Annual high-dose vitamin D₃ and mental well-being: randomised controlled trial

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Background
Epidemiological evidence supports a relationship between vitamin D and mental well-being, although evidence from large-scale placebo-controlled intervention trials is lacking.

Aims
To examine if vitamin D supplementation has a beneficial effect on mood in community-dwelling older women; if a single annual large dose of vitamin D has a role in the prevention of depressive symptoms; and if there is an association between serum 25-hydroxyvitamin D levels and mental health.

Method
A double-blind, randomised, placebo-controlled trial of women aged 70 or older (the Vital D Study: ISRCTN83409867 and ACTR12605000658617). Participants were randomly assigned to receive 500 000 IU vitamin D₃ (cholecalciferol) orally or placebo every autumn/winter for 3–5 consecutive years. The tools utilised at various time points were the General Health Questionnaire, the 12-item Short Form Health Survey, the Patient Global Impression–Improvement scale and the WHO Well-Being Index. Serum 25-hydroxyvitamin D levels were measured in a subset of 102 participants.

Results
In this non-clinical population, no significant differences between the vitamin D and placebo groups were detected in any of the measured outcomes of mental health. Serum 25-hydroxyvitamin D levels in the vitamin D group were 41% higher than the placebo group 12 months following their annual dose. Despite this difference, scores from the questionnaires did not differ. Furthermore, there was no interaction between those on antidepressant/anxiety medication at baseline and the treatment groups.

Conclusions
The lack of improvement in indices of mental well-being in the vitamin D group does not support the hypothesis that an annual high dose of vitamin D₃ is a practical intervention to prevent depressive symptoms in older community-dwelling women.

Declaration of interest
M.B. and S.D. have relationships with Stanford Medical Research Foundation, NHMRC, Beyond Blue, Eli Lilly, GlaxoSmithKline, Organon, Mayne Pharma and Servia. M.B. has relationships with MBF, Geelong Medical Research Foundation, Bristol-Myers Squibb, Novatis, AstraZeneca, Janssen-Cilag, Lundbeck, Pfizer, Sanofi Synthelabo, Solvay and Wyeth. S.D. has a relationship with Rotary that might have an interest in the submitted work in the previous 3 years.

Depression and other psychiatric conditions with a mood component are common and debilitating chronic illnesses that are often difficult to treat. A high prevalence of vitamin D insufficiency has been reported among most Western societies and the level of insufficiency is most marked among elderly people. In Australia, the prevalence of insufficiency (25-hydroxyvitamin D (25D) below 50 nmol/l) is approximately 50% among older community-dwelling women. Clinical psychiatric cohorts may have even higher rates of vitamin D insufficiency. In particular, it is postulated that low levels of vitamin D, known to be common in winter, may contribute to seasonal affective disorder and that older adults with vitamin D deficiency are more likely to have depressed mood.

Recent advances in the understanding of neural physiology strengthen the argument for a link between vitamin D status and mental health. Using animal models, cross-talk between vitamin D and glucocorticoids has been demonstrated in the hippocampus, and these signalling pathways are germane to disorders with dysregulated glucocorticoid signalling such as depression. The enzymes vitamin D 25-hydroxylase and 25D-1α-hydroxylase, necessary for the hydroxylation of 25D to active 1,25-dihydroxyvitamin D (1,25(OH)₂D) are present in various areas of the human brain including the hypothalamus, cerebellum, substantia nigra as well as retinal neurons. Locally produced 1,25(OH)₂D has a documented role in brain function.

Since vitamin D insufficiency is a treatable condition, vitamin D repletion in older adults may prevent or improve depressive symptoms. Despite epidemiological and in vitro evidence supporting a positive association between vitamin D levels and mental health there remains a dearth of evidence from large clinical trials. Among the small intervention trials there is heterogeneity in dose and inconsistent, albeit, suggestive findings. The Vital D study (ISRCTN83409867 and ACTR12605000658617) is the first large randomised placebo-controlled trial to investigate the impact of vitamin D supplementation on mood and depressive symptoms in a community-based cohort of older women. Furthermore, the utility of a single large annual dose of vitamin D is also investigated since previous trials reporting no benefit in the prevention of fractures have suggested that the likelihood of positive findings were hampered by low to moderate adherence to treatment regimes.

