

Vitamin B

Introduction

Vitamin B12, B6 and folate play important roles in the development, maintenance and function of the brain. Vitamin B is important for critical cellular processes such as the synthesis of nucleic acids for DNA, and the metabolism of amino acids and other vitamins. However, any relationship between vitamin B levels and risk of psychiatric disorders remains unclear.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ([PRISMA](#)) checklist which describes a preferred way to present a meta-analysis¹. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that

some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation ([GRADE](#)) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)². The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three systematic reviews that met our inclusion criteria³⁻⁵.

- Moderate quality evidence suggests decreased blood folate levels in people with schizophrenia, particularly Caucasian and Asian people, and people aged under 50 years. High quality evidence finds no differences in vitamin B12 levels.
- Moderate quality evidence also finds a medium-sized effect of lower folate and high quality evidence finds no differences in B12 in people with first-episode psychosis.

Cao B, Wang DF, Xu MY, Liu YQ, Yan LL, Wang JY, Lu QB

Vitamin B12 and the risk of schizophrenia: A meta-analysis

Schizophrenia Research 2016; 172: 216-7

[View review abstract online](#)

Comparison	Vitamin B12 levels in people with schizophrenia compared to controls.
Summary of evidence	High quality evidence (large sample, consistent, precise, direct) suggests no differences in vitamin B12 levels in people with schizophrenia compared to controls.
B12 levels	
<p><i>No significant differences between patients and controls;</i> 13 studies, N = 2,113, $d = 0.09$, 95%CI -0.03 to 0.22, $p = 0.067$, $I^2 = 40\%$ Moderator analyses indicated that results varied significantly across geographic areas (Asia, Europe, America, Africa; pooled subgroup results are not reported). There were no effects of patient age, source (serum/plasma), or method of assessment on the effect size. Authors report no evidence of publication bias.</p>	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Firth J, Carney R, Stubbs B, Teasdale S, Vancampfort D, Ward P, Berk M, Sarris J

Nutritional Deficiencies and Clinical Correlates in First-Episode Psychosis: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2018; 44: 1275-92

[View review abstract online](#)

Comparison	Nutritional deficits in people with first-episode psychosis vs. controls
Summary of evidence	Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests people with first-episode psychosis have a medium-sized effect of lower levels of folate than controls. High quality evidence (large sample, consistent, precise, direct) finds no differences in B12.
<p><i>A significant, medium-sized effect of lower blood levels of folate;</i> 6 studies, N = 827, $g = -0.624$, 95%CI -1.176 to -0.072, $p = 0.027$, $I^2 = 92\%$ Lower levels of folate were related to increased psychiatric symptoms.</p> <p><i>No differences were found in B12;</i> 4 studies, N = 620, $g = -0.059$, 95% CI -0.22 to 0.10, $p = 0.468$, $I^2 = 0\%$ There was no evidence of publication bias.</p>	
Consistency in results	Inconsistent for folate, consistent for B12.
Precision in results	Imprecise for folate, precise for B12.
Directness of results	Direct

Wang D, Zhai JX, Liu DW

Serum folate levels in schizophrenia: A meta-analysis

Psychiatry Research 2016; 235: 83-89

[View review abstract online](#)

Comparison	Serum folate levels in people with schizophrenia compared to controls.
Summary of evidence	Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests decreased folate levels in people with schizophrenia, particularly Caucasian and Asian people, and people aged under 50 years.
Folate levels	

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<p><i>Significant effect of decreased serum folate in people with schizophrenia;</i> 26 studies, N = 3,703, WMD = -1.57, 95%CI -2.11 to -1.02, $p < 0.00001$, $I^2 = 90%$, $p < 0.00001$ Subgroup analyses found that the effect was significant in Caucasian and Asian samples, but not in African, Latino, or mixed population samples. The effect was significant in samples with age < 50 years but not > 50 years. There were no moderating effects of publication language, duration of illness, medication status, or sex.</p>	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, d = Cohens' d and g = Hedge's g = standardised mean difference, I^2 = level of heterogeneity across study results, N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus, WMD = weighted mean difference

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect⁶.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. InOR stands for logarithmic OR where an InOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An r^2 of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered

imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed⁷.

|| Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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References

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2. GRADE Working Group (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
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4. Cao B, Wang DF, Xu MY, Liu YQ, Yan LL, Wang JY, *et al.* (2016): Vitamin B12 and the risk of schizophrenia: A meta-analysis. *Schizophrenia Research* 172: 216-7.
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7. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 3.2 for Windows*.