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Correlation between Vitamin D Deficiency and Depression

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ABSTRACT

Aim of the Study: To conduct a systematic review and meta-analysis of prospective cohort studies of the association of vitamin D deficiency with onset of depression in non- depressed individuals.

Methods: A systematic review of the electronically searched publications of the scientific literature. We searched the Cochrane Hepato Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE (1946 to 2017), EMBASE (1974 to 2017), and Science Citation Index Expanded (1900 to 2017). Initially all randomized clinical trials which studied the correlation of Vitamin D with depression were included, articles were then selectively screened according to the eligibility criteria. **Results:** the search yielded 11 studies, A meta-analysis of all studies without flaws demonstrated a statistically significant improvement in depression with Vitamin D supplements (+0.72 CI +0.28, +1.31). Nevertheless, studies with biological flaws were mainly inconclusive

Conclusion: Our analyses are consistent with the hypothesis that Vitamin D supplementation (≥800 I.U. daily) was supported in the management of depression.

Keywords: Depression, biological plausibility, meta-analysis, systematic review, 25OHD, Vitamin D supplementation.

INTRODUCTION

Vitamin D is a unique secosteroid hormone formed mainly by photosynthesis, so an indoor lifestyle and sun-avoidance leads to deficiency (25OHD <50 nmol/L) [(1)]. Vitamin D deficiency is now a global public health problem affecting a billion people worldwide [(2)]. Even in sunny Australia, deficiency affects one third of the population [(3)], with much higher rates observed in migrant populations [(4)]. There has been an increase in the prevalence of Vitamin D deficiency and a ten-fold increase in spending on supplements in the US over the last decade [(5)].

Vitamin D plays a vital role in bone health and researchers are now discovering that vitamin D may play a role in many other areas of health as well. Vitamin D receptors have been found in many parts of the brain [(6)]. Receptors are found on the surface of a cell where they receive chemical signals. By attaching themselves to a receptor, these chemical signals direct a cell to do something, for example to act in a certain way, or to divide or die. Some of the receptors in the brain are receptors for vitamin D, which means that vitamin D is acting in some way in the brain. These receptors are found in the areas of the brain that are linked to the development of depression. For this reason, vitamin D has been linked with depression and with other mental health problems [(6)].

On a separate note, depression is a biological disease, like multiple sclerosis, it has a strong genetic characteristic. Depression can be triggered by a number of different things. Sometimes there is one main trigger, such as the death of a loved one, but there are a number of different factors that may play a part [(7)]. Although the factors leading to depression differs between individuals, the most common triggers include: Physical illness, family history of depression, major life changes, early life experiences or genetic predisposition and regular heavy drinking [(7)]. Depression affects 350 million people worldwide, it is the leading cause of disability and the fourth-leading cause of the global disease burden [(8)].

Epidemiological evidence shows that vitamin D deficiency is associated with an 8%–14%

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increase in depression [9] and a 50% increase in suicide [10]; nevertheless, causality and efficacy of supplementation remain controversial [11] awaiting confirmation by systematic review and meta-analysis. Exactly how vitamin D works in the brain isn't fully understood. One theory is that vitamin D affects the amount of chemicals called monoamines, such as serotonin, and how they work in the brain. Many anti-depressant medications work by increasing the amount of monoamines in the brain. Therefore, researchers have suggested that vitamin D may also increase the amount of monoamines, which may help treat depression [12].

Other theories suggested that since vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development[13], making it biologically plausible that this vitamin might be associated with depression and that its supplementation might play an important part in the treatment of depression. Over two-thirds of the populations of the USA and Canada have suboptimal levels of vitamin D [14].

Some studies have demonstrated a strong relationship between vitamin D and depression [15], whereas others have shown no relationship[16]. To date there have been eight narrative reviews on this topic [17], with the majority of reviews reporting that there is insufficient evidence for an association between vitamin D and depression.

The present study is intended to conduct a systematic review and meta-analysis to dig deep and understand the association between vitamin D deficiency and depression in adults and whether vitamin D deficiency increases the risk of developing depression in cohort studies in adults; and whether vitamin D supplementation improves depressive symptoms in adults with depression compared with placebo, or prevents depression compared with placebo, in healthy adults in randomized controlled trials (RCTs).