The aims of the mental well-being study were to determine in community-dwelling older women whether a single annual dose of vitamin D supplementation has a beneficial effect on mood and is a practical health intervention for the prevention of depressive symptoms; and whether there is an association between serum vitamin D levels and mood and well-being. The study’s hypothesis was that older women treated with a large annual dose of vitamin D (500 000 IU cholecalciferol) would perform better than women treated with placebo on mood-related psychiatric assessments. In a biochemistry substudy we hypothesised higher serum 25D levels would be predictive of better mental well-being compared with women with a lower vitamin D status.
Method

Study design
The Vital D study was a single-centre, large-scale double-blind, randomised, placebo-controlled trial involving women 70 years or older. The participants were randomly assigned to receive either an oral dose of vitamin D3 500,000 IU or matched placebo once each year for 3–5 years (in the autumn/winter). The primary end-point was falls and fractures, and participants were selected on the basis of hip fracture risk. These results have been reported elsewhere.23 The Vital D study concurrently investigated the effect of the vitamin D3 supplementation on mental well-being. This analysis relates to the three sets of mental well-being data that were prospectively collected.

The study was approved by the institutional ethical research boards of Barwon Health and the University of Melbourne and carried out in compliance with the Helsinki Declaration. An early protocol amendment enabled baseline data on mental well-being to be collected from participants recruited to the study during 2005. All women provided written informed consent and those enrolled in the substudy consented to the extra assessments.

Participants
The Vital D Study recruited 2317 community-dwelling women between 2003 and 2005.22 Invitation letters were sent to all women aged at least 70 years on the electoral roll of the Barwon and Mornington Peninsula regions (latitude approximately 38° South). Voting and voter registration is compulsory in Australia. Inclusion criteria has been previously described, but briefly included females ≥70 years who had an identified risk factor for hip fracture such as maternal hip fracture, self-reported ‘faller’, fracture since aged 50, and/or at high risk of low vitamin D and osteoporosis.24 The exclusion criteria were: inability to provide informed consent or falls/fracture data; permanent resident of high-level care facility; albumin-corrected calcium >2.65 mmol/l; vitamin D supplementation >400 IU/day; and other parameters relating to bone health.

Randomisation and intervention
Eligible participants were randomised to receive either 500,000 IU vitamin D3 or placebo. The allocation of treatment arm was performed by an independent statistician using computer randomisation of participants’ study identification number (Minitab). The participants and study staff were masked to the treatment allocation until completion of the study.

Identical tablets of placebo and 50,000 IU vitamin D3 were supplied by PSM Healthcare, Auckland, New Zealand. Study medication (10 tablets) was posted to participants annually during autumn/winter (March to August, determined by recruitment month), with instructions to take all 10 tablets on 1 day. Study staff confirmed ingestion by written or verbal confirmation within 2 weeks of postage.

Outcome measures
Age, calcium intake and fracture risk profile were documented at baseline in all participants. Three sets of mental well-being outcomes were included in the study; The General Health Questionnaire (GHQ)25 was completed at three time points: baseline, 12 months post-dose (immediately prior to the second dose of study medication) and at 15 months post-dose (3 months after the second dose). The data do not include the first 693 participants recruited into the study as the GHQ was added after a protocol amendment in April 2005. As baseline GHQ data were not available for these participants the GHQ data include all participants except those recruited prior to this amendment. The 12-item Short Form Health Survey (SF-12)26 questionnaire provided physical and mental component summary scores and was completed once by all participants immediately prior to their study completion in 2008, corresponding to an intervention period of 3–5 years.

The third set of mental health outcomes was collected only in a subgroup of participants who underwent serial biochemistry including serum 25D. These substudy participants were randomly selected from the entire group of participants and completed all the study data collection requirements at the same time points as all other participants. Additional mental well-being questionnaires were completed to coincide with the serial assessments of 25D status done in this subgroup of participants (as described below).

Substudy participants: biochemistry and mental well-being testing
Substudy participants (n = 150) were randomly selected (masked to treatment status) using their study identification numbers in a statistical program (Minitab, version 13 for Windows). These participants completed the two mood-related psychiatric questionnaires at six time points concurrently, with blood sampling during 2006 and 2007. The World Health Organization (WHO) Well-Being Index27 and the Patient Global Impression Improvement (PGI-I) scale28 questionnaires were completed and serum levels of 25D were assessed at: pre-dose (immediately prior to the current dose of study medication and corresponding to 12 months following last year’s annual dose), 1 and 3 months post-dose of study medication. Samples were frozen at −80°C until being batch analysed. Serum 25D was measured using radioimmunoassay (DiaSorin; Stillwater, Minnesota, USA).

