophrenia risk and treatment outcomes does not restrict the strength of our findings.

3.5.2 Possible mechanisms of action

Although the precise mechanism explaining the current findings are unclear, multiple pathways may be considered with regard to the role of folate and vitamin B_{12} in development of schizophrenia. The most studied is the homocysteine hypothesis[66]: low concentrations or availability of folate in the body results in elevated levels of homocysteine, which induces vascular impairment of the brain and causes alterations of neurotransmitters that contributes to psychiatric disorders. Toxicity of homocysteine to neuronal cells[67,68] have been implicated in loss of neural plasticity and development of neurodegenerative disorders[69] and schizophrenia[9,12,70,71]. As the brain lacks the pathways to eliminate homocysteine, i.e., betaine re-methylation or transsulfuration[72], it is more vulnerable to the damaging effects of high homocysteine. This hypothesis is supported by our findings, in which the risk of schizophrenia was significantly higher among individuals who had low blood concentrations of folate or a variant of the *MTHFR* gene that enables re-methylation of homocysteine into methionine[73,74].

Another possibly related mechanism is the involvement of folate and vitamin B_{12} in the production of S-adenosylmethionine (SAM), a universal methyl donor involved in numerous methylation reactions and neural functions[73,75-77]. Deficiency in these vitamins has been related to impaired production of monoamine neurotransmitters[78,79] and brain atrophy[80], leading to impaired function of the central nervous system and mood.

A mediating role of tetrahydrobiopterin (BH4) may also be considered[81]. BH4 is critically involved in the production of neurotransmitters, i.e., serotonin, dopamine, and norepinephrine[82-84], and it is synthesized by dihydrofolate reductase (DHFR) or 5-methyltetradrofolate[85]. It can be hypothesized that folate deficiency or disturbances in the folate metabolism may lead to BH4 deficiency[81], which is found in 30% of schizophrenia patients[86,87].

3.5.3 Gaps in the evidence

We noted several gaps in the current body of evidence. First, there were limited number of studies for each exposure-outcome category and most of these had small sample sizes. Supplementation studies in particular were very scarce and too small in scale to allow for

further stratification by dosage, duration of vitamin use, or severity of illness. The genetic polymorphism studies in the African populations were also underpowered to reach conclusions. While prior research has shown that the frequencies of *MTHFR* C677T and A1298C mutations are the lowest in the African ethnicity compared to Hispanics, "Caucasians", and Asians[88,89], more larger genotyping studies on the African population in relation to schizophrenia risk will be helpful in building credible evidence.

Second, the meta-analyses of the effect of biomarkers consisted entirely of retrospective studies, in which temporal sequence of exposure and outcome could not be ascertained. We could not find systematic reviews or meta-analyses that synthesized prospective studies using dietary intake or supplementation of folate as exposure. These studies did not report on the impact of potential confounders such as age, sex, socioeconomic level, underlying comorbidities, and use of medications known to interfere with folate metabolism. Baseline folate and vitamin B_{12} concentrations, duration/ severity of illness, and presence of mandatory folic acid fortification policies are also important considerations in assessing the effect of these vitamins in both biomarker and supplementation studies. For example, a broad mandatory fortification of food with folic acid has been shown to dilute the genetic effects of impaired folate metabolism[50,90] and some antipsychotics are reported to impair folic acid absorption[17]. However, these factors were not examined in the included evidence syntheses.

Third, risk of bias assessment was not conducted in over half of the evidence syntheses identified. This may be because all of the evidence syntheses examining the effect of biomarkers (including *MTHFR* genotypes) comprised of small-scale case-control studies with limited information. Only two syntheses conducted sensitivity analyses based on the quality of the component studies. In this review, for each exposure-outcome category, we selected articles that had the highest methodological quality.

Lastly, we found inconsistencies in classification of ethnicity. For example, people from Iran were classified as "Asian"[50,52] or "Caucasian"[51]; from Mexico as "Caucasian"[31,32,54], "American"[50,52] or "Latino"[51]; from USA as "Mixed"[51] or "Caucasian"[31,32,54]. Such

inconsistencies made it difficult to compare the pooled results of subgroups across the syntheses and may mask the effects of folic acid fortification in specific countries.

3.5.4 Strengths and limitations

This set of umbrella reviews presents a comprehensive picture of the current knowledge on the relationship between folate, vitamin B_{12} and schizophrenia, using broad search strategies to systematically identify relevant literature. We addressed the limitations of the previous evidence syntheses by integrating various measures of the exposure and focusing on clinically defined schizophrenia as outcome. Our synthesis of the positive association between *MTHFR* 677TT genotype and risk of schizophrenia further strengthened the findings from plasma/serum concentrations. We also conducted additional statistical analyses, i.e., 95% prediction interval and test of excess significance, to strengthen our credibility assessment. Most importantly, we were able to identify gaps in the current evidence both in quantity and quality. However, our reviews were limited by the design of an umbrella review: we may not have captured most recent original analyses that are yet to be incorporated into systematic reviews or meta-analyses, as these were outside the scope of our reviews.

3.6 Conclusion

We found suggestive level of evidence that higher plasma/serum folate concentrations or the variant *MTHFR* 6777TT genotype were each associated with decreased and increased risk, respectively. The current evidence on the effect of folic acid or vitamin B_{12} supplements as an adjunctive treatment for schizophrenia symptoms was not sufficient to draw conclusions. More research is needed to investigate the role of folate intake or status at different lifecycle stages or under different conditions, e.g., maternal folate intake during pregnancy, folate intake during childhood, or use of drugs known to interfere with folate metabolism, in development or treatment of schizophrenia.

3.7 References

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3.8 Figures and Tables

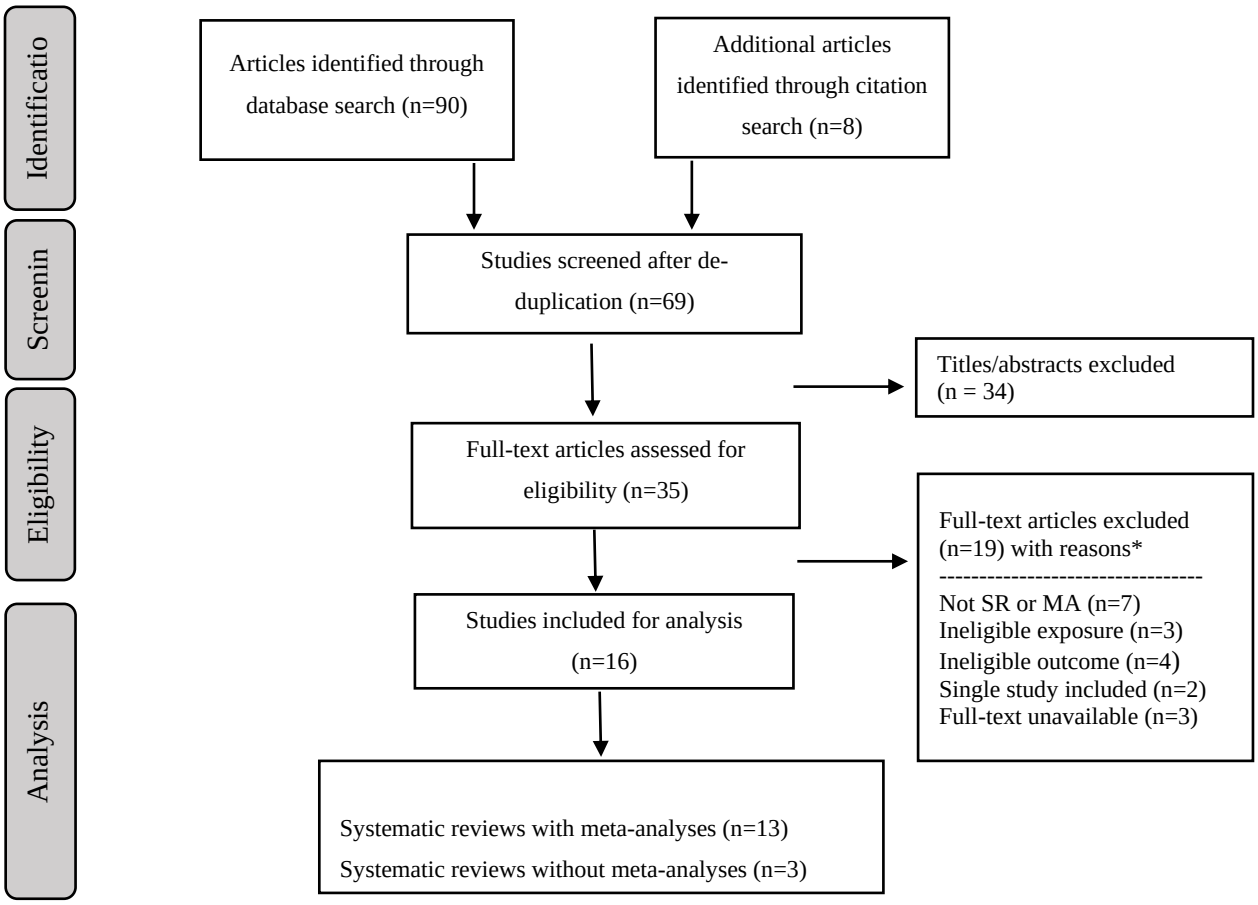

Figure 3-1. PRISMA diagram of the process used to identify evidence on the association between folate and vitamin B_{12} status and schizophrenia onset and treatment outcome

***** Ineligible exposures: broad-spectrum micronutrients, nutritional status, food items; Ineligible outcomes: neurodevelopment, general mental illness, schizophrenia secondary to metabolic disorder .

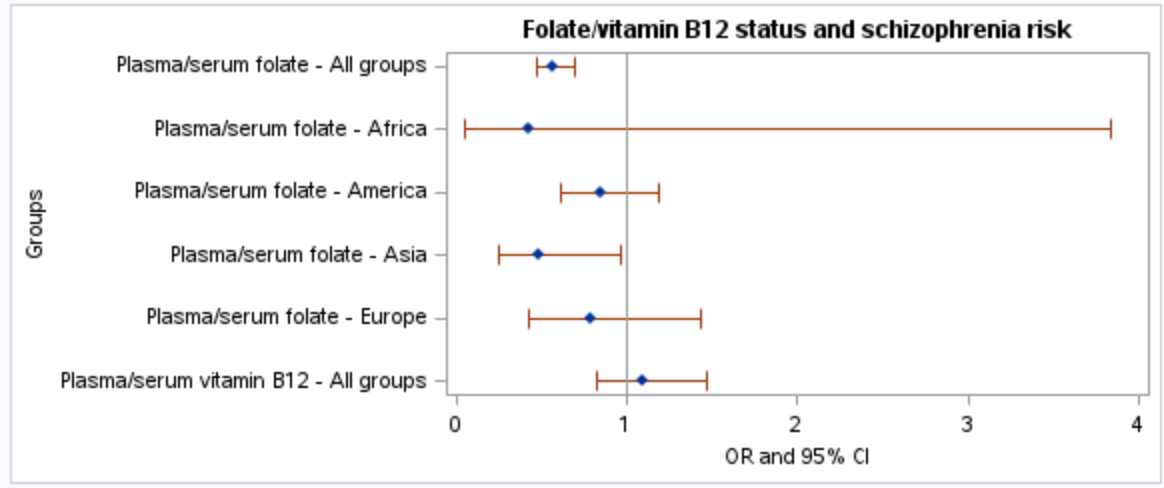

Figure 3-2. Association between plasma/serum concentration of folate and vitamin B_{12} and schizophrenia onset

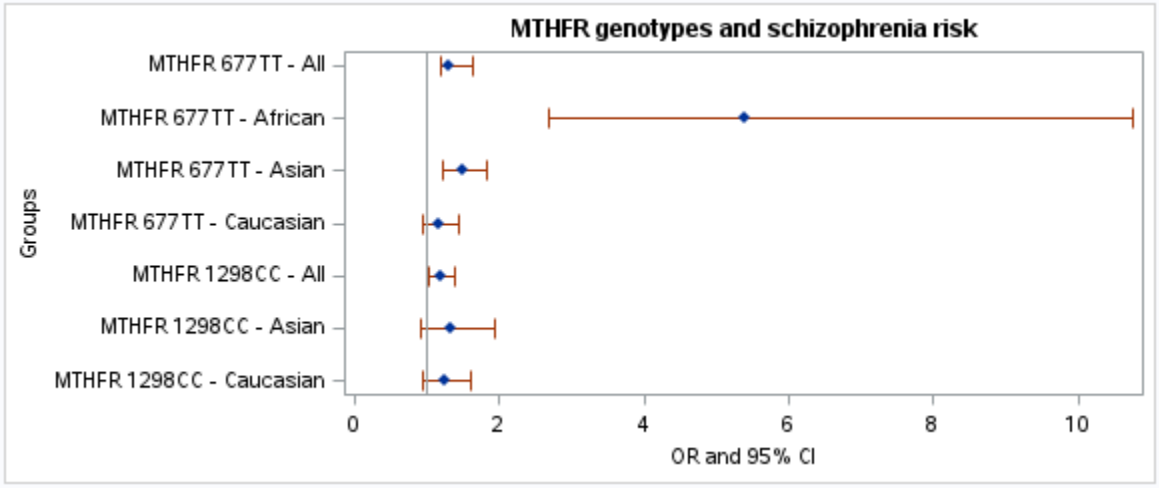

Figure 3-3. Association of *MTHFR* 677TT vs. *MTHFR* 677CC and *MTHFR* 1298CC vs *MTHFR* 1298AA genotypes and schizophrenia onset

Table 3-1. Characteristics of the evidence syntheses included in the review of the association between folate and vitamin B_{12} status with schizophrenia onset and treatment outcome

Author (year)	Exposure	Outcome	# Studies	Component study designs	# Total (# Cases)	Age (mean (SD)) Sex (Male%)	Included countries
Association between folate or vitamin B_{12} status and the risk of schizophrenia							
Cao (2016)[50]	Folate (plasma/serum)	Schizophrenia (DSM-4)	20	Case-control	2,739 (1,463)	22.1 (5.0) – 40.4 (10.5) years	China, Greece, Iran, Korea, Mexico, the Netherlands, Poland, Serbia, Spain, Tunisia, Turkey
Wang (2016)[51]	Folate (plasma/serum)	Schizophrenia	26	Case-control (25) Cross-sectional (1)	3,453 (1,773)	NR	China, Denmark, England, Greece, Iran, Israel, Korea, Mexico, Poland, Serbia, Spain, Tunisia, Turkey, USA
Cao (2016)[52]	Vitamin B_{12} (plasma/serum)	Schizophrenia (DSM-4)	13	Case-control	2,113 (1,092)	20.1 – 40.4 (10.5) years	China, Greece, Iran, Korea, Kuwait, Mexico, the Netherlands, Poland, Serbia, Spain, Tunisia, Turkey
Firth (2018)[53]	Folate (serum)	FEP	6	Cross-sectional	872 (421)	23-34 years 51-60%	China, India, Poland, Spain, Turkey
	Vitamin B_{12} (serum)	FEP	4	Cross-sectional	620 (313)		
Lewis (2005)[54]	*MTHFR* C677T	Schizophrenia	6	Case-control	2,427 (1,119)	NR	Canada, Japan, the Netherlands, Spain, Turkey
Muntjewerff (2006)[9]	*MTHFR* C677T	Schizophrenia	10	Case-control	4,986 (2,265)	NR	Canada, China, Japan, the Netherlands, Scotland, Singapore, Spain, Turkey
Gilbody (2006)[30]	*MTHFR* C677T	Schizophrenia	12	Case-control	6,125 (2,762)	NR	Canada, China, Netherlands, Poland, Scotland, Singapore, Spain, Turkey

Zintzaras (2006)[29]	*MTHFR* C677T	Schizophrenia	10	Case-control	5,232 (2,3890)	39.4 - 55.2 years	Canada, China, Japan, Netherlands, Spain, Turkey
Hu (2015)[32]	*MTHFR* C677T	Schizophrenia	13	Case-control	6,752 (3,073)	NR	Canada, China, Japan Korea, Poland, Scotland, Singapore, Spain, Turkey, USA
Yadav (2016)[55]	*MTHFR* C677T	Schizophrenia (DSM/ICD)	38	Case-control	23,441 (10,069)	NR	Bulgaria, Canada, China, Czech Republic, Denmark, Egypt, Greece, Iran, Japan, Korea, Mexico, the Netherlands, Norway, Poland, Scotland, Singapore, Spain, Sweden, Syria, Tunisia, Turkey, USA
Gilbody (2006)[30]	*MTHFR* A1298C	Schizophrenia	2	Case-control	994 (427)	NR	Turkey
Zintzaras (2006)[29]	*MTHFR* A1298C	Schizophrenia	4	Case-control	2,565 (1,111)	41.2 – 55.4 years	China, Scotland, Spain, Turkey
Hu (2015)[32]	*MTHFR* A1298C	Schizophrenia	15	Case-control	8,942 (3,871)	NR	Bulgaria, China, Denmark, Korea, Norway, Poland Scotland, Spain, Sweden, Turkey
Peerbooms (2011)[31]	*MTHFR* A1298C	Schizophrenia	13	Case-control, cross-sectional	7,066 (2,914)	NR	Bulgaria, China, Denmark, Korea, Norway, Poland, Romani, Scotland, Spain, Sweden, Turkey
Rai (2017)[53]	*MTHFR* A1298C	Schizophrenia	19	Case-control	9,537 (4,049)	NR	Bulgaria, China, Denmark, Korea, Norway, Poland, Romania, Scotland, Spain, Sweden, Syria, Turkey
Effect of folic acid/ B12 supplementation on treatment							

Chia (2015)[57]*	FA FA+B12 FA+B6+B12	Schizophrenia symptoms	3	RCT	49 (26) 139 (93)	42-45.3 years 71.3%	UK, USA
Firth (2017)[58]*	FA FA+B12	Schizophrenia symptoms	3	RCT	180 (112)	44.1-46.3 years 53-81% male	USA
Sakuma (2018)[59]	FA	Total symptoms, negative symptoms	10	RCT	925 (NR)	45.3 years 69.6%	Australia, China, Finland, Germany, Israel, Italy, UK, USA
Vander Burg (2021)[60]*	FA FA+B12 FA+B6+B12	Schizophrenia symptoms	4	RCT	89 (NR) 139 (NR) 123 (NR)	NR	Australia, USA
	MTHFR C677T, *FOLH1* C484T, *MTR* G1298A, *COMT* G675A, *COMT* 158ValMet	Schizophrenia symptoms	6	RCT	153 (NR) 139 (NR) 123 (NR)	NR	Australia, Finland, USA

* systematic review without meta-analysis

COMT: catechol-O-methyltransferase; DSM: Diagnostic and Statistical Manual of Mental Disorders ; FA: folic acid; FEP: first-episode psychosis; FOLH1: folate hydrolase 1; ICD: International Classification of Diseases; MTHFR: methylene tetrahydrofolate reductase; MTR: methionine synthase; NR: not reported; SD: standard deviation

Table 3-2. Pooled associations and assessment of the strength of evidence of the association between folate and vitamin B_{12} status with onset of schizophrenia and first episode psychosis

Reference	Exposure Outcome	Population (# sample)	# Cases/ Controls	Summary effect (95% CI, p-value)	95% prediction interval	Heterogeneity I^2 (p-value)	Small study effects (P_{Egger})	Excess significance p-value	Credibility
Cao (2016)[50]	Plasma/serum folate Schizophrenia	All (20)	1,463/ 1,276	OR=0.57 (0.47, 0.70) p<0.001	(0.25, 1.28)	82.8% (p<0.01)	p=0.435	p=0.706	Suggestive
		Asia (11)	888/712	OR=0.49 (0.39, 0.61) p<0.001	(0.25, 0.96)	76.7% (p<0.01)	p=0.325	p=0.868	Suggestive
		Europe (6)	411/413	OR=0.79 (0.60, 1.03) p=0.078	(0.43, 1.43)	69.05% (p<0.01)	p=0.821	p=0.004	Weak
		Africa (2)	94/81	OR=0.43 (0.12, 1.57) p=0.201	(0.05, 3.84)	93.79% (p<0.01)	NA	p=1.0	Weak
		America (1)	70/70	OR=0.85 (0.61, 1.19) p=0.350	(0.61, 1.19)	NA	NA	p=0.665	Weak
Cao (2016)[52]	Plasma/serum B_{12} Schizophrenia	All (13)	1,092/ 1,021	OR=1.10 (0.98, 1.24)	(0.83, 1.47)	40.0% (p=0.07)	p=0.583	p=0.328	Weak
Firth (2018)[53]	Plasma/serum folate first episode psychosis	All (6)	421/406	g= -0.62 (-1.18, -0.07) p=0.03	Unavailable	92.4% (p<0.01)	p=0.16	Unavailable	Weak
	Plasma/serum B_{12} first episode psychosis	All (4)	313/307	g= -0.06 (-0.22, 0.10) p=0.47	Unavailable	0% (p=0.468)	NR	Unavailable	Weak
Yadav (2016)[55]	*MTHFR* 677TT Schizophrenia	All (38)	5,559/ 7,488	OR=1.31 (1.20, 1.64) p<0.001	(0.71, 2.80)	61.0% (p<0.001)	p=0.09	p<0.0001	Suggestive
		Asian (17)	3,092/ 3,892	OR=1.50 (1.23, 1.84) p<0.001	(0.81, 2.80)	60.9% (p<0.01)	p=0.001	p<0.005	Suggestive
		"Caucasian" (18)	2,311/ 3,379	OR=1.16 (0.94, 1.44) p=0.14	(0.61, 2.24)	51.27% (p<0.01)	p=0.625	p=0.001	Weak

		African (3)	156/ 217	OR=5.39 (2.70, 10.75) p<0.001	(2.71, 10.76)	0% (p=0.84)	p=0.672	p=0.541	Inconclusive
Rai (2017)[56]	*MTHFR* 1298CC Schizophrenia	All (19)	2,531/ 3,443	OR=1.20 (1.03, 1.39) p=0.02	(0.76, 2.12)	36.69% (p=0.06)	p=0.11	p=0.127	Weak
		Asian (7)	1,212/ 1,304	OR=1.34 (0.93, 1.93) p=0.11	(0.69, 2.64)	36.99% (p=0.15)	p=0.243	p=0.305	Weak
		"Caucasian" (12)	1,319/ 2,139	OR=1.24 (0.96, 1.62) p=0.10	(0.71, 2.18)	36.46% (p=0.10)	p=0.43	p=0.148	Weak

* CI: confidence interval; FA: folic acid; NA: not applicable; NR: not reported; NS: Not significant

3.9 Appendices

Appendix 3-A. MEDLINE search strategy

exp Folic Acid/
((vitamin* or vit or co?enzym*) adj2 (b9 or b 9 or m)).tw,kw.
(folate or folic acid or folacin or folvite or pteroylglutamic acid or acfol or acifolic or acidofolico or filicine or folacid or folart or folavit or folavite or foldivie or foliamin or folicid or folicet or folina or folinsyre or folitab or folium acid or folivit or folsan or folsau or folveriam or folvite or ingafol or gravi-fol or lafol or lexpec or megafol or neocepri or pteroyl glutamate or pteroyl monoglutamate or pteroyl monoglutamic acid or rubiefol or unifol).tw,kw.
or/1-3
exp Vitamin B 12/
((vitamin* or vit or co?enzym*) adj2 (b12 or b 12)).tw,kw.
(cobalamin* or hydro?cobalamin* or c?anocobalamin* or adenosylcobalamin* or methylcobalamin* or dibencozid* or cobamaid* or cobamid* or eriton or deoxyadenosinecobalamin*).tw,kw.
or/5-7
4 or 8
diet/ or eating/ or drinking/
((calorie or calories or caloric or diet* or feed* or macronutrient* or micronutrient* or nutrient* or nutritional) adj2 (intake or intakes)).tw,kw.
ingest*.tw,kw.
Dietary Supplements/
((diet* or food or herbal) adj2 supplement*).tw,kw.
(neutraceutical* or nutracentrical*).tw,kw.
Food preferences/
exp Nutrition Therapy/
Foods, Fortified/
((fortified or enriched or supplement*) adj2 food*).tw,kw.
Nutritional Status/
((nutrition* or food*) adj2 status*).tw,kw.
exp Homocysteine/
exp Plasma/
Erythrocytes/
exp Serum/
((biologic* or clinical or biochemical or serum or immun*) adj2 (marker or markers)).tw,kf.
((end point or end points or endpoint or endpoints) adj surrogate).tw,kf.
homocysteine.tw,kf.
or/10-28
9 and 29
exp Schizophrenia/
exp Psychotic Disorders/
(psychosi?s or psychotic or schizophreni* or paranoid disorder* or severe mental disorder* or hebephrenic or oligophrenic or chronic mental illness).tw,kw.
(schizophrenia spectrum and other psychotic disorders).mp.

or/31-34

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30 and 35

meta-analysis/ or "systematic review"/

exp Systematic Review as Topic/

(systematic adj2 review*).tw,kw.

systematic review.pt.

(system* adj3 review*).tw.

exp Meta-Analysis as Topic/

(meta analys* or metaanalys*).tw,kw.

meta analysis.pt.

(meta-analy* or metaanaly* or metanaly*).tw,kw.

(((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw.

or/37-46

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36 and 47

Appendix 3-B. Assessment of methodological quality of included syntheses (AMSTAR-2)

Reference No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Review planning				Independent screening & extraction			Descriptive analysis	RoB	Funding source	MA method	RoB MA	RoB discussion	Between study difference	Small study effects	CoI
50	N	N	N	N	N	Y	N	Y	Y	N	Y	N	N	Y	Y	Y
51	N	N	N	PY	N	Y	N	N	N	N	Y	N	N	N	Y	Y
52	N	N	N	N	N	N	N	Y	Y	N	Y	N	N	Y	Y	Y
53	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	Y	Y
54	N	N	N	PY	N	N	N	N	N	N	N	N	N	Y	Y	N
9	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	N
30	N	N	PY	N	N	Y	N	PY	N	N	N	N	N	Y	Y	Y
29	N	N	N	N	N	N	N	Y	N	N	N	N	N	Y	Y	N
31	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	Y	N
32	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y
55	N	N	N	PY	N	Y	N	N	Y	N	Y	N	N	N	Y	Y
56	N	N	N	PY	N	N	N	N	N	N	N	N	N	N	Y	Y
58	N	N	N	Y	Y	N	N	Y	Y	N	N/A	N/A	N	N	N/A	Y
59	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y
57	N	N	N	N	N	N	N	Y	N	N	N/A	N/A	N	N	N/A	N
60	N	N	N	N	N	N	N	Y	Y	N	N/A	N/A	N	N	N/A	Y

CoI: Conflict of Interest; MA: Meta-Analysis; N: No; N/A: Not Applicable; PY: Partial Yes; RoB: Risk of Bias; Y: Yes

Q1: Did the research questions and inclusion criteria for the review include the components of PICO?

Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

Q3: Did the review authors explain their selection of the study designs for inclusion in the review?

Q4: Did the review authors use a comprehensive literature search strategy?

Q5: Did the review authors perform study selection in duplicate?

Q6: Did the review authors provide a list of excluded studies and justify the exclusion?

Q7: Did the review authors provide a list of excluded studies and justify the exclusions?

Q8: Did the review authors describe the included studies in adequate detail?

Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

Q10: Did the review authors report on the sources of funding for the studies included in the review?

Q11: If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?

Q12: If meta-analysis waws performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Q15: If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review

Chapter 4: Is there a causal link between folate status and schizophrenia? Evidence from genetic association studies

In Context

Our umbrella review on the association of folate and vitamin B_{12} status with schizophrenia (chapter 3) suggested an inverse relationship from limited evidence available. With respect to the risk of schizophrenia onset, all of the included syntheses comprised of retrospective studies with lack of consideration of important sociodemographic and clinical covariates. Evidence on the effect of folate or vitamin B_{12} on improvement of schizophrenia symptoms was severely limited.

As the next step in the inquiry, we investigated the nature of the relationship between folate, vitamin B_{12} and schizophrenia. We aimed to synthesize relevant evidence that utilized instrumental variable analysis approach, which is designed to inform on causal nature of the association of interest. More specifically, we sought to gain insights from Mendelian randomization studies, which use genetic variants as instrumental variables to infer causality.

This chapter describes our systematic review and meta-analysis of Mendelian randomization studies investigating the relationship between folate, vitamin B_{12} and schizophrenia.

Journal Submission

- Published in *Nutritional Neuroscience* (December, 2024)
- Authors: Samantha Yoo, Azita Montazeri, Helen McNulty, Monique Potvin Kent, Julian Little
- Author contributions: SY, HMcN, MPK, JL conceptualized the study. SY adapted the search strategies from Research 1 and executed the search. SY and AM screened articles, extracted data, and conducted methodological quality assessment of all included articles. SY synthesized the evidence and drafted the manuscript. AM, HMcN, MPK, and JL provided critical input in development of the manuscript. All authors read and approved the final version of the manuscript.

4.1 Abstract

Background: It is plausible that folate and vitamin B_{12} status, through their critical involvement in DNA synthesis and methylation, may be causally related to the risk of schizophrenia. However, associations with blood status measures may reflect reverse causation or inadequate control for confounders. The Mendelian randomization approach may mitigate these problems. Among multiple genes involved in the folate pathway, methylenetetrahydrofolate reductase (*MTHFR*) plays a crucial role in folate metabolism and in subsequent methylation reactions in the brain. Two common variants of this gene, *MTHFR* C677T and A1298C, result in lower blood folate and reduced enzyme activity, and have been associated with higher risk of schizophrenia. The objective of this study was to synthesize evidence on the possible causal link between folate and vitamin B_{12} status and schizophrenia using genetic variants as instrumental variables.

Methods: MEDLINE, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews were searched for Mendelian Randomization studies that investigated a causal relationship between genetic instruments for folate and vitamin B_{12} status and schizophrenia onset or symptom scores. The risk of bias of the included studies was assessed using Newcastle Ottawa Scale. Odds ratios and 95% confidence intervals were estimated using random effects models.