MATERIALS AND METHODS

Data Sources

Literature electronic search of Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE (1946 to 2017), EMBASE (1974 to 2017), and Science Citation Index Expanded (1900 to 2017). Initially all randomized clinical trials which investigated the correlation of vitamin D deficiency with depression were included then articles were then selectively screened according to the eligibility criteria.

The reference lists of identified articles were reviewed for additional studies.

Search Terms

(Vitamin D, baseline 25OHD levels, DSM, Depression) were used in combinations and together with the Boolean operators OR and AND. 1371 articles initially matched the stipulated criteria and were included in the current review.

Study Selection and Criteria

Search results were screened by scanning abstracts for the following

Inclusion Criteria

1- Articles conducted in or translated to English or Arabic language
2- All randomized clinical trials, case–control studies, cross-sectional studies and cohort studies. That investigated the association of depression with vitamin D deficiency.
3- Age group: Adults (over 18 years).
4- Articles that reported depression as the outcome of interest and vitamin D measurements as a risk factor or intervention.
5- Study outcome: Cross-sectional and cohort studies were required to report depression outcomes for participants with vitamin D deficiency

Exclusion Criteria

1. Articles in other languages than Arabic and English.
2. a clinical diagnosis of a depressive disorder, depressive episode or depression not otherwise specified.
3. a diagnosis of depression using an established cut-off point on a validated rating scale,

Quality of articles was critically appraised with PEDro[18]. Trials were rated with a checklist, the PEDro scale. This considers two aspects of trial quality; internal validity of the trial and whether the trial contains sufficient statistical information to make it interpretable. It does not rate external validity or the effect size.

DATA EXTRACTION

Data was extracted for participants, 25OHD levels, study timeframes, interventions, outcome measures, measures of effect, methodological quality scores, and biological flaws.

Change in depressive symptoms using a validated rating scale. This secondary outcome was not used for RCTs that enrolled non-depressed participants or other study designs because it was not meaningful in those contexts.

Meta-Analysis

We used MedCalc where data was available on diagnosis, dose, outcome measure, and biological flaws. Estimates of the size of effect using the standardized mean difference (SMD) were compared according to the presence of biological flaws in primary studies.

For meta-analysis of studies with a continuous measure, MedCalc uses the "Hedges g" statistic as a formulation for the SMD under the fixed effects model. The SMD is the difference between the two means divided by the pooled standard deviation, with a correction for small sample bias.

Next the heterogeneity statistic is incorporated to calculate the summary SMD under the random effects model. The total SMD with 95% CI is given both for the fixed effects model and the random effects model. A value of 0.2 indicates a small effect, a value of 0.5 indicates a medium effect, and a value of 0.8 or larger indicates a large effect.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Uncertain risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

The study was done according to the ethical board of King Abdulaziz university.

RESULTS

The initial search was broad, accepting any article related to evaluation of depression with vitamin D deficiency to ensure a comprehensive view of available work, and generated 1371 articles. Preliminary application of study criteria identified 454 potential studies for inclusion that met one or more criteria. Further review of these investigations by two independent reviewers yielded 145 studies that fully met all inclusion criteria. No individual authors were contacted for information. No further review of methodological quality of the studies was conducted beyond that it appeared in a peer review journal and comprised an RCT.

The 145 eligible articles were again closely examined and data extracted using a standard protocol regarding target population, sample size, program provider, program content, intervention components, processes, and outcomes. Another 134 articles were excluded, 16 of which were not retrieved, 66 had irrelevant endpoints/outcome while 52 publication had the same cohort.

Comparison among provider type was computation of differences between percent of successful program to number attempted. No further statistical analyses were employed.

Finally, 11 studies were included according to Prisma and detailed as the focus for the present study (Figure 1) [(19)].

