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Correlates of Vitamin D in Psychotic Disorders: A comprehensive Systematic Review

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Abstract (199/ 200)

People with psychosis have high prevalence of low vitamin D levels but the correlates and relevance of this deficiency are unclear. A systematic search of major databases from inception to 03/2016 was undertaken investigating correlates of vitamin D in people with psychosis. Data was summarised with a best evidence synthesis. Across 23 included studies (n=1,770 psychosis, n= 8,171 controls) a mean difference in vitamin D levels between both groups of -11.14 ng/ml ±0.59 was found. 53 unique correlations between vitamin D and outcomes in people with psychosis were identified. The evidence base was broadly equivocal although season of blood sampling (67% of studies found a positive correlation with warmer seasons) and parathyroid hormone (100% of studies found a negative correlation) were associated with vitamin D levels. The most commonly non-correlated variables were: BMI (83% found no correlation), age (73%), gender (86%), smoking (100%), duration of illness (100%) and general assessment of functioning score (100%). In conclusion, whilst many unique correlates have been investigated, there is weak and inconclusive evidence regarding the consistency and meaning of the correlates of vitamin D levels in people with psychosis. Future longitudinal studies should consider the correlates of vitamin D in people with psychosis.

Key words: Schizophrenia; Psychosis; vitamin D; hypovitaminosis D; 25-hydroxyvitamin D; 25-OHD

1. Introduction

Psychotic disorders are one of the largest contributers to the global burden of disease (Whiteford et al., 2013). The prevalence of psychotic disorders varies among different geographical locations, with increased rates in cold climates and high latitudes (Kinney et al., 2009). Furthermore, prevalence increases in individuals born in Winter/Spring months compared to Summer/Autumn babies (Kinney et al., 2009; Saha et al., 2005). These ecological findings suggest sun exposure and therefore vitamin D is a risk factor for psychotic disorders. These findings are consistent with the increased rates of psychotic disorders observed in Black ethnic migrant groups (Cantor-Graae and Selten, 2005;

Dealberto, 2010) partially due to darker skin pigments being less able to absorb Ultraviolet B (UVB) radiation, higher rates in urban compared with rural areas and the high ratio of patients diagnosed being born in winter months (McGrath, 1999; McGrath et al., 2004).

The association between vitamin D and psychotic disorders has become of increasing interest. Recently vitamin D deficiency was demonstrated in two meta-analyses in patients with psychotic disorders versus controls (Belvederi Murri et al., 2013; Valipour, Saneei & Esmaillzadeh, 2014). Low vitamin D levels have been reported in established (Lally et al., 2016) and first episode psychosis (FEP) (Crews et al., 2013). However, to what extent hypovitaminosis D is related to disease mechanisms or influences health outcomes among this population is unknown. One study examining the effects of supplementation with vitamin D in the first year of life found that an intake of 2000 international units (IU) or more per day was associated with a significant reduced risk of developing a psychotic disorder in males (RR = .23, CI = .06-.95) (McGrath et al., 2004). Furthermore, low vitamin D prenatally could impact on fetal neural development, increasing one's risk of developing a psychotic disorder later in life (Eyles et al., 2013). These findings suggest an association between vitamin D and psychotic disorders.

In the general population, vitamin D deficiency has been linked to increased risk of Cardiovascular Disease (CVD) and related disorders such as stroke, hypertension and heart failure (Liu et al., 2012). Evidence suggests that low vitamin D is associated with some physical health factors such as high body mass index (BMI) (Vimaleswaran et al., 2013), larger waist circumference (Lally et al., 2016) and increased rates of smoking (Cutillas-Marco et al., 2012), all risk factors for CVD. Furthermore, hypovitaminosis D is a risk factor for osteoporosis in certain age groups (van Schoor et al., 2008) and type 2 diabetes mellitus in women (Lindqvist et al., 2010). Emerging evidence suggests that hypovitaminosis D may be a risk-modifying factor for psychotic disorders as well as for other chronic illnesses including, type 1 diabetes, multiple sclerosis, rickets, heart disease, osteomalacia and cancer (Kaludjerovic & Vieth, 2010). More recently in human studies, vitamin D deficiency has been linked to dysfunction of the hippocampus, a region thought to be involved in the pathogenesis of psychotic disorders, and a positive correlation between vitamin D and regional grey matter volume (Shivakumar et al., 2015).