Results: Thirty-four case-control studies were identified. None of the studies used a formal instrumental variable analysis. Most of the studies had high methodological quality for assessing genetic association. The *MTHFR* polymorphisms (C677T, A1298C) were most studied and homozygosity for the variants showed significant positive associations with the risk of schizophrenia (OR $_{677TT\ vs\ 677CC}$= 1.26 (1.03, 1.55), OR $_{1298CC\ vs\ 1298AA}$=1.58 (1.17, 2.13)). Heterozygosity for the variants showed attenuated associations in the same direction as homozygosity. Subgroups of age, sex, ethnicity, and folic acid fortification implementation were mostly underpowered to detect effects with precision. Evidence on the association of *MTHFR* polymorphisms with specific schizophrenia symptoms or the relationship between *Methylenetetrahydrogenase-1*

(MTHFD-1) and *methionine synthase (MTRR)* and risk of schizophrenia was severely limited.

Conclusion: Significant associations were identified between the *MTHFR* C677T and A1298C polymorphisms and the risk of schizophrenia at an aggregate level. Subgroup analyses by age group, sex, and ethnicity produced non-significant results or estimates with wide confidence intervals. Considering complexity and heterogeneity of schizophrenia, more detailed delineation of the study population may be needed to understand the key risk factors in its etiology. Composite genetic index or epigenetic investigations may also be relevant in the study of schizophrenia.

4.2 Introduction

Schizophrenia is a complex neuropsychiatric disorder with substantial heritability[1-3] and susceptibility to environmental exposures[4]. The heritability of the disorder ranges between 64-81% based on family and twin studies[5,6], while strong associations with environmental factors such as urbanicity and migration have been suggested by epidemiological studies[7-11].

Folate and vitamin B_{12} have been studied in the context of schizophrenia with conflicting results. Our recent umbrella review found a significant inverse association between folate, vitamin B_{12} status and the risk of schizophrenia (chapter 3). However, most of this evidence is limited by a retrospective study design, small sample size, and large heterogeneity among the populations studied; these limitations prevented examination of the relationship in subgroups that may be differentially affected by folate and vitamin B_{12} status.

The postulated link between folate, vitamin B_{12} and schizophrenia is based on the crucial role of methylenetetrahydrofolate (*MTHFR*) gene in folate metabolism and subsequent methylation reactions and neurodevelopment. *MTHFR* converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a bioactive form that donates a methyl group required to produce S-adenosylmethionine[12], which, in turn, catalyzes

various methylation reactions in the brain[13,14]. These methylations are involved in the synthesis of monoamines, such as dopamine, serotonin, and norepinephrine[15]. Two common variants of the gene, C677T (rs1801133) and A1298C (rs1801131), result in lower blood folate and 30-60% reductions in the enzyme activity[16-18] and are associated with several neurological conditions, such as neural tube defects[19-21], motor and gait dysfunction[22].

Both of these common variants of *MTHFR* were among the 24 genetic variants identified in the initial *Schizophrenia Gene* database[23] as associated with schizophrenia risk (*MTHFR* C677T OR=1.16 (1.05, 1.30) based on 3,327 cases and 4,093 controls; *MTHFR* A1298C OR=1.16 (1.07, 1.34) based on 1,211 cases and 1,795 controls)[23]. Risk estimates for these two alleles have since been updated to 677T OR=1.29 (1.07, 1.56)[24] and 1298A OR=1.07 (0.96, 1.18)[25]. However, these associations have not been replicated in studies examining predominantly or entirely non-European populations[26,27].

Besides *MTHFR*, evidence is accumulating around the roles of other genes that are critically involved in the one-carbon metabolism, such as methionine synthase reductase (*MTRR*)[28] and methylenetetrahydrofolate dehydrogenase-1 (*MTHFD*)[29], and their association with various health conditions[30].

Mendelian Randomization (MR) analysis has become an established methodology for investigating a relationship between a risk factor and a health outcome using genetic variants as instrumental variables, and may support causality because random segregation mimics the randomization in randomized controlled trials (RCTs) and because the design reduces the risk of reverse causality compared with conventional observational study designs[31,32]. Briefly, this approach uses genetic variant(s) that are biologically or statistically strongly associated with a risk factor as an instrumental variable and measures its association with the outcome to compute a causal estimate. Core assumptions and methodologies of the MR approach are described in detail elsewhere[31,33,34].

Given the critical role of *MTHFR* in one-carbon metabolism and its suggested association with schizophrenia, this gene may be a candidate for providing further insights into the putative link between folate, vitamin B_{12} and schizophrenia. However, the current literature is limited to retrospective observations of heterogeneous populations. We sought to investigate whether a causal relationship exists between folate and schizophrenia by synthesizing MR analyses of folate and vitamin B_{12} status and schizophrenia.

4.3 Methods

The protocol for this study was registered with the PROSPERO database CRD 42023418118. We performed a systematic review and meta-analysis of MR studies that examined a causal relationship between folate and/or vitamin B_{12} status and schizophrenia.

4.3.1 Eligibility criteria

The exposure was folate or vitamin B_{12} status. Eligible instrumental variables were any biologically plausible determinant of the status of either vitamin or polymorphic variants of genes known to be involved in one-carbon metabolism, including *MTHFR*, and the genes encoding cystathionine beta synthase *(CBS)*, methylenetetrahydrofolate dehydrogenase-1 *(MTHFD1)*, and methionine synthase reductase *(MTRR)*.

The outcome was diagnosis of schizophrenia or treatment outcomes of schizophrenia, i.e., improvement in positive or negative scores. We restricted the outcome definition to clinical diagnosis of schizophrenia by trained psychiatrists according to the criteria specified in any editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD). The treatment outcome could be measured by any validated symptoms scales or any tool of functional assessment. In order to minimize heterogeneity in the analyses, we excluded schizoaffective disorder, mood disorders with psychotic features, or psychoses induced by other conditions or medications. We did not limit schizophrenia in terms of severity, duration of illness, or

use of antipsychotics. Comparators were healthy controls without current, past, or family history of schizophrenia.

We did not limit the type of MR study by whether it was a one-sample or two-sample design. There was no restriction in terms of age, sex, ethnicity, geographical region of the study populations.

4.3.2 Data sources and search strategy

We searched four electronic databases: PubMed/MEDLINE, Embase, PsycINFO, and Cochrane Database of Systematic Reviews from inception to March 21, 2023. The search strategies broadly captured genetic polymorphisms that determined folate and/or vitamin B_{12} status and schizophrenia in humans. No restriction was placed on the year of publication. Language restriction was not imposed on the search strategy in order to avoid bias[35]. We also conducted an extensive search of the reference lists of the included studies. The full search strategy for MEDLINE is provided in Appendix 4-A. The searches in the other databases were built on the MEDLINE search.

4.3.3 Screening and extraction

All articles identified in the searches were imported to the Covidence software[36] for two-stage screening and data extraction. Two independent reviewers (SY, AM) conducted two-stage screening and resolved conflicts by discussion and consensus. Data extraction was also conducted by two independent reviewers (SY, AM) using a predefined template, which included the following key information from each article: (1) basic study information (first author, title of the study, year of publication, country in which the study was conducted, conflict of interest, source of funding); (2) methodology used in the study (eligibility criteria, case definition, control definition, matching variables, type of sample used, year of data collection, genotyping method); (3) study population (number of participants, age, sex, ethnicity, comorbidities, socioeconomic position of both cases and controls, age of onset, severity, use of antipsychotics for cases); (4) exposure (genetic instrument used, allele frequency, genotype distribution, statistical significance, Hardy-Weinberg equilibrium); and (5) quantitative analysis (risk estimates by allele contrast,

risk estimates by genotype, causal estimate, subgroup analyses). All discrepancies were resolved by discussion and consensus.

4.3.4 Risk of bias assessment

We assessed the risk of bias of all included studies using Newcastle-Ottawa Quality Assessment Scale (NOS)[37]. This assessment tool is widely used for observational studies. We used a specific version for case-control studies, which consists of three domains: assessment of selection bias (total 4 points), assessment of comparability between cases and controls (total 2 points), and assessment of ascertainment bias (total 4 points). Two independent reviewers (SY, AM) assessed the risk of bias and resolved conflicts by consensus.

Use of NOS was a deviation from the registered protocol, in which we originally planned to use STROBE-MR[38] and Q-GENIE[39] to assess methodological quality. We chose NOS to best accommodate the articles finally included in our analysis, which were entirely case-control studies.

4.3.5 Evidence synthesis

We organized the studies according to the outcome: (1) risk of schizophrenia and (2) treatment outcomes of schizophrenia. The studies were subsequently categorized by the genotypes used as instrumental variables. We further stratified the studies by age group, sex, ethnicity, and the implementation of folic acid food fortification program in the country studied.

For stratification of age groups, we used the categories of 15-30 years, 31-45 years, and 45 years or older in order to account for the typical age of onset of schizophrenia for both sexes (from late adolescence to the late 20s among males and from the early 20s to the early 30s among females)[40-42]. Ethnicity was classified based on the authors' descriptions as well as the geographical location of the country of study. The classifications were "European", "East Asian", "Middle Eastern/West Asian", and "Mixed ethnicities". The latter included participants described as a mixture of ancestries. For presence of folic acid

fortification programs, we used data from the Food Fortification Initiative (FFI)[43], a public-private-civic partnership that implements and monitors fortification programs of industrially milled grains across the globe. We grouped each country of study as either having mandatory fortification or not having mandatory fortification during the period of study.

We used a random effects model to synthesize odds ratios and 95% confidence intervals of the risk estimates from the included studies. We also calculated 95% prediction intervals to understand the dispersion of effect sizes[44]. Egger's test of asymmetry was used to assess potential small study effects (significance threshold $p<0.10$)[45]. All statistical analyses were performed using Review Manager version 5.4.1[46] and Metafor package[47] in R software[48].

4.4 Results

4.4.1 Overview

Our database and manual citation searches retrieved 150 and 59 articles, respectively. After deduplication, a total of 188 articles remained and were screened over two stages. Studies examining interactions between multiple genetic polymorphisms or examining broad mental health conditions without including a subgroup analysis on schizophrenia were excluded in the full-text screening. Four articles were not published in English. Thirty-four articles were included in the final analysis (Figure 4-1).

None of the studies used a formal instrumental variable analysis. All 34 articles reported case-control studies examining the association of genetic polymorphisms and risk or severity of schizophrenia. Thirty-two of the articles reported the risk of schizophrenia associated with genetic variants and three reported differences in severity of schizophrenia symptoms associated with genetic variants. Across the 32 articles that investigated the risk of schizophrenia, four genetic polymorphisms were studied in 35 datasets comprising 11,159 individuals with diagnosis of schizophrenia and 13,831 healthy controls: *MTHFR* C677T (32 studies), *MTHFR* A1298C (10 studies), *MTHFD-1* G1958A (1 study), and *MTRR A66G* (1 study). The three studies that reported on the

genetic association with schizophrenia symptoms examined *MTHFR* C677T (3 studies, in aggregate 2,238 affected individuals) and *MTHFR* A1298C (1 study, 200 affected individuals).

The included studies were conducted in East Asia (14 out of 37 datasets), Europe (12 datasets), Middle East/ West Asia (6 datasets), North America (4 datasets), and Africa (1 dataset). The size of the datasets ranged from 50 to 3,891 participants. Most of the authors used broad descriptions of ethnicity, i.e., “Caucasian”, “European”, and “Han Chinese”. A total of 14 datasets were matched on age, sex and/or ethnicity.

All of the studies recruited cases from inpatient wards or outpatient clinics of psychiatry hospitals using DSM or ICD criteria. Controls were unrelated individuals selected from the community after ruling out family or past history or current presence of psychiatric disorders (23 out of 35 datasets). Across the studies, the mean age of the participants ranged from 29 to 58 years across the studies. In most of the studies, information on severity, duration of illness, or use of antipsychotics was not reported. Characteristics of the included studies are summarized in Table 4-1.

4.4.2 Risk of bias assessment

Most of the included studies were rated as of high quality according to the NOS. Of the 32 studies (excluding two studies that analyzed genotypes among patients with schizophrenia), 30 (94.7%) scored 6 points or higher out of total 9. While all studies scored fully in the exposure domain (comparable method of diagnosis and response rate in both groups), variations were observed in selection and comparability domains, particularly in relation to representativeness of the cases, definition of controls, and comparability of cases and controls. Only two studies randomly selected cases from a pool of potential candidates or described representativeness of the cases. Twenty-three out of 32 studies screened the controls for presence of mental disorders. Ten studies used individual matching of controls to cases based on ethnicity, age and/or sex. Details of the matching technique (e.g., use of age bands) were not reported in any of these studies. One

study used a conditional logistic regression model and all of the 10 studies reported crude risk estimates.

4.4.3 *MTHFR* genotypes and risk of schizophrenia

4.4.3.1 *MTHFR* C677T variants

The datasets included in the analysis of the association with the *MTHFR* C677T polymorphism comprised of 10,637 cases and 13,216 controls. The data subset for 677TT vs 677CC genotype comparison included 6,037 cases and 7,646 controls. Overall, compared to the homozygous common variant 677CC, individuals with the homozygous variant 677TT had a significantly higher risk of having schizophrenia (OR=1.26, 95% confidence interval: (1.03, 1.55)) (Figure 4-2). Heterogeneity among the datasets was high (I^2=80.12%, p<0.01) but there was no evidence of small study effects (P_{Egger}= 0.07) (Table 4-2.)

We did not find strong evidence of modification of the effect of 677TT genotype by age group, sex, or ethnicity. Some of the subgroups were underpowered (< 300 cases) to produce precise estimates. Levels of heterogeneity varied across the subgroups (I^2= 9.8% - 87.5%). Among the subgroups with ≥ 1,000 cases, three groups showed significant associations: East Asians (OR=1.31 (1.07, 1.61), I^2=62.09%); 31-45 years age-group (OR=1.38 (1.01, 1.89), I^2=85.90%); and countries without folic acid fortification (OR=1.28 (1.03, 1.59, I^2=81.65%); however, 95% prediction intervals included the null for all three subgroups (Table 4-2).

We pooled 9,094 cases and 11,633 controls for comparison of the *MTHFR* 677CT genotype to the 677 CC genotype; the result was similar in direction to, albeit with somewhat lower magnitude (OR=1.10 (1.01, 1.19)) than the association observed for the 677TT vs 677CC comparison, with less heterogeneity (I^2=41.66%, p=0.01). Small study effects were not observed (P_{Egger}=0.29).

When stratified by age group, sex, ethnicity, and presence of folic acid fortification program, the risk estimates and heterogeneity were comparable within the categories of each subgroup with the width of the confidence intervals largely reflecting sample size.

4.4.3.2 *MTHFR* A1298C variants

The dataset available for analysis of the *MTHFR* A1298C polymorphism was smaller than that for *MTHFR* C677T, and included a total of 2,417 cases and 3,454 controls; there were 1,507 cases and 2,325 controls homozygous for either variant. Individuals homozygous for the C variant (*MTHFR* 1298CC) had a higher risk of schizophrenia than those homozygous for the A variant (1298AA; OR=1.58 (1.17, 2.13); Figure 4-3). The pooled analysis had moderate heterogeneity (I^2=48.2% (p=0.03)) and no evidence of small study effects (P_{Egger}= 0.20).

Subgroup analyses comparing homozygotes were limited to two age groups (31-45 years, > 45 years), sex, and three ethnicity groups (European, East Asian, Middle Eastern/West Asian). None of the included studies was conducted in a country with folic acid fortification. Total sample size across all subgroup categories ranged from 524 to 2,959 participants, with most analyses been based on analytical samples 300 – 500 cases. One subgroup with ≥ 1,000 cases (31-45 years age group) reported a significant association (OR=1.60 (1.10, 2.33), I^2=57.1%). Across all subgroups, the estimated risks were comparable and in the same direction, ranging from OR=1.06 ((0.81, 1.39), I^2=0%) to OR=2.15 ((0.92, 5.01), I^2=60.3%).

In the comparison of *MTHFR* 1298CA heterozygotes vs homozygotes for the common variant (1298AA) (2,278 cases and 3,475 controls), the overall association was in the same direction as for homozygotes for the common variant, but weaker (OR=1.19 (0.99, 1.44), I^2=63.5%). Subgroups comprised from 816 to 4,698 participants (344 to 1,734 cases) and showed attenuated associations in the same direction compared the comparison of the homozygotes with the risk estimates ranging from OR=1.02 ((0.86, 1.21), I^2=0%) to OR=1.48 ((0.96, 2.28), I^2=82%).

4.4.4 *MTHFR* genotypes and schizophrenia symptoms

Three studies examined the association of *MTHFR* C677T and A1298C genotypes with different symptoms of schizophrenia. Roffman et al. studied differences in levels of impairment of executive function[49] and negative symptoms (absence or lack of normal mental functions, such as avolition, anhedonia, and social withdrawal)[50] in association with both variants in the same pool of outpatients with chronic, stable schizophrenia (n=200) in the USA. Mean age of the participants ranged from 41.8 ± 11.0 years to 45.7±7.7 years across the genotypes. The proportion of males was 65-70% in each genotype group. Ethnicity was mixed in the overall group (78.5% "Caucasian", 20% African American, 1% East/Southeast Asian, and 0.5% Latino) and the composition of ethnicities varied across the genotype groups studied. The mean duration of illness was 17.7 – 22.2 years in the study population. Compared to the 677CC group, individuals with 677TT had significantly more impairment on some, but not all, executive function scales[49] and significantly more negative symptoms[50] measured on the Positive and Negative Syndrome Scale (PANSS)[51]. Overall, the C677T variants accounted for 2.1% of the variations in negative symptoms and 2.4% of the variations in positive symptoms. The A1298C polymorphism did not show significant association with negative symptoms.

Zhang et al.[24] investigated the association between *MTHFR* C677T polymorphisms and episodic memory among 33 individuals with schizophrenia and 29 healthy controls in China (entirely Han Chinese). Age, sex, and educational attainment were comparable across the two groups. Mean age was 23 years and male sex accounted for approximately 60% in each group. The authors found a significant impairment of episodic memory among the individuals with schizophrenia compared to controls, and a significant association between the T allele and impairment of episodic memory only in the group diagnosed with schizophrenia[24].

4.4.5 Other genotypes and risk of schizophrenia

MTRR A66G and *MTHFD-1* G1958A genotypes and their relationships with risk of schizophrenia were examined in one study each. First, in a small study in Syria (85 cases

and 126 controls, mean age 37±10 years, male proportion 63% in cases - 71% in controls), Lajin et al.[52] reported that the association between schizophrenia and the *MTRR* 66GG and 66GA genotypes compared to 66AA were compatible with the null (OR=1.12 (0.57, 2.53) and OR=0.84 (0.45, 1.57), respectively). Second, the *MTHFD-1* G1958A genotypes were studied in a Russian "Caucasian" study population of 116 cases and 62 controls. The cases were older (median age=33 years) and had more male (52.6%) compared to the controls (median age=29 years, male 35.5%). All of the cases were on antipsychotic treatment. The authors found significant associations of 1958AA (OR=3.15 (1.13, 4.72)) with risk of schizophrenia, but not of 1958GA (OR=1.82 (0.87, 3.79)), compared to 1958GG.

4.5 Discussion

We systematically synthesized the current evidence on associations between schizophrenia and variants of genes involved in the folate pathway. We did not find any MR analyses with estimates of the effect of folate and vitamin B_{12} based on formal analysis of genetic instrumental variables on the risk or symptom severity of schizophrenia.

From the genetic association studies available, we identified small, but significant associations of the two common polymorphisms of *MTHFR* with schizophrenia. The risk alleles of 677T and 1298C may have additive effects, considering larger magnitudes of risk estimates with the homozygous variants compared to the heterozygous variants. Although some were underpowered to detect effects with precision, most of the subgroup risk estimates were not significant or had wide confidence intervals. Studies on the associations of genetic variants with schizophrenia symptoms or on the effects of other genetic polymorphisms, such as *MTHFD-1* G1958A and *MTRR* A66G were limited.

The evidence on the relationship between the two common variants of *MTHFR* and severity of schizophrenia symptoms was not sufficient to draw firm conclusions. While the 677T allele correlated to a statistically significant level of executive function deficits and negative symptoms compared to 677CC genotype, the biological mechanisms under

which the risk allele affects certain symptoms more than others remain unclear. Of note is the heterogeneous nature of negative symptoms (consequence of positive symptoms or antipsychotics use)[50]. More evidence from larger and more homogenous studies replicating these findings may help our understanding of the clinical significance of the variants and guide strategies for better treatment of negative symptoms.

Our meta-analysis of genetic associations with schizophrenia is an extension of the previous work by Yadav et al.[53] and Rai et al.[54] There are several important distinctions of our work: first, we narrowly defined schizophrenia and excluded studies that examined schizoaffective disorders or other affective psychoses in their study populations. This somewhat reduced the size of our analytical samples but decreased heterogeneity among the study population. Considering the inherent limitations of schizophrenia diagnosis that depends on clinical observations or self-reported symptoms rather than biological markers, restricting heterogeneity is important. Second, we conducted subgroup analyses by age groups, sex, and folic acid fortification program in addition to ethnicity to gain further evidence on potential effect modifications. Age at onset is an important variable in schizophrenia that often serves as a proxy for severity and/or prognosis[55,56] and is reported to interact with sex[41,42,57]. Sex differences in severity of schizophrenia symptoms have also been widely reported[58-60].

The biological link between the *MTHFR* C677T polymorphisms and folate and vitamin B_{12} metabolism is well-established[16] and has been validated by numerous reports and meta-analyses[61-63]. However, due to substantial variations in the frequency distributions of the T allele by ethnicity[64-68], caution must be exercised in aggregating risk estimates across different ethnicities. Strength of the causal relationship, if any, between folate metabolism and risk of schizophrenia may vary by ethnicity or geographical region.

The genetic associations we found in this synthesis align with our previous findings on the relationship between plasma/serum concentrations of folate and the risk of schizophrenia (chapter 3). Folate status was inversely associated with the risk of schizophrenia in the overall and the East Asian subgroup. The genotype analysis also

suggests a potentially load-dependent relationship between the risk allele and schizophrenia risk. These findings reduce the possibility of reverse causation and confounding in the association seen with the biomarkers.

The largely weak genetic associations found in our subgroup analyses suggest several possibilities. First, folate metabolism may vary across the lifespan, susceptible to factors such as comorbidities, use of antipsychotics and other medications that affect folate homeostasis (e.g., methotrexate, neuroleptics, antiepileptics[69]), socioeconomic status, as well as age. Failure to address heterogeneity across these potential confounders may result in imprecise conclusions.

Second, there may be compounded effects of multiple polymorphisms of multiple genes that are involved in folate metabolism. The *MTHFR* gene is reported to have over a dozen mutations, with some being more rare than others but associated with greater severity of enzyme restriction[70-72]. Some researchers have also studied the combined effects of the C677T and A1298C genotypes or haplotypes[52,73-77] and reported that different genetic models, i.e., dominant, recessive, homozygous codominant, heterozygous codominant, may be at work for each polymorphism in the context of schizophrenia risk[52,76]. Studies on other genes involved in the one-carbon metabolism and their interplay with the more common polymorphisms are still scarce. A composite risk index[26,78] that comprises of carefully weighted polymorphisms involved in the folate metabolism may help us better understand the nature of the association between the vitamins and schizophrenia.

Third, we note the possibility of multiple mediation pathways linking folate metabolism and schizophrenia, each depending on complex interplays with other genes. In addition to the most established hypothesis of excess homocysteine inducing vascular impairment[79] and neuronal toxicity and neurodegeneration[80,81], disturbances in folate metabolism compromise the re-synthesis of tetrahydrobiopterin (BH4)[82], which is an important cofactor in the production of neurotransmitters and associated with schizophrenia risk[30,83,84]. Complex interactions between the *MTHFR* C677T variants and G324A polymorphisms of the *catechol-o-methyltransferase (COMT)* gene have also been widely

reported[24,74,85-87]. The latter gene is involved in the turnover of monoamines[88] and dopamine[74] and has been associated with schizophrenia[86,89,90]. These two genes share metabolic pathways[91], with the *MTHFR* polymorphism influencing the expression of the *COMT* gene[92]. Neuroinflammation may be another pathway, in which deficiency in folate and vitamin B_{12} compromises the functions of cytokines[93,94], which result in inflammations in the brain that have been linked to the onset of schizophrenia[95-97]. Future research on these potential mediation pathways involving one-carbon metabolism may provide insights into the biological mechanisms linking folate and schizophrenia risk.

Last, the etiopathology of schizophrenia may be more epigenetic than genetic. Schizophrenia is increasingly described as a neurodevelopmental disorder[98-100], while also having neurodegenerative components[101]. SAM, generated from homocysteine with a methyl group from 5-methyltetrahydrofolate, is crucially involved in key methylations and neural functions[102-105] throughout the lifespan. Adding further weight on the epigenetics hypothesis are observations that schizophrenia does not show typical pattern of Mendelian inheritance[85] and that the sex-specific genetic associations remain unexplained[106]. Knowledge on the potential epigenetic mechanisms of schizophrenia has been accumulating[107-110]; yet, more remains to be understood about the involvement of one-carbon nutrients and trajectories of epigenetic modifications.

4.6 Strengths and limitations

We conducted a comprehensive search of the literature inclusive of all genetic associations that might indicate folate and vitamin B_{12} associations with schizophrenia. Most of the included studies were matched for ethnicity and/or geography, which ruled out population stratification bias and allowed for less confounded assessment of the association of interest.

Nevertheless, there might have been heterogeneity among the study populations, particularly in important confounders such as antipsychotics use (dosage, duration), duration of illness, and socioeconomic status. Such information was not available from the studies and may have resulted in confounded estimations.

In addition, we did not find any studies that used formal MR or other causal inference approaches[111]. Identifying causality of the effect of folate and vitamin B_{12} on schizophrenia may be challenging due to potential misclassification of schizophrenia in clinical practice, variations of symptoms within individuals, and difficulty in precise measurement of folate and vitamin B_{12} status. Our synthesis of genetic association studies, however, may serve as triangulating evidence in the broad question on the relationship of folate and vitamin B_{12} with schizophrenia.

4.7 Conclusion

We identified associations between the *MTHFR* C677T and A1298C polymorphisms and the risk of schizophrenia at an aggregate level. Subgroup analyses by age group, sex, and ethnicity produced non-significant results or risk estimates with wide confidence intervals. Considering the complexity and heterogeneity of the schizophrenia spectrum disorder, more detailed delineation of the study population may be important in understanding the key risk factors in its etiology. Use of a composite genetic index or epigenetic investigations may also be relevant in the study of schizophrenia.