Scoring of mental well-being assessments
The GHQ-12 questionnaire25 is a well-validated instrument for the identification and measurement of non-psychotic psychiatric disorders in community and medical settings.29 The self-reported GHQ-12 consists of 12 questions, each with a choice of four responses: ‘better than usual’ or ‘same as usual’ are both scored as ‘0’, whereas ‘less than usual’ or ‘much less than usual’ are both scored as ‘1’. Using the GHQ scoring method there is a maximum total score of 12 and a cut-off threshold of 3 analysed as a binary ‘yes/no’ outcome. A total score of 3 or greater has been reported as being indicative of a psychiatric disorder.29

The SF-12 consists of 12 questions with standardised categorical answers and is a widely used health survey relevant across all ages and disease categories. Data were scored according to the users’ manual30 providing both a physical component summary score and a mental component summary score for each individual.

The WHO Well-Being Index (version 2, 1998)27 is a 5-item self-report questionnaire, each question with a choice of five responses: ‘all of the time’ (scores 5); ‘most of the time’ (scores 4); ‘more than half of the time’ (scores 3); ‘less than half of the time’ (scores 2); ‘some of the time’ (scores 1); or ‘at no time’ (scores 0). The score for each question was totalled. Individuals were considered to have poor well-being and depression if their total score was <13 or if they answered 0 or 1 for any of the five items.30

The PGI-I scale is a validated adaptation of the Clinical Global Impression Scale28 that consists of one question that was altered
slightly as indicated in italics: ‘Circle the number that best describes how you have felt overall since you began taking the Vital D Study medication.’ There are seven answer choices ranging from ‘very much better’ (score, 1) to ‘very much worse’ (score, 7): this score was used in the analysis.

**Sample size**
The power calculations for the Vital D study were based on the primary outcome relating to a difference in fracture rates between the treatment groups. Nevertheless, given the large cohort required for the primary outcome, the study is adequately powered to detect a 50% relative difference in the proportion of participants with a score of three or greater in the GHQ questionnaire when 15% of the placebo group score three or greater (80% power and 0.05 level of significance).31

**Statistical methods**
All analyses were intention-to-treat. The physical and mental component summary scores from the SF-12 were compared between groups using t-tests. Since participants completed the GHQ, WHO Well-Being Index and the PGI-I scale on multiple occasions, a generalised estimating equation approach with robust standard errors and exchangeable correlation was used to allow for within-participant correlation. A linear link function was used for the WHO Well-Being score, and a logistic link function for the dichotomised WHO Poor Well-Being Index and the dichotomised GHQ score. For the GHQ score, baseline GHQ was adjusted for, to increase the statistical precision of the analysis. Results are presented as estimated differences in means (SF-12, WHO Well-Being, PGI-I scale) or estimated odds ratios (binary GHQ, binary WHO score) and 95% confidence intervals with Wald-test P-values.

To investigate the a priori hypothesis that the effect of vitamin D on mental well-being would differ by baseline antidepressant use, an interaction between trial arm and antidepressant was added to each of the models above. Wald tests for the interaction are presented with estimates of treatment effect within each subgroup. No adjustment was made for multiple testing. All P-values are two-sided. Analyses were performed in Stata 10.1 for Windows.

**Results**
Randomisation of participants, assessments and the number of participants who withdrew are shown in Fig. 1. There were no differences between the vitamin D and placebo groups in age or baseline use of antidepressants/anxiety medication (Table 1). Ingestion of study medication was high; over the course of the study 58 participants (33 in the vitamin D group and 25 in the placebo group) declined study medication and study medication was not dispensed to 105 participants (44 in the vitamin D group and 61 in the placebo group) as they reported taking greater than 400 IU of vitamin D supplementation. These participants were included in the intention-to-treat analysis.

**GHQ-12**
In total, 92% (n = 1434) of the 1565 Vital D participants recruited in 2005 completed the GHQ-12 at baseline. The proportion of...
participants in either treatment group with a psychiatric disorder as indicated by a GHQ score of $\geq 3$ varied between 14 and 18% across the three time points (Table 2). There was no difference in scores between the vitamin D and placebo groups at any time point ($P=0.69$, Table 3). There was no evidence of an interaction between treatment arm and use of antidepressant/anxiety medication.