Previous systematic reviews have concentrated on comparing the mean difference in vitamin D levels between psychotic disorders and healthy controls (Belvederi Murri, et al., 2013; Valipour et al., 2014). Whilst previous reviews have confirmed people with psychosis experience low levels of vitamin D, no systematic review to our knowledge has considered the correlates of vitamin D deficiency in this patient group. Therefore, a review systematically examining the correlates of vitamin D in people with psychosis is needed in order to understand the association between vitamin D level and other examined variables.

The aims of this review was to provide an update on vitamin D levels in psychotic disorders and systematically examine the correlates of vitamin D in people with psychosis.

1. Methods

This systematic review was conducted in line with the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1 Inclusion criteria

The Inclusion criteria for this systematic review were studies that; (1) included participants with psychotic disorders (schizophrenia, schizoaffective disorder or psychotic disorder NOS), formally diagnosed according to established criteria (e.g., DSM-IV, (APA, 2000) or ICD-10, (World Health Organisation, 1992)). (2) Included a measurement of vitamin D levels (25-hydroxyvitamin D (25-OHD)) within a psychotic disorder population. (3) are published in an international peer review journal in the English language.

2.2 Exclusion criteria

The exclusion criteria for this review were studies that; (1) did not differentiate between different diagnoses when presenting data, i.e. put all mental disorders together as one group. (2) Did not report vitamin D mean values. (3) Conference abstracts.

2.3 Information sources and searches

The study author searched; MEDLINE, PsycINFO and EMBASE from database inception until 4th March 2016, using the key words 'Vitamin D' AND 'Schizophrenia' OR 'schiz*' OR 'psychosis'. In addition, reference lists of two previous reviews of vitamin D and Schizophrenia or psychosis were screened to identify additional studies (Belvederi Murri et al., 2013; Valipour, Saneei, & Esmaillzadeh, 2014).

2.4 Study selection

After removal of duplicates, author JA screened the titles and abstracts of all potentially eligible articles. These were then double-checked by an independent researcher (BS) to confirm that the eligibility criteria were adhered to. After applying the eligibility criteria, a list of full text articles was developed through consensus. The full texts of included articles were then considered and a final list of included articles was reached through consensus.

2.5 Outcomes

The outcomes of interest were the mean and standard deviation (SD) of vitamin D levels (ng/ml) in people with psychotic disorders compared to healthy controls. If vitamin D levels were measured using alternative units of measurement (e.g. nmol/L, mcg/L) they were converted into nanograms per millilitre (ng/ml). Additional outcomes were any correlate of vitamin D among people with psychosis, as described in the primary study data.

2.6 Data Extraction

Author JA extracted the data using Microsoft Excel, including: study setting (inpatients, outpatients, community or mixed), geographical country and region, study design, first episode psychosis, mental illness type (schizophrenia, psychosis or other[specified]), duration of illness, sex, age, proportion with vitamin D deficiency, deficiency level cut-off , plasma or serum vitamin D samples, BMI, tobacco smoking, proportion prescribed antipsychotic medication and finally, the mean and SD for vitamin D in people with and without psychosis was collected.

2.7 Correlate Outcomes

Information on all reported significant and non-significant correlates of vitamin D levels in psychotic disorders were collated (as defined by primary author's papers). To assess the effect and direction of the relationship between vitamin D and other variables within psychosis we sought to standardise the statements about statistical significance in line with guidance from the Canadian Agency for Drugs and Technology in Health (https://www.cadth.ca/interventions-directed-professionals, CADTH, 2011). For the purpose of this study the categories were defined as the following:

- 0% of studies found a significant association = no evidence for an association.
- 1-33% of studies found a significant association = largely no evidence for an association.
- 34-66% of studies found a significant association = mixed evidence for an association.
- 67% + of studies found a significant association = good to strong evidence of an association.

This method was used for all variables measured in ≥3 different studies.

2.8 Quality of included studies

Methodological quality of the included studies, looking at correlates of vitamin D, was assessed using the Newcastle-Ottawa Scale (NOS) (NOS; (Wells, G., Shea., B., O'Connell, D., Peterson, J., Welch, V., Loscos, M, et al.,)). The scale provides an assessment of the quality of nonrandomized studies and its content validity and inter-rated reliability have been established (Wells et al.). The scale consists of three broad categories: (1) The selection of study participants. (2) The comparability of the groups. (3) Outcomes. Each study is rated on 9 items with a possible overall score of up to 9 points with a higher score indicating a better methodological quality study.