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4.9 Figures and Tables

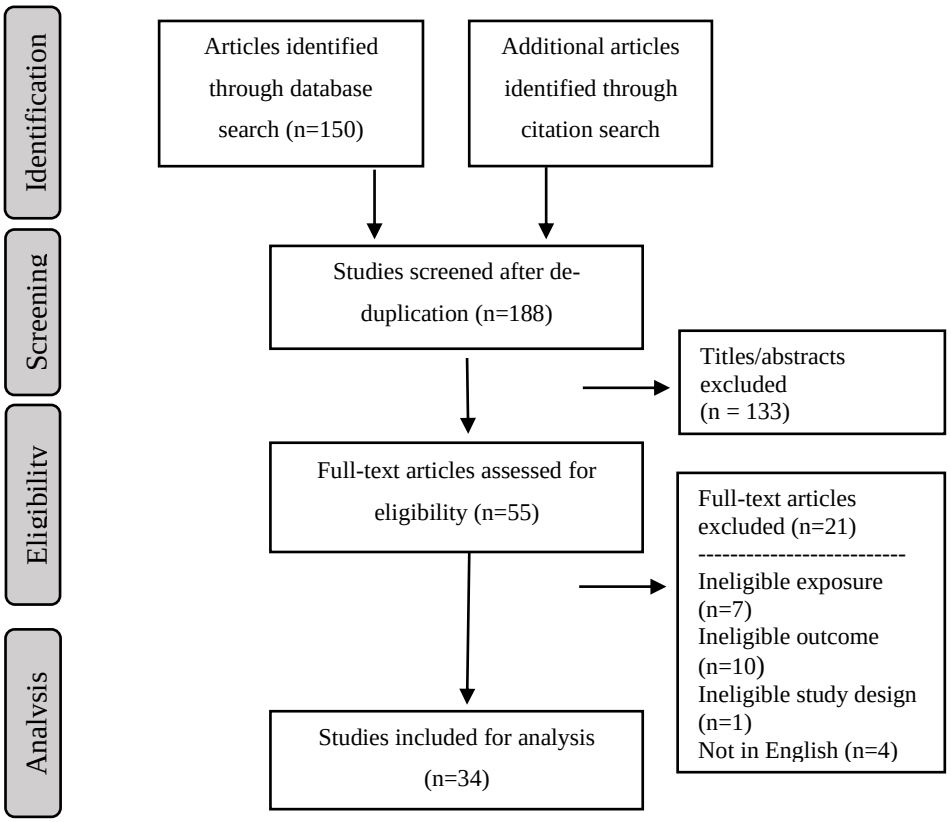

Figure 4-1. PRISMA diagram of the process used to identify evidence on the association between folate and vitamin B_{12} status and schizophrenia onset and treatment outcome

***** Ineligible exposures: interaction among multiple genes; Ineligible outcomes: schizoaffective disorder, general mental illness

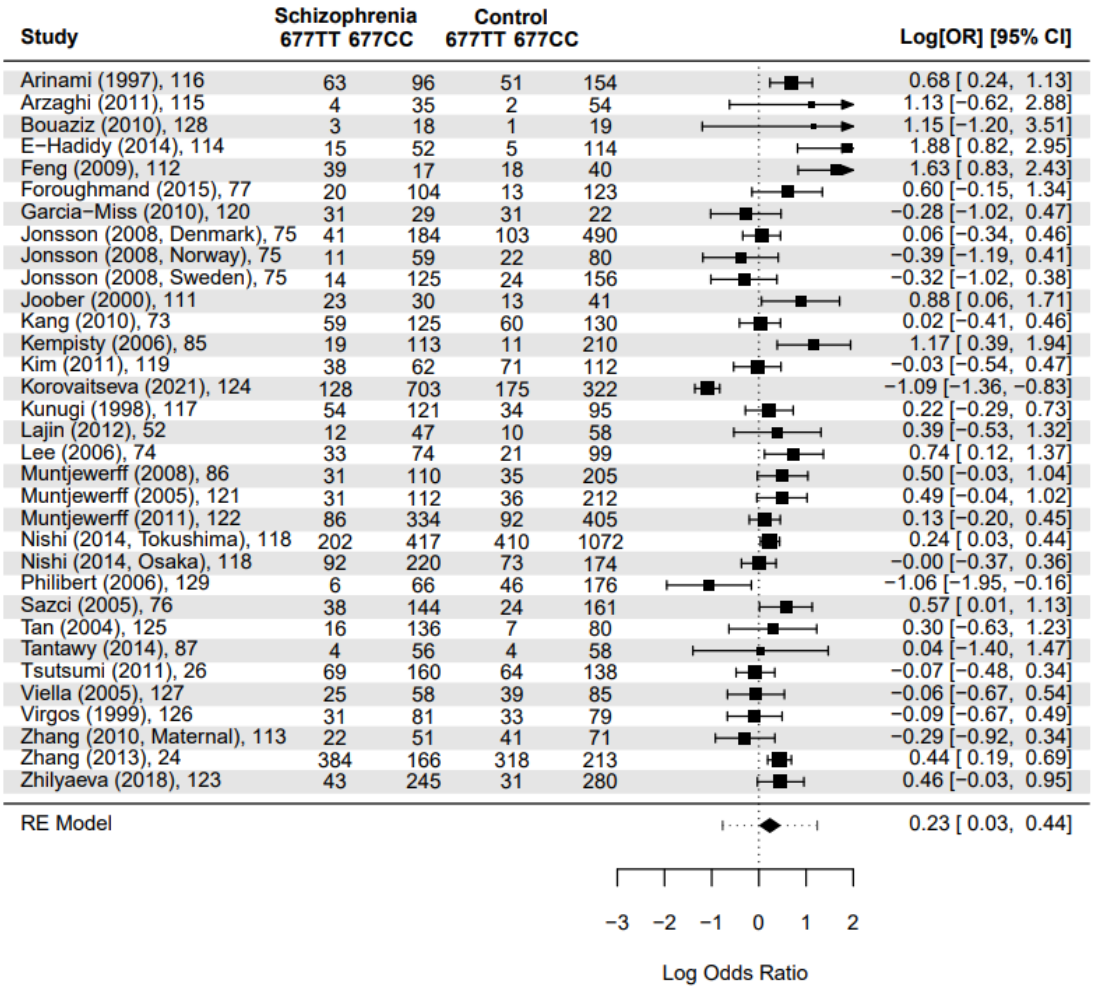

Figure 4-2. Forest plot of the association between *MTHFR* 677TT vs 677CC and schizophrenia

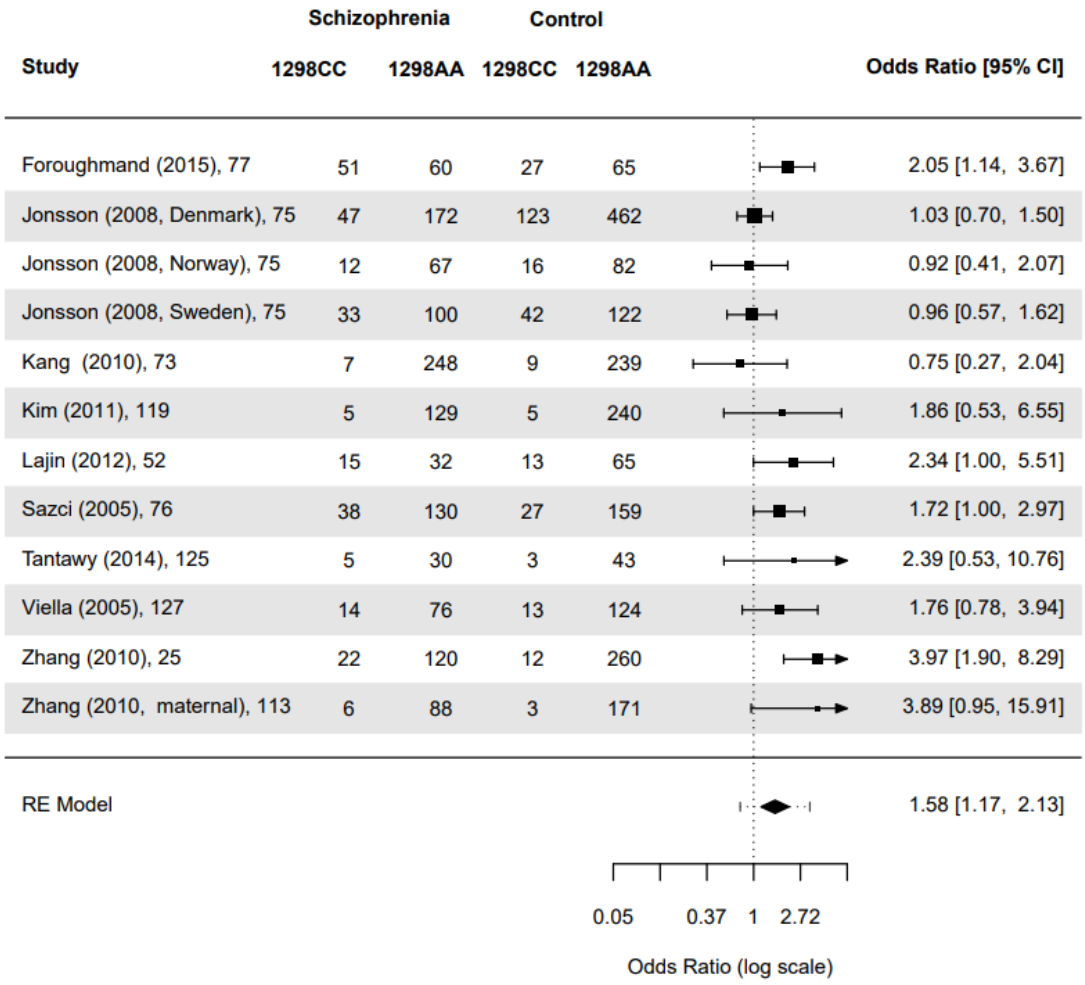

Figure 4-3. Forest plots of the association between *MTHFR* 1298CC vs 1298AA and schizophrenia

Table 4-1. Characteristics of the studies of associations between genotypes related to folate status and schizophrenia included in the analysis

First author (Year)	Country (Ethnicity*)	Case definition	Control definition	Sample (case : control)	Age (years) (mean, SD)	Sex (M-F)	NOS score
MTHFR C677T – risk of schizophrenia							
Joober et al. (2000)[111]	Canada, hospitals in Montreal and Ottawa ("Caucasian")	Diagnosis of SZ Responders: complete/quasi-complete remission when on conventional neuroleptics Non-responders: non-remitting symptoms in spite of adequate treatment with conventional neuroleptics	Healthy volunteers screened for DSM-IV axis I mental disorders	105:90	Case: Responders 38.7 (6.9) Non-responders 40.6 (10.5) Control: significantly older than cases	Case: NR Control: significantly more female than cases	6
Feng et al. (2009)[112]	China (Han Chinese)	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	Volunteers	123:123	Case: 31.7 Control: 33.8	Case:50-73 Control:53-70	7
Zhang et al. (2010)[113]	China (Han Chinese)	Healthy mothers with SZ-afflicted offspring Diagnosis of SZ under DSM-IV	Healthy mothers with healthy offspring	143:235	Case: mother 47.4 (4.6) child 18.8 (5.0) Control: mother 49.2 (5.9) child 18.6 (6.0)	Case: child 56-55 Control: child NR	8
Zhang et al. (2013)[24]	China (Han Chinese)	Unrelated individuals Diagnosis of SZ under DSM-4	Healthy individuals in community Screened against history of mental health or neurological diseases	1002: 1036	Case: 31.2 (9.9) Control: 32.5 (8.3)	Case: 540-462 Control: 602-434	8

Jonsson et al. (2008)[75]	Denmark ("Caucasian")	In/outpatients of psychiatry Diagnosis of SZ under ICD-10 No history of mania/bipolar disorder	Healthy, unrelated blood donors	388:1006	Case: 44.4 (12.2) Control: 44.2 (11.8)	Case: 226-162 Control: 449-557	6
El-Hadidy et al. (2014)[114]	Egypt (Arab)	Diagnosis of SZ under DSM-IV-TR	Healthy volunteers No personal/family history of psychiatric disorders Unrelated to cases	103:149	Case: 33.9 (9.4) Control: 34.3 (6.0)	Case: 68-35 Control: 76-73	6
Arzaghi et al. (2011)[115]	Iran (Iranian)	Unrelated individuals Diagnosis of SZ under DSM-IV	No personal/family history of psychiatric, neurological, metabolic conditions	66:94	Case: 29 (4) Control: 31 (6)	Case: 45-21 Control:53-41	8
Foroughmand et al. (2015)[77]	Iran (NR)	Unrelated individuals with SZ	Healthy blood donors	200:200	Case: 43.3 (11.3) Control: 39.4 (11.1)	Case: 117-83 Control:117-83	6
Arinami et.al (1997)[116]	Japan (Japanese)	Unrelated individuals Diagnosis of SZ under DSM-III-R	Unrelated individuals	297:419	Case: 45.2 (13.0) Control: 48.5 (8.7)	Case: 168-128 Control: 218-138	6
Kunugi et al. (1998)[117]	Japan (Japanese)	Unrelated individuals In/outpatients of psychiatry Diagnosis of SZ under DSM-IV 81% had history of hospitalization	Healthy, unrelated individuals	343:258	Case: 42.2 (12.8) Control: 31.3 (11.3)	Case: 167-176 Control:129-129	6

Tsutsumi et al. (2011)[26]	Japan (Japanese)	Inpatients Diagnosis of SZ under DSM-IV-TR	Volunteers	407:384	Case: 47.2 Control: 42.1	Case: 221-186 Control: 194-190	7
Nishi et al. (2014)[118]	Japan - Tokushima (Japanese)	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	Volunteers	1,149: 2,742	Case: 54.6 (14.9) Control: 38.8 (12.6)	Case: 676-473 Control: 1,230-1,512	5
Nishi et al. (2014)[118]	Japan - Osaka, (Japanese)	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	Volunteers	621:486	Case: 46.5 (15.8) Control: 35.0 (12.7)	Case: 302-318 Control: 231-255	5
Lee et al. (2006)[74]	Korea (Korean)	Inpatients of psychiatry on antipsychotic treatment Diagnosis of SZ under DSM-IV-TR No history of physical, neurological or other mental disorders	Volunteers No history of physical, mental or heritable disease	235:235	NR	Case: 100-135 Control: 100-135	7
Kang et al. (2010)[73]	Korea (Korean)	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV Past and current history of aggressive behavior	Healthy volunteers No history of psychiatric episodes or violent episodes	360:348	Case: 38.3 (3.9) Control: 38.3 (5.5)	Case: 194-166 Control: 195-153	8

Kim et al. (2011)[119]	Korea (Korean)	Diagnosis of SZ under DSM-IV No history of organic abnormality of the brain, alcohol-related mental problems, drug abuse or other physical illness manifested as psychiatric symptoms	No history of psychiatric disorders, organic mental disorders, illegal substance abuse, medical conditions that may give rise to mental symptoms No first-degree relative with suspected psychiatric illness	201:350	Case: 32.9 (7.8) Control: 25.9 (6.6)	Case: 133-68 Control: 174-176	7
Garcia-Miss et al. (2010)[120]	Mexico (Mayan and Spanish)	Inpatients on treatment Diagnosis of SZ under DMS-IV-TR	Healthy volunteers No evidence of medical or mental disorders	105:108	NR	Case:74-31 Control: 55-53	7
Muntjewerff et al. (2005)[121]	Netherlands ("Caucasian")	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	Individuals recruited from general practice	254:414	Case: 41 (14) Control: 51 (14)	Case: 183-71 Control: 178-236	6
Muntjewerff et al. (2008)[86]	Netherlands ("Caucasian")	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	Individuals free of psychiatric illness, recruited from general practice	252:405	Case: 41 (14) Control: 51 (14)	Case: 184-68 Control: 166-239	6
Muntjewerff et al. (2011)[122]	Netherlands ("Caucasian")	Unrelated in/outpatients Diagnosis of SZ under DSM-IV	Unrelated volunteers No history of any psychiatric condition	742:884	Case: 39 (14) Control: 52 (20)	Case: 557-185 Control: 407-477	7
Jonsson et al. (2008)[75]	Norway ("Caucasian")	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	No history of head injury, neurological disorder, mental retardation	132:177	Case: 36.6 (9.8) Control: 39.7 (10.3)	Case: 80-52 Control: 79-98	6

Kempisty et al. (2006)[85]	Poland ("Caucasian")	Inpatients Diagnosis of SZ under DSM-IV and ICD-10	Blood donors	200:300	Case: M 29.6 (11) F 32.7 (12) Control: M 45 (9) F 40 (11)	Case: 101-99 Control:159-141	6
Zhilyaeva et al. (2018)[123]	Russia ("Caucasian")	Inpatients and day-stay patients Diagnosis of SZ under ICD-10	Healthy blood donors No presence of mental disorders, addictions, severe somatic disorders, blood-borne infections	500:499	Case: 43.2 (12.7) Control: 42.6 (11.5)	Case: 277-223 Control: 277-222	9
Korovaitseva et al. (2021)[124]	Russia (>95% Russian)	Diagnosis of SZ under ICD-10	Mentally healthy individuals No inherited burden of mental disease	1,397:711	Case: 36.9 (13.9) Control: 29.7 (12.9)	Case: 533-864 Control: 393-318	6
Tantawy et al. (2014)[87]	Saudia Arabia (NR)	In/outpatients Diagnosis of SZ under ICD-10	Healthy, unrelated blood donors Absolutely free of personal or family history of any psychiatric illness	79:82	Case: NR Control: 27.2 (11.1)	Case: 57-22 Control: 49-36	7
Tan et al. (2004)[125]	Singapore (Han Chinese)	Diagnosis of SZ under DSM-IV No other psychiatric diagnoses	Unrelated individuals No manifestation of psychiatric symptoms or history of mental illness	236:120	Case: 55.2 (10.3) Control: 44.7 (16.3)	Case: 179-57 Control: 48-72	7
Virgos et al. (1999)[126]	Spain ("European Caucasian")	Unrelated inpatients Diagnosis of SZ under ICD-9	Unrelated individuals No personal record of psychiatric disease	210:218	Case: 58 Control: 58	Case: 141-69 Control: 193-25	7

Viella et al. (2005)[127]	Spain ("Mediterranean Caucasian")	Unrelated inpatients Diagnosis of SZ under ICD-9 No vitamin or folic acid supplement	Unrelated healthy individuals No history of psychiatric disease or Goldberg score >6 No evidence renal insufficiency, hepatic damage, neoplasia, oligophrenia or dementia No vitamins or drugs interfering with Hcy metabolism	158:234	Case: 55.4 (12.1) Control: 46.4 (14.5)	Case: 94-64 Control: 129-105	7
Jonsson et al. (2008)[75]	Sweden ("Caucasian")	Outpatients of psychiatry clinic Diagnosis of SZ under DSM-III-R/ DSM-IV	Individuals from biological psychiatry research or administrative register	233:293	Case: 55.7 (15.6) Control: 51.2 (10.1)	Case:146-87 Control: 183-112	6
Lajin et al. (2012)[52]	Syria (Arab-Syrian)	Diagnosis of SZ under DSM-IV Otherwise healthy individuals	Healthy individuals	85:126	Case: 37 (10) Control: 40 (10)	Case: 60-25 Control: 79-47	5
Bouaziz et al. (2010)[128]	Tunisia (Tunisian)	Inpatients, naïve to antipsychotics or antipsychotics-free for 3 months Diagnosis of SZ under DSM-IV-TR	Healthy volunteers No personal/family history of psychiatric disorder	25:25	Case: 36.6 (9.0) Control: 37.1 (9.6)	Case: all male Control: all male	8

Sazci et al. (2005)[76]	Turkey (NR)	Unrelated outpatients Diagnosis of SZ under DSM-IV	Unrelated individuals No history of SZ for at least three generations	297:341	Case: 41.2 (9.4) Control: 40.9 (8.1)	Case: 168-129 Control: 192-149	7
Philibert et al. (2006)[129]	USA (NR)	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	Iowa newborn registry	132:359	NR	Case: 91-41 Control: 182-177	6
MTHFR C677T – schizophrenia severity/progression							
Zhang, Y et al. (2013)[24]	China (Han Chinese)	Unrelated individuals Diagnosis of SZ under DSM-IV	Healthy individuals No history of mental or neurological diseases	1,002:1,036	Case: 31.2 (9.9) Control: 32.5 (8.3)	Case: 540-462 Control: 602-434	8
Roffman et al. (2007)[49]	USA (mixed)**	Outpatients Diagnosis of SZ under DSM-IV	No control	200	41.8 – 45.7 across genotype	M 130-148 across genotype	
Roffman et al. (2008)[50]	USA (mixed)**	Chronic, stable outpatients Diagnosis of SZ under DSM-IV	No control	200	41.8 – 45.7 across genotype	M 130-148 across genotype	
MTHFR A1298C – risk of schizophrenia							
Zhang et al. (2010)[25]	China (Han Chinese)	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	Blood donors Self reportedly no history of mental disorders or severe physical disorders	379:380	Case: 32.1 (9.7) Control: 31.5 (8.6)	Case: 220-159 Control: 215-165	7
Zhang et al. (2010)[113]	China (Han Chinese)	Healthy mothers with SZ-afflicted offspring Diagnosis of SZ under DSM-IV	Healthy mothers with healthy offspring	143:235	Case: mother 47.4 (4.6) child 18.8 (5.0) Control: mother 49.2 (5.9) child 18.6 (6.0)	Case: child 56-55 Control: child NR	8

Jonsson et al. (2008)[75]	Denmark ("Caucasian")	Diagnosis of SZ under ICD-10 No history of mania/bipolar disorder	Healthy, unrelated blood donors	387:1004	Case: 44.4 (12.2) Control: 44.2 (11.8)	Case: 225-162 Control: 586-418	6
Foroughmand et al. (2015)[77]	Iran (Iranian)	Unrelated individuals with SZ	Healthy blood donors	200:200	Case: 43.3 (11.3) Control: 39.4 (11.1)	Case: 117-83 Control: 117-83	6
Kang et al. (2010)[73]	Korea (Korean)	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV Past and current history of aggressive behavior	Healthy volunteers No history of psychiatric episodes or violent episodes	360:348	Case: 38.3 (3.9) Control: 38.3 (5.5)	Case: 194-166 Control: 195-153	8
Kim et al. (2011)[119]	Korea (Korean)	Diagnosis of SZ under DSM-IV No history of organic abnormality of the brain, alcohol-related mental problems, drug abuse or other physical illness manifested as psychiatric symptoms	No history of psychiatric disorders, organic mental disorders, illegal substance abuse, medical conditions that may give rise to mental symptoms No first-degree relative with suspected psychiatric illness	201:350	Case: 32.9 (7.8) Control: 25.9 (6.6)	Case: 133-68 Control: 174-176	7
Jonsson et al. (2008)[75]	Norway ("Caucasian")	In/outpatients of psychiatry Diagnosis of SZ under DSM-IV	No history of head injury, neurological disorder, mental retardation	132:177	Case: 36.6 (9.8) Control: 39.7 (10.3)	Case: 80-52 Control: 79-98	6
Jonsson et al. (2008)[75]	Sweden ("Caucasian")	Outpatients of psychiatry clinic Diagnosis of SZ under DSM-III-R/ DSM-IV	Individuals from biological psychiatry research or administrative register	233:293	Case: 55.7 (15.6) Control: 51.2 (10.1)	Case:146-87 Control: 183-112	6

Lajin et al. (2012)[52]	Syria (Arab Syrian)	Diagnosis of SZ under DSM-IV Otherwise healthy individuals	Healthy individuals	85:126	Case: 37 (10) Control: 40 (10)	Case: 60-25 Control: 79-47	5
Sazci et al. (2005)[76]	Turkey (NR)	Unrelated outpatients Diagnosis of SZ under DSM-IV	Unrelated individuals No history of SZ for at least three generations	297:341	Case: 41.2 (9.4) Control: 40.9 (8.1)	Case: 168-129 Control: 192-149	7
MTHFR A1298C – schizophrenia severity/progression							
Roffman et al. (2008)[50]	USA (mixed)**	Chronic, stable outpatients Diagnosis of SZ under DSM-IV	No control	200	41.8 – 45.7 across genotype	M 130-148 across genotype	8
MTHFD1 G1958A – risk of schizophrenia							
Zhilyaeva et al. (2022)[130]	Russia ("Caucasian")	In/outpatients of psychiatry Diagnosis of SZ under DSM-V No synthetic vitamins, anti-inflammatory drugs or antioxidants for >1 month before inclusion	Healthy individuals No history of mental disorders, social maladaptation, substance abuse, chronic somatic disease, neurological disorders associated with hyperhomocysteinemia No synthetic vitamins, anti-inflammatory drugs or antioxidants for >1 month before inclusion	116:62	Case***: 33 (23) Control***: 29 (16)	Case: 61-55 Control: 22-40	7
MTRR A66G – risk of schizophrenia							
Lajin et al.[52]	Syria (Arab-Syrian)	Diagnosis of SZ under DSM-IV Otherwise healthy individuals	Healthy individuals	85:126	Case: 37 (10) Control: 40 (10)	Case: 60-25 Control: 79-47	5

* as reported by the authors
** 78.5% Caucasian, 20.0% African American, 1.0% East/Southeast Asian, 0.5% Latino
*** median (IQR)
DSM: Diagnostic ; F: female; M: male; NR: not reported; SZ: schizophrenia

Table 4-2. Meta-analyses of association between *MTHFR* C677T and *MTHFR* A1298C polymorphisms and risk of schizophrenia

Comparison	Stratification	Subgroups	Case	Control	OR (95% CI)	I^2 (p-value)	P_{Egger}	95% PI
MTHFR 677 TT vs CC	All	All	6,037	7,646	**1.26 (1.03, 1.55)**	80.12% (p<0.01)	P=0.07	(0.46, 3.44)
	Ethnicity	European	2,637	3,179	1.13 (0.75, 1.70)	87.50% (p<0.01)	P=0.10	(0.29, 4.37)
		East Asian	2,716	3,546	**1.31 (1.07, 1.61)**	62.09% (p<0.01)	P=0.28	(0.75, 2.29)
		Middle Eastern/West Asian	552	646	**2.04 (1.39, 3.00)**	9.80% (p=0.35)	P=0.54	(1.23, 3.38)
		Mixed ethnicities	132	275	0.54 (0.25, 1.14)	41.8% (p=0.19)	NA	(0.19, 1.50)
	Sex	Male	727	815	1.41 (0.96, 2.07)	39.5% (p=0.10)	P=0.45	(0.64, 3.13)
		Female	463	673	1.13 (0.75, 1.70)	21.4% (p=0.26)	P=0.24	(0.58, 2.19)
	Age	15-30 years	244	389	1.77 (0.57, 5.54)	77.70% (p=0.01)	P=0.51	(0.23, 13.54)
		31-45 years	3,953	4,666	**1.38 (1.01, 1.89)**	85.90% (p<0.01)	P=0.11	(0.38, 5.06)
		> 45 years	1,858	2,693	1.17 (0.95, 1.44)	41.9% (p=0.09)	P=0.88	(0.75, 1.81)
	Fortification	Yes	348	680	1.19 (0.56, 2.53)	71.00% (p<0.01)	P=0.49	(0.25, 5.79)
		No	5,689	7,125	**1.28 (1.03, 1.59)**	81.65% (p<0.01)	P=0.05	(0.47, 3.46)
MTHFR 677 CT vs CC	All	All	9,094	11,633	**1.10 (1.01, 1.19)**	41.66% (p<0.01)	P=0.29	(0.82, 1.47)
	Ethnicity	European	4,088	4,717	1.11 (0.98, 1.25)	43.80% (p=0.05)	P=0.03	(0.82, 1.49)
		East Asian	4,050	5,569	1.10 (0.99, 1.22)	23.38% (p=0.21)	P=0.16	(0.90, 1.34)
		Middle Eastern/West Asian	756	958	1.06 (0.73, 1.56)	67.00% (p<0.01)	P=0.80	(0.44, 2.57)
		Mixed ethnicities	200	389	0.91 (0.51, 1.65)	56.10% (p=0.13)	NA	(0.38, 2.18)
	Sex	Male	1,080	1,190	1.16 (0.98, 1.38)	0.00% (p=0.47)	P=0.27	(0.98, 1.38)
		Female	721	1,016	1.09 (0.87, 1.37)	18.80% (p=0.28)	P=0.79	(0.76, 1.56)
	Age	15-30 years	364	575	1.15 (0.69, 1.90)	61.10% (p=0.08)	P=0.73	(0.53, 2.44)
		31-45 years	5,830	6,861	**1.15 (1.02, 1.29)**	53.74% (p<0.01)	P=0.16	(0.78, 1.69)
		> 45 years	2,805	4,196	1.04 (0.94, 1.15)	0.00% (p=0.75)	P=0.87	(0.94, 1.15)
	Fortification	Yes	524	745	1.21 (0.89, 1.64)	37.20% (p=0.17)	P=0.58	(0.72, 2.02)
		No	8,570	10,888	1.08 (1.00, 1.18)	42.82% (p<0.01)	P=0.30	(0.81, 1.45)
MTHFR 1298 CC vs AA	All	All	1,507	2,325	**1.58 (1.17, 2.13)**	48.20% (p=0.03)	P=0.20	(0.75, 3.33)
	Ethnicity	European	521	984	1.06 (0.81, 1.39)	0.00% (p=0.62)	P=0.56	(0.81, 1.39)
		East Asian	625	939	2.15 (0.92, 5.01)	60.30% (p=0.06)	P=0.96	(0.46, 10.12)
		Middle Eastern/West Asian	361	402	**1.97 (1.38, 2.79)**	0.00% (p=0.92)	P=0.63	(1.38, 2.79)
	Sex	Male	503	562	**1.72 (1.09, 2.71)**	0.00% (p=0.91)	P=0.76	(1.09, 2.71)
		Female	352	471	**1.76 (1.02, 3.04)**	0.00% (p=0.53)	P=0.70	(1.02, 3.04)
	Age	31-45 years	1,155	1,804	**1.60 (1.10, 2.33)**	57.10% (p=0.02)	P=0.87	(0.68, 3.76)
		> 45 years	223	301	1.20 (0.68, 2.12)	34.10% (p=0.22)	NA	(0.56, 2.55)

MTHFR 1298 CA vs AA	All	All	2,278	3,475	1.19 (0.99, 1.44)	63.50% (p<0.01)	P=0.74	(0.69, 2.05)
	Ethnicity	European	804	1,514	1.02 (0.86, 1.21)	0.00% (p=0.70)	P=0.50	(0.86, 1.21)
		East Asian	933	1,284	1.48 (0.96, 2.28)	82.00% (p<0.01)	P=0.98	(0.60, 3.62)
		Middle Eastern/West Asian	541	677	1.09 (0.87, 1.38)	1.60% (p=0.38)	P=0.20	(0.86, 1.39)
	Sex	Male	725	819	1.11 (0.90, 1.38)	0.00% (p=0.54)	P=0.79	(0.90, 1.38)
		Female	509	660	1.25 (0.97, 1.60)	0.00% (p=0.78)	P=0.24	(0.97, 1.60)
	Age	31-45 years	1,734	2,694	1.19 (0.92, 1.54)	74.20% (p<0.01)	P=0.98	(0.61, 2.31)
		> 45 years	344	472	1.03 (0.78, 1.36)	0.00% (p=0.51)	NA	(0.78, 1.36)

CI: confidence interval; NA: not applicable; PI: prediction interval; **bold** indicates statistical significance

4.10 Appendices

Appendix 4-A. MEDLINE search strategy

exp Folic Acid/
((vitamin* or vit or co?enzym*) adj2 (b9 or b 9 or m)).tw,kw.
(folate or folic acid or folacin or folvite or pteroylglutamic acid or acfol or acifolic or acidofolico or filicine or folacid or folart or folavit or folavite or foldivie or foliamin or folicid or folicet or folina or folinsyre or folitab or folium acid or folivit or folsan or folsau or folveriam or folvite or ingafol or gravi-fol or lafol or lexpec or megafol or neocepri or pteroyl glutamate or pteroyl monoglutamate or pteroyl monoglutamic acid or rubiefol or unifol).tw,kw.
or/1-3
exp Vitamin B 12/
((vitamin* or vit or co?enzym*) adj2 (b12 or b 12)).tw,kw.
(cobalamin* or hydro?cobalamin* or c?anocobalamin* or adenosylcobalamin* or methylcobalamin* or dibencozid* or cobamaid* or cobamid* or eriton or deoxyadenosinecobalamin*).tw,kw.
or/5-7
4 or 8
diet/ or eating/ or drinking/
((calorie or calories or caloric or diet* or feed* or macronutrient* or micronutrient* or nutrient* or nutritional) adj2 (intake or intakes)).tw,kw.
ingest*.tw,kw.
Dietary Supplements/
((diet* or food or herbal) adj2 supplement*).tw,kw.
(neutraceutical* or nutracentrical*).tw,kw.
Food preferences/
exp Nutrition Therapy/
Foods, Fortified/
((fortified or enriched or supplement*) adj2 food*).tw,kw.
Nutritional Status/
((nutrition* or food*) adj2 status*).tw,kw.
exp Homocysteine/
exp Plasma/
Erythrocytes/
exp Serum/
((biologic* or clinical or biochemical or serum or immun*) adj2 (marker or markers)).tw,kf.
((end point or end points or endpoint or endpoints) adj surrogate).tw,kf.
homocysteine.tw,kf.
or/10-28
9 and 29
exp Schizophrenia/
exp Psychotic Disorders/

(psychosi?s or psychotic or schizophreni* or paranoid disorder* or severe mental disorder* or hebephrenic or oligophrenic or chronic mental illness).tw,kw.