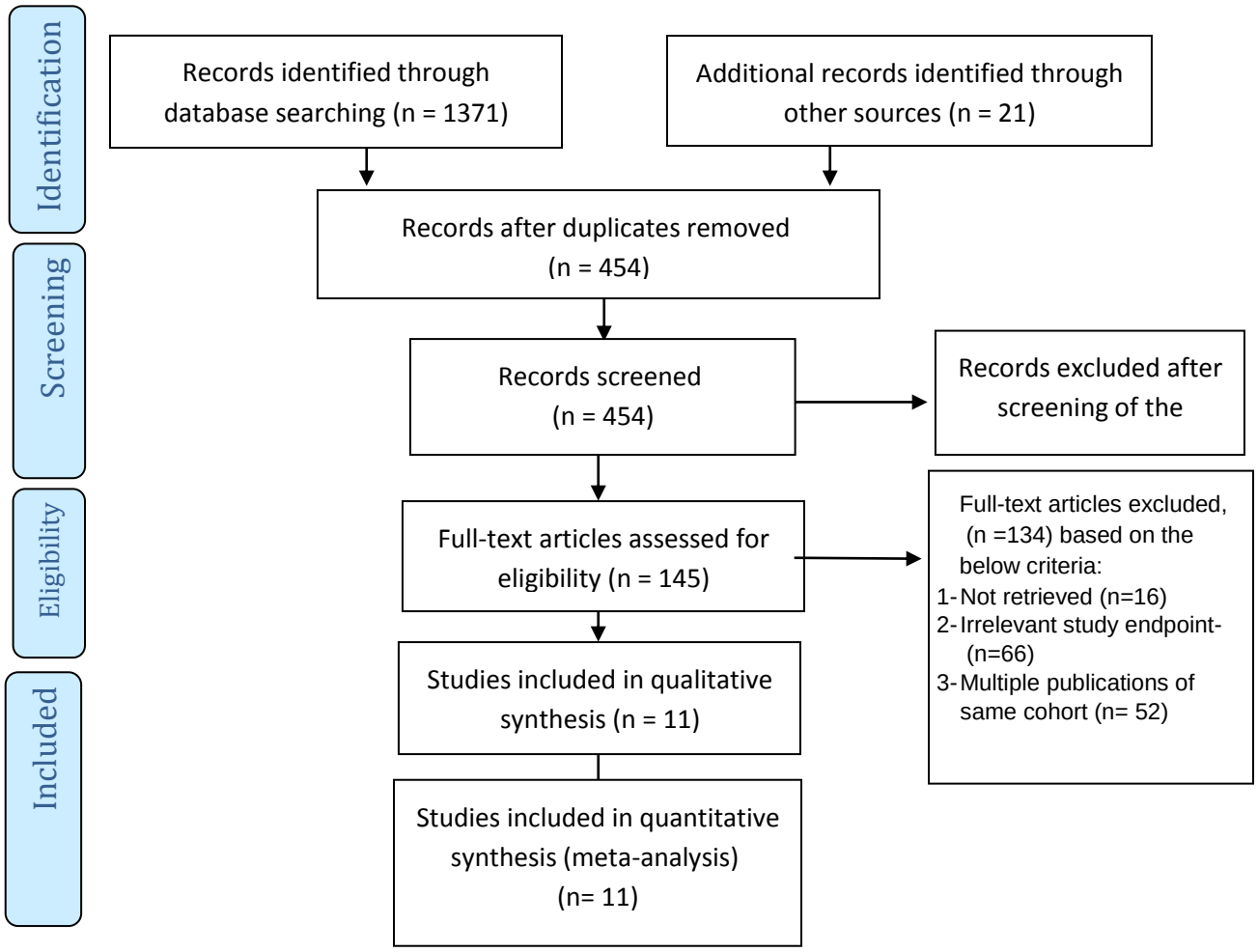

Figure 1: PRISMA flow diagram showing the selection criteria of assessed the studies[19].

There was wide variation in study methodology. The study populations were diverse. Smaller studies were performed in patients with specific disorders (depression, seasonal affective disorder, obesity, post-menstrual tension and hospitalized patients)- Table 1.

Table 1. Characteristics of the included studies and group (population, no of patients and Quality score ((PEDro Scale))

	No of Patients				
Publication (Author, Year)	**Control**	**Intervention**	**Total**	**Population**	**Quality Score**
Veith *et al.*, 2004[20]	32	32	64	Adults with serum 25(OH)D <61 nmol/L in summer, expected to develop 25(OH)D concentrations <40 nmol/L by winter	10
Dumville *et al.*, 2006[21]	1205	912	2117	Older women with seasonal affective disorder	11
Jorde *et al.*, 2008[22]	149	292	441	Overweight and obese adults	8
Khajehei *et al.*, 2009[23]	60	120	180	University female students with premenstrual syndrome	9
Arvold *et al.*, 2009[24]	50	50	100	Individuals with Vitamin D deficiency (10–25 ng/mL) seen for medical care at a primary healthcare clinic	10
Belcaro *et al.*, 2010[25]	32	33	65	Menopausal women with signs of depression and mood disorder	8
Sanders *et al.*, 2011[26]	1011	1001	2012	Community dwelling older women with seasonal mood disorders	11
Zhang *et al.*, 2011[27]	15	17	32	Hospitalized patients	9
Dean *et al.*, 2011[28]	65	63	128	Young healthy adults (University students)	11
Bertone-Johnson *et al.*, 2012[29]	18106	18176	36282	PostmenopausalWomen with depressive symptoms	11
Khoraminya *et al.*, 2013[30]	20	20	40	Adults with major depressive disorder based on DSM-IV criteria, without psychosis	10
Total	20745	20716	41461	Average Score	9.8