**SF-12**

At study completion, 99% ($n=1011$) of participants completed the SF-12. There was no difference between the vitamin D and placebo groups in the mean scores from either the physical (41.4 v. 41.2, $P=0.66$) or the mental component summary (52.5 v. 52.6, $P=0.75$, Table 2). There was no interaction between treatment groups and use of antidepressant/anxiety medication, although there was a trend for those taking medication for treatment of anxiety or depression to score higher (i.e. better) on the SF-12 mental component summary if they were randomised to receive vitamin D rather than placebo ($P=0.11$, Table 3). However, there was no significant difference between the groups in the proportion of participants from each group who either commenced antidepressant/anxiety medication during the study or ceased antidepressants during the intervention period (vitamin D v. placebo group: commenced these medications: 5.2% v. 7.1%, $P=0.12$; proportion of participants taking these medications at baseline and ceased them during the intervention period: 24.6% v. 25.4%, $P=0.89$).

**WHO Well-Being Index and PGI-I scale**

In total, 91% (137/150) of those invited consented to the biochemistry substudy. The analysis included 118 participants (61 in the vitamin D group and 57 in placebo group) who completed at least one questionnaire. There were no differences in the scores from the WHO Well-Being questionnaires at any time point ($P=0.47$, Table 3). No interaction trend was found between treatment group and use of antidepressant/anxiety medication. Those taking medication for treatment of anxiety or depression did not score differently on the WHO Well-Being Index if they were randomised to receive vitamin D or placebo (Table 3 and Fig. 2). There was no difference between the vitamin

### Table 2 Outcome measures from 12-item Short Form Health Survey (SF-12) and General Health Questionnaire (GHQ)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Vitamin D group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-12 (completed in 2008)</td>
<td>1001</td>
<td>1011</td>
</tr>
<tr>
<td>Physical component score (normed), mean (s.d.)</td>
<td>41.4 (11.3)</td>
<td>41.2 (10.9)</td>
</tr>
<tr>
<td>Mental component score (normed), mean (s.d.)</td>
<td>52.5 (9.8)</td>
<td>52.6 (9.9)</td>
</tr>
<tr>
<td>GHQ-12, score of $\geq 3$, indicator for psychiatric disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (2005), % ($n$)</td>
<td>728</td>
<td>706</td>
</tr>
<tr>
<td>12 months post-dose (2006), % ($n$)</td>
<td>14.0 (102)</td>
<td>15.0 (106)</td>
</tr>
<tr>
<td>15 months post-dose (2006), % ($n$)</td>
<td>13.8 (91)</td>
<td>13.7 (89)</td>
</tr>
</tbody>
</table>

### Table 3 Estimated treatment effects: results from the questionnaires of the vitamin D group compared with placebo group$^a$

<table>
<thead>
<tr>
<th>Measure</th>
<th>Estimate</th>
<th>95% CI</th>
<th>$P$</th>
<th>$P$ interaction$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-item Short Form Health Survey, $\beta$ (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.22</td>
<td>$-0.75$ to $1.19$</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>0.23</td>
<td>$-0.88$ to $1.34$</td>
<td>0.69</td>
<td>0.98</td>
</tr>
<tr>
<td>Medication</td>
<td>0.27</td>
<td>$-2.40$ to $2.94$</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Mental component summary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>$-0.14$</td>
<td>$-1.00$ to $0.72$</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>$-0.39$</td>
<td>$-1.36$ to $0.57$</td>
<td>0.42</td>
<td>0.11</td>
</tr>
<tr>
<td>Medication</td>
<td>1.66</td>
<td>$-0.67$ to $3.98$</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>General Health Questionnaire, OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.06</td>
<td>$0.81$ to $1.37$</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>1.14</td>
<td>$0.84$ to $1.55$</td>
<td>0.39</td>
<td>0.31</td>
</tr>
<tr>
<td>Medication</td>
<td>0.82</td>
<td>$0.46$ to $1.45$</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>WHO Well-Being Index, OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO well-being score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>$-0.04$</td>
<td>$-1.52$ to $1.44$</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>$-0.18$</td>
<td>$-1.75$ to $1.38$</td>
<td>0.82</td>
<td>0.47</td>
</tr>
<tr>
<td>Medication</td>
<td>1.56</td>
<td>$-2.92$ to $6.03$</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>WHO poor well-being score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.85</td>
<td>$0.45$ to $1.61$</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>0.88</td>
<td>$0.45$ to $1.73$</td>
<td>0.89</td>
<td>0.73</td>
</tr>
<tr>
<td>Medication</td>
<td>0.61</td>
<td>$0.08$ to $4.47$</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

WHO, World Health Organization.