(schizophrenia spectrum and other psychotic disorders).mp.

or/31-34

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30 and 35

meta-analysis/ or "systematic review"/

exp Systematic Review as Topic/

(systematic adj2 review*).tw,kw.

systematic review.pt.

(system* adj3 review*).tw.

exp Meta-Analysis as Topic/

(meta analys* or metaanalys*).tw,kw.

meta analysis.pt.

(meta-analy* or metaanaly* or metanaly*).tw,kw.

(((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw.

or/37-46

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36 and 47

Chapter 5: Global Evaluation of the Impact of Food Fortification with Folic Acid on Rates of Schizophrenia

In Context

Our research studies have informed us that there may be a potentially causal relationship between folate status and schizophrenia onset. A series of comprehensive literature searches also informed us that more evidence – in quantity and quality – is needed to better understand how folate status may be associated with onset of schizophrenia or severity of symptoms in different subgroups.

This chapter describes our next and final endeavor examining public health policies in the realm of folate and schizophrenia. Guided by our literature search, we focused on food fortification of folic acid, which has been adopted by countries in various forms over the past 30 years. More specifically, we assessed the impact of folic acid fortification on age-adjusted prevalence and incidence rates of schizophrenia in 194 jurisdictions.

Journal Submission

- Under review at *Schizophrenia Research* (November 2024)
- Authors: Samantha Yoo, Derrick Bennett, Azita Montazeri, Helen McNulty, Monique Potvin Kent, Julian Little
- Author contributions: SY, DB, JL conceptualized the study. SY obtained data from public databases, curated the data, and conducted statistical analyses. SY drafted the manuscript. DB provided critical input on the statistical approach. AM, HMcN, MPK, and JL provided critical input on the epidemiological aspect of the manuscript. All authors read and approved the final version of the manuscript.

5.1 Abstract

Introduction Low folate status is one of the multiple factors thought to contribute to the development of schizophrenia. To date, nearly 70 countries have legislated mandatory folic acid fortification of their key grain products; however, impact of the fortification on schizophrenia has not been comprehensively investigated.

Methods Assessment was conducted of the impact of mandatory folic acid fortification policies on changes in the schizophrenia rates in 194 jurisdictions between 1990 and 2019 using fortification data from published reviews and global data repositories, and schizophrenia data from the Global Burden of Disease 2019 study. Weighted regression models were used adjusting for sociodemographic index, sociopolitical conflict, experience of natural disasters, and baseline schizophrenia rate.

Results Age-adjusted prevalence and incidence of schizophrenia increased marginally between 1990 and 2019. The schizophrenia rates were positively correlated with the countries' sociodemographic index in all geographic regions and across fortification status. More countries with lower sociodemographic index reported mandatory fortification compared to countries with higher index. Males reported higher rates of schizophrenia compared to females. In the overall population, schizophrenia rates were inversely related to mandatory fortification, and comparable between the sexes, with modest magnitudes. The duration of fortification policies did not have a strong impact. The folic acid dose used in the fortification policies did not appear to influence the distribution of schizophrenia in the overall population. However, in the 15-39 year age-group, both mandatory fortification (β= -13.14 (-22.60, -3.68)) and duration of fortification (β= -0.82 (-1.40, -0.23)) had directional consistent and larger magnitude in both males and females. The highest dose tertile was reported to have the lowest incidence rate and the smallest increase in prevalence rate in the 15-39 year age-group.

Conclusion Having mandatory folic acid fortification measures and the duration of any folic acid fortification policies were independently associated with declines in the prevalence rates of schizophrenia in 15-39 years age-group, but not in the overall

population. Results of this study suggest that folic acid fortification may potentially be a beneficial population intervention strategy in lowering schizophrenia prevalence rates among adolescents and young adults.

5.2 Introduction

Schizophrenia is a severe neuropsychiatric disorder of complex etiology[1,2] with a lifetime prevalence of 1%[3]. The disorder is characterized by positive (i.e., delusions, hallucinations), negative (i.e., avolition, anhedonia), and cognitive symptoms (i.e., deficits in memory and executive functions)[1] and is often accompanied by other chronic diseases[4,5]. Individuals with schizophrenia often experience poor psychosocial functioning, lower quality of life, and long-term disability[6,7]. Typical onset occurs in adolescence or early adulthood[8-10] with some reported differences between male and female sex[11-13].

Low folate status is one of the multiple factors thought to contribute to the development of schizophrenia. Over the years, numerous epidemiological studies have reported an inverse relationship, in varying magnitudes, between blood concentrations of folate and the risk of schizophrenia[14,15]. This link has been triangulated by genetic association studies examining associations of methylenetetrahydrofolate reductase (*MTHFR*) gene variants, known to impair folate metabolism[16,17], with the risk of schizophrenia[18,19]. The role of folate in schizophrenia is biologically plausible because this vitamin is required for critical metabolic roles including DNA synthesis and methylation[20,21], homocysteine remethylation[22,23], and production of neurotransmitters[24,25].

Folate status may also work together with other known environmental risk factors for schizophrenia. For example, a growing body of evidence discusses early life adversity, migration experience, and urban living as potential risk factors[1,2]. These factors correlate with poor diet quality, food insecurity, or lower socioeconomic positions[26-28], which are in turn associated with lower intake of micronutrients[29-31].

Naturally occurring food folates, such as green leafy vegetables, are however insufficient in achieving optimal status owing to the well-recognized poor stability and incomplete bioavailability of natural folate forms compared to the synthetic vitamin, folic acid[32]. Thus, the achievement of optimal status among individuals and populations requires the provision of folic acid, either as a supplement or via food fortification[33].

Mandatory food fortification with folic acid started to be introduced in the late 1990s after landmark research demonstrating the beneficial effect of periconceptional folic acid in preventing of both first occurrence[34] and recurrence[35] of neural tube defects. The mandatory fortification program is an upstream population-based public health intervention that is cost-effective and that has greater reach than a downstream intervention at the individual level (e.g., public education and campaigns), which relies heavily on targeting individuals' awareness, motivation, and economic means for success[36]. To date, nearly 70 countries in the world have legislated mandatory folic acid fortification of their key grain products (i.e., wheat, maize, rice), with an additional 46 countries encouraging manufacturers to voluntarily fortify their grain products[37]. These measures have been reported to have significantly reduced the prevalence at birth of neural tube defects[38-40] and incidence of cardiovascular events[38,41], while benefits of this population intervention have been under debate for some other diseases[42,43].

The impact of folic acid fortification on schizophrenia, however, has not been investigated. Our literature search (as of February 2024) for population-level interventions involving folate in the context of neuropsychiatric diseases did not identify any formal intervention. Besides food fortification, we found guidelines on pre- and peri-conceptional use of folic acid supplements, issued by national/provincial governments and international organizations; however, these predominantly focused on prevention of congenital anomalies. The recently updated clinical guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce[44] recommended 1-15 mg/d of methyl folate for treatment of negative symptoms of schizophrenia. These guidelines were based on a

meta-analysis of randomized controlled trials[45] conducted in the US and UK, but did not discuss whether folic acid fortification was taken into consideration.

Here, we aimed to investigate the impact of mandatory folic acid fortification policies on schizophrenia rates in the population globally. More specifically, we sought to identify (a) if mandatory measures were associated with any changes in schizophrenia rates and if so, the direction and magnitude of change; (2) if mandatory fortification had any impact on schizophrenia rates among the 15-39 years age-group, which may reflect most sensitively any impact of folic acid fortification; and (3) if dosage of folic acid in fortification differentially impacted the distribution of schizophrenia among the countries with mandatory measures.

5.3 Methods

5.3.1 Data sources

Information on folic acid fortification policies was obtained from four sources: two recent systematic reviews[41,46], the WHO Global Database on the Implementation of Nutrition Action (GINA)[47], and the Global Fortification Data Exchange (GFDx)[37]. The latter two non-profit data repositories provide up-to-date information on the various food fortification and/or nutritional intervention policies across different countries.

Schizophrenia prevalence data were extracted from the well-established Global Burden of Disease (GBD) study[48], which provides data for public access[49]. The most recent GBD 2021 dataset provides multiple indicators (e.g., prevalence, incidence, disability-adjusted life years, years lived with disability) of a total of 288 causes of death in 204 countries annually from 1990 to 2019. Schizophrenia is defined using International Classification of Diseases (ICD)-9/10 or Diagnostic and Statistical Manual of Mental Disorders (DSM)-4/4-TR[48]. Methodologies used in the GBD studies are available in detail elsewhere[48,50].

5.3.2 Rates of schizophrenia

Based on the complexity and heterogeneity in the disease trajectory of schizophrenia, i.e., burden of comorbidities, onset secondary to other diseases, variations in the diagnostic

practice among countries, we examined both incidence and prevalence rates. Accordingly, we examined three rates of schizophrenia: (1) age-standardized prevalence rate, (2) age-standardized incidence rate (all ages), and (3) incidence and prevalence rates among the 15-39 years age group. We separately examined the 15-39 years age group because the onset of schizophrenia typically occurs between late adolescence and early/mid adulthood[8-10]. Early years are also more sensitive to the effects of inadequate folate status given previously illustrated roles of folate in DNA, RNA syntheses and methylation reactions. We also examined the role of sex (male/female) as a moderator[11,12] in the trajectory of schizophrenia development and distribution.

5.3.3 Classification of folic acid fortification policies

Folic acid fortification policy status was categorized as mandatory fortification policy, voluntary fortification policy, or no fortification policy for each country. For countries that introduced mandatory fortification policies for different grain products over multiple years, we took the year of the first grain fortified. For countries that had a voluntary fortification policy prior to introducing a mandatory policy, we classified them into mandatory fortification policy and took the year of the mandatory measure. For countries that introduced multiple mandatory measures targeting different grain products in a sequential fashion, we took the year of the first measure. For countries with mandatory fortification policies, we further obtained information on the number of targeted grain products and the dose, both in mg per kg and in percent of the WHO recommended levels (400 mcg/d)[51].

5.3.4 Classification of country indicators

As schizophrenia is a complex disorder with etiology involving both genetic and environmental factors, we extracted information on geographic region, income level, and sociodemographic index. Geographic classification was based on the WHO regional groups (African, the Americas, Southeast Asia, European, Eastern Mediterranean and Western Pacific). As a measure of the socio-economic environment of each country, we used the sociodemographic index (SDI) published in the GBD study[50], a composite indicator of per capita income, population average educational attainment, and total

fertility rate[52]. The SDI has five levels (low, low-middle, middle, high-middle, high). We also extracted data on sociopolitical conflict from one of the cause indicators available in the GBD database (conflict and terrorism variable). Countries with any mortality attributable to conflict or terrorism in the study period were coded as having experienced sociopolitical conflict. Lastly, we extracted information on countries' experience of natural disasters (any mortality during the study period due to the force of nature). Sociopolitical instability and fatal natural disasters are important factors that may compromise public and private resources for policy implementation and compliance[53].

5.3.5 Statistical analyses

Weighted regression analyses were performed to investigate associations between folic acid fortification and schizophrenia prevalence or incidence. In order to account for variations in the precision of the data collected from each country, we applied an inverse of the variance as weights in the regression models[54].

In the primary analyses, we employed eight models: models A.1-4 examined the effect of fortification status (mandatory vs none) as the main exposure and models B.1-4 the effect of duration of the fortification program. Outcomes were changes in the age-adjusted prevalence rate between 1990 and 2019, and changes in the age-adjusted incidence rate between 1990 and 2019. Countries with voluntary fortification policies were excluded from the regression models A.

All regression models were adjusted for SDI, sociopolitical conflict, natural disasters, and baseline age-adjusted prevalence or incidence rates. All models were repeated stratified by sex.

We performed two subgroup analyses. First, we examined whether the associations of interest were different in direction or magnitude among the 15-39 year age-group. All models were stratified by sex. Second, we investigated whether dosage of folic acid differentially impacted the distribution of schizophrenia among the countries with mandatory fortification measures. Dose levels were categorized into tertiles and countries

with missing dose information (n=4) were excluded from the subgroup analysis. We also excluded the countries with voluntary fortification measures because they lacked detailed guidelines (e.g., vehicle, dose, composition) and information on self-compliance was insufficient. One-way ANOVA and subsequently Tukey post-hoc pair-wise comparisons were conducted.

We performed a set of sensitivity analyses to ensure the findings from our main analyses were robust to influential jurisdictions with large populations and high levels of heterogeneity. The main regression models were repeated excluding USA, China, and India each at a time. USA has a large diversity in ethnicities, income, and lifestyles across the country and reports the highest age-adjusted prevalence and incidence rates of schizophrenia. In China, mandatory measures are not in place; however, the government has implemented a nationwide, free supplementation of folic acid for target groups in the population since 2009[55,56]. India has a high prevalence of veganism or low intake of vitamin B_{12}[57], which may compromise one-carbon metabolism and result in functional folate deficiency[58,59].

In all regression analyses, we report beta-coefficients with 95% confidence intervals. SAS[60] version 9.4 was used for all statistical analyses; R software[61] version 4.1.3 was used for visualization of Figure 5-1.

5.4 Results

5.4.1 Overview

Data on distribution of schizophrenia were available on a total of 204 jurisdictions, of which information on folic acid fortification policies was identifiable for 194. The jurisdictions excluded due to missing or unclear fortification policy data were Bermuda, Greenland, Niue, Taiwan, Tokelau, and five unincorporated territories of the United States (American Samoa, Guam, Northern Mariana Islands, Puerto Rico, and United States Virgin Islands). All subsequent analyses were conducted on the 194 jurisdictions with complete data. Categorizing the 194 jurisdictions by WHO Region, 48 were in the African Region, 35 in the Americas, 22 in the Eastern Mediterranean, 53 in the European,

11 in the Southeast Asian, and 25 in the Western Pacific. One jurisdiction (Palestine) was not included in the WHO regional categorization. A full mapping of the jurisdictions with SDI, fortification status, and schizophrenia disease burden indicators are available in Appendix 5-A.

5.4.2 Policy on folic acid fortification of food

Food fortification with folic acid was first legislated in 1985 in Malaysia as a voluntary measure before being introduced in other countries a decade later. The number of countries adopting mandatory fortification policies peaked in 2009-2011, while those with voluntary fortification measures stayed steadily low except in 2006 when the European Union permitted voluntary fortification of foods in that region (Regulation EC 1925/2006), impacting 29 countries[62].

As of 2023, a total of 117 countries had formalized policies on folic acid fortification; 72 countries had mandatory policies specifying target grain and dose, while 46 countries recommended voluntary fortification by food manufacturers (Figure 5-1). By region, Africa and the Americas had the largest number of countries that adopted mandatory fortification measures. By SDI, countries in the two lowest categories showed the highest rates of mandatory fortification. Conversely, voluntary fortification measures were predominantly used in countries with higher SDI or located in Europe (Figure 5-2, Table 5-1). The number of countries without any fortification measures increased in line with the SDI, except in the top index group which was mostly represented by European countries with voluntary fortification policies.

Among the countries with mandatory fortification, 50 (69.4%) targeted a single type of grain product, while 19 (26.4%) had policies for two grain types and three countries had policies for three grain types. Wheat products were the most commonly used vehicle (69 countries, 95.8%).

5.4.3 Prevalence of schizophrenia (2019)

The age-standardized prevalence rate of schizophrenia per 100,000 persons varied substantially by geographic region with the mean ranging from 220.45 in the African region to 295.65 in the West Pacific region (Table 5-2). In all regions, the age-adjusted prevalence rates showed an increasing trend by SDI: the variations in the rates between the lowest and the highest SDI categories within regions (22.11-119.84) were larger compared to those between the regions (0.29-75.2). The age-adjusted prevalence rates were higher among males compared to females in all regions and SDI categories (Appendix 5-B).

By fortification status, the countries with mandatory fortification legislations showed the lowest age-adjusted prevalence rates (254.77) compared to the countries with voluntary policies (279.04) and those without any fortification policies (267.15) (Table 5-3). Across all levels of fortification status, the rates were higher in places with higher SDI: with greater within-SDI variations (74.22-158.56) compared to within-fortification group variation (12.00-24.79). The rates were higher among males compared to females in all fortification categories and SDI groups (Appendix 5-C).

5.4.4 Incidence of schizophrenia (2019)

Trends in age-standardized incidence rates reflected those observed for prevalence. Thus, the incidence of schizophrenia per 100,000 persons ranged from the lowest in Africa (14.28) to the highest in the Western Pacific (18.06). Within each region, the rates increased in line with the SDI. Again, the variations in the incidence rates between the lowest and the highest SDI categories within regions (0.54-4.58) were wider compared to those observed between the regions (0.04-3.78). The age-adjusted incidence rates were higher among males compared to females in all regions and SDI categories (Appendix 5-B).

Age-standardized incidence rates were the lowest in the mandatory fortification group (15.62) compared to others (16.09-16.25). The rates mostly increased in line with the SDI for all levels of fortification, exhibiting similarly larger within-SDI variations (2.48-6.71)

compared to within-fortification group variations (0.17-0.48). Males were reported to have higher age-adjusted incidence rates compared to females (Appendix 5-C).

5.4.5 Changes in the age-adjusted prevalence and incidence rates of schizophrenia

Age-adjusted prevalence rates and incidence rates of schizophrenia increased over the 30 years of the observation period (Table 5-4). The mean changes in the age-adjusted prevalence rates increased by 2.78 per 100,000 persons, with substantial variation among countries (range from -17.54 to 30.86). The magnitude of change was slightly higher among male (mean 2.89, 95% confidence interval (1.92, 3.86)) compared to female (mean 2.69 (1.72, 3.65)). The mean changes in the age-adjusted incidence rates was an increase of 0.01 per 100,000 persons (range from -1.32 to 1.19). The change in the incidence rate appeared to be greater among female (mean 0.04 (0.00, 0.08)) compared to male (mean 0.01 (-0.02, 0.05)).

In all SDI categories, the age-adjusted prevalence rates increased; however, the magnitude of increase peaked in the middle group (mean 5.11 (2.89, 7.33)). The age-adjusted incidence rates increased in low-middle (mean 0.01 (-0.05, 0.07)), middle (mean 0.06 (0.00, 0.12)), and middle-high (mean 0.03 (-0.05, 0.11)) categories.

The countries with mandatory fortification policies had a smaller increase in age-adjusted prevalence rates (mean 2.57 (1.51, 3.63)) compared to countries without any fortification policies (mean 3.31 (1.57, 5.05)), but larger compared to those with voluntary policies (mean 2.22 (-0.11, 4.55)). The change in age-adjusted incidence rates was lower among the countries with mandatory fortification policies (mean -0.01 (-0.06, 0.04)) and voluntary fortification policies (mean -0.01 (-0.12, 0.09) compared to those with no policies (mean 0.05 (-0.01, 0.10)).

5.4.6 Changes in the schizophrenia prevalence and incidence in 15-39 year age group

Among individuals aged 15-39 years, the prevalence rate increased, on average, by 19.36 per 100,000; and the incidence rate decreased by 0.02 per 100,000 over the 30 years (Table 5-5). The magnitudes of change were comparable between males and females. In terms of SDI, the trends for changes in prevalence were similar to the overall group, showing increases in all categories and the largest increases occurred in middle and high-middle groups. The age-adjusted incidence rates did not show a clear pattern in any direction.

Countries with mandatory fortification policies reported the smallest increase in the prevalence rates (mean 14.32 (8.57, 20.07)) compared to those with voluntary policies (mean 23.13 (16.66, 29.59)) and no policies (mean 21.37 (14.59, 28.15)). The incidence rates declined both in countries with mandatory fortification policies (mean -0.05 (-0.30, 0.20)) and those without any policies (mean -0.11 (-0.38, 0.17)).

5.4.7 Impact of folic acid fortification on distribution of schizophrenia

We investigated whether any policies of folic acid fortification policy (status and/or duration) were associated with the changes in the age-adjusted distributions of schizophrenia. The regression coefficients (and 95% CI) of mandatory folic acid fortification policy, compared to no fortification policy, with age-adjusted rates of prevalence and incidence were β= -0.94 (-3.16, 1.28) and β= -0.01 (-0.09, 0.07), respectively (Table 5-6). The relationship between duration of any folic acid fortification policies and the changes in age-adjusted distributions of schizophrenia was non-statistically significant: β= -0.08 (-0.22, 0.07) for changes in age-adjusted prevalence rates and β= -0.00 (-0.01, 0.01) for changes in age-adjusted incidence rates. There was no evidence of effect modification by sex in sex-specific analyses; however, the effect sizes were somewhat larger for female in the models examining the impact of mandatory fortification compared to none (Table 5-6).

5.4.8 Subgroup analysis 1: Impact of folic acid fortification in 15-39 years age-group

Among the 15-39 years age-group, mandatory fortification policy was associated with decreases in age-adjusted prevalence rates of schizophrenia (β= -13.14 (-22.60, -3.68))

(Table 5-6, Figure 5-3). The direction and magnitude of this association were comparable in sex-stratified analyses (β_{male}= -13.37 (-23.95, -2.78), β_{female}= -12.03 (-20.49, -3.57)). Duration of fortification policies was inversely associated with age-adjusted prevalence rates of schizophrenia (β= -0.82 (-1.40, -0.23)). Sex-specific beta-coefficients showed comparable effects (β_{male}= -0.76 (-1.40, -0.12), β_{female}= -0.86 (-1.41, -0.31)).
There was no evidence of an association in changes of age-adjusted rates of incidence with mandatory fortification policy (β= -0.10 (-0.46, 0.26)) or with duration of fortification policies (β= 0.00 (-0.02, 0.03). Sex-specific effects were consistent with the aggregate findings in direction, magnitude and statistical significance.

5.4.9 Subgroup analysis 2: Effects of folic acid fortification dosage

The dose of folic acid prescribed for fortification ranged from 0.4 mg/kg to 5.10 mg/kg across 72 countries with mandatory policies. Generally, we did not find any evidence of differences in age-adjusted rates for prevalence or incidence of schizophrenia (2019) among dose tertiles (low, medium, high). However, in the 15-39 years age-group, the high dose group reported lower incidence rates (mean difference (MD)= -5.69 (-8.58, -2.80)) and prevalence rates (MD= -88.65 (-145.19, -32.10)) compared to the medium dose group. Sex-specific analyses among the 15-39 years age-group showed comparable patterns for both age-adjusted prevalence and incidence rates.

In terms of the changes in age-adjusted prevalence or incidence rates of schizophrenia, we found evidence of differences among the dose tertiles in three strata. Among females, the low dose group reported the largest decrease in age-adjusted incidence rate compared to the medium (MD= -0.12 (-0.23, -0.00)) and high dose groups (MD= -0.12 (-0.24, -0.01)) (p=0.020). Among the 15-39 year age-group, the high dose group reported the smallest increase in age-adjusted prevalence rate compared to the medium dose group (MD= -25.89 (-40.19, -11.58)) and the low dose group (MD= -10.84 (-25.15, 3.46)) (p=0.001). The latter pattern was replicated among the 15-39 year-old male ($MD_{High\ vs\ medium}$= -29.72 (-44.98, -14,46), $MD_{High\ vs\ low}$= -11.92 (-27.17, 3.34)) (p=0.000) and female stratum ($MD_{High\ vs\ medium}$= -22.13 (-35.12, -9.14), $MD_{High\ vs\ low}$= -9.16 (-22.15, 3.83)) (p=0.002).

5.4.10 Sensitivity Analyses

Analyses excluding USA, China, and India, one at a time, did not produce differences in effect sizes in the overall population or in the 15-39 years age-group. The association of mandatory folic acid fortification or duration of fortification with changes in age-adjusted rates of prevalence and incidence remained unchanged after removing any one of the three countries (Appendix 5-D).

5.5 Discussion

5.5.1 Summary of findings

We observed a marginal increase in the prevalence and incidence rates of schizophrenia across the examined jurisdictions over the last 30 years. Geographically, these rates were lowest in Africa and the East Mediterranean regions, followed by Europe and Southeast Asia, and highest in the American and the Western Pacific regions. Within each region, the rates were correlated with the countries' SDI: both prevalence and incidence were higher in countries with better socioeconomic environment. This pattern remained unchanged when countries were stratified by folic acid fortification status, i.e., schizophrenia rates increased in accordance with the SDI across all fortification strata. Not surprisingly, we noted greater differences between SDI strata compared to between fortification strata. We also observed that the mandatory fortification policies were more common among the countries with low SDI. Males were reported to have higher incidence and prevalence rates of schizophrenia compared to females across all geographic regions, SDI groups and fortification strata.

In the overall population, the association between folic acid fortification policy (mandatory vs. none, duration of fortification policies) and schizophrenia appeared to be inversely related, but in small magnitudes and non-statistically significant. The associations were comparable between the sexes. The folic acid dose used in the mandatory fortification policies did not appear to influence the distribution of schizophrenia in the overall population. In the 15-39 year age-group, however, there was evidence of a larger magnitude of impact of mandatory fortification, compared to none,

on schizophrenia prevalence and incidence rates, both in males and females. In this age-group of typical onset of schizophrenia, the highest dose tertile was reported to have the lowest incidence rate and the smallest increase in prevalence rate.

5.5.2 Heterogeneity and fidelity of folic acid fortification policies

The prescribed dosage of folic acid, as reported in the Global Fortification Data Exchange, varies substantially across the countries with mandatory policies. Another potential variation in the data is the fidelity of the implementation of the fortification program. Data on fortification quality or compliance are not available for all countries: for example, among the countries with mandatory fortification policies for wheat, maize, and rice, only ten, three, and two countries report compliance data on the proportion or amount of the grain products fortified[37]. For imported food vehicles, only 30 countries have formalized monitoring protocols available[37]. The proportion of the population covered by fortified foods is less well-reported and may also vary substantially across and within the countries. Such heterogeneity makes it more challenging to compare and identify the outcomes of food fortification among countries.

Nonetheless, mandatory folic acid fortification has largely been effective in addressing folate inadequacy on multiple levels. Most of the studies reported higher plasma, serum or erythrocyte concentrations of folate among cohorts exposed to folic acid-fortified foods compared to unexposed cohorts[41,46,63-65], although one national study reported persistence of high folate inadequacy despite two decades of fortification[66]. Folic acid fortification policies have also been associated with significant reductions in neural tube defects[39-41,46], anemia[46], cardiovascular diseases[67,68], and certain cancers[69-72].

5.5.3 Complexity in schizophrenia epidemiology

Schizophrenia is a complex disorder that has been associated with a multitude of genetic and environmental factors. Recent research is converging on the multifactorial model of interplay between genes and environmental risks[1,2,73]. While folate may be an important environmental risk factor for susceptibility to schizophrenia[14,18], our current knowledge is not sufficient to fully understand the comparative importance of various risk factors when

presented together and their interactive effects over the life course. For example, interventions with folic acid fortification may be effective in reducing susceptibility to schizophrenia among subgroups of population who are exposed to fewer other risk factors; or differential dosage of folic acid may be more effective in population subgroups that on average carry a higher load of risk alleles. Addressing folate inadequacy in early life may reduce incidence at the typical ages of onset and, after accumulated time, contribute to lowering population-level prevalence.

We also note potential heterogeneity in the clinical and sociocultural settings around the world, which may result in differential diagnosis rates, treatment rates, and treatment outcomes. Schizophrenia is increasingly understood as a neuropsychiatric disorder on a spectrum with clusters of symptoms often overlapping with one another[74-76] and the conventional practice of relying on observed or self-reported symptoms for clinical diagnosis[77,78] leaves room for potential bias. Lower rates of diagnosis of schizophrenia in countries with lower SDI compared to countries with higher SDI[79] may be an artefact of the quality of the data in those countries. Timely access to psychiatric healthcare and professional resources is still a considerable challenge in many less developed jurisdictions, often coinciding with stigmatization and consequent deprivation and shorter lifespan[80-82]. Countries with lower SDI may also have other competing priorities in healthcare policy, such as combating communicable diseases and reducing infant mortality.

Another challenge in detecting associations between schizophrenia and risk factors is the relative low life-time prevalence[3], which may explain the stable trends in age-adjusted incidence and prevalence globally for the past 30 years[79,83,84].

5.5.4 Potential role of socioeconomic environment

A large and growing body of epidemiological research reports on the relationship between socioeconomic environment and the risk of schizophrenia. Some of the most studied socioeconomic risk factors include migrant status[85-88], urbanicity[89-93], and childhood adversity[94-97], while some authors suggest the potential role of income

inequality[98]. With emerging epigenetic evidence supporting these environmental factors as important moderators or mediators in the development of schizophrenia[99-102], we observe with interest the consistent trend of SDI stratification in the distribution of schizophrenia in all geographic regions and fortification groups in our ecological analysis. In line with this observation, some authors have reported similar trends of lower prevalence of mental disorders in lower income countries compared to higher income counterparts[103,104]. Other than stress, which we observe as one of the key underlying themes behind the known socioeconomic risk factors above, other authors proposed social capital[105], resilience[106], or sense of deprivation[107] as protective factors working in favor of lower income countries.

On the other hand, in the context of folate intake, socioeconomic deprivation may confound the relationship between folate status and the risk of schizophrenia as individuals with lower socioeconomic position are less likely to consume folate-rich diet or supplements[108-110]. This concern may be widely relevant today as more countries are facing acute food insecurity amid challenges arising from armed conflicts, climate change, and poverty. The World Food Program estimates that 333 million people across 78 countries are facing acute levels of food insecurity as of 2023[111].

5.5.5 Strengths and limitations

Our analysis marks a novel attempt at examining the impact of folic acid fortification on the distribution of schizophrenia worldwide. In addition to providing comprehensive descriptions of the latest age-adjusted incidence and prevalence rates of schizophrenia and the changes in these rates over 30 years, we stratified all data by geographic region, SDI, and sex, which are known risk factors in development of schizophrenia. We also weighted our regression models to address the variability in the estimates for each country.

As an ecological study, relationships identified in our analysis cannot be inferred to apply to individuals. Additional information on clinical settings, such as antipsychotics prescription rates, accessibility to psychiatric care, and social stigmatization, was not

available for our analysis. We also note that for two jurisdictions (Ethiopia, Mexico) which introduced voluntary policies prior to mandatory policies, the status and year of mandatory fortification were used for analyses. The time between voluntary and mandatory fortification was 3 and 7 years, respectively. Given the small number of countries, short duration until mandatory regulation, and the marginal change in schizophrenia rates across the countries, it is unlikely that the classification of these two countries might have impacted our findings.