2.9 Data Synthesis

The review is presented in a best evidence synthesis.

2. Results

The initial search yielded 867 hits. After the removal of duplicates 638 abstracts and titles were screened. At the full text review stage 69 articles were considered and 46 were subsequently excluded (see Figure 1). Overall, 23 unique studies were included in the systematic review. Full details of the included studies are summarised in Table 1.

INSERT FIGURE 1 HERE (PRISMA)

Across the 23 unique studies there were 1,770 individuals with a Psychotic disorder (mean age 42.76±12.37 years, 52.72% male (range 0-100%) with mean illness duration of 11.34±11.31 years). Two unique studies looked at First Episode Psychosis and only one study included longitudinal vitamin D results. Overall, the mean BMI among participants was 27.5±3.08 and 42.62%±13.31 smoked. There were 8,171 healthy control participants (mean age 40.29±12.13 years, 47.61% male (range 0-100%) with a BMI of 25.95±1.69, of whom 22.83%±5.13 smoked (smoking only reported in 3 studies).

Vitamin D was obtained in plasma and serum samples across six and 17 comparisons, respectively and vitamin D levels were standardised to ng/ml to allow for cross comparison. Mean vitamin D levels in the patient population were 18.62±8.35 ng/ml and in the healthy control population 29.76±12.13 ng/ml, a mean difference of 11.14 ng/ml ($p<.0001$, $d=.96$). Vitamin D deficiency rates ranged from 0-100% with a mean of 63.24%, depending on the level considered deficient which ranges from 10-40 ng/ml. In studies categorising the deficiency levels conservatively at 10ng/ml the deficiency rates in the patient populations were 0% and 48.8% (Bergemann, Parzer, Mundt, & Auler, 2008; Lally et al., 2016, respectively).

There are more comparisons than included studies as a number of studies reported vitamin D levels stratified by diagnosis, length of stay or by first or multiple episodes of psychosis. Overall six, six and eleven comparisons were available in Asia, North America and Europe respectively. For a detailed summary of included studies see Table 1.

INSERT TABLE 1 HERE

3.1 Quality of included studies

The quality of the included studies was assessed using the NOS 9-point scale, with a higher score indicating a better quality methodological study. The average quality score across the included 23 studies was 4.94±1.34 and ranged from 3 to 7 points out of the possible 9, a summary of the scores is presented in Table 2.

INSERT TABLE 2 HERE

3.2 Correlates of vitamin D among people with psychosis

Full details of the correlates are summarised in tables 2 and 3. In total, 16 studies out of the 23 included within the review report a total of 53 different correlations. Correlates with mixed or significant findings were: Season of blood sampling (4 significant findings, 67%) suggesting good to strong evidence of a positive correlation with summer months (more daylight exposure); ethnicity (2 sig, 50%) suggesting mixed evidence for a correlation; Parathyroid Hormone (PTH) Level (3 sig, 100%) suggesting good to strong evidence of a negative correlation. The top five most reported correlations all included one or more contradicting results, the only correlations reported more than twice which have 100% agreement are smoking, duration of illness, GAF score and PTH level.

3. Discussion

The results from this systematic review confirm earlier meta-analyses demonstrating that patients with psychotic disorders have significantly lower mean levels of vitamin D compared to healthy controls. Furthermore, this patient group demonstrated a mean prevalence of vitamin D deficiency of 63.24% across the included studies. This supports previous reviews findings of general hypovitaminosis D in this patient population with one review findings 59.14% and the other 65.3% (Belvederi Murri et al., 2013; Valipour et al., 2014, respectively) and suggests that on average over half of psychotic patients are deficient of vitamin D at any one time. This is in line with research in other areas suggesting that low vitamin D is also common in other mental health disorders such as depression and anorexia (Anglin et al., 2013; Veronese et al., 2015, respectively).

The results of our comprehensive review considering the correlates of vitamin D among people with psychosis found that the evidence base is equivocal. However, there is evidence to suggest that vitamin D among people with psychosis is correlated with the season of blood sampling (Belzeaux et al., 2015; Berg et al., 2010; Crews et al., 2013; Grønli et al., 2014; Lally et al., 2016; Zhu et al., 2015) and parathyroid hormone levels (Bergemann et al., 2008; Rey-Sánchez et al., 2009; Schneider et al., 2000), the latter being negatively correlated to vitamin D. What this review highlights are a multitude of variables that have been found to not significantly correlate with vitamin D within the patient population including but not limited to: BMI, age, gender, smoking, duration of illness and GAF score.