*a. Medication or no medication refers to participants taking medication for anxiety or depression at baseline. The estimate from the SF-12 results is the $\beta$ coefficient and the 95% confidence interval around this estimate, for the effect of the vitamin D group compared with the placebo group. The estimates for the results from the General Health Questionnaire and WHO Well-Being Index are the odds ratio and the 95% confidence around this ratio, of the effect of the vitamin D group compared with the placebo group. The subgroup of those with poor well-being was also analysed separately. Poor well-being and depression were indicated for those with a total score of $<13$ or for those who answered 0 or 1 to any of the five items.*

*b. The interaction $P$-value refers to a differing effect between the vitamin D and placebo groups when participants are grouped according to whether they were taking antidepressants or anti-anxiety medication at baseline.*
Annual high-dose vitamin D3 and mental well-being

Biochemical changes in serum 25D

There was no difference in serum 25D between the groups at baseline (Table 1). Approximately half the substudy participants had serum 25D of 50 nmol/l or lower (46 and 61%, vitamin D and placebo groups respectively) but less than 3% had levels <25 nmol/l (1.8 and 2.7% respectively).

Detailed biochemistry data were collected on 102 (86%) of these substudy participants during 2006 and 2007, coinciding with their second to fifth annual dose of study medication. Immediately prior to the annual dose of study medication, the vitamin D group had mean serum 25D levels 41% higher than the placebo group (ratio of geometric means 1.41 95% CI 1.27–1.57; P < 0.001) at approximately 70 nmol/l. One month post-dose the mean serum 25D levels of the vitamin D group was approximately 122 nmol/l (median 2006 and 2007 respectively: 121 and 124 nmol/l). By 3 months post-dose the median 25D level decreased to approximately 90 nmol/L (median 2006 and 2007 respectively: 87 and 94 nmol/l).

Relationship between serum 25D and mental well-being

There was no significant relationship between serum 25D levels and the assessments of mental well-being completed at the time of blood sampling (Fig. 3). Despite the changes in serum 25D levels (Fig. 3(a)), there was no evidence of any apparent trends between serum 25D and the scores from either the WHO Well-Being Index or the PGI-I scale (see 1-month post-dose data Fig. 4(a) and 4(b)).

Adverse events

A similar number of participants reported an adverse event in each group: 19.7% (223/1131) in the vitamin D group and 17.8% (200/1125) in the placebo group. Overall, 33 participants (2.9%) from the vitamin D group and 22 participants (1.9%) from the placebo group reported more than one adverse event. The most commonly reported adverse events were ‘injury
improved scores on the SF-12 mental health component summary medication for treatment of anxiety or depression to have medication. There was a non-significant trend for those taking participants had ingested at least three annual doses of study groups when administered 12 months post-dose and after the SF-12 did not differ between the vitamin D and placebo groups at any of the three assessments (baseline, 6 months after adjusting for age and mental health outcomes measured 1, 3 or 12 months following the annual dose of study medication, the indices of mental well-being did not appear to be influenced by the abrupt changes in serum 25D levels as demonstrated in our nested substudy.

**Main findings**

In this large randomised trial investigating the potential benefits of a single, annual dose of 500 000 IU vitamin D₃, no consistent significant differences were detected between the vitamin D and placebo groups in any of the measured outcomes of mental health. Results from the GHQ-12 indicate that fewer than 20% of the cohort of almost 1600 older women had scores consistent with a non- psychotic psychiatric disorder, and this proportion did not differ between the groups at any of the three assessments (baseline, 12 months and 15 months post-dose). Similarly, the mental health and the physical health component summary scores from the SF-12 did not differ between the vitamin D and placebo groups when administered 12 months post-dose and after participants had ingested at least three annual doses of study medication. There was a non-significant trend for those taking medication for treatment of anxiety or depression to have improved scores on the SF-12 mental health component summary if they received vitamin D rather than placebo; however, this was not a consistently observed pattern.