5.5.6 Policy implications

Folic acid fortification is one of the most effective and well-established population-level interventions against congenital anomalies and other health conditions. Our analysis shows that supplementing folic acid through fortification may potentially benefit adolescents and young adults in lowering the rates of schizophrenia. While more studies are needed to validate the findings in different subgroups under different conditions, folic acid fortification can be considered a broad preventive tool for the age of typical onset. More rigorous monitoring and reporting of compliance and quality will benefit policymakers in adjusting dosage of the folic acid used in the fortification or expanding the coverage of the policies to other grain products.

5.6 Conclusion

Across 194 jurisdictions, we observed a stable trend of schizophrenia incidence and prevalence over 30 years. Schizophrenia rates were higher among male compared to female; higher in countries with higher socioeconomic index; and lower in countries with mandatory food fortification with folic acid compared to countries with voluntary or no policies. Having mandatory folic acid fortification policies and the duration of any folic acid fortification policies were independently associated with declines in the prevalence rates of schizophrenia in 15-39 years age-group, but not in the overall population. Our results suggest that folic acid fortification may potentially be a beneficial population intervention strategy in lowering schizophrenia prevalence rates among adolescents and young adults.

5.7 References

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5.8 Figures and Tables

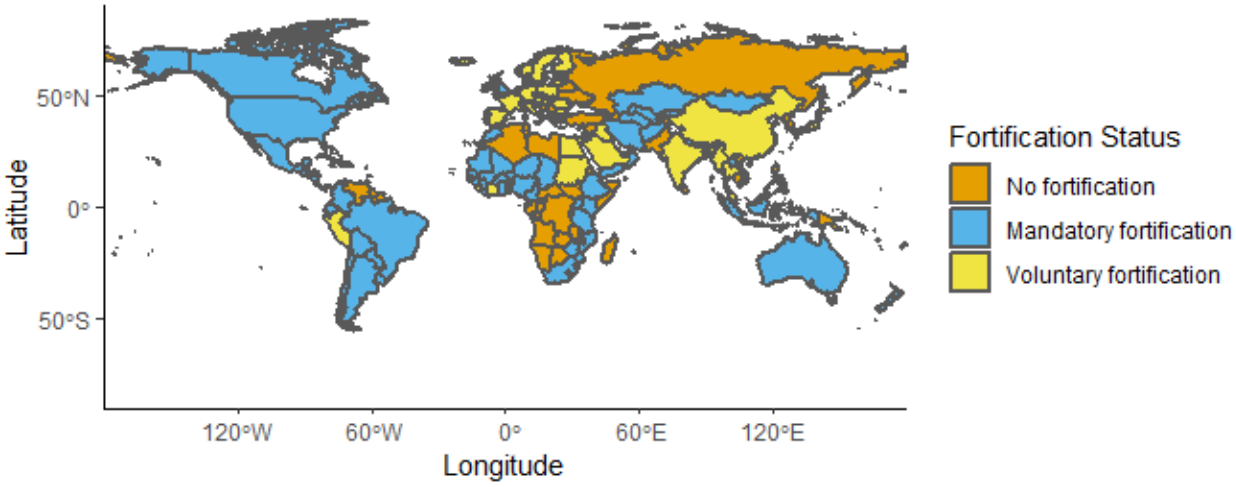

Figure 5-1. Folic acid fortification status of 194 jurisdictions

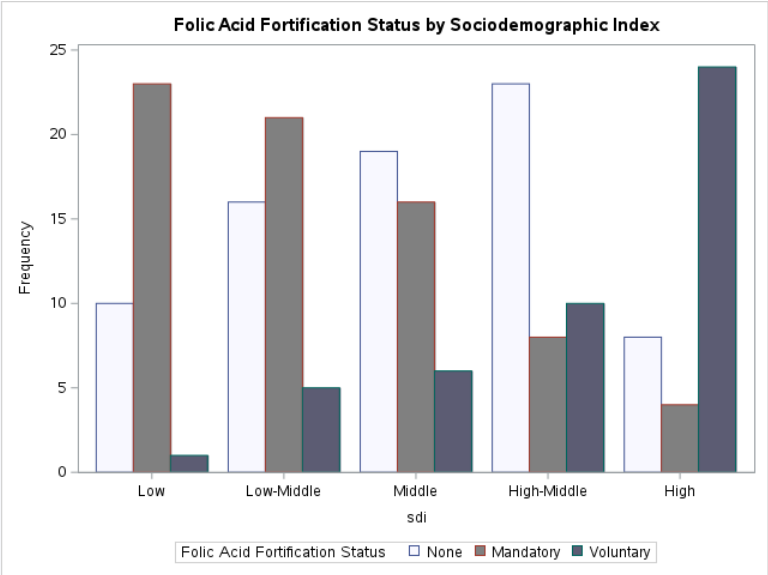

Figure 5-2. Distribution of folic acid fortification policies by sociodemographic index

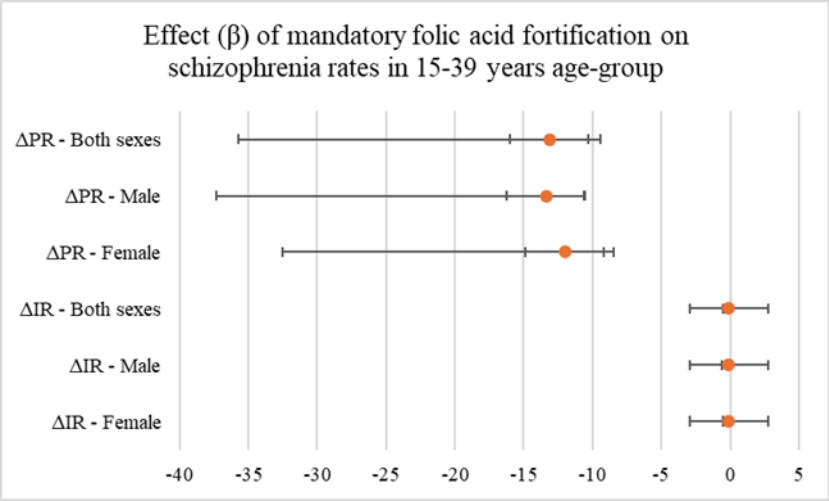

Figure 5-3. Effect of mandatory folic acid fortification on schizophrenia rates in 15-39 years age-group

Table 5-1. Distribution of folic acid food fortification policies by geographic region and SDI* (2019)

	Low	Low-Middle	Middle	Middle-High	High	Total
AFR	18 (1)	8 (1)	1 (0)	0 (0)	-	27 (2)
AMR	1 (0)	7 (0)	8 (1)	3 (0)	2 (0)	20 (2)
EMR	2 (0)	2 (1)	1 (2)	3 (0)	0 (4)	8 (7)
EUR	-	1 (0)	2 (1)	2 (9)	0 (18)	5 (28)
SEAR	1 (0)	0 (3)	1 (1)	0 (0)	-	2 (4)
WPR	1 (0)	2 (0)	3 (1)	0 (1)	2 (2)	8 (4)
NR	-	1 (0)	-	-	-	1 (0)
Total	23 (1)	21 (5)	16 (6)	8 (10)	4 (24)	72 (46)

* numbers in parentheses indicate the number of countries with voluntary fortification with folic acid
AFR: African region; AMR: American region; EMR: Eastern Mediterranean region; EUR: European region; NR: Not reported; SDI: sociodemographic index; SEAR: Southeast Asian region; WPR: West Pacific region

Table 5-2. Distribution of age-standardized prevalence and incidence rates of schizophrenia (per 100,000) in 2019 by geographic region and SDI

Region	SDI	Jurisdictions	aPR Mean (SD)	aPR Median (IQR)	aIR Mean (SD)	aIR Median (IQR)
AFR	1	26	209.33 (6.82)	208.88 (6.25)	13.97 (0.21)	13.90 (0.20)
	2	13	216.53 (7.28)	216.92 (7.17)	13.96 (0.22)	13.93 (0.27)
	3	6	231.23 (9.99)	227.42 (11.21)	14.20 (0.31)	14.10 (0.36)
	4	3	312.27 (1.63)	312.71 (3.18)	18.47 (0.10)	18.51 (0.18)
	5	0	-	-	-	-
	Subtotal	48	220.45 (25.97)	213.33 (14.67)	14.28 (1.12)	13.98 (0.27)
AMR	1	1	241.31 (-)	241.31 (-)	15.23 (-)	15.23 (-)
	2	8	269.35 (5.73)	269.65 (8.65)	15.96 (0.20)	15.80 (0.29)
	3	15	278.28 (5.78)	277.82 (4.90)	16.28 (0.19)	16.26 (0.20)
	4	9	293.84 (15.87)	286.89 (27.45)	17.08 (0.97)	16.55 (1.83)
	5	2	361.15 (102.54)	361.15 (145.01)	19.81 (5.59)	19.81 (7.91)
	Subtotal	35	283.92 (29.72)	277.87 (11.74)	16.58 (1.42)	16.26 (0.46)
EMR	1	4	227.69 (37.71)	221.73 (49.19)	14.32 (0.46)	14.14 (0.54)
	2	3	232.11 (11.01)	232.68 (21.99)	14.40 (0.15)	14.34 (0.28)
	3	5	248.55 (4.78)	247.57 (6.27)	14.76 (0.15)	14.74 (0.15)
	4	5	258.73 (8.63)	255.06 (10.71)	15.12 (0.30)	15.00 (0.46)
	5	4	274.23 (9.05)	274.06 (11.8)	15.66 (0.39)	15.61 (0.53)
	Subtotal	21	249.54 (23.27)	252.46 (21.87)	14.88 (0.56)	14.84 (0.66)
EUR	1	0	-	-	-	-
	2	2	262.88 (1.13)	262.88 (1.60)	15.95 (0.07)	15.95 (0.10)
	3	6	283.02 (7.92)	282.67 (6.49)	16.46 (0.19)	16.49 (0.11)
	4	21	280.66 (11.75)	282.44 (16.67)	16.35 (0.57)	16.44 (0.30)
	5	24	284.99 (27.44)	281.01 (20.63)	16.49 (1.60)	16.27 (0.85)
	Subtotal	53	282.22 (20.28)	281.92 (17.46)	16.41 (1.13)	16.40 (0.54)
SEAR	1	1	266.99 (-)	266.99 (-)	13.83 (-)	13.83 (-)
	2	7	280.54 (17.61)	278.20 (23.99)	16.06 (1.71)	16.33 (2.98)
	3	2	297.37 (5.21)	297.37 (7.37)	17.90 (0.16)	17.90 (0.23)
	4	1	300.82 (-)	300.82 (-)	18.03 (-)	18.03 (-)
	5	0	-	-	-	-
	Subtotal	11	284.21 (17.03)	285.23 (33.82)	16.37 (1.79)	16.88 (3.65)
WPR	1	2	263.09 (11.10)	263.09 (15.69)	17.25 (0.22)	17.25 (0.32)
	2	8	271.19 (7.07)	272.55 (4.91)	17.22 (0.45)	17.37 (0.30)
	3	7	297.00 (14.47)	292.13 (23.33)	18.15 (0.64)	17.91 (0.71)
	4	2	307.31 (13.42)	307.31 (18.98)	18.43 (0.27)	18.43 (0.38)
	5	6	333.67 (43.12)	311.65 (87.78)	19.23 (2.12)	18.11 (3.97)
	Subtotal	25	295.65 (33.58)	291.05 (31.49)	18.06 (1.32)	17.73 (0.83)

aPR: age-adjusted prevalence rate; aIR: age-adjusted incidence rate; AFR: African region; AMR: American region; EMR: Eastern Mediterranean region; EUR: European region; IQR: inter-quartile range; SD: standard deviation; SDI: sociodemographic index; SEAR: Southeast Asian region; WPR: West Pacific region

Table 5-3. Age-standardized prevalence and incidence rates of schizophrenia (per 100,000) by fortification status and SDI

Fortification	SDI	Jurisdictions	aPR Mean (SD)	aPR Median (IQR)	aIR Mean (SD)	aIR Median (IQR)
None	1	10	220.41 (31.08)	209.89 (25.58)	14.45 (1.11)	14.13 (0.47)
	2	16	260.98 (28.55)	269.59 (33.66)	16.17 (1.60)	16.61 (3.17)
	3	19	264.29 (23.48)	275.63 (40.34)	15.80 (1.28)	16.19 (1.94)
	4	23	284.56 (17.63)	285.05 (20.56)	16.66 (1.10)	16.45 (0.97)
	5	8	294.63 (12.85)	295.54 (16.76)	16.93 (0.75)	16.78 (0.93)
	Subtotal	76	267.15 (31.51)	276.53 (37.29)	16.09 (1.42)	16.33 (2.41)
Mandatory	1	23	216.33 (16.48)	211.24 (8.34)	14.16 (0.71)	13.94 (0.20)
	2	21	243.22 (25.60)	248.20 (46.23)	15.05 (1.06)	14.77 (1.77)
	3	15	279.49 (21.09)	280.53 (12.48)	16.61 (1.27)	16.39 (1.60)
	4	8	285.54 (25.01)	276.70 (45.97)	16.71 (1.45)	16.37 (2.86)
	5	4	374.89 (61.29)	388.63 (72.52)	20.87 (3.46)	21.94 (4.19)
	Subtotal	72	254.77 (46.43)	255.57 (65.41)	15.62 (2.05)	15.30 (2.38)
Voluntary	1	1	208.04 (-)	208.04 (-)	13.82 (-)	13.82 (-)
	2	5	257.98 (30.62)	276.19 (45.52)	14.87 (1.44)	14.34 (0.85)
	3	6	280.33 (25.00)	283.89 (53.49)	16.50 (1.45)	16.56 (3.28)
	4	10	285.52 (15.13)	288.56 (19.26)	16.60 (0.86)	16.53 (0.85)
	5	24	283.52 (28.06)	277.55 (19.99)	16.44 (1.67)	16.17 (1.06)
	Subtotal	46	279.04 (28.21)	278.28 (22.93)	16.25 (1.56)	16.17 (1.28)

aPR: age-adjusted prevalence rate; aIR: age-adjusted incidence rate; IQR: inter-quartile range; SD: standard deviation; SDI: sociodemographic index

Table 5-4. Changes in age-standardized prevalence and incidence rates of schizophrenia between 1990 and 2019, stratified by sex, SDI, and fortification status

		Mean (SD)	Median (IQR)	95% CI	Min	Max
Δ aPR						
Sex	Both sexes	2.78 (6.68)	2.00 (6.40)	(1.83, 3.72)	-17.54	30.86
	Male	2.89 (6.85)	2.07 (6.26)	(1.92, 3.86)	-22.97	31.79
	Female	2.69 (6.81)	1.63 (6.15)	(1.72, 3.65)	-15.37	31.13
SDI	Low	0.41 (4.04)	0.18 (6.76)	(-1.00, 1.82)	-6.69	8.63
	Low-Middle	3.96 (7.13)	2.79 (6.48)	(1.73, 6.18)	-13.70	22.59
	Middle	5.11 (7.03)	4.32 (6.90)	(2.89, 7.33)	-17.54	30.86
	Middle-High	3.19 (6.31)	1.71 (6.53)	(1.20, 5.18)	-11.21	17.56
	High	0.50 (7.08)	-0.31 (6.00)	(-1.90, 2.89)	-16.32	25.50
Fortification	None	3.31 (7.62)	1.92 (7.63)	(1.57, 5.05)	-17.54	30.86
	Mandatory	2.57 (4.51)	2.09 (5.49)	(1.51, 3.63)	-6.69	17.04
	Voluntary	2.22 (7.85)	0.85 (7.33)	(-0.11, 4.55)	-16.32	25.50
Δ aIR						
Sex	Both sexes	0.03 (0.25)	0.01 (0.18)	(-0.00, 0.07)	-0.80	1.48
	Male	0.01 (0.26)	0.02 (0.20)	(-0.02, 0.05)	-1.32	1.19
	Female	0.04 (0.27)	-0.01 (0.18)	(0.00, 0.08)	-0.53	1.78
SDI	Low	-0.03 (0.14)	-0.00 (0.10)	(-0.08, 0.02)	-0.49	0.06
	Low-Middle	0.01 (0.19)	-0.00 (0.19)	(-0.05, 0.07)	-0.46	0.91
	Middle	0.06 (0.18)	0.08 (0.14)	(0.00, 0.12)	-0.57	0.56
	Middle-High	0.03 (0.25)	0.02 (0.31)	(-0.05, 0.11)	-0.48	0.70
	High	-0.02 (0.44)	-0.01 (0.27)	(-0.17, 0.12)	-0.80	1.48
Fortification	None	0.05 (0.23)	0.05 (0.24)	(-0.01, 0.10)	-0.57	0.91
	Mandatory	-0.01 (0.21)	0.02 (0.13)	(-0.06, 0.04)	-0.49	0.46
	Voluntary	-0.01 (0.35)	0.02 (0.32)	(-0.12, 0.09)	-0.80	1.48

Table 5-5. Changes in age-standardized prevalence and incidence rates of schizophrenia (1990-2019) among individuals aged 15-39 years, stratified by sex, SDI, and fortification status

		Mean (SD)	Median (IQR)	95% CI	Min	Max
Δ aPR						
Sex	Both sexes	19.36 (18.03)	20.13 (28.25)	(15.76, 22.95)	-16.85	73.66
	Male	19.08 (19.40)	19.33 (30.80)	(15.21, 22.95)	-22.88	72.71
	Female	19.48 (17.79)	18.66 (23.04)	(15.93, 23.02)	-23.38	74.69
SDI	Low	1.37 (9.82)	-2.31 (15.99)	(-4.46, 6.10)	-12.32	23.79
	Low-Middle	19.79 (14.12)	18.60 (17.16)	(12.26, 27.31)	-0.71	49.38
	Middle	28.27 (17.51)	27.34 (19.73)	(20.70, 35.84)	-16.85	73.66
	Middle-High	29.45 (13.43)	34.00 (17.18)	(23.50, 35.41)	-0.07	54.10
	High	14.50 (18.17)	11.66 (35.11)	(5.75, 23.26)	-16.59	40.01
Fortification	None	21.37 (18.80)	22.39 (27.07)	(14.59, 28.15)	-16.85	54.10
	Mandatory	14.32 (16.99)	13.20 (30.73)	(8.57, 20.07)	-12.32	48.11
	Voluntary	23.13 (17.62)	20.13 (25.57)	(16.66, 29.59)	-14.99	73.66
Δ aIR						
Sex	Both sexes	-0.02 (0.86)	0.02 (0.83)	(-0.19, 0.15)	-3.65	3.70
	Male	-0.03 (0.91)	0.03 (0.92)	(-0.21, 0.16)	-4.33	2.89
	Female	-0.05 (0.84)	0.00 (0.75)	(-0.22, 0.12)	-2.60	4.55
SDI	Low	0.01 (0.41)	0.06 (0.67)	(-0.19, 0.20)	-0.95	0.54
	Low-Middle	0.31 (0.58)	0.29 (0.79)	(-0.00, 0.62)	-0.65	1.43
	Middle	0.05 (0.72)	0.07 (0.76)	(-0.26, 0.36)	-1.25	1.68
	Middle-High	-0.34 (1.02)	-0.44 (0.78)	(-0.80, 0.11)	-3.64	1.22
	High	-0.04 (1.21)	0.01 (1.02)	(-0.63, 0.54)	-2.40	3.70
Fortification	None	-0.11 (0.77)	-0.09 (1.10)	(-0.38, 0.17)	-1.72	1.68
	Mandatory	-0.05 (0.75)	0.07 (0.59)	(-0.30, 0.20)	-3.64	0.96
	Voluntary	0.10 (1.05)	0.03 (0.91)	(-0.29, 0.48)	-2.40	3.70

Table 5-6. Association between fortification policies and age-standardized distributions of schizophrenia

		Fortification*† (β, 95% CI)	Fortification years**† (β, 95% CI)
ΔaPR			
	Both sexes	-0.94 (-3.16, 1.28)	-0.08 (-0.22, 0.07)
	Male	-0.63 (-2.81, 1.56)	-0.08 (-0.21, 0.06)
	Female	-0.84 (-2.98, 1.31)	-0.07 (-0.22, 0.07)
15-39 years	Both sexes	-13.14 (-22.60, -3.68)	-0.82 (-1.40, -0.23)
	Male	-13.37 (-23.95, -2.78)	-0.76 (-1.40, -0.12)
	Female	-12.03 (-20.49, -3.57)	-0.86 (-1.41, -0.31)
ΔaIR			
	Both sexes	-0.01 (-0.09, 0.07)	-0.00 (-0.01, 0.00)
	Male	-0.01 (-0.09, 0.07)	-0.00 (-0.01, 0.01)
	Female	-0.06 (-0.14, 0.03)	-0.00 (-0.01, 0.00)
15-39 years	Both sexes	-0.10 (-0.46, 0.26)	0.00 (-0.02, 0.03)
	Male	-0.11 (-0.52, 0.29)	0.00 (-0.03, 0.03)
	Female	-0.09 (-0.40, 0.22)	0.00 (-0.02, 0.03)

* mandatory vs none, total n=148 countries

** duration of any folic acid fortification policies, total n=194 countries

† adjusted for sociodemographic index category, sociopolitical conflict, and baseline rate (1990)

5.9 Appendices

Appendix 5-A. Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Africa									
Benin	1	Mandatory	2010	Wheat	Both sex	210.73	213.54	13.85	13.89
					Male	218.29	220.61	14.77	14.71
					Female	204.40	206.97	13.07	13.13
Burkina Faso	1	Mandatory	2010	Wheat	Both sex	202.52	207.89	13.72	13.78
					Male	209.94	215.19	14.68	14.64
					Female	196.52	201.58	12.94	13.02
Burundi	1	Mandatory	2015	Wheat	Both sex	202.45	200.41	14.00	14.06
				Maize	Male	209.00	207.23	14.89	14.97
					Female	196.55	193.33	13.20	13.12
Chad	1	Mandatory	2021	Wheat	Both sex	205.61	210.59	13.81	13.84
				Maize	Male	213.39	218.87	14.71	14.73
					Female	198.90	202.58	13.02	13.00
Cote d'Ivoire	1	Mandatory	2007	Wheat	Both sex	213.43	213.54	13.89	13.88
					Male	220.39	221.38	14.65	14.70
					Female	205.75	204.86	13.08	13.00
Ethiopia	1	Mandatory	2022	Wheat	Both sex	206.97	213.38	14.72	14.66
					Male	213.67	220.76	15.68	15.61
					Female	200.62	206.10	13.81	13.72
Gambia	1	Mandatory	2020	Wheat	Both sex	212.14	212.32	13.94	13.90
					Male	218.55	219.64	14.74	14.78
					Female	205.36	205.25	13.12	13.08
Guinea	1	Mandatory	2006	Wheat	Both sex	208.54	209.05	13.82	13.79
					Male	217.42	218.05	14.72	14.71
					Female	200.75	201.20	13.04	12.99
Liberia	1	Mandatory	2017	Wheat	Both sex	209.11	207.03	13.91	13.89
					Male	218.25	215.48	14.84	14.75
					Female	200.39	198.29	13.06	13.01
Malawi	1	Mandatory	2011	Wheat	Both sex	199.84	201.84	13.99	14.00
				Maize	Male	205.68	208.94	14.85	14.94
					Female	194.35	195.22	13.18	13.12
Mali	1	Mandatory	2010	Wheat	Both sex	206.40	211.24	13.82	13.88
					Male	216.30	220.77	14.77	14.80
					Female	197.38	202.07	12.97	13.02

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Mozambique	1	Mandatory	2016	Wheat	Both sex	195.31	203.94	14.02	13.99
				Maize	Male	199.40	210.26	14.93	14.93
					Female	191.83	198.37	13.25	13.16
Niger	1	Mandatory	2010	Wheat	Both sex	208.01	207.69	13.89	13.86
					Male	215.57	215.80	14.75	14.77
					Female	200.48	200.11	13.07	13.01
Senegal	1	Mandatory	2009	Wheat	Both sex	215.12	216.23	13.97	13.94
					Male	222.84	224.42	14.83	14.82
					Female	208.00	208.52	13.18	13.10
Togo	1	Mandatory	2013	Wheat	Both sex	208.46	208.71	13.85	13.86
					Male	216.50	215.85	14.76	14.72
					Female	201.54	202.34	13.05	13.08
Uganda	1	Mandatory	2011	Maize	Both sex	200.90	207.95	14.02	14.03
				Wheat	Male	206.54	215.01	14.86	14.93
					Female	195.54	201.60	13.22	13.21
United Republic Tanzania	1	Mandatory	2010	Wheat	Both sex	208.18	213.27	14.06	14.06
				Maize	Male	215.307	221.08	14.96	14.95
					Female	201.74	206.17	13.24	13.26
Rwanda	1	Voluntary	2019	Wheat	Both sex	205.32	209.99	14.06	14.06
				Maize	Male	211.44	217.91	14.91	15.01
					Female	199.79	202.85	13.28	13.18
Sierra Leone	1	Voluntary	2010	Wheat	Both sex	207.86	208.04	13.80	13.82
					Male	215.51	215.31	14.67	14.67
					Female	200.67	220.77	13.00	12.99
Comoros	1	None	-	-	Both sex	217.60	217.20	14.20	14.25
					Male	224.41	224.92	15.03	15.12
					Female	211.20	209.52	13.42	13.37
DRC	1	None	-	-	Both sex	207.99	204.36	13.85	13.86
					Male	215.38	211.46	14.72	14.72
					Female	201.32	197.23	13.05	13.00
Eritrea	1	None	-	-	Both sex	202.28	207.45	14.04	14.07
					Male	206.24	213.39	14.87	14.95
					Female	198.46	201.51	13.26	13.18
Guinea Bissau	1	None	-	-	Both sex	203.18	203.76	13.74	13.73
					Male	210.52	211.09	14.64	14.64
					Female	196.94	197.24	12.97	12.92
Madagascar	1	None	-	-	Both sex	213.22	212.34	14.18	14.15
					Male	219.62	220.02	14.98	15.04
					Female	207.1	204.83	13.41	13.27

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
South Sudan	1	None	-	-	Both sex	229.74	229.35	14.40	14.33
					Male	235.23	236.96	15.08	15.16
					Female	223.15	222.33	13.62	13.58
Cabo Verde	2	Mandatory	2014	Wheat	Both sex	221..55	229.56	14.03	14.21
					Male	226.21	234.34	14.87	14.90
					Female	218.02	224.53	13.38	13.48
Cameroon	2	Mandatory	2011	Wheat	Both sex	213.68	213.16	13.86	13.85
					Male	222.19	221.23	14.74	14.68
					Female	205.81	205.28	13.06	13.05
Ghana	2	Mandatory	2010	Wheat	Both sex	210.62	216.92	13.87	13.92
					Male	218.32	224.66	14.73	14.74
					Female	203.35	210.08	13.06	13.18
Kenya	2	Mandatory	2012	Wheat	Both sex	214.26	216.64	14.33	14.35
				Maize	Male	221.95	224.79	15.20	15.24
					Female	206.78	208.66	13.49	13.47
Lesotho	2	Mandatory	2020	Wheat	Both sex	195.73	204.73	13.53	13.64
				Maize	Male	201.99	211.08	14.41	14.45
					Female	189.78	198.56	12.70	12.84
Mauritania	2	Mandatory	2010	Wheat	Both sex	217.59	220.32	13.99	14.01
					Male	227.90	230.48	14.90	14.91
					Female	208.40	210.89	13.14	13.19
Nigeria	2	Mandatory	2014	Wheat	Both sex	218.86	222.61	14.21	14.14
				Maize	Male	226.70	231.59	15.06	15.04
					Female	209.56	214.75	13.28	13.34
Zimbabwe	2	Mandatory	2016	Wheat	Both sex	206.95	202.48	13.67	13.60
				Maize	Male	214.23	209.73	14.53	14.48
					Female	200.11	196.16	12.88	12.83
Eswatini	2	Voluntary	2013	Wheat	Both sex	211.57	217.62	13.70	13.80
					Male	218.94	224.51	14.55	14.59
					Female	205.41	211.46	12.98	13.08
Angola	2	None	-	-	Both sex	213.98	219.83	13.92	13.93
					Male	220.60	227.87	14.70	14.79
					Female	207.10	212.65	13.12	13.15
Congo	2	None	-	-	Both sex	214.74	215.30	13.87	13.83
					Male	223.02	223.59	14.72	14.68
					Female	207.11	207.06	13.07	13.00

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Sao Tome and Principe	2	None	-	-	Both sex	219.96	222.82	14.03	14.10
					Male	228.34	230.85	14.91	14.92
					Female	212.20	214.66	13.21	13.27
Zambia	2	None	-	-	Both sex	208.69	212.87	14.03	14.06
					Male	214.59	220.00	14.86	14.92
					Female	203.11	205.78	13.25	13.21
South Africa	3	Mandatory	2003	Wheat Maize	Both sex	222.72	224.81	14.04	14.08
					Male	230.64	232.54	14.86	14.88
					Female	215.47	217.45	13.28	13.30
Algeria	3	None	-	-	Both sex	250.22	249.14	14.90	14.77
					Male	262.37	261.11	15.85	15.69
					Female	238.08	237.03	13.93	13.83
Botswana	3	None	-	-	Both sex	214.30	225.16	13.76	13.97
					Male	222.11	232.91	14.62	14.74
					Female	207.54	217.81	13.01	13.23
Central African Republic	3	None	-	-	Both sex	197.09	191.39	13.71	13.61
					Male	202.84	197.26	14.57	14.49
					Female	191.77	185.85	12.92	12.78
Equatorial Guinea	3	None	-	-	Both sex	205.17	236.03	13.80	14.34
					Male	212.94	244.73	14.74	15.08
					Female	198.90	227.49	13.04	13.52
Gabon	3	None	-	-	Both sex	229.99	229.68	14.19	14.12
					Male	237.25	237.69	14.91	14.91
					Female	222.62	222.19	13.45	13.40
Namibia	3	None	-	-	Both sex	216.89	222.56	13.82	13.93
					Male	224.83	229.85	14.66	14.71
					Female	209.47	215.95	13.02	13.21
Cook Islands	4	None	-	-	Both sex	307.29	312.71	18.44	18.54
					Male	326.24	333.57	19.87	20.12
					Female	286.52	293.70	16.91	17.13
Mauritius	4	None	-	-	Both sex	293.65	310.46	17.75	18.36
					Male	311.54	326.09	19.18	19.65
					Female	276.01	294.88	16.30	17.05
Seychelles	4	None	-	-	Both sex	300.34	313.63	17.94	18.51
					Male	318.64	328.16	19.35	19.69
					Female	281.59	296.51	16.48	17.09