Previous meta-analyses have focused on the mean vitamin D difference between a patient group and a control comparison. The first meta-analysis finding a medium effect size for lower vitamin D in psychotic disorders versus healthy controls (Belvederi Murri, et al., 2013). However, this study only included seven studies in their final report due to restrictive inclusion criteria and did not consider any correlational analysis. A more recent review included more studies and found similar results however again it did not include any correlational analysis (Valipour et al., 2014). Moreover, the review found significantly lower levels of vitamin D in case-control studies though not in cross-sectional studies. This systematic review goes further to include correlational analysis as an attempt to establish the consistency of correlates across the included studies and not the magnitude of effect.

The season of blood sampling was found across 4 included studies to be associated with vitamin D levels in psychotic disorders (Berg et al., 2010; Grønli et al., 2014; Lally et al., 2016; Zhu et al., 2015). This is perhaps not surprising since UVB irradiation intensity varies over the year and it is known that in healthy populations vitamin D levels change with UVB intensity. In one healthy sample participants were 55% deficient during January to March but the same sample was only 11% deficient between July and September, ($p<.001$) (Klingberg et al., 2015). This highlights the importance to control for the season of blood sampling when comparing vitamin D levels across groups. Within the same sample group, it was found that there was a negative correlation between BMI and vitamin D. This was not replicated in the current systematic review with only two out of 12 studies finding this association in psychotic disorder patients.

Parathyroid hormone was the only correlation with unanimous agreement among the included studies with a negative correlation to vitamin D in this patient population with three studies finding the same significant correlation. This relationship is expected as PTH increases the activity of enzymes which covert 25-hydroxycholecalciferol 25(OH)D, inactive vitamin D, into an active form of vitamin D (1,25(OH)2 D) in the kidney (Nussey and Whitehead, 2001). Therefore, with increasing PTH levels we would expect to see decreased 25(OH)D levels, the vitamin D level examined in the included studies.

There is insufficient evidence identified from this systematic review to support the hypothesis that vitamin D might mediate cardiovascular disease risk factors in psychosis. There is evidence to suggest that BMI does not correlate with vitamin D levels in people with psychosis, with only two out of 12 studies finding a negative correlational relationship. Hypertension was only measured in two included studies, with one finding a significant negative correlation with vitamin D (Lally et al., 2016) and the other finding no significant effects (McCue et al., 2012). Finally, only one included study examined waist circumference finding a significant negative correlation with vitamin D (Lally et al., 2016). This highlights that the relationship between waist circumference, hypertension and vitamin D is understudied and this should be a priority for future research since cardiovascular disease is one of the leading causes for premature mortality in psychosis (Lawrence et al., 2013). Thus, the relationship between vitamin D and cardiovascular outcomes in people with psychosis are not clear.

Whilst the results of the review are novel, some considerations should be noted. Interestingly, only one included study used a longitudinal design (Thakurathi et al., 2013), which is another key limitation in the current evidence base. The only other identified longitudinal study combined many mental disorders, and not just psychotic disorders, to create a patient group (Abdullah et al., 2012). This made the longitudinal findings difficult to generalise to psychotic disorders. Most of the included studies used a cross-sectional design, this only allowed us to examine the role of vitamin D in psychotic disorders at one time point, and no inference on the directionality of the association between vitamin D and psychotic disorders can be made. Future studies with longitudinal design are required to enable a greater understanding of causal inference(Levin, 2006).

Second, there was a vast amount of heterogeneity of the variables used, the variation of thresholds set and the multiple definitions of each variable. Third, there was limited data on many of the variables in the review. In particular, there was limited data on psychotropic medication and vitamin D and clinical outcomes. Future studies need to consider using variables that are consistent with variables from past literature in order to strengthen known or unknown associations.

4.1 Conclusion

To the best of the author's knowledge, this review is the first to systematically review correlates of vitamin D and highlight the gaps in the current literature. Only the season of blood sampling and parathyroid hormone were consistently associated with vitamin D. Future research needs to consider using similar correlates to that of previous research to aid the understanding of associations and address the heterogeneity in the current literature, secondly to consider filling the gaps in the current literature including: depression, pain and quality of life measures and finally to improve on the current sparsity of longitudinally designed studies to suggest causality.

Conflict of interest

JA, BS, LA, JL and AK declare that they have no conflicts of interests in relation to the planning, drafting and publication of this manuscript.

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