TECHNICAL COMMENTARY

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Vitamin D

Introduction

Vitamin D is a fat soluble vitamin and steroid hormone. It can be ingested through a diet containing fish, eggs, vegetable oils, butter, liver, fortified milk and margarine, or may also be gained through exposure to the sun. Vitamin D has been linked to cell growth and foetal development, and low maternal concentration may adversely impact the developing brain.

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 given priority 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-analysis[1]. Reviews reporting less than 50% of items 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 criteria[3-5].

- Moderate to high quality evidence suggests a medium effect of more Vitamin D deficiency in people with schizophrenia compared to controls. Moderate quality evidence suggests people with first-episode psychosis also have lower levels of vitamin D.
- High quality evidence suggests a small effect of lower Vitamin D in people with schizophrenia compared to people with other psychoses.
- Moderate to high quality evidence suggests no differences in Vitamin D between people with schizophrenia and people with major depression.

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Vitamin D

Belvederi Murri M, Respino M, Masotti M, Innamorati M, Mondelli V, Pariante C, Amore M

Vitamin D and psychosis: Mini meta-analysis

Schizophrenia Research 2013; 150: 235-239

View review abstract online

Comparison	**Vitamin D levels in people with schizophrenia vs. controls, and vs. other psychoses or depression.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests a large effect of lower Vitamin D in people with schizophrenia compared to controls.** **High quality evidence (large samples, consistent, precise, direct) suggests a small effect of lower Vitamin D in people with schizophrenia compared to people with other psychoses.** **Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests no differences in Vitamin D between people with schizophrenia and people with major depression.**

Vitamin D

A significant, large effect of lower Vitamin D levels in people with schizophrenia vs. controls;

6 studies, N = 7,924, g = -1.23, 95%CI -1.87 to -0.59, $p < 0.001$, I^2 = 95%, $p < 0.001$

A small trend effect of lower Vitamin D in people with schizophrenia vs. other psychoses;

3 studies, N = 342, g = -0.26, 95%CI -0.53 to 0.01, $p = 0.059$, I^2 = 31%, $p = 0.23$

No significant differences in Vitamin D between people with schizophrenia and people with major depression;

3 studies, N = 338, g = -0.35, 95%CI -0.89 to 0.18, $p = 0.19$, I^2 = 74%, $p = 0.02$

Consistency‡	Consistent for schizophrenia vs. other psychoses, inconsistent for schizophrenia vs. controls and schizophrenia vs. major depression.
Precision§	Precise for schizophrenia vs. other psychoses and schizophrenia vs. major depression, imprecise for schizophrenia vs. controls.
Directness‖	Direct

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

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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 samples, inconsistent, imprecise, direct) suggests people with first-episode psychosis have a large effect of lower levels of vitamin D.**
A significant, large effect of lower blood levels of vitamin D (matched for age and ethnicity); 6 studies, N = 906, *g* = -1.055, 95%CI -1.990 to -0.119, *p* = 0.027, I^2 = 97% Lower vitamin D was related to increased psychiatric symptoms. There was no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Valipour G, Saneei P, Esmaillzadeh A

Serum Vitamin D Levels in Relation to Schizophrenia: A Systematic Review and Meta-Analysis of Observational Studies

Journal of Clinical Endocrinology and Metabolism 2014; 99: 3863-3872

View review abstract online

Comparison	**Vitamin D levels in people with schizophrenia vs. controls, and vs. other psychoses or depression.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests a medium effect of increased Vitamin D deficiency in people with schizophrenia compared to controls.**
Vitamin D deficiency	

Vitamin D

Significant reduced mean Vitamin D levels in people with schizophrenia vs. controls; 13 studies, N = 7290, MD = -5.91, 95%CI -10.68 to -1.14, $p < 0.05$, Q test $p < 0.0001$, $I^2 = 97.6\%$ Subgroup analysis showed studies using biomarker $25(OH)D_3$ reported homogenous results. *Significant, medium effect of increased odds of Vitamin D deficiency (< 20 vs. > 20 ng/mL) in people with schizophrenia vs. controls;* 8 studies, N = 785, OR = 2.16, 95%CI 1.32 to 3.56, $p < 0.05$, Q test $p < 0.068$, $I^2 = 48.8\%$ *Significant increase in the prevalence of Vitamin D deficiency (< 10- 30 ng/mL) in people with schizophrenia vs. controls;* 8 studies, N = 591, prevalence = 0.65, 95%CI 0.46 to 0.84, $p < 0.05$, Q test $p < 0.0001$, $I^2 = 84.8\%$	
Consistency	Consistent for odds ratios only.
Precision	Imprecise
Directness	Direct

Explanation of acronyms

CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect size) I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; 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[6].

† Different effect measures are reported by different reviews.

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.

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).

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[6].

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, a 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. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r 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 independent 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.

‡ Inconsistency refers to differing estimates of 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 considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[6];

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

§ 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, these criteria should be relaxed[8].

‖ 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, which 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 and is therefore 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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