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
The Americas									
Haiti	1	Mandatory	2017	Wheat	Both sex	244.20	241.31	15.37	15.23
					Male	254.95	253.86	16.33	16.28
					Female	234.70	230.14	14.49	14.28
Belize	2	Mandatory	1998	Wheat	Both sex	265.73	270.70	15.93	16.03
				(Rice)	Male	271.58	278.41	16.65	16.82
					Female	259.52	263.17	15.18	15.26
Bolivia	2	Mandatory	1997	Wheat	Both sex	260.33	266.55	15.78	15.91
					Male	271.56	277.96	16.71	16.81
					Female	249.77	255.31	14.90	15.00
Dominican Republic	2	Mandatory	2009	Wheat	Both sex	267.65	277.87	15.98	16.27
				(Maize)	Male	274.59	286.12	16.75	17.04
					Female	261.06	269.50	15.25	15.49
El Salvador	2	Mandatory	2007	Wheat	Both sex	262.84	268.61	15.82	15.89
				Maize	Male	265.56	273.90	16.51	16.65
					Female	260.38	264.37	15.20	15.25
Guatemala	2	Mandatory	2001	Wheat	Both sex	261.10	262.77	15.77	15.70
				Maize	Male	267.69	270.63	16.55	16.53
					Female	254.84	255.98	15.04	14.97
Honduras	2	Mandatory	2007	Wheat	Both sex	259.68	261.68	15.74	15.70
					Male	269.67	271.82	16.65	16.61
					Female	250.19	252.68	14.88	14.88
Nicaragua	2	Mandatory	2007	Wheat	Both sex	270.04	270.73	16.06	16.04
				Rice	Male	276.45	277.50	16.84	16.77
					Female	264.08	264.43	15.35	15.29
Venezuela	2	None	-	-	Both sex	277.37	275.89	16.24	16.14
					Male	284.46	283.10	17.01	16.91
					Female	270.48	269.05	15.50	15.41
Brazil	3	Mandatory	2002	Maize	Both sex	274.04	277.64	16.34	16.36
				Wheat	Male	280.95	285.07	17.45	17316
					Female	267.41	270.60	15.56	15.59
Columbia	3	Mandatory	1996	Wheat	Both sex	276.14	279.88	16.25	16.26
					Male	281.87	286.90	16.97	17.03
					Female	270.64	273.32	15.57	15.53
Costa Rica	3	Mandatory	1997	Wheat	Both sex	281.18	285.97	16.40	16.48
				Maize	Male	287.57	293.75	17.12	17.27
				Rice	Female	274.94	278.85	15.70	15.76

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Cuba	3	Mandatory	2012	Wheat	Both sex	279.73	280.53	16.38	16.39
					Male	288.16	290.43	17.17	17.23
					Female	271.34	270.52	15.58	15.51
Ecuador	3	Mandatory	1996	Wheat	Both sex	271.47	275.63	16.10	16.18
					Male	278.59	283.31	16.85	16.96
					Female	264.53	268.19	15.38	15.42
Mexico	3	Mandatory	2009	Wheat	Both sex	281.78	283.89	16.57	16.56
				Maize	Male	288.89	291.59	17.34	17.36
					Female	275.12	276.72	15.84	15.81
Panama	3	Mandatory	2003	Wheat	Both sex	278.97	288.11	16.34	16.53
				Rice	Male	286.68	296.66	17.11	17.29
					Female	271.05	279.49	15.55	15.77
Paraguay	3	Mandatory	1998	Wheat	Both sex	273.50	277.82	16.17	16.25
					Male	282.65	287.14	17.04	17.09
					Female	264.25	268.30	15.30	15.39
Peru	3	Voluntary	2006	Wheat	Both sex	272.68	279.54	16.16	16.31
				Rice	Male	282.45	291.00	17.02	17.21
					Female	263.17	268.43	15.32	15.40
Grenada	3	None	-	-	Both sex	269.42	279.21	16.03	16.30
					Male	277.89	289.01	16.82	17.14
					Female	261.41	268.74	15.26	15.41
Guyana	3	None	-	-	Both sex	253.86	263.01	15.62	15.80
					Male	260.31	271.60	16.42	16.65
					Female	247.58	254.74	14.85	14.97
Jamaica	3	None	-	-	Both sex	275.30	276.14	16.22	16.20
					Male	285.38	287.81	17.09	17.13
					Female	265.72	264.76	15.39	15.28
Saint Lucia	3	None	-	-	Both sex	272.71	276.92	16.14	16.19
					Male	279.70	284.92	16.91	16.99
					Female	266.29	268.94	15.41	15.38
St. Vincent & Grenadines	3	None	-	-	Both sex	267.50	274.23	16.01	16.15
					Male	275.43	284.32	16.79	17.01
					Female	259.73	263.68	15.23	15.25
Suriname	3	None	-	-	Both sex	271.29	275.63	16.09	16.19
					Male	278.97	284.87	16.88	17.03
					Female	263.65	266.69	15.30	15.37
Argentina	4	Mandatory	2002	Wheat	Both sex	310.78	311.54	18.34	18.27
					Male	328.01	329.98	19.78	19.80
					Female	293.76	293.49	16.93	16.76

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Chile	4	Mandatory	2000	Wheat	Both sex	311.38	317.76	18.36	18.50
					Male	327.48	335.29	19.75	19.95
					Female	295.82	300.22	17.01	17.03
Uruguay	4	Mandatory	2006	Wheat	Both sex	311.38	313.49	18.35	18.32
					Male	328.44	331.24	19.79	19.77
					Female	294.68	296.31	16.92	16.90
Antigua and Barbuda	4	None	-	-	Both sex	283.61	288.66	16.47	16.56
					Male	291.90	298.53	17.27	17.38
					Female	276.06	279.40	15.73	15.78
Bahamas	4	None	-	-	Both sex	285.16	284.81	16.48	16.44
					Male	294.46	295.15	17.30	17.29
					Female	276.56	275.20	15.70	15.64
Barbados	4	None	-	-	Both sex	281.83	282.56	16.39	16.40
					Male	291.19	291.43	17.22	17.21
					Female	273.33	274.31	15.61	15.63
Dominica	4	None	-	-	Both sex	270.54	274.77	16.11	16.18
					Male	279.03	284.89	16.90	17.05
					Female	262.34	264.01	15.30	15.26
Saint Kitts and Nevis	4	None	-	-	Both sex	27.22	284.09	16.20	16.45
					Male	282.56	293.36	17.00	17.25
					Female	266.31	274.64	15.43	15.64
Trinidad and Tobago	4	None	-	-	Both sex	276.08	286.89	16.22	16.55
					Male	282.90	296.40	16.94	17.36
					Female	269.29	277.18	15.50	15.71
Canada	5	Mandatory	1998	Wheat Pasta (Rice)	Both sex	288.60	288.64	15.86	15.85
					Male	312.14	312.25	17.20	17.46
					Female	265.21	265.35	14.50	14.21
United States of America	5	Mandatory	1996	Wheat Maize Rice	Both sex	435.86	433.65	24.09	23.76
					Male	460.29	437.32	25.78	24.46
					Female	411.37	429.53	22.36	23.05
Eastern Mediterranean									
Afghanistan	1	Mandatory	2014	Wheat	Both sex	223.21	217.78	14.18	13.99
					Male	236.23	229.97	15.27	14.97
					Female	272.37	279.08	15.50	15.62
Yemen	1	Mandatory	2001	Wheat	Both sex	231.50	225.68	14.46	14.17
					Male	242.13	234.95	15.46	15.06
					Female	220.84	216.45	13.48	13.28

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Pakistan	1	None	-	-	Both sex	283.76	278.89	15.39	15.00
					Male	317.06	312.93	17.29	16.95
					Female	246.86	243.77	13.28	13.00
Somalia	1	None	-	-	Both sex	192.24	188.42	14.06	14.11
					Male	196.06	192.89	14.88	15.06
					Female	188.47	183.85	13.25	13.14
Djibouti	2	Mandatory	2013	Wheat	Both sex	221.01	220.83	14.32	14.30
					Male	226.87	228.01	15.02	15.10
					Female	214.08	212.81	13.48	13.41
Morocco	2	Mandatory	2005	Wheat	Both sex	240.96	242.82	14.66	14.57
					Male	253.18	255.02	15.65	15.55
					Female	229.09	230.69	13.69	13.60
Sudan	2	Voluntary	2011	Wheat	Both sex	230.67	232.68	14.45	14.34
					Male	241.45	243.06	15.44	15.27
					Female	220.11	222.41	13.50	13.42
Iran (Islamic Republic of)	3	Mandatory	2006	Wheat	Both sex	252.25	254.16	15.08	14.97
					Male	261.07	264.10	15.94	15.84
					Female	242.99	243.96	14.18	14.07
Egypt	3	Voluntary	2008	Wheat	Both sex	245.35	247.70	14.83	14.74
					Male	255.88	257.56	15.77	15.58
					Female	234.47	236.88	13.86	13.85
Iraq	3	Voluntary	2000	Wheat	Both sex	248.84	246.18	14.88	14.68
					Male	259.45	256.63	15.81	15.58
					Female	237.78	235.21	13.92	13.73
Syrian Arab Republic	3	None	-	-	Both sex	245.57	242.37	14.82	14.57
					Male	256.92	254.24	15.78	15.55
					Female	233.76	232.23	13.83	13.75
Tunisia	3	None	-	-	Both sex	251.41	252.46	14.96	14.84
					Male	261.17	263.02	15.85	15.72
					Female	241.62	242.26	14.06	13.98
Bahrain	4	Mandatory	2002	Wheat	Both sex	271.01	270.95	15.62	15.50
					Male	280.34	280.18	16.37	16.25
					Female	255.65	255.01	14.50	14.42
Jordan	4	Mandatory	2002	Wheat	Both sex	255.30	255.06	15.12	15.00
					Male	268.31	266.77	16.10	15.87
					Female	240.78	240.90	14.01	13.95
Oman	4	Mandatory	1996	Wheat	Both sex	264.39	264.24	15.47	15.37
					Male	272.09	271.18	16.13	15.95
					Female	250.22	249.68	14.32	14.22

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Lebanon	4	None	-	-	Both sex	253.60	253.52	15.00	14.91
					Male	263.80	264.28	15.90	15.79
					Female	243.97	243.60	14.13	14.04
Libya	4	None	-	-	Both sex	261.10	249.90	15.28	14.80
					Male	271.07	260.27	16.08	15.67
					Female	248.50	238.73	14.30	13.89
Kuwait	5	Voluntary	2015	Wheat	Both sex	276.61	273.81	15.81	15.55
					Male	285.23	284.65	16.54	16.38
					Female	261.99	260.86	14.72	14.62
Qatar	5	Voluntary	2015	Wheat	Both sex	282.87	284.95	16.14	16.17
					Male	290.08	290.90	16.71	16.62
					Female	263.09	264.14	14.76	14.74
Saudi Arabia	5	Voluntary	2015	Wheat	Both sex	264.94	262.86	15.42	15.24
					Male	273.74	272.10	16.13	15.96
					Female	251.10	248.92	14.39	14.21
United Arab Emirates	5	Voluntary	2015	Wheat	Both sex	284.81	275.32	16.15	15.67
					Male	292.45	282.38	16.77	16.31
					Female	265.50	256.24	14.80	14.44
Europe									
Kyrgyzstan	2	Mandatory	2009	Wheat	Both sex	265.99	262.08	16.09	15.90
					Male	273.01	269.94	16.92	16.79
					Female	259.31	254.60	15.27	15.02
Tajikistan	2	None	-	-	Both sex	269.36	263.68	16.20	16.00
					Male	279.68	274.43	17.12	16.95
					Female	259.18	253.00	15.29	15.04
Turkmenistan	3	Mandatory	2006	Wheat	Both sex	272.05	281.01	16.22	16.48
					Male	281.72	291.41	17.12	17.36
					Female	262.92	270.21	15.35	15.51
Uzbekistan	3	Mandatory	2011	Wheat	Both sex	264.84	270.15	16.05	16.13
					Male	273.87	280.65	16.93	17.06
					Female	256.10	260.10	15.20	15.20
Croatia	3	Voluntary	2006	NR	Both sex	292.67	294.13	16.66	16.70
					Male	301.14	302.19	17.45	17.45
					Female	284.21	286.01	15.86	15.93

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Albania	3	None	-	-	Both sex	281.20	287.50	16.33	16.42
					Male	289.26	296.02	17.11	17.22
					Female	272.37	279.08	15.50	15.62
Armenia	3	None	-	-	Both sex	277.50	282.62	16.42	16.53
					Male	284.52	291.12	17.20	17.39
					Female	270.91	274.82	15.67	15.71
Azerbaijan	3	None	-	-	Both sex	277.47	282.71	16.39	16.51
					Male	286.02	292.19	17.25	17.35
					Female	269.64	273.56	15.59	15.66
Kazakhstan	4	Mandatory	2008	Wheat	Both sex	274.56	282.44	16.30	16.49
					Male	282.38	292.08	17.11	17.39
					Female	267.37	273.62	15.52	15.63
Republic of Moldova	4	Mandatory	2012	Wheat	Both sex	381.78	268.85	16.34	16.26
					Male	279.85	276.14	17.18	17.07
					Female	264.58	262.00	15.55	15.45
Bulgaria	4	Voluntary	2006	NR	Both sex	283.86	288.10	16.55	16.62
					Male	293.68	297.96	17.42	17.46
					Female	274.16	278.01	15.67	15.74
Greece	4	Voluntary	2006	NR	Both sex	273.11	272.23	16.00	16.01
					Male	274.95	275.21	16.51	16.54
					Female	270.63	268.67	15.47	15.45
Hungary	4	Voluntary	2006	NR	Both sex	287.00	291.49	16.44	16.55
					Male	295.82	300.60	17.23	17.35
					Female	278.49	282.52	15.66	15.74
Italy	4	Voluntary	2006	NR	Both sex	299.70	291.21	17.68	17.20
					Male	301.17	291.58	18.18	17.56
					Female	297.05	289.96	17.15	16.80
Malta	4	Voluntary	2006	NR	Both sex	274.16	277.11	16.05	16.15
					Male	278.03	283.00	16.64	16.80
					Female	269.11	270.20	15.42	15.45
Poland	4	Voluntary	2006	NR	Both sex	284.82	294.53	16.57	16.86
					Male	291.82	302.14	17.35	17.63
					Female	277.89	286.92	15.79	16.08

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Portugal	4	Voluntary	2006	NR	Both sex	268.40	269.07	15.85	15.87
					Male	269.14	270.67	16.33	16.34
					Female	266.58	266.73	15.35	15.37
Romania	4	Voluntary	2006	NR	Both sex	282.48	289.02	16.32	16.50
					Male	291.09	297.61	17.10	17.29
					Female	273.92	280.31	15.53	15.69
Spain	4	Voluntary	2006	NR	Both sex	265.33	265.62	15.64	15.59
					Male	302.40	302.37	17.98	17.85
					Female	228.55	228.64	13.24	13.27
Belarus	4	None	-	-	Both sex	271.44	277.32	16.36	16.51
					Male	276.71	284.84	17.11	17333
					Female	266.62	270.34	15.64	15.70
Bosnia Herzegovina	4	None	-	-	Both sex	276.96	286.66	16.20	16.40
					Male	285.62	295.68	17.03	17.20
					Female	268.14	277.72	15.33	15.59
Russian Federation	4	None	-	-	Both sex	280.10	281.81	16.60	16.62
					Male	289.04	291.10	17.44	17.48
					Female	271.93	273.33	15.79	15.78
Georgia	4	None	-	-	Both sex	278.49	277.27	16.41	16.33
					Male	285.85	283.96	17.22	17.11
					Female	271.79	270.85	15.64	15.56
Israel	4	None	-	-	Both sex	305.93	299.14	17.67	17.30
					Male	314.70	305.15	18.50	17.95
					Female	296.81	292.42	16.82	16.62
Montenegro	4	None	-	-	Both sex	289.89	288.89	16.55	16.48
					Male	299.45	297.90	17.40	17.25
					Female	279.70	279.92	15.68	15.69
North Macedonia	4	None	-	-	Both sex	286.41	287.66	16.44	16.44
					Male	296.53	297.34	17.28	17.25
					Female	276.22	277.39	15.58	15.57
Serbia	4	None	-	-	Both sex	283.91	285.05	16.35	16.33
					Male	293.13	294.36	17.14	17.18
					Female	274.67	275.66	15.53	15.46
Turkey	4	None	-	-	Both sex	246.80	248.93	14.56	14.51
					Male	256.11	258.62	15.39	15.30
					Female	237.28	238.91	13.72	13.68

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Ukraine	4	None	-	-	Both sex	276.16	271.43	16.56	16.33
					Male	284.41	277.68	17.46	17.13
					Female	268.68	265.74	15.71	15.56
Austria	5	Voluntary	2006	NR	Both sex	275.93	276.75	16.07	16.16
					Male	278.51	280.45	16.62	16.71
					Female	271.47	272.09	15.49	15.56
Belgium	5	Voluntary	2006	NR	Both sex	274.51	274.17	16.02	16.04
					Male	277.56	278.84	16.58	16.65
					Female	270.19	269.04	15.45	15.43
Iceland	5	Voluntary	2006	NR	Both sex	278.49	278.35	16.16	16.20
					Male	282.18	283.04	16.74	16.80
					Female	273.98	272.75	15.56	15.56
Ireland	5	Voluntary	2006	NR	Both sex	356.52	352.67	19.97	19.81
					Male	364.73	354.79	20.51	19.90
					Female	347.81	350.50	19.43	19.69
Latvia	5	Voluntary	2006	NR	Both sex	280.09	266.01	16.59	16.77
					Male	288.02	294.40	17.42	17.56
					Female	272.92	278.13	15.80	15.98
Lithuania	5	Voluntary	2006	NR	Both sex	280.89	288.42	16.59	16.83
					Male	288.34	297.05	17.38	17.63
					Female	274.15	280.44	15.84	16.03
Luxemburg	5	Voluntary	2006	NR	Both sex	278.88	281.92	16.15	16.30
					Male	281.49	286.69	16.68	16.86
					Female	274.83	276.71	15.63	15.72
Netherlands	5	Voluntary	2006	NR	Both sex	384.29	367.97	22.77	21.97
					Male	392.42	371.74	24.27	23.03
					Female	373.25	363.44	21.21	20.87
Norway	5	Voluntary	2006	NR	Both sex	283.34	282.72	16.46	16.42
					Male	286.48	286.42	16.95	16.90
					Female	279.03	278.39	15.95	15.92
Cyprus	5	Voluntary	2006	NR	Both sex	274.50	273.98	16.08	16.08
					Male	277.32	277.86	16.60	16.58
					Female	270.68	269.46	15.50	15.47
Czech Republic	5	Voluntary	2006	NR	Both sex	292.70	296.58	16.27	16.40
					Male	300.79	304.75	17.02	17.14
					Female	284.63	288.13	15.52	15.64

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Denmark	5	Voluntary	2006	NR	Both sex	215.88	241.38	12.71	14.19
					Male	208.45	229.30	12.60	13.78
					Female	221.93	253.06	12.81	14.59
Estonia	5	Voluntary	2006	NR	Both sex	281.01	290.10	16.60	16.91
					Male	288.56	298.56	17.40	17.70
					Female	274.06	281.84	15.83	16.09
Finland	5	Voluntary	2006	NR	Both sex	264.35	264.08	15.12	15.12
					Male	262.41	263.25	15.09	15.11
					Female	264.93	264.30	15.14	15.13
France	5	Voluntary	2006	NR	Both sex	269.68	268.28	15.85	15.83
					Male	271.96	271.03	16.41	16.39
					Female	266.37	265.07	15.28	15.26
Germany	5	Voluntary	2006	NR	Both sex	261.82	262.70	15.78	15.81
					Male	243.62	245.37	14.90	14.92
					Female	278.29	279.75	16.69	16.74
Sweden	5	Voluntary	2006	NR	Both sex	282.48	270.26	16.23	15.86
					Male	303.06	293.86	17.66	17.34
					Female	260.21	245.07	14.72	14.26
United Kingdom	5	Voluntary	2006	NR	Both sex	251.37	246.26	13.93	13.72
					Male	271.36	263.40	15.53	15.20
					Female	231.17	228.64	12.34	12.21
Andorra	5	None	-	-	Both sex	290.23	286.52	16.57	16.48
					Male	294.10	292.77	17.09	17.07
					Female	285.06	280.00	16.00	15.84
Monaco	5	None	-	-	Both sex	295.21	295.40	16.79	16.84
					Male	299.98	300.74	17.35	17.34
					Female	289.62	289.90	16.21	16.26
San Marino	5	None	-	-	Both sex	284.29	280.11	16.34	16.25
					Male	287.75	286.50	16.89	16.86
					Female	279.90	274.59	15.84	15.63
Slovakia	5	None	-	-	Both sex	288.73	295.68	16.53	16.72
					Male	297.19	304.26	17.33	17.49
					Female	280.51	287.02	15.73	15.94
Slovenia	5	None	-	-	Both sex	294.34	299.51	16.71	16.85
					Male	303.07	307.54	17.49	17.58
					Female	285.70	290.99	15.92	16.07

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Switzerland	5	None	-	-	Both sex	282.27	279.98	16.29	16.23
					Male	285.91	284.55	16.84	16.76
					Female	276.97	274.70	15.69	15.67
Southeast Asia									
Nepal	1	Mandatory	2011	Wheat	Both sex	273.68	266.99	14.32	13.83
					Male	307.29	302.87	16.28	15.82
					Female	240.48	237.29	12.48	12.16
Bangladesh	2	Voluntary	2008	Wheat Rice	Both sex	280.60	276.19	14.47	14.01
					Male	314.18	312.27	16.41	15.98
					Female	243.02	241.97	12.49	12.20
India	2	Voluntary	2018	Wheat Rice	Both sex	279.97	285.23	14.94	14.86
					Male	314.12	319.15	16.91	16.75
					Female	242.70	249.98	12.84	12.86
Myanmar	2	Voluntary	2019	Rice	Both sex	255.31	278.20	16.77	17.35
					Male	275.39	295.29	18.42	18.77
					Female	236.71	263.07	15.16	16.05
Mongolia	2	Mandatory	2018	Wheat	Both sex	261.86	272.49	15.95	16.19
					Male	269.60	282.82	16.78	17.11
					Female	254.12	262.79	15.11	15.29
Bhutan	2	None	-	-	Both sex	282.00	286.71	14.55	14.37
					Male	314.02	320.02	16.26	16.13
					Female	246.06	249.26	12.55	12.38
Democratic People's Republic of Korea	2	None	-	-	Both sex	274.96	261.26	17.31	16.88
					Male	295.99	280.62	18.94	18.33
					Female	256.76	241.39	15.84	15.31
Maldives	2	None	-	-	Both sex	293.31	313.49	17.72	18.63
					Male	317.11	329.63	19.41	19.75
					Female	266.91	266.93	15.98	16.76
Timor Leste	2	None	-	-	Both sex	250.71	262.72	15.96	16.33
					Male	271.74	281.81	17.50	17.79
					Female	228.89	243.41	14.34	14.88
Tuvalu	2	None	-	-	Both sex	266.34	275.51	17.22	17.59
					Male	289.24	294.62	18.94	19.02
					Female	247.97	254.87	15.78	16.00
Indonesia	3	Mandatory	2009	Wheat	Both sex	280.83	293.69	17.40	17.78
					Male	304.03	313.11	13.14	19.25
					Female	258.27	274.00	15.72	16.28

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Thailand	3	Voluntary	1998	NR	Both sex	284.95	301.06	17.46	18.02
					Male	302.46	315.94	18.93	19.32
					Female	268.26	286.83	16.03	16.74
Tonga	3	None	-	-	Both sex	288.59	291.05	17.83	17.91
					Male	309.73	311.82	19.42	19.47
					Female	269.11	271.71	16.33	16.45
Sri Lanka	4	None	-	-	Both sex	285.14	300.82	17.50	18.03
					Male	301.15	314.03	18.95	19.26
					Female	269.06	288.63	16.04	16.87
Western Pacific									
Solomon Islands	1	Mandatory	2010	Wheat Rice	Both sex	256.53	255.24	17.09	17.09
					Male	277.01	276.11	18.64	18.68
					Female	233.98	234.24	15.45	15.50
Papua New Guinea	1	None	-	-	Both sex	270.22	270.93	17.42	17.41
					Male	290.62	291.04	18.95	18.95
					Female	248.15	249.63	15.79	15.80
Kiribati	2	Mandatory	2014	Wheat	Both sex	261.07	255.89	17.14	17.04
					Male	282.62	276.44	18.78	18.67
					Female	241.10	237.51	15.60	15.52
Cambodia	2	None	-	-	Both sex	257.22	273.50	16.73	17.27
					Male	279.00	291.04	18.48	18.72
					Female	240.13	257.51	15.29	15.88
Lao PDR	2	None	-	-	Both sex	261.91	280.32	16.88	17.42
					Male	282.89	298.08	18.54	18.83
					Female	242.47	262.55	15.35	16.01
Marshall Islands	2	None	-	-	Both sex	271.96	272.61	17.45	17.48
					Male	292.36	291.99	19.01	18.98
					Female	250.01	252.31	15.79	15.89
Micronesia	2	None	-	-	Both sex	269.75	269.29	17.37	17.36
					Male	288.93	288.26	18.89	18.89
					Female	249.34	249.87	15.78	15.77
Vanuatu	2	None	-	-	Both sex	271.17	269.89	17.42	17.37
					Male	289.25	287.74	18.93	18.88
					Female	251.49	251.65	15.86	15.88
Vietnam	3	Mandatory	2016	Wheat	Both sex	306.51	323.55	19.00	19.46
					Male	321.80	336.14	20.53	20.75
					Female	293.29	311.29	17.63	18.17

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Samoa	3	Mandatory	2017	Wheat	Both sex	284.40	286.65	17.81	18.81
					Male	304.19	306.15	19.29	19.29
					Female	263.53	265.90	16.19	16.23
Fiji	3	Mandatory	2009	Wheat	Both sex	289.66	292.68	17.89	17.95
					Male	310.02	313.31	19.40	19.47
					Female	269.06	271.45	16.35	16.36
China	3	Voluntary	2012	Wheat	Both sex	300.55	309.98	18.41	18.47
				Rice	Male	307.73	317.97	19.28	19.26
					Female	292.70	301.74	17.47	17.66
Nauru	3	None	-	-	Both sex	300.50	282.96	18.23	17.66
					Male	322.01	303.78	19.77	19.16
					Female	276.90	263.34	16.61	16.17
Philippines	3	None	-	-	Both sex	282.54	292.13	17.43	17.76
					Male	301.43	307.34	18.99	19.01
					Female	263.81	276.61	15.87	16.38
Malaysia	4	Voluntary	1985	Meat	Both sex	299.25	316.80	17.92	18.62
				Vegetable	Male	317.64	332.20	19.36	19.85
				Yeast	Female	280.79	300.16	16.47	17.27
Palau	4	None	-	-	Both sex	296.41	297.82	18.12	18.24
					Male	316.28	314.96	19.60	19.51
					Female	275.57	275.74	16.54	16.52
Australia	5	Mandatory	2009	Wheat	Both sex	389.10	388.65	21.77	21.70
					Male	441.41	441.96	24.85	24.83
					Female	335.81	335.31	18.61	18.41
New Zealand	5	Mandatory	2021	Wheat	Both sex	390.52	388.61	22.23	22.18
					Male	441.04	440.78	25.15	25.11
					Female	340.27	339.06	19.28	19.13
Brunei Darussalam	5	Voluntary	2001	NR	Both sex	307.50	304.10	17.88	17.86
					Male	329.69	331.35	19.52	19.73
					Female	280.06	272.58	16.04	15.69
Japan	5	Voluntary	1995	NR	Both sex	300.89	300.83	17.71	17.57
					Male	323.51	323.81	19.29	19.15
					Female	277.29	276.83	16.08	15.91
Republic of Korea	5	None	-	-	Both sex	292.69	300.63	17.46	17.73
					Male	313.88	324.86	19.17	19.54
					Female	269.93	273.31	15.69	15.68
Singapore	5	None	-	-	Both sex	306.98	319.20	18.00	18.36
					Male	335.57	353.41	19.93	20.69
					Female	277.87	282.83	15.97	16.10

Appendix 5-A (Cont'd). Geographic/sociodemographic classification, fortification status, and distribution of schizophrenia in the 194 jurisdictions included in the analyses (by region, SDI, fortification status, country name)

Country information		Folic acid fortification				Distribution of schizophrenia†			
Country	SDI*	Status	Year	Grain	Sex	aPR (1990)	aPR (2019)	aIR (1990)	aIR (2019)
Not Reported									
Palestine	2	Mandatory	2010	Wheat	Both sex	247.70	248.20	14.92	14.77
					Male	257.26	257.79	15.83	15.64
					Female	238.93	238.28	14.04	13.87

* 1: Low, 2: Low-Middle, 3: Middle, 4: Middle-High, 5: High; † rounded to two decimal places

aIR: age-adjusted incidence rate; aPR: age-adjusted prevalence rate; DPRK: Democratic People's Republic of Korea; DRC: Democratic Republic of Congo; SDI: sociodemographic index;

Appendix 5-B. Distribution of age-standardized prevalence and incidence rates of schizophrenia (per 100,000) in 2019 by geographic region and SDI, stratified by sex