In Table 2, we can observe a validated outcome measures of depression included Beck Depression Index in three studies[22,28,30] ,the profile of Mood States in one study[27] and the mental component score of the SF12 in one study [21]. Questionnaires about pre-menstrual syndrome[23], fibromyalgia[24], and menopause[25] included depression as a domain. There was no significant differences at baseline measures and methodological quality of studies was generally high (9 out of 11)

Table 2. Key depression outcome measures, within and between group findings

Publication (Author, Year)	Follow-up Time Period	Outcome Measures	Within Group Findings	Between Group Findings
Veith *et al.*, 2004[20]	2–6 M	Self-developed Wellbeing Scale	Pre-post mean (SD): 600 I.U. 2.2 (2.0); 2.3 (2.3) ($p > 0.05$)	Significant enhancement in wellbeing, promoting higher dose of Vitamin D
Dumville *et al.*, 2006[21]	6 M	SF12 mental component	Mean difference (95%CI) between intervention and control at baseline −0.6 (−1.5 to 0.3) ($p > 0.05$); follow up 1.8 (−0.8 to 1.2) ($p > 0.05$)	Mean adjusted (age- and baseline score) between group difference (95%CI) −0.49 (−1.34 to 0.81) $p > 0.05$
Jorde *et al.*, 2008[22]	12 M	Beck Depression Index (total score)	Baseline: DD group 4.5 (0.0–24.0); DP group 5.0 (0.0–28.0); PP group 4.0 (0.0–24.0). Follow-up: DD group 3.0 (0.0–23.0) ($p < 0.05$); DP group 4.0 (0.0–26.0) ($p < 0.05$); PP group 3.8 (0.0–18.0)	DD and DP groups change was similar ($p > 0.05$) but significantly greater from PP ($p < 0.05$)
Khajehei *et al.*, 2009[23]	Premenstrual for 2 cycles	PMS symptom rating form which captured psychological and physical symptoms including depression	Mean % total symptoms	The dydrogesterone and calcium plus Vitamin D treatments were significantly more effective than placebo in lessening the severity of PMS symptoms ($p < 0.05$)
Arvold *et al.*, 2009[24]	8 WK	Fibromyalgia impact questionnaire	FIQ score Mean pre-post difference total (95%CI) intervention −3.71 (−7.5 to 0.1) ($p < 0.03$), control 1.91 (−2.9 to 6.7) ($p > 0.05$)	$p < 0.05$
Belcaro *et al.*, 2010[25]	8 WK	Menopause symptoms questionnaire	Total average symptom score reduced by 48% for intervention group ($p < 0.05$), control group increased by 10% ($p > 0.05$).	$p < 0.05$
Sanders *et al.*, 2011[26]	3–5 YR	General health questionnaire SF12 (PCS, Sanders MCS), WHO Wellbeing Index	Intervention: no intervention	Treatment effects SF12 effect size (95%CI) PCS 0.22 (−70.75 to 1.19); MCS 70.14 (−71.00 to 0.72)

Zhang *et al.*, 2011[27]	8 D	Profile of Mood States questionnaire	Vitamin D group pre-post 23.1 ± 27.2; 22.4 ± 22.4 p > 0.05	p < 0.05
Dean *et al.*, 2011[28]	6 WK	Beck Depression Index	Baseline: follow up mean (95%CI): Intervention 7.24 (5.58–8.90); 6.40 (4.73–8.07) (p > 0.05); control 5.72 (4.09–7.36); 5.38 (3.74–7.02) (p > 0.05)	p > 0.05
Bertone-Johnson *et al.*, 2012[29]	At 2 WK, then twice yearly for 2 years	Burnam Depression Scale	Mean overall change (SD) 0.004 (0.143) intervention, −0.002 (0.113) (control)	p > 0.05
Khoraminya *et al.*, 2013[30]	Every 2 WK for 8 WK	24-item Hamilton Depression Rating Scale (HDRS) (1°), 21-item Beck Depression Inventory (BDI) (2°	BDI Intervention: Wk0 32.45 ± 7.35; Wk2 27.73 ± 7.50; Wk4 20.44 ± 6.56; Wk6 16.73 ± 8.11; Wk8 13.2 ± 8.64 (p < 0.05) Control: Wk0 31.65 ± 7.33; Wk2 29.17 ± 6.78; Wk4 25.18 ± 6.93; Wk6 21.00 ± 6.81; Wk8 17.95 ± 6.31 (p < 0.05)	p < 0.05 for both outcomes,

META-ANALYSIS

Meta-Analysis of Studies without Biological Flaws

Two studies (Jorde *et al.* [22] and Khoraminya *et al.* [30] were included as they used the same outcome measure; the Beck Depression Inventory.

The standardized mean difference for these studies without flaws is shown in the.? It shows a statistically significant positive effect of vitamin D in depression of 0.78 (CI 0.24, 1.27). The random effects model was used due to the diverse populations studied.

he ???Jorde *et al.* [22] trial (n = 387) had three study groups; two interventions with different doses of vitamin D and a control. The Khoraminya *et al.* [30] trial (n = 40) compared vitamin D plus fluoxetine to fluoxetine alone. The studies had similar baseline level of 25OHD (Jorde *et al.* [22] 55 nmol/L) (Khoraminya *et al.* [30] 57 nmol/L), and the doses of vitamin D over 800 nmol/L in both studies. The participants in both studies were patients; Khoraminya *et al.* [30] depressed patients and Jorde *et al.* [22] obese patients. Depression and obesity overlap, as there is a reciprocal relationship between obesity and depression indicated by the 50% increase in one condition when the other is present [31].

Meta-Analysis of Studies with Biological Flaws

Options for meta-analysis were examined and performed combining for Dumville *et al.* [21] due to the diverse outcome variables used in other studies. There was a statistically significant negative effect of vitamin D administration evident from the forest plot in the standardized mean differences. The effect size was −1.1 (CI −0.7, −1.5) (random effects). These studies were of high methodological quality, had similar subjects (community dwelling women aged >70 years) and baseline 25OHD, and used the same outcome measure. The studies differed in the dosing schedule, daily and annually.

DISCUSSION

Our key outcome in the present systematic review and meta-analysis was that all studies without flaws and the meta-analysis of studies without biological flaws support the efficacy of vitamin D supplementation for depression, as compared with the negative results of meta-analysis for studies with biological flaws. The women Health

Initiative [29], with more participants that all the other studies combined, had the highest methodological quality and the most biological flaws leading to non-significant outcomes for both bone strength and mood. Due to its sheer size, the WHI has dominated previous meta-analysis leading to null results.

Furthermore, a review of antidepressant efficacy published in the NEJM [32] shows that the effect size of antidepressant medication was increased by selective publication of trials and altering the effect size. Nevertheless, the overall mean weight effect size value for antidepressants was only 0.15 (CI 0.08, 0.22) for unpublished studies and 0.37 (CI 0.33, 0.41) for published studies. Thus, the effect size of vitamin D demonstrated in our meta-analysis may be comparable with that of anti-depressant medication. For the meta-analysis of studies with biological flaws, the size of the effect was statistically significant and negative being −1.1 (CI −0.7, −1.5), indicating that vitamin D supplementation in flawed studies may lead to deterioration in depression.

Moreover, a study in Sweden found that those who attempted suicide had significantly lower vitamin D levels than non-suicidal depressed patients or healthy controls [33].They also had higher concentrations of pro-inflammatory cytokines, which have been observed in other suicidal patients. Cytokines are small proteins emitted by cells to signal other cells. Vitamin D is known to reduce the levels of pro-inflammatory cytokines.

A 20-year study in Iowa found that for people with major depressive disorder, there was a slight increase in depressive symptoms in the winter months, peaking in March. However, new episodes were highest from October through January, peaking in January [34].

A study in Netherlands involving 1102 people aged 18-65 years with current depressive disorder and 790 with former but not current depressive disorder found lower vitamin D levels among those with current depressive disorder and lower symptom severity for those with higher vitamin D levels. There was also a significant correlation between vitamin D status and developing depressive symptoms at a 2-year follow up[35].