Region	SDI	Countries	Sex	aPR Mean (SD)	aPR Median (IQR)	aIR Mean (SD)	aIR Median (IQR)
AFR	1	26	Both sexes	209.33 (6.82)	208.88 (6.25)	13.97 (0.21)	13.90 (0.20)
			Male	216.83 (7.44)	216.88 (7.37)	14.86 (0.22)	14.79 (0.24)
			Female	202.18 (6.51)	201.83 (6.89)	13.13 (0.20)	13.09 (0.18)
	2	13	Both sexes	216.53 (7.28)	216.92 (7.17)	13.96 (0.22)	13.93 (0.27)
			Male	224.21 (7.44)	224.66 (9.25)	14.80 (0.23)	14.79 (0.25)
			Female	209.27 (7.25)	210.08 (6.87)	13.16 (0.20)	13.18 (0.22)
	3	6	Both sexes	231.23 (9.99)	227.42 (11.21)	14.20 (0.31)	14.10 (0.36)
			Male	239.80 (11.68)	235.30 (12.18)	15.00 (0.36)	14.89 (0.34)
			Female	222.98 (8.06)	220.00 (10.04)	13.41 (0.23)	13.35 (0.29)
	4	3	Both sexes	312.27 (1.63)	312.71 (3.18)	18.47 (0.10)	18.51 (0.18)
			Male	329.28 (3.86)	328.16 (7.48)	19.82 (0.26)	19.69 (0.47)
			Female	295.03 (1.41)	294.88 (2.81)	17.09 (0.04)	17.09 (0.08)
	5	0	-	-	-	-	-
	Subtotal	48	Both sexes	220.45 (25.97)	213.33 (14.67)	14.28 (1.12)	13.98 (0.27)
			Male	228.73 (28.32)	220.93 (15.27)	15.17 (1.24)	14.85 (0.28)
			Female	212.50 (23.53)	205.94 (13.35)	13.42 (0.98)	13.17 (0.30)
AMR	1	1	Both sexes	241.31 (-)	241.31 (-)	15.23 (-)	15.23 (-)
			Male	253.86 (-)	253.86 (-)	16.28 (-)	16.28 (-)
			Female	230.14 (-)	230.14 (-)	14.28 (-)	14.28 (-)
	2	8	Both sexes	269.35 (5.73)	269.65 (8.65)	15.96 (0.20)	15.80 (0.29)
			Male	277.43 (5.33)	277.73 (7.90)	16.77 (0.17)	16.79 (0.23)
			Female	261.81 (6.40)	263.77 (11.09)	15.19 (0.22)	15.26 (0.36)
	3	15	Both sexes	278.28 (5.78)	277.82 (4.90)	16.28 (0.19)	16.26 (0.20)
			Male	287.23 (5.75)	287.14 (6.13)	17.10 (0.17)	17.13 (0.23)
			Female	269.46 (6.23)	268.74 (6.62)	15.46 (0.22)	15.41 (0.22)
	4	9	Both sexes	293.84 (15.87)	286.89 (27.45)	17.08 (0.97)	16.55 (1.83)
			Male	306.25 (19.85)	296.40 (36.62)	18.12 (1.29)	17.36 (2.52)
			Female	281.64 (12.15)	277.18 (18.65)	16.04 (0.66)	15.71 (1.12)

	5	2	Both sexes	361.15 (102.54)	361.15 (145.01)	19.81 (5.59)	19.81 (7.91)
			Male	374.89 (88.44)	374.79 (125.07)	20.96 (4.94)	20.96 (6.99)
			Female	347.44 (116.09)	347.44 (164.18)	18.63 (6.25)	18.63 (8.83)
	Subtotal	35	Both sexes	283.92 (29.72)	277.87 (11.74)	16.58 (1.42)	16.26 (0.46)
			Male	293.93 (29.97)	287.14 (12.05)	17.48 (1.48)	17.13 (0.38)
			Female	274.18 (29.81)	268.94 (12.36)	15.69 (1.40)	15.41 (0.46)
EMR	1	4	Both sexes	227.69 (37.71)	221.73 (49.19)	14.32 (0.46)	14.14 (0.54)
			Male	242.68 (50.45)	232.46 (62.51)	15.51 (0.96)	15.06 (0.99)
			Female	212.29 (24.96)	210.77 (35.63)	13.09 (0.14)	13.07 (0.23)
	2	3	Both sexes	232.11 (11.01)	232.68 (21.99)	14.40 (0.15)	14.34 (0.28)
			Male	242.03 (13.53)	243.06 (27.01)	15.30 (0.23)	15.27 (0.45)
			Female	221.97 (8.95)	222.41 (17.89)	13.48 (0.10)	13.42 (0.19)
	3	5	Both sexes	248.55 (4.78)	247.57 (6.27)	14.76 (0.15)	14.74 (0.15)
			Male	259.11 (4.26)	257.56 (6.40)	15.65 (0.12)	15.58 (0.14)
			Female	238.11 (4.90)	236.88 (7.05)	13.87 (0.15)	13.85 (0.23)
	4	5	Both sexes	258.73 (8.63)	255.06 (10.71)	15.12 (0.30)	15.00 (0.46)
			Male	268.54 (7.62)	266.77 (6.90)	15.91 (0.22)	15.87 (0.16)
			Female	245.58 (6.68)	243.60 (8.78)	14.10 (0.22)	14.04 (0.27)
	5	4	Both sexes	274.23 (9.05)	274.06 (11.8)	15.66 (0.39)	15.61 (0.53)
			Male	282.51 (7.82)	283.51 (10.54)	16.32 (0.27)	16.35 (0.36)
			Female	257.54 (6.60)	258.55 (9.92)	14.50 (0.23)	14.53 (0.35)
	Subtotal	21	All	249.54 (23.27)	252.46 (21.87)	14.88 (0.56)	14.84 (0.66)
			Male	260.24 (25.54)	263.02 (17.86)	15.76 (0.53)	15.72 (0.41)
			Female	236.37 (19.50)	240.90 (17.62)	13.84 (0.51)	13.89 (0.79)
EUR	1	0	-	-	-	-	-
	2	2	Both sexes	262.88 (1.13)	262.88 (1.60)	15.95 (0.07)	15.95 (0.10)
			Male	272.18 (3.17)	272.18 (4.49)	16.87 (0.11)	16.87 (0.16)
			Female	253.80 (1.13)	253.80 (1.30)	15.03 (0.01)	15.03 (0.02)
	3	6	Both sexes	283.02 (7.92)	282.67 (6.49)	16.46 (0.19)	16.49 (0.11)
			Male	292.26 (7.07)	291.80 (4.90)	17.30 (0.14)	17.35 (0.18)
			Female	273.96 (8.70)	274.19 (8.87)	15.61 (0.24)	15.64 (0.20)
	4	21	Both sexes	280.66 (11.75)	282.44 (16.67)	16.35 (0.57)	16.44 (0.30)
			Male	289.33 (12.17)	292.08 (14.90)	17.16 (0.57)	17.25 (0.35)

			Female	271.90 (14.97)	273.62 (11.25)	15.52 (0.77)	15.59 (0.29)
	5	24	Both sexes	284.99 (27.44)	281.01 (20.63)	16.49 (1.60)	16.27 (0.85)
			Male	289.88 (29.36)	286.59 (21.30)	17.05 (1.73)	16.88 (0.91)
			Female	279.75 (27.77)	277.42 (15.19)	15.90 (1.61)	15.69 (0.61)
	Subtotal	53	Both sexes	282.22 (20.28)	281.92 (17.46)	16.41 (1.13)	16.40 (0.54)
			Male	289.27 (21.35)	291.41 (19.06)	17.12 (1.21)	17.20 (0.66)
			Female	275.00 (21.60)	274.70 (11.64)	15.68 (1.20)	15.63 (0.47)
SEAR	1	1	Both sexes	266.99 (-)	266.99 (-)	13.83 (-)	13.83 (-)
			Male	302.87 (-)	302.87 (-)	15.82 (-)	15.82 (-)
			Female	237.29 (-)	237.29 (-)	12.16 (-)	12.16 (-)
	2	7	Both sexes	280.54 (17.61)	278.20 (23.99)	16.06 (1.71)	16.33 (2.98)
			Male	305.54 (19.62)	312.27 (38.21)	17.64 (1.42)	15.82 (2.64)
			Female	253.72 (16.43)	249.26 (21.10)	14.35 (1.85)	14.88 (3.67)
	3	2	Both sexes	297.37 (5.21)	297.37 (7.37)	17.90 (0.16)	17.90 (0.23)
			Male	314.52 (2.00)	314.52 (2.83)	19.29 (0.05)	19.29 (0.07)
			Female	280.42 (9.07)	280.42 (12.83)	16.51 (0.32)	16.51 (0.46)
	4	1	Both sexes	300.82 (-)	300.82 (-)	18.03 (-)	18.03 (-)
			Male	314.03 (-)	314.03 (-)	19.26 (-)	19.26 (-)
			Female	288.63 (-)	288.63 (-)	16.87 (-)	16.87 (-)
	5	0	-	-	-	-	-
	Subtotal	11	Both sexes	284.21 (17.03)	285.23 (33.82)	16.37 (1.79)	16.88 (3.65)
			Male	307.70 (15.82)	313.11 (23.87)	17.92 (1.50)	18.33 (3.13)
			Female	260.25 (20.37)	249.98 (44.86)	14.77 (1.98)	15.31 (4.36)
WPR	1	2	Both sexes	263.09 (11.10)	263.09 (15.69)	17.25 (0.22)	17.25 (0.32)
			Male	283.57 (10.55)	283.57 (14.93)	18.81 (0.19)	18.81 (0.27)
			Female	241.93 (10.88)	241.93 (15.39)	15.65 (0.21)	15.65 (0.30)
	2	8	Both sexes	271.19 (7.07)	272.55 (4.91)	17.22 (0.45)	17.37 (0.30)
			Male	288.87 (6.82)	289.65 (8.02)	18.64 (0.63)	18.86 (0.24)
			Female	253.63 (8.10)	253.59 (9.26)	15.78 (0.25)	15.88 (0.30)
	3	7	Both sexes	297.00 (14.47)	292.13 (23.33)	18.15 (0.64)	17.91 (0.71)
			Male	313.79 (10.96)	311.82 (11.82)	19.50 (0.57)	19.29 (0.31)
			Female	280.29 (18.62)	271.71 (35.85)	16.77 (0.80)	16.38 (1.43)
	4	2	Both sexes	307.31 (13.42)	307.31 (18.98)	18.43 (0.27)	18.43 (0.38)

		Male	323.58 (12.19)	323.58 (17.24)	19.68 (0.24)	19.68 (0.35)
		Female	287.95 (17.27)	287.95 (24.42)	16.90 (0.53)	16.90 (0.76)
5	6	Both sexes	333.67 (43.12)	311.65 (87.78)	19.23 (2.12)	18.11 (3.97)
		Male	369.36 (56.79)	342.38 (115.93)	21.51 (2.73)	20.21 (5.29)
		Female	296.65 (31.63)	279.83 (62.00)	16.82 (1.54)	16.00 (2.71)
Subtotal	25	Both sexes	295.65 (33.58)	291.05 (31.49)	18.06 (1.32)	17.73 (0.83)
		Male	317.52 (42.13)	307.34 (33.82)	19.67 (1.74)	19.16 (0.65)
		Female	273.23 (26.66)	271.45 (21.95)	16.39 (0.98)	16.01 (0.65)

aPR: age-adjusted prevalence rate; aIR: age-adjusted incidence rate; AFR: African region; AMR: American region; EMR: Eastern Mediterranean region; EUR: European region; IQR: inter-quartile range; SD: standard deviation; SDI: sociodemographic index; SEAR: Southeast Asian region; WPR: West Pacific region;

Appendix 5-C. Age-standardized prevalence and incidence rates of schizophrenia (per 100,000) by fortification status and SDI, stratified by sex

Fortification	SDI	Countries	Sex	aPR Mean (SD)	aPR Median (IQR)	aIR Mean (SD)	aIR Median (IQR)
None	1	10	Both sexes	220.41 (31.08)	209.89 (25.58)	14.45 (1.11)	14.13 (0.47)
			Male	231.20 (39.71)	216.70 (25.86)	15.51 (1.39)	15.05 (0.44)
			Female	209.57 (22.49)	203.17 (25.10)	13.40 (0.87)	13.16 (0.37)
	2	16	Both sexes	260.98 (28.55)	269.59 (33.66)	16.17 (1.60)	16.61 (3.17)
			Male	276.48 (33.43)	285.42 (40.67)	17.41 (1.80)	18.06 (3.36)
			Female	244.50 (23.18)	250.76 (28.17)	14.86 (1.38)	15.36 (2.65)
	3	19	Both sexes	264.29 (23.48)	275.63 (40.34)	15.80 (1.28)	16.19 (1.94)
			Male	275.18 (25.57)	284.87 (37.95)	16.74 (1.46)	17.01 (1.80)
			Female	253.77 (21.78)	263.68 (39.49)	14.87 (1.11)	15.28 (1.91)
	4	23	Both sexes	284.56 (17.63)	285.05 (20.56)	16.66 (1.10)	16.45 (0.97)
			Male	295.12 (19.75)	295.15 (20.31)	17.58 (1.27)	17.25 (0.82)
			Female	273.86 (15.93)	275.66 (9.58)	15.72 (0.93)	15.64 (0.96)
	5	8	Both sexes	294.63 (12.85)	295.54 (16.76)	16.93 (0.75)	16.78 (0.93)
			Male	306.83 (22.82)	302.50 (26.56)	17.92 (1.42)	17.41 (1.60)
			Female	281.67 (7.13)	281.42 (13.82)	15.90 (0.23)	15.89 (0.41)
	Subtotal	76	Both sexes	267.15 (31.51)	276.53 (37.29)	16.09 (1.42)	16.33 (2.41)
			Male	279.03 (34.71)	288.03 (37.30)	17.10 (1.61)	17.16 (2.46)
			Female	255.02 (29.07)	264.38 (36.88)	15.04 (1.27)	15.57 (2.17)
Mandatory	1	23	Both sexes	216.33 (16.48)	211.24 (8.34)	14.16 (0.71)	13.94 (0.20)
			Male	226.31 (22.45)	219.64 (8.94)	15.14 (0.87)	14.93 (0.28)
			Female	206.93 (11.67)	202.85 (5.78)	13.24 (0.61)	13.10 (0.19)
	2	21	Both sexes	243.22 (25.60)	248.20 (46.23)	15.05 (1.06)	14.77 (1.77)
			Male	252.11 (26.44)	257.79 (48.43)	15.93 (1.14)	15.64 (1.88)
			Female	234.81 (25.20)	237.51 (45.09)	14.20 (1.01)	13.87 (1.92)
	3	16	Both sexes	279.76 (20.41)	280.77 (10.74)	16.60 (1.23)	16.43 (0.96)
			Male	290.77 (22.61)	290.92 (17.22)	17.58 (1.45)	17.25 (1.26)

			Female	268.77(19.12)	270.56 (8.32)	15.62 (1.03)	15.56 (0.62)
	4	8	Both sexes	285.54 (25.01)	276.70 (45.97)	16.71 (1.45)	16.37 (2.86)
			Male	297.86 (29.38)	286.13 (56.95)	17.76 (1.80)	17.23 (3.68)
			Female	271.40 (23.00)	267.81 (42.56)	15.55 (1.26)	15.54 (2.51)
	5	4	Both sexes	374.89 (61.29)	388.63 (72.52)	20.87 (3.46)	21.94 (4.19)
			Male	408.08 (63.92)	439.05 (66.59)	22.97 (3.68)	24.64 (4.01)
			Female	342.31 (67.30)	337.19 (83.96)	18.70 (3.62)	18.77 (4.78)
	Subtotal	71	Both sexes	254.36 (46.63)	255.24 (64.49)	15.61 (2.06)	15.23 (2.37)
			Male	265.85 (52.01)	269.94 (66.06)	16.63 (2.34)	15.95 (2.32)
			Female	243.04 (42.28)	238.28 (63.02)	14.59 (1.82)	14.21 (2.39)
Voluntary	1	1	Both sexes	208.04 (-)	208.04 (-)	13.82 (-)	13.82 (-)
			Male	215.31 (-)	215.31 (-)	14.67 (-)	14.67 (-)
			Female	200.77 (-)	200.77 (-)	12.99 (-)	12.99 (-)
	2	5	Both sexes	257.93 (30.62)	276.19 (45.52)	14.87 (1.44)	14.34 (0.85)
			Male	278.85 (42.56)	295.29 (69.21)	16.27 (1.61)	15.98 (1.49)
			Female	237.78 (20.83)	241.97 (27.57)	13.52 (1.48)	13.08 (0.56)
	3	6	Both sexes	279.74 (27.34)	283.83 (53.49)	17.40 (1.66)	17.33 (3.68)
			Male	290.22 (27.46)	296.60 (58.37)	17.40 (1.52)	17.36 (3.68)
			Female	269.18 (27.76)	277.22 (49.96)	15.55 (1.56)	15.66 (2.89)
	4	10	Both sexes	285.52 (15.13)	288.56 (19.26)	16.60 (0.86)	16.53 (0.85)
			Male	295.33 (17.24)	297.79 (19.14)	17.47 (0.97)	17.41 (0.83)
			Female	275.21 (19.36)	279.16 (18.25)	15.69 (1.05)	15.72 (0.63)
	5	24	Both sexes	283.52 (28.06)	277.55 (19.99)	16.44 (1.67)	16.17 (1.06)
			Male	290.25 (31.21)	285.54 (22.83)	17.10 (1.89)	16.75 (1.25)
			Female	274.85 (28.74)	272.34 (16.57)	15.66 (1.70)	15.56 (1.27)
	Subtotal	47	Both sexes	279.15 (27.91)	278.35 (22.93)	16.26 (1.55)	16.17 (1.28)
			Male	288.55 (30.39)	291.00 (30.09)	17.08 (1.66)	16.86 (1.32)
			Female	268.72 (29.02)	270.20 (27.39)	15.37 (1.64)	15.56 (1.54)

aPR: age-adjusted prevalence rate; aIR: age-adjusted incidence rate; IQR: inter-quartile range; SD: standard deviation; SDI: sociodemographic index;

Appendix 5-D-1. Sensitivity analyses of main regression models (mandatory fortification and changes in age-adjusted prevalence and incidence rates of schizophrenia) without USA, China, and India, stratified by sex

		Fortification*† (β, 95% CI)			
		All countries	Without USA	Without China	Without India
ΔaPR					
	Both sexes	-0.94 (-3.16, 1.28)	-0.94 (-3.16, 1.28)	-0.94 (-3.16, 1.28)	-0.94 (-3.16, 1.28)
	Male	-0.63 (-2.81, 1.56)	-0.63 (-2.81, 1.56)	-0.63 (-2.81, 1.56)	-0.63 (-2.81, 1.56)
	Female	-0.84 (-2.98, 1.31)	-0.84 (-2.98, 1.31)	-0.84 (-2.98, 1.31)	-0.84 (-2.98, 1.31)
15-39 years	Both sexes	-13.14 (-22.60, -3.68)	-13.14 (-22.60, -3.68)	-12.64 (-22.02, -3.26)	-13.14 (-22.60, -3.68)
	Male	-13.37 (-23.95, -2.78)	-13.37 (-23.95, -2.78)	-12.76 (-23.25, -2.28)	-13.37 (-23.95, -2.78)
	Female	-12.03 (-20.49, -3.57)	-12.03 (-20.49, -3.57)	-11.60 (-20.05, -3.16)	-12.03 (-20.49, -3.57)
ΔaIR					
	Both sexes	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)
	Male	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)
	Female	-0.06 (-0.14, 0.03)	-0.06 (-0.14, 0.03)	-0.06 (-0.14, 0.03)	-0.06 (-0.14, 0.03)
15-39 years	Both sexes	-0.10 (-0.46, 0.26)	-0.10 (-0.46, 0.26)	-0.10 (-0.46, 0.26)	-0.10 (-0.46, 0.26)
	Male	-0.11 (-0.52, 0.29)	-0.11 (-0.52, 0.29)	-0.11 (-0.52, 0.29)	-0.11 (-0.52, 0.29)
	Female	-0.09 (-0.40, 0.22)	-0.09 (-0.39, 0.22)	-0.09 (-0.39, 0.22)	-0.09 (-0.39, 0.22)

Appendix 5-D-2. Sensitivity analyses of main regression models (duration of folic acid fortification policy and changes in age-adjusted prevalence and incidence rates of schizophrenia) without USA, China, and India, stratified by sex

		Fortification years**† (β, 95% CI)			
		All countries	Without USA	Without China	Without India
ΔaPR					
	Both sexes	-0.08 (-0.22, 0.07)	-0.08 (-0.22, 0.07)	-0.07 (-0.22, 0.07)	-0.08 (-0.22, 0.07)
	Male	-0.08 (-0.21, 0.06)	-0.08 (-0.32, 0.06)	-0.07 (-0.21, 0.06)	-0.07 (-0.21, 0.06)
	Female	-0.07 (-0.22, 0.07)	-0.07 (-0.22, 0.07)	-0.07 (-0.22, 0.08)	-0.07 (-0.22, 0.08)
15-39 years	Both sexes	-0.82 (-1.40, -0.23)	-0.82 (-1.40, -0.23)	-0.74 (-1.30, -0.18)	-0.84 (-1.43, -0.25)
	Male	-0.76 (-1.40, -0.12)	-0.76 (-1.40, -0.12)	-0.68 (-1.29, -0.07)	-0.78 (-1.43, -0.13)
	Female	-0.86 (-1.41, -0.31)	-0.86 (-1.41, -0.31)	-0.80 (-1.33, -0.27)	-0.87 (-1.43, -0.31)
ΔaIR					
	Both sexes	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)
	Male	-0.00 (-0.01, 0.01)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)
	Female	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)	-0.00 (-0.01, 0.00)
15-39 years	Both sexes	0.00 (-0.02, 0.03)	0.00 (-0.02, 0.03)	0.00 (-0.02, 0.03)	0.00 (-0.02, 0.03)
	Male	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)
	Female	0.00 (-0.02, 0.03)	0.00 (-0.02, 0.03)	0.00 (-0.02, 0.03)	0.00 (-0.02, 0.03)

Chapter 6: Integrated Discussion

6.1 Overview of Research Activities

This chapter aims to provide an integrated perspective on this dissertation: its overarching objectives; a series of studies conducted under these objectives; convergence of findings from the individual studies; collective contribution to the overarching objective and to the existing knowledge; strengths and limitations of the studies, and finally, overall implications for future research drawing from across all components of this dissertation.

The key objective of the dissertation was to investigate and identify a relationship between folate and vitamin B_{12} and schizophrenia. Integrating and triangulating evidence originating from various study designs was an important aspect of the proposed research considering the complex nature of the exposure of interest (status of micronutrient), outcome (schizophrenia spectrum), and potential mechanisms of action (etiology not fully understood). Four research projects were designed with this objective in mind, with each informing the subsequent project (Figure 6-1).

In chapter 2, we conducted a high-level synthesis of the existing evidence to understand the relationship between vitamin B_{12} and various health outcomes. This umbrella review showed that while evidence is fragmented and heterogeneous, vitamin B_{12} may have a role in some neurological disorders and cancers. We then narrowed the focus to schizophrenia and adapted the evidence synthesis accordingly (chapter 3). In this umbrella review, we identified significantly lower plasma/serum concentrations of folate, but not vitamin B_{12}, among individuals with schizophrenia compared to healthy controls. This association was consistent in the subgroup of studies conducted in Asia. We also found a significant, positive association of the *MTHFR* 677TT genotype with increased risk of schizophrenia compared to the 677CC genotype, consistent in direction across ethnicity subgroups. These findings suggested a potentially causal role of folate and vitamin B_{12} in schizophrenia as the *MTHFR* C677T genotypes critically determine the bio-availability of folate. Building on this understanding, we undertook the next synthesis (chapter 4), in which we meta-analyzed instrumental variable analysis that examined the

link between folate and schizophrenia using genetic variants as instrumental variables. Here, we identified small, but significant associations of the two common polymorphisms of *MTHFR* with schizophrenia: C677T and A1298C. Our analysis also suggested that the risk alleles of 677T and 1298C may have additive effects, considering larger magnitudes of risk estimates with the homozygous variants compared to the heterozygous variants.

Drawing not only upon our own findings, but also upon the ever-growing literature suggesting potential mechanisms and pathways that are yet to be explored further, we next conducted a global policy analysis aiming to assess the impact of folic acid fortification on schizophrenia at a population level. In chapter 5, we used linear regression models to assess if mandatory folic acid fortification policy was associated with any changes in the age-standardized prevalence or incidence rates of schizophrenia over 30 years (1990 through 2019) across 147 countries. In the overall population, mandatory folic acid fortification appeared to be inversely related to the schizophrenia rates, but in small magnitudes and non-statistically significant. However, in the 15-39 year age-group, which was separately examined as a period of first diagnosis and sensitivity to optimal folate intake, we found a larger impact of mandatory fortification, compared to none, on schizophrenia prevalence and incidence. The highest tertile of folic acid dose in fortification was reported to have the lowest incidence rate and the smallest increase in prevalence rate in this age group of typical onset.

Pulling together the individual components of this dissertation to answer the overarching research question, we identified a broad converging of evidence with regard to the relationship between folate and vitamin B_{12} and schizophrenia: folate status appears to be inversely related to the risk of developing schizophrenia (chapters 3, 4, 5). This relationship may potentially be causal with variations across ethnic groups (chapters 4). The potentially beneficial role of folate in schizophrenia remained consistent at the population level (chapter 5), particularly in reducing the prevalence and incidence among adolescents and young adults who often experience the first onset.

We did not find convincing evidence on the relationship between vitamin B_{12} and schizophrenia (chapters 2, 3) – the volume and the quality of the available evidence was severely limited. The evidence on vitamin B_{12} consisted entirely of retrospective studies utilizing smaller samples compared to the evidence on folate and using a single type of measurement (serum concentration). However, we note the established role of this vitamin in neurodevelopment and neuropathy from numerous intervention trials (chapter 2). Moreover, vitamin B_{12} status is closely intertwined with the bioavailability of folate: vitamin B_{12} deficiency may impair folate metabolism as 5-methyltetrahydrofolate (5-MTHF) becomes metabolically trapped and functionally unavailable in the absence of vitamin B_{12}[1]. Thus, we consider folate and vitamin B_{12} together in their relations to schizophrenia.

National or international policies with regard to folate and vitamin B_{12} intake were scarce. Most of the public health interventions documented are built around mandatory or voluntary fortification of foods with folic acid or recommendations of folic acid supplementation for women of reproductive age (chapter 5); and both of these policy approaches had been designed primarily to prevent NTD and other congenital anomalies. When examined globally, mandatory folic acid fortification (mainly wheat products) appeared to have positive impact, compared to no fortification, on lowering incidence rates of schizophrenia among the 15-39 years age group (chapter 5).

Further insight we obtained from across the research is that folate and vitamin B_{12} may be among the many factors that are involved in a complex web of pathways contributing to schizophrenia, including joint effects of the two vitamins or interactive effects of genetic variants, and potential epigenetic pathways (chapters 2, 3, 4). These findings are summarized in Table 6-1.

6.2 Discussion of the Research Findings

The subsequent sections in this chapter present some of the reflections on our findings in light of the broader literature; notably the overall insights we gained from the series of research activities and the key challenges that remain to be addressed in research

examining the health effects of folate and vitamin B_{12} or risk factors of neuropsychiatric disorders in general. The discussion will be presented as below:

1. How do folate and vitamin B_{12} relate to schizophrenia in the big picture?
2. What are the key knowledge gaps in the context of the association between folate and vitamin B_{12} and schizophrenia?
3. What are the methodological limitations in studying the effects of folate and vitamin B_{12}?
4. What are important considerations in studying schizophrenia?
5. Should our research findings be translated into public health policies at national or international levels, and if so, how?

6.2.1 Folate and vitamin B_{12} status and the risk of schizophrenia - the bigger picture

Several hypotheses provide biological frameworks that explain the link between folate and vitamin B_{12} and schizophrenia; more specifically, they involve the neurotoxicity of elevated homocysteine, neuroinflammation, impairment of synthesis of neurochemicals, and epigenetic modifications (chapters 1 through 4). Some have also reported interactions between multiple genetic variants and their compounded effect on the risk of schizophrenia (chapter 4). We believe these frameworks are mutually complementary and jointly paint a comprehensive picture of the association between folate, vitamin B_{12} and schizophrenia.

These mechanisms will not be discussed here in detail to avoid redundancy. Briefly, folate and vitamin B_{12} deficiency may result from a combination of factors, such as poor intake of dietary sources of these vitamins, older age, use of medications that affect folate homeostasis, and having one or more of the *MTHFR* C677T variants. Growing food insecurity in many global regions due to armed conflicts and climate change, increasing popularity of veganism, and unbalanced dietary habits contribute to the poor intake of these vitamins. Older age is a known risk factor for malabsorption of vitamin B_{12}[2,3]. Also known to interfere with folate metabolism are disease modifying antirheumatic drugs[4], antimicrobials[5], antiepileptic medications[6,7], oral contraceptives[8], proton pump inhibitors, metformin, and histamine 2 receptor antagonists[9-11]. Research further shows that the

MTHFR C677T variant result in lower blood concentration of folate and 30-60% reductions in the methylenetetrahydrofolate enzyme activity, converting 5,10-methylenetetrahydrofolate into a bioactive 5-methyltetrahydrofolate[12-14].

Low folate and vitamin B_{12} status results in elevated homocysteine, which induces vascular impairment[15] and damages neurons[16,17] and is associated with an increased risk of schizophrenia[18,19]. Folate metabolism is also involved in the synthesis of BH4, a cofactor in the production of neurotransmitters such as dopamine, norepinephrine, epinephrine, and serotonin[20], as dihydrofolate reductase (DHFR), dependent on 5-methyltetrahydrofolate (5-MTHF), converts 7,8-dihydrobiopterin (BH2) into BH4[21]. BH4 deficiency has been associated with increased risk of schizophrenia[22,23]. As evidence evolves beyond the dopamine hypothesis in examining the etiology of schizophrenia[24], BH4 deficiency may be one of the potential mechanisms for central nervous system disorders including schizophrenia[23,25,26]. In addition, folate and vitamin B_{12} status is associated with biomarkers of immune function, such as total immunoglobulin E[27,28], survival of regulatory T cells[29,30], proliferation of CD8+ T cells[31], and maturation of dendritic cells[32]. Deficiency in these vitamins also compromises cytokine functions[33,34], which may result in neuroinflammation and consequently in schizophrenia[35,36].