The importance of vitamin D to many brain processes including neuroimmunomodulation and neuroplasticity suggests that it might have a role in psychiatric illness such as depression. The biological plausibility of the association between vitamin D and depressive illness has been strengthened by the identification of vitamin D receptors in areas of the brain implicated in depression,the detection of vitamin D response elements in the promoter regions of serotonin genes[36], and demonstration of interactions between vitamin D receptors and glucocorticoid receptors in the hippocampus[37].

LIMITATION OF THE REVIEW

The main limitation of the current review was:

- Diversity of study methodology preventing a wide-ranging meta-analyses, and leaving only two studies in each meta-analysis.
- Variability in outcome measures and reporting suggest agreement should be sought within the research community to reinforce standard conduct and reporting of future studies to support meta-analysis.

CONCLUSION

It was clear that vitamin D deficiency is associated with an increased risk developing depression, furthermore, vitamin D supplementation in the right dose is comparable with the effect of anti-depressant medication which in turn favors vitamin D supplementation in the treatment for depression.

More prospective observational studies may be needed to provide more evidence on the correlation and to determine whether vitamin D can also contribute in the prevention of depression in some cases.

REFERENCES

1. **Holick M (2010):** The Vitamin D deficiency pandemic: A forgotten hormone important for health, Public Health Rev.,32:267–283.
2. **Hollick M(2007):** Vitamin D deficiency. N. Engl. J. Med., 357:266–281.
3. **Daly R, Gagnon C, Lu Z *et al.* (2011):** Prevalence of Vitamin D deficiency and its determinants in Australian adults aged 25 years and older: A national, population-based study. Clin. Endocrinol.,77:26–35.
4. **Thacher T, Fischer P, Strand M, Pettifor J(2006):** Nutritional rickets around the world: Causes and future directions. Ann. Trop. Paediatr., 26:1–16.