Epigenetic modifications, although not investigated in the dissertation, is another important link between folate and vitamin B_{12} and schizophrenia as these vitamins play an integral role in providing methyl donors and facilitating the transmethylation pathway[37]. Research on the correlation between methyl-donor micronutrients and epigenetic marks has been growing steadily since the early 2000s[38-40]. Both folate and vitamin B_{12} are reported to impact key modes of epigenetic modification: DNA methylation, histone modification, and non-coding RNA expression[39]. However, these effects seem to vary in direction and magnitude depending on the samples taken (i.e., leukocyte, saliva, adipose tissue), type of epigenetic modification (i.e., global DNA methylation, single target candidate gene), type of folate measure (i.e., supplementation, dietary intake) and study population (i.e., age, sex, comorbidities). Recent systematic

reviews on the effects of folate and vitamin B_{12} on DNA methylations[38,40] reported highly heterogeneous evidence and inconclusive results.

It should also be noted that epigenetics research is still evolving on the markers of schizophrenia and schizophrenia symptoms[37,41,42]. More work is needed to validate and synthesize the fragmented findings on multiple candidate genes explored across different samples[41,43]. As briefly discussed in chapter 1, current evidence is very limited in linking folate and vitamin B_{12} status directly with epigenetic marks of schizophrenia.

Likewise, thinking beyond the scope of this dissertation, we may consider potential roles of other environmental risk factors, particularly the risks with established associations from epidemiological studies, i.e., childhood adversity, urbanicity, and substance use[44]. Investigation into multiple environmental risk factors in a comparative manner is scarce and our knowledge to date is still limited in understanding relative importance of one environmental risk over another. Nevertheless, we note that folate and vitamin B_{12} status is one of the earliest environmental exposures related to neuropsychiatric outcomes and directly involved in neurodevelopment and syntheses of neurochemicals. More well-designed epidemiological investigations on the interactions between folate/ vitamin B_{12} status and other environmental factors will advance our understanding of schizophrenia.

6.2.2 Key knowledge gaps on the association between folate, vitamin B_{12} and schizophrenia

We identified several areas where evidence is still developing and more insight is yet to become available. First, inter-dependent effects of folate and vitamin B_{12} status on development of susceptibility to schizophrenia need to be understood better. Because of their roles in one-carbon metabolism as discussed earlier, these two vitamins are hypothesized to have joint effects or moderating effects on many health outcomes. The homocysteine-lowering effect of folic acid and vitamin B_{12} in a combination regimen is well established[45-47]. Folate and vitamin B_{12} each have a regulatory role in the homocysteine metabolism and the strength of their inverse relationship with homocysteine concentration varies depending on the serum concentration of each

vitamin[48]. A combined use of folic acid and cyanocobalamin (≤ 0.05 mg/d) was associated with a 25% reduced risk of stroke in a meta-analysis involving 28,450 participants[49]. In another trial, supplementing folic acid (400 μg/d) combined with vitamin B_{12} (100 μg/d) was associated with higher overall cognitive function among 900 older adults compared to placebo[50]. Examining all micronutrients involved in the one-carbon metabolism, thus additionally including vitamin B_2, vitamin B_6, and choline, may also provide further insights. Compared to administering folic acid (2 mg/d) and vitamin B_{12} (400 μg/d) only, which did not have an impact on schizophrenia symptoms[51], providing vitamin B_6 (25 mg/d) in addition was reported to mitigate the symptoms[52]. However, the current evidence on the joint effects of folate and vitamin B_{12} in relation to the schizophrenia risk is limited in quantity and quality.

In the same vein, there remains more to be understood on the effects of combined genotypes or haplotypes of *MTHFR* C677T and A1298C polymorphisms on the risk of schizophrenia. Several studies reported that certain compound genotypes (i.e., 677CT/1298AA, 677TT/1298AA) were significantly associated with higher risk of schizophrenia compared to 677CC/1298AA[53-55], however, these findings are at variance with other reports[56,57]. Some investigators also speculate that the effect of *MTHFR* polymorphisms on health outcomes are modified by geographical regions or average folate status of the population[58,59]. Larger studies are needed to validate these findings and hypotheses.

Second, interactions among different genotypes that share metabolic pathways and affect methylations linked to schizophrenia need to be studied more. *MTHFR* and *COMT* genes are known to interact by way of the former gene influencing the expression of the latter gene's promoter region[60], which is associated with production of monoamine neurotransmitters and with schizophrenia symptoms[61,62]. Having risk alleles from both genes was associated with an increased risk of schizophrenia compared to having either genotype alone in a Dutch study[63], but not in a Korean study[64]. Another study reported that the risk alleles of these two genes may interact to impact executive functions in individuals with schizophrenia[62].

Third, another substantial knowledge gap comes from the limited evidence on the effect of folate and vitamin B_{12} on the treatment of schizophrenia. Compared to the growing research on the role of these vitamins in susceptibility, the evidence on the use of folic acid with or without vitamin B_{12} as an adjunctive therapy for schizophrenia is rather fragmented. We identified only three small-scale randomized controlled trials[65-67] that examined the effects of folic acid alone, one study[51] that examined the effects of folic acid with vitamin B_{12}, and one study[52] that provided a combination of folic acid, vitamin B_{12} and vitamin B_6. Moreover, these studies varied in terms of the folic acid dosage used (2-500 mg/d), duration of supplementation (12-26 weeks), composition of sex of participants (male 45.5-95.2%), and concomitant antipsychotics used. More and larger trials are needed to more precisely understand the effects of folate and vitamin B_{12} in different settings and guide clinicians in the care of individuals with schizophrenia.

6.2.3 Methodological limitations in studying the effects of folate and vitamin B_{12}

The investigation of folate and vitamin B_{12} in the context of health outcomes is inherently complex, because the status of these vitamins is not a fixed variable: folate and vitamin B_{12} status varies in time and it is also dependent on a large number of factors as considered in 6.2.1. In addition to poor dietary intake, deficient status may be a consequence of life-stage factors (e.g., increased requirement during pregnancy, loss of intrinsic factor in older age), life-style factors (e.g., alcohol use, substance use), or health-related factors (e.g., use of antifolate drugs)[68]. Therefore, when investigating the health effects of folate and vitamin B_{12}, it is important to consider and ideally stratify by these factors.

Another consideration is that folate and vitamin B_{12} deficiency may not fully reflect the critical time period contributing to disease susceptibility. For example, in cross-sectional studies where only a single measurement was taken from the participants or in retrospective cohort or case-control studies where a look-back time window reaches far beyond what the folate and vitamin B_{12} biomarkers inform (e.g., previous 3-4 months for erythrocyte folate concentration), it will be difficult to understand the nature of

relationship between the vitamins and the disease. Utilizing multiple measurements to understand the average level during a time period of interest or to examine a trajectory of folate and vitamin B_{12} concentration prior to diagnosis may provide additional insight.

In prospective studies, the vitamin status at baseline should be an important consideration. Some studies report that beneficial effects of vitamin supplement or increased intake are achieved individuals with low or deficient status[69-71], as optimizing the vitamin concentration can restore or even reverse the physiological harm caused by the deficiency. Related to the concern of better accounting for the baseline status, information on folic acid fortification can also be useful, although a very crude measure for baseline. Individuals in countries where mandatory folic acid fortification of key grain products has been implemented for decades may have different baseline status of folate compared to those in countries where no policy action has been taken. Across the research activities in the dissertation, we did not come across many studies, whether primary investigations or reviews, that described the baseline or fortification status or conducted a sensitivity analysis.

Lastly and particularly for vitamin B_{12}, different biomarkers have been used in clinical and research settings to determine vitamin status, i.e., serum/ plasma total vitamin B_{12}, holotranscobalamin (holoTC), and methylmalonic acid (MMA)[72,73], thereby presenting a challenge for synthesizing findings. Variations in the cutoff values to categorize vitamin intake levels also add to the challenges in evidence synthesis.

6.2.4 Important considerations in studying schizophrenia

One of the defining features of schizophrenia is its clinical heterogeneity[74]: a large variation among the affected individuals in symptom manifestations, disease trajectory, and response to treatment. Over the past years, epidemiological studies have described heterogeneity in cognitive functions[75], treatment responses[76,77], and genetic factors[78]. Multiple endeavors have been made to identify subtypes or phenotypes of schizophrenia to reduce the heterogeneity[79,80]; however, no consensus has been reached[81].

Earlier, we briefly introduced the concept of schizophrenia on a psychosis spectrum (chapter 1). Given the substantial overlap in psychotic symptoms among several neuropsychiatric disorders and the fluctuating symptoms within individuals, the argument for a psychosis spectrum disorder has value. Some further use the notion of psychosis continuum, citing approximately 5% median prevalence of transient, subclinical, psychosis-like experiences in the general population[82]. One of the criticisms of the conventional diagnostic framework – that is, diagnosing schizophrenia based on clinical observations and self-reported symptoms and having a set of strict criteria for the diagnosis of schizophrenia – is that it results in a biased selection of individuals with most severe psychosis and with the poorest outcomes[83].

In the context of research, on the one hand having a narrow definition of the disorder reduces heterogeneity but on the other hand, the restricted operationalization may also mean less relevance to a larger number of individuals experiencing similar symptoms on a spectrum. Whether to adopt a broad, multidimensional versus a clinical, pragmatic approach to schizophrenia will depend on the research question at hand. Examining endophenotypes or using the RDoC approach (chapter 1) may provide an alternative way of studying schizophrenia in a broader context with other neuropsychiatric disorders – by enabling the examination of manifested symptoms and underlying neurobiological mechanisms simultaneously. Evidence on the relationship between folate, vitamin B_{12} and schizophrenia based on endophenotypes is still scarce but has been growing rapidly[84]. In our research, clinical heterogeneity may have contributed to small effect sizes or imprecise effect estimation.

Turning to the socioeconomic and cultural factors related to schizophrenia, we observed a proportional correlation between SDI and schizophrenia prevalence and incidence rates globally and within each geographical region (chapter 5). We cannot rule out the possibility of under-diagnosis or under-detection of schizophrenia in low-income countries, attributable to higher stigmatization, limited access to mental health services for individuals, limited availability of resources for healthcare professionals, and other pressing health issues facing the society.

We understand from the growing epidemiological and epigenetic evidence that childhood adversity[85-91], migration[92-94], and substance use[95-98] are associated with the increased risk of schizophrenia; however, exposures to these risk factors at the individual level could not be captured in our ecological analysis (chapter 5) or evidence syntheses (chapters 3, 4). We found that sociodemographic factors were rarely reported or discussed in the primary studies or reviews included in our syntheses. A wider use of established frameworks such as PROGRESS-Plus[99] may benefit researchers and readers alike to gain most insight from the research findings and potentially highlight most vulnerable subgroups for targeted intervention.

Meanwhile, some studies propose potentially protective factors that exist in lower-income countries, such as stronger social capital[100], resilience[101], and lower sense of deprivation[102] due to less income inequality. Much remains to be known regarding the interplay or counterbalance between factors at individual and societal levels, which may vary at different life stages and depend on robust, validated tools of measurement.

6.2.5 Translation of the research findings into public health policies at national and international levels

Translating epidemiological research findings into public health policy is an important endeavor[103]: public health interventions should be informed by the best available scientific evidence and scientific knowledge should not be destined to the shelves of an archive. Fortunately, in the realm of folate and vitamin B_{12}, we have seen a faster growth in the body of evidence in the past two decades compared to that of other micronutrients[104]. Moreover, motivated by the landmark research on the role of folic acid in the prevention of first[105] and second[106] occurrence of NTD, folic acid fortification has been widely introduced globally since 1996 in order to optimize folate status in the general population.

Mandatory folic acid fortification has been described as the most effective policy vehicle to reach the population[107,108] compared to voluntary fortification or public education for

individual supplementation. Mandatory fortification is a structural upstream intervention[109], much like the strategies employed to address the socioeconomic barriers to optimal health described in Frieden's five-tier health impact pyramid[110].

While various health benefits of mandatory folic acid fortification have been described[107,108,111-113], concerns exist around potentially excessive intake of folate in fortified countries[114-116]. These concerns largely center around potential harms arising from high folate intake, particularly among individuals with poor vitamin B_{12} status or with *MTHFR* 677TT genotype. At present, epidemiological evidence surrounding these concerns is equivocal[116,117]. Continuous monitoring of health effects of folic acid fortification, taking into consideration the changing trends in dietary habits, lifestyle, and chronic diseases, will be important in ensuring benefits for the population.

Here, we present wider policy challenges in optimizing folate and vitamin B_{12} intake at a population level and some practical strategies to address them. First, surveillance of policy compliance appears to be lacking in many jurisdictions where mandatory folic acid fortification has been implemented (chapter 5). For policy interventions to achieve their intended goals, it is important to ensure that the policies as executed as designed (i.e., dose, method, coverage, distribution)[103]. For example, relevant food authorities can conduct routine inspections of grain manufacturers' or importers' facilities and/or perform a sampling test of commercially available grain products to ensure compliance.

Second, evaluation of the impact of folic acid fortification should be performed in a systematic manner. Organizing health surveys and documenting changes in blood concentrations of folate will help identify geographic areas or subgroups that may still lack access to the fortified products or that are not benefiting from the policy intervention. Results of these monitoring endeavors can in turn inform the relevant authorities to amend or expand the existing policies to ensure more substantial benefits across the population.

Third, many countries have yet to implement mandatory fortification for various reasons. Concerns of potential harms of excessive folate intake have been key barriers against mandatory folic acid fortification in Europe[108], while lack of urgency, lack of planning, or associated costs may serve as barriers in others. In these countries, individuals are responsible for accessing voluntarily fortified products or supplements – which is reported to be ineffective in achieving optimal folate status[118-120]. While the necessary steps for mandatory fortification are taken, targeted approaches may be considered, specifically women in the reproductive age, children, and older adults who are known to have higher requirements for these vitamins or who are at a higher risk of deficiency[68] – such as offering routine serum folate and vitamin B_{12} screening in primary care settings or engaging physicians or pharmacists in counselling of patients who are prescribed medications that interfere with folate homeostasis.

Fourth, folic acid fortified foods could be provided to countries experiencing food insecurity due to conflicts, poverty, or climate change as humanitarian aid. Food insecurity and undernourishment is an ongoing threat to public health in many parts of the world. As of 2016, over 800 million people in the world are chronically undernourished[121]. Food insecurity is invariably linked to child development[122,123], poor overall health[124], and poor mental health outcomes[125]. Supplementing folic acid in the form of fortified food aid would be beneficial for broad health outcomes, particularly to the vulnerable populations in these affected regions.

Fifth, a structured process of evidence-based policymaking should be considered. Routine roundtable discussions involving policymakers and scientists, where latest epidemiological, clinical, preclinical, and epigenetic evidence is examined in an integrated manner, will not only inform the policy decisions but also build public trust. Further, understanding interactive effects of micronutrients in different subgroups with varying requirements and susceptibilities will be critical, as we collectively learned from the β-carotene research in cancer[126] and colorectal adenoma[127,128].

6.3 Overarching Limitations of Dissertation

We note several limitations that apply broadly to all or most of the research components in the dissertation. First, the available evidence was very limited. While studies on vitamin B_{12} were more scarce compared to those on folate, the overall volume of evidence on these two vitamins in relation to schizophrenia was low. Many of the studies we examined were also small in scale and retrospective in their inquiry.

Second, most of the evidence came from high-income countries. Studies we retrieved for syntheses were conducted predominantly in high-income countries and this skewness was most pronounced in our meta-analysis of genetic association studies (chapter 4). Likewise, the data collected from less developed countries for our ecological analysis (chapter 5) had larger variances, which we addressed using weights. Although we made efforts to stratify by ethnicity or geography (chapters 3, 4), we acknowledge that lower income countries were less represented in the data examined in the dissertation and thus our findings may not be generalizable to all countries.

Third, the study populations were poorly described in most of the evidence we examined. Information on common confounders in epidemiological studies, such as socioeconomic status, comorbidities, and use of medications, were often unavailable and authors of evidence syntheses did not report on any adjustment. Additional covariates that may also potentially confound the relationship between folate and vitamin B_{12} and schizophrenia, such as use of antipsychotics and duration of illness, were not available for most studies. Combined with the high level of clinical heterogeneity in schizophrenia, as described in 6.2.4, unavailability of important clinical and sociodemographic information did not allow for stratified analyses and may have masked effects that exist in subgroups.

6.4 Next Steps in the Research on Folate, Vitamin B_{12} and Schizophrenia

One of the knowledge gaps repeatedly discussed throughout the dissertation is epigenetic mechanisms linking folate and vitamin B_{12} and schizophrenia. More evidence is becoming available with the advance of technologies and tools for research in genomics, proteomics, metabolomics, and transcriptomics (collectively "*omics*"). An integrative

multi-omics approach[128,129] has also been introduced to provide further triangulated evidence to various research questions in a holistic manner. In the context of folate and vitamin B_{12}, the omics research will enable a granular understanding of the biological processes involving these vitamins, potentially identifying risk factors for individuals with different susceptibilities.

An exploratory scan of the literature informed us that evidence on a direct epigenetic link was scarce; however, we also identified a large volume of research on epigenetic marks of other known environmental risk factors of schizophrenia. We thus set out to conduct a scoping review to broadly synthesize all evidence on epigenetic modifications associated with six selected risk factors of schizophrenia: childhood adversity, migration, urbanicity, maternal infection, and folate and vitamin B_{12} exposure. Given the volume and complexity of the work, we are undertaking this project outside the scope of this dissertation (chapter 1). Here, we briefly discuss the progress and preliminary observations thus far.

We systematically searched the literature (MEDLINE, EMBASE, and PsycINFO) on December 9, 2023 using separate search strategies for the six topics listed above. We included all types of epigenetic marks and did not use restrictions on years of publication or language. Reviews, commentaries, animal or in-vitro studies, or studies using postmortem samples were excluded. We retrieved 24,456 articles from the databases and additional 108 articles from citations search. After de-duplication and two stages of screening, we identified a total of 477 articles across the six topics (Figure 6-2). Epigenetic investigations of schizophrenia accounted for 34.4% (n=164) of the final pool of evidence, followed by childhood adversity (33.1%, n=154), folate and vitamin B_{12} status (27.5%, n=131). Studies on migration, urbanicity, and maternal infection were small in number (n=4, n=10, n=8, respectively).

We observed substantial heterogeneity in the process of screening and identification of the evidence. For example, more recent studies tended to report on global DNA methylation in contrast to single target genes; analytical samples varied (peripheral blood,

saliva, buccal mucosa, umbilical cord blood, etc.); and different testing devices/methods were used across the studies. Definition of exposure was not uniform: studies on urbanicity examined exposures to different types of particulate matters; studies on maternal infection investigated different virus or bacteria; and migration status was defined variably.

As we start to synthesize the evidence, we expect to gain more understanding of the current research landscape and common patterns of epigenetic modifications or susceptible genes involved in the development of schizophrenia. Heterogeneity in the evidence will benefit us in broadening the scope of our inquiry into the role of folate and vitamin B_{12} in the epigenetic mechanisms surrounding schizophrenia.

6.5 Overall Conclusion

We set out to investigate the relationship between folate and vitamin B_{12} status and schizophrenia risk and treatment outcomes. We designed a comprehensive evidence synthesis approach, in which studies examining different exposure measures, such as dietary intake, biomarker measurement, and supplementation, can be integrated to triangulate the findings. Across four research studies, we examined (1) the overall health effects of vitamin B_{12}, which has been less studied and hypothesized to be associated with neurological outcomes; (2) the association between folate, vitamin B_{12} and schizophrenia in an umbrella review; (3) the causal link between folate, vitamin B_{12} and schizophrenia; and (4) the impact of folic acid fortification on schizophrenia at a population level in 194 countries.

The current evidence on the relationship between folate, vitamin B_{12} and schizophrenia broadly converged across the research studies: (1) we found suggestive level of evidence on the association of vitamin B_{12} status with neurological outcomes; (2) inadequate folate status was associated with higher risk of schizophrenia in the general population; (3) folate status may be causally linked to schizophrenia; and (4) mandatory folic acid fortification policy was associated with reduction in incidence rates of schizophrenia among individuals aged 15-39 years. The significant finding in the 15-39 year age-group,

which marks typical age of onset of schizophrenia, suggests that optimizing folate intake through mandatory measures may be beneficial at a population level.

Overall, the volume of available evidence was not sufficient to examine subgroups in detail. The field of micronutrients and their impact on mental health is still evolving and further insights will be gained as more studies expand to under-studied populations and address potential confounding factors. The importance of optimal folate and vitamin B_{12} status should also be considered in the context of public health policy, prioritizing at-risk populations without structural interventions in place.

6.6 References

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6.7 Figures and Tables

Research component				Outcome	Exposure	Evidence base	Finding
1	2	3	4				
■	■			Schizophrenia risk	Vitamin B_{12} (dietary intake)	No	
■	■				Vitamin B_{12} (biomarker)	Yes	Lower status – higher risk
■	■				Vitamin B_{12} (supplementation)	No	
	■				Folate (dietary intake)	No	
	■				Folate (biomarker)	Yes	Lower status – higher risk
	■	■			Folate (*MTHFR* C677T, A1298C)	Yes	677TT, 1298CC – higher risk
	■				Folic acid (supplementation)	Yes	Lowers risk
			■		Folic acid (fortification)	Yes	Lowers risk among 15-39 years
■	■			Schizophrenia symptoms	Vitamin B_{12} (dietary intake)	No	
■	■				Vitamin B_{12} (supplementation)	No	
	■				Folate (dietary intake)	No	
	■				Folic acid (supplementation)	Limited	Potential benefit for overall and negative symptoms

Figure 6-1. Visual summary of the evidence synthesized across the research components of the dissertation

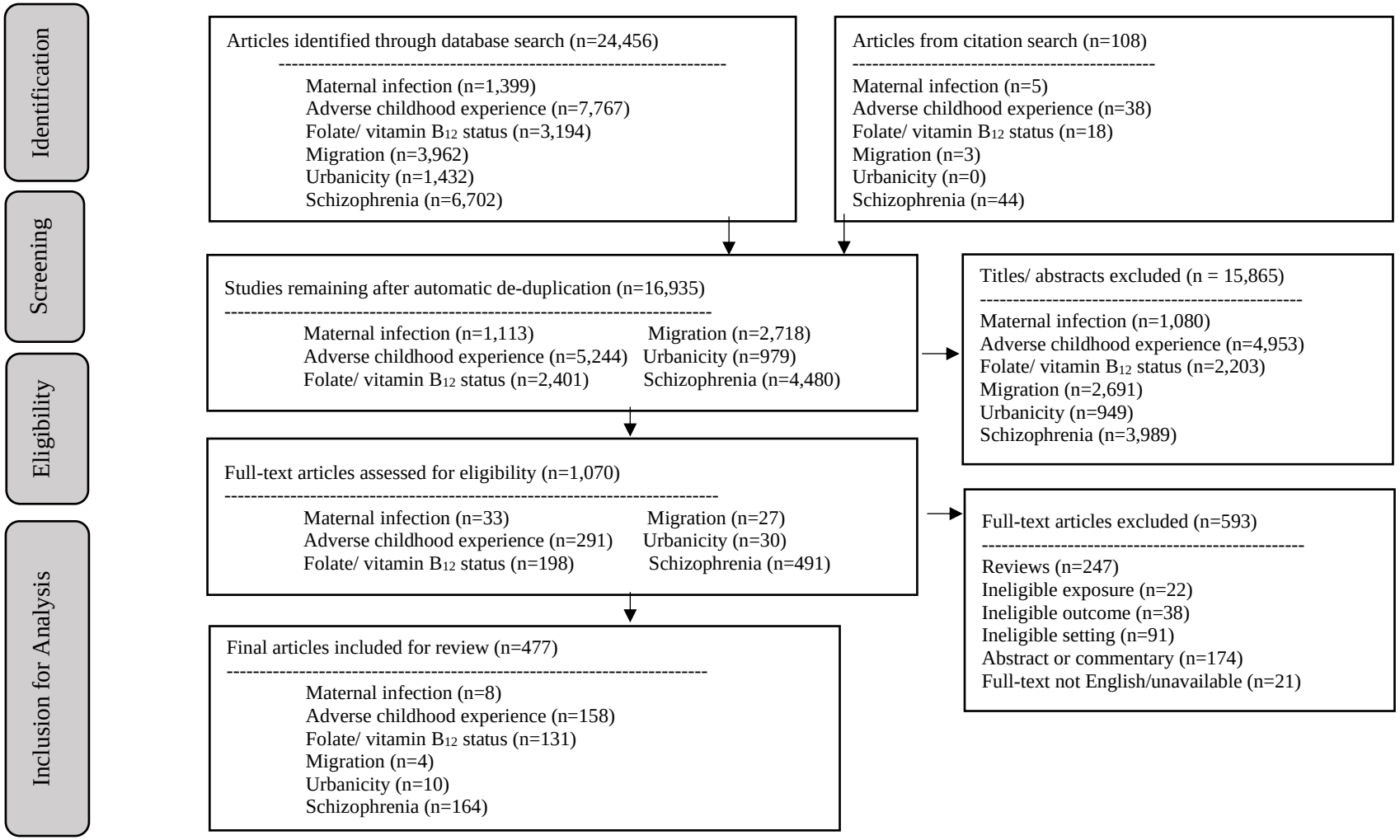

Figure 6-2. PRISMA diagram describing screening and selection of articles examining epigenetic marks of schizophrenia

Table 6-1. Summary of the findings from across the research components of the dissertation

	Research Activity				
	Chapter 2	**Chapter 3**	**Chapter 4**	**Chapter 5**	**Convergence of evidence and implications for future work**
Research question	What are the health effects of vitamin B_{12}?	What are associations of folate and vitamin B_{12} status with schizophrenia onset and schizophrea symptoms?	Is there a causal link between folate, vitamin B_{12} and schizophrenia?	Global evaluation of the impact of food fortification with folic acid on rates of schizophrenia	
Findings	Identified four associations with a suggestive level of credibility: associations total intake - colorectal cancer; dietary intake - esophageal cancer; dietary intake - depression; and serum concentration - peripheral neuropathy.	Plasma/serum concentration of folate, but not vitamin B_{12}, was significantly lower among individuals diagnosed with schizophrenia compared to healthy controls. This finding was consistent only in the subgroup of Asians.	Folate status was inversely associated with the risk of schizophrenia in the overall and the East Asian subgroup.	In the overall population, the association between folic acid fortification policy and schizophrenia rates appeared to be inversely related, but in small magnitudes and non-statistically significant. There was a larger magnitude of impact of mandatory fortification on schizophrenia prevalence and incidence rates, both in males and females.	Folate status may be inversely related to the risk of schizophrenia in the overall population and in the East Asian subgroup.

	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Convergence of evidence and implications for future work
		Identified a significant, positive pooled association of the *MTHFR* 677TT genotype with increased risk of schizophrenia compared to the 677CC genotype. This finding was consistent in direction across the ethnicity subgroups, although the results did not reach statistical significance threshold in all subgroups.	There may be a load-dependent relationship between the risk allele and schizophrenia risk.	Geographically, schizophrenia rates were lowest in Africa and the East Mediterranean regions, followed by Europe and Southeast Asia, and highest in the American and the Western Pacific regions. Males were reported to have higher incidence and prevalence rates of schizophrenia compared to females across all geographic regions, SDI groups and fortification strata.	
		The variant *MTHFR* 1298CC genotype showed a smaller but significant overall effect on the schizophrenia risk; however, the effect diminished in the ethnicity subgroups.			The inverse relationship of folate and schizophrenia risk may be causal.

	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Convergence of evidence and implications for future work
		The effect of folic acid supplementation with or without vitamin B_{12} on management of schizophrenia symptoms was weak and statistically not significant; however, the evidence was underpowered to detect meaningful effect.		In the overall population, the folic acid dose used in the mandatory fortification policies did not appear to influence the distribution of schizophrenia. Among individuals aged 15-39 years, the highest dose tertile was reported to have the lowest incidence rate and the smallest increase in prevalence rate.	More research is needed to examine the effect of folate on management of symptoms among individuals diagnosed with schizophrenia.
				In all regions, across all fortification status, schizophrenia rates were positively correlated with the countries' SDI. Differences in schizophrenia rates were greater between SDI strata compared to between fortification strata.	

	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Convergence of evidence and implications for future work
	Methodological quality of the syntheses retrieved was low and we did not find convincing level of evidence on any measure of vitamin B_{12} for any health outcome at the population level.	Overall, the articles included were rated to be weak to moderate quality. Risk of bias assessment was not conducted in over half of the evidence syntheses identified.	Most of the included studies were rated as of high quality; however, variations were observed in terms of representativeness of the cases, definition of controls, and comparability of cases and controls.		More robustly designed studies are needed to gain insights on the relationship between folate, B_{12} and schizophrenia.
	None of the included syntheses reported adjustment for or stratification by known confounders of vitamin B_{12} status – health, such as the baseline status, older age, use of certain medications.	The included studies did not report on potential confounders such as age, sex, socioeconomic level, underlying comorbidities, and use of medications known to interfere with folate metabolism. Baseline folate, vitamin B_{12} concentrations, duration/ severity of illness, and presence of folic acid fortification policies were not reported in the included syntheses.	Folate metabolism may vary across the lifespan, susceptible to factors such as comorbidities, use of antipsychotics and other medications that affect folate homeostasis, socioeconomic status, as well as age.		More well-designed studies are needed accounting for potential confounding effects.

	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Convergence of evidence and implications for future work
	There is heterogeneity in the types of biomarkers used in clinical and research settings, each with its strengths and limitations.	There was limited number of studies for each exposure-outcome category and mostly small sample sizes. Studies in the African populations are scarce.		Substantial heterogeneity exists in folic acid fortification policies and in schizophrenia treatment environment. Lack of data on fidelity of the implementation of fortification policies.	Lack of data and a high level of heterogeneity present a challenge to integrating the existing evidence.

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