5. **Maxmen A(2011):** Nutrition advice: The Vitamin D-lemma. A vociferous debate about vitamin-D supplementation reveals the difficulty of distilling strong advice from weak evidence. Nature,475:23–25.
6. **Eyles D, Smith S, Kinobe R *et al.*(2005):** *Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain.* J Chem Neuroanat., 29(1): p. 21-30.
7. **Scott AI(2005):** The ECT handbook: the third report of the Royal College of Psychiatrists' Special Committee of ECT. RCPsych Publications.
8. **Hyman S, Chisholm D, Kessler R *et al.*(2006):** Mental disorders. In Disease Control Priorities in Developing Countries, 2nd ed.; Jamison, D.T., Breman, J.G., Measham, A.R., Alleyne, G., Claeson, M., Evans, D.B., Jha, P., Mills, A., Musgrove, P., Eds.; Oxford University Press: New York, NY, USA, pp. 605–626.
9. **Kjærgaard M, Joakimsen R, Jorde R(2011):** Low serum 25-hydroxyVitamin D levels are associated with depression in an adult Norwegian population. Psychiatry Res., 190:221–225.
10. **Umhau J, George D, Heaney R *et al.*(2013):**Low Vitamin D status and suicide: A case-control study of active duty military service members. PLoS One,8:e51543.
11. **Li G, Mbuagbaw L, Samaan Z, Zhang S *et al.*(2013):**ThabaneL Efficacy of vitamin D supplementation in depression in adults: a systematic review protocol. Syst. Rev., 2:64.
12. **Kjaergaard ., Waterloo K, Wang C *et al.*(2012):** *Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial.* Br J Psychiatry, 201(5): 360-8.
13. **Fernandes de Abreu D, Eyles D, Feron F.*Vitamin D(2009): A neuroimmunomodulator: implications for neurodegenerative and autoimmune diseases. Psychoneuroendocrinology , 34 (1): S265–77.***
14. **Langlois K, Greene-Finestone L, Little J, Hidiroglou N, Whiting S*(2010): Vitamin D Status of Canadians as Measured in the 2007 to 2009 Canadian Health Measures Survey. Health Reports 82-003-XPE: 8. Statistics Canada.***
15. **May HT, Bair TL, Lappe DL, Anderson JL, Horne BD, Carlquist JF *et al.(2010): Association of vitamin D levels with incident depression among a general cardiovascular population. Am Heart J ., 159: 1037–43.***
16. **Pan A, Lu L, Franco OH, Yu Z, Li H, Lin X(2009):** Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. Journal of affective disorders,118(1):240-3.
17. **Humble MB. Vitamin D(2010):** light and mental health. Journal of Photochemistry and Photobiology B: Biology,101(2):142-9.
18. **Sherrington C, Herbert R, Maher C A(2000):** database of randomized trials and systematic reviews in physiotherapy. *Man. Ther., 5*:223–226.
19. **Moher D, Liberati A, Tetzlaff J, Altman DG (2009):** *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med., 6(7):11-22.
20. **Veith R, Kimball S, Hu A, Walfish P(2004):** Randomized comparison of the effects of the Vitamin D3 adequate intake *versus* 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. *Nutr. J., 3*:8.
21. **Dumville J, Miles J, Porthouse J *et al.*(2006):**Can Vitamin D supplementation prevent winter-time blues? A randomised trial among older women. *J. Nutr. Health Aging , 10*: 151–153.
22. **Jorde R, Sneve M, Figenschau Y *et al.*(2008):**Effects of Vitamin D supplementation on symptoms of depression in overweight and obese subjects: Randomized double blind trial. *J. Intern. Med., 264*:599–609.
23. **Khajehei M, Abdali K, Parsanezhad M, Tabatabaee H(2009):** Effect of treatment with dydrogesterone or calcium plus Vitamin D on the severity of premenstrual syndrome. *Int. J. Gynecol. Obstet., 105*:158–161.
24. **Arvold D, Odean M, Dornfeld M *et al.*(2009):** Correlation of symptoms with Vitamin D deficiency and symptom response to cholecalciferol treatment: A randomized controlled trial. *Endocr. Pract., 15*:203–212.
25. **Belcaro G, Cesarone M, Cornelli U(2010):** Dugall, M. MF Afragil® in the treatment of 34 menopause symptoms: A pilot study. *Panminerva Med., 52*: 49–54.
26. **Sanders K, Stuart A,Williamson *E et al.*(2011):***Annual* high-dose Vitamin D3 and mental well-being: randomised controlled trial. *Br. J. Psychiatry , 198*: 357–364.
27. **Zhang M, Robitaille L, Eintracht S, Hoffer L(2011):** Vitamin C provision improves mood in acutely hospitalized patients. *Nutrition,27*: 530–533.
28. **Dean A, Bellgrove M, Hall *T et al.*(2011):***Effects* of Vitamin D supplementation on cognitive and emotional functioning in young adults—A randomised controlled trial. *PLoS One,6*:e25966.
29. **Bertone-Johnson E, Powers S, Spangler L(2012):**Vitamin D supplementation and depression in the women's health initiative calcium and Vitamin D trial. *Am. J. Epidemiol., 176*:1–13.
30. **Khoraminya N, Tehrani-Doost M, Jazayeri *S et al.*(2013):***Therapeutic* effects of Vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. *Aust. N.Z. J. Psychiatry , 47*:271–275.
31. Luppino F, Wit L, Bouvy P(2010): Overweight, obesity and depression. A systematic review and

meta-analysis of longitudinal studies. *Arch. Gen. Psychiatry* , *67*:220–229.

32. **Turner E, Matthews A, Linardatos *E et al.*(2008):***Selective* publication of antidepressant trials and its influence on apparent efficacy. *N. Engl. J. Med.*, *358*: 252–260
33. **Grudet C, Malm J, Westrin A *et al.*(2014):** *Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood.* Psychoneuroendocrinology, 50: 210-9.
34. **Cobb BS, Coryell WH, Cavanaugh J *et al.*(2014):** Seasonal variation of depressive symptoms in unipolar major depressive disorder. Compr Psychiatry,55(8):1891-9.
35. **Milaneschi Y, Hoogendijk W, Lips P *et al.*(2014):**The association between low vitamin D and depressive disorders. Mol Psychiatry,19(4):444-51.
36. **Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ(2005):** Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat., 29: 21–30.
37. **Wang TT, Tavera-Mendoza LE, Laperriere D, Libby E, MacLeod NB, Nagai Y *et al.* (2006):**Large-scale in silico and microarray-based identification of direct 1,25-dihydroxyvitamin D3 target genes. Mol Endocrinol 2005; 19: 2685–95. 61 Obradovic D, Gronemeyer H, Lutz B, Rein T. Cross-talk of vitamin D and glucocorticoids in hippocampal cells. J Neurochem.,96: 500–9.