The relationship between serum vitamin D status and mental well-being was tested in more detail in the nested subset of participants who had serial biochemistry samples taken at baseline and during the intervention period. Biochemistry results demonstrate that serum 25D were low to moderate at baseline and typical of this population of community-dwelling older women; remained low to moderate in the placebo group; initially spiked in the vitamin D group (approximately 120 nmol/l at 1-month post-dose) and remained in the high to normal range at 12-month post-dose (approximately 70 nmol/l). At each blood sampling taken 12 months post-dose, serum 25D levels were, on average, 41% higher in the vitamin D group compared with the placebo group. Despite these biochemical changes, vitamin D status was not a significant predictor of mental well-being when assessed using either the WHO Well-Being Index or the PGI-I scale scores. Since there were no significant differences in mental health outcomes measured 1, 3 or 12 months following the annual dose of study medication, the indices of mental well-being did not appear to be influenced by the abrupt changes in serum 25D levels as demonstrated in our nested substudy.

**Discussion**

There are inconsistent findings on the association between vitamin D and mental health. Epidemiological studies have reported associations between vitamin D insufficiency and the presence of mood disorder and depression. A low level of serum 25D was significantly associated with a high depression score in a small observational study. Similarly, no difference in questionnaire scores (Fibromyalgia Impact Questionnaire) were detected using 400 000 IU vitamin D₃ over 8 weeks when given to individuals with frank vitamin D deficiency (serum 25D, less than 10 nmol/ml (25 nmol/l)) nor when given to a group randomised to receive 400 000 IU vitamin D₃ or placebo. Although serum 25D levels increased in these two groups by a mean of 93 and 68 nmol/l respectively, there was no significant improvement in depression (including seasonal), fatigue or musculoskeletal symptoms. Our results demonstrating no improvement in mental health scores are also consistent with those of a UK randomised unmasked trial of 1621 women aged 70 years and older. Participants completed the SF-12 questionnaire both at baseline and at 6 months. Those randomised to the treatment group received 800 IU vitamin D₃ and 1000 mg calcium each day. Women allocated to the control group did not receive any study medication or placebo. There was no difference in the mental component summary score between the groups at 6 months after adjusting for age and baseline mental component summary score (P = 0.262). In a small study of individuals comparing 100 000 IU of vitamin D with phototherapy for seasonal affective disorder, depressive symptoms improved in those who received vitamin D, but not the phototherapy group. Following the administration of vitamin D₃ in late winter, improved positive affect and reduced negative affect has been reported. In a randomised trial of overweight or obese people, high-dose vitamin D (20 000 or 40 000 IU per week) for 1 year had a beneficial effect on depressive symptoms compared with the placebo group; however, the study’s cross-sectional analysis suggested a threshold effect. In those with baseline 25D levels >40 nmol/l there was no apparent change in the group receiving the vitamin D. Although we only have 25D levels in a subset of 137 participants, few of these Vital D participants were clearly deficient at baseline with the interquartile range of 25D being 40–63 nmol/l. A review of the evidence linking vitamin D deficiency to brain dysfunction concludes that direct effects of

![Fig. 4 Scatterplots for (a) World Health Organization (WHO) Well-Being Index score against serum vitamin D at 1 month post-dose, and (b) Patient Global Impression Improvement (PGI-I) scale score against serum vitamin D at 1 month post-dose.](image-url)
vitamin D inadequacy on cognition/behaviour appear to be subtle with current experimental evidence not fully satisfying usual criteria. 

Although currently available evidence strongly suggest a role for 1,25(OH)2D in the nervous system, Garcia and colleagues have postulated that 1,25(OH)2D functions might overlap with other signalling pathways and may be protected in the central nervous system. 

The role of 1,25(OH)2D therefore might not be apparent in the absence of other pathogenic processes. Similarly, other signalling pathways relevant to psychological end-points may overlap with no obvious phenotypic symptoms. Interestingly, a recent population-based case-control study has reported a U-shaped relationship between neonatal 25D status and risk of developing schizophrenia by the age of 24 years. 

The relative risk was increased for neonates in each of the three lowest quintiles of 25D. The authors report that neonates in the highest quintile also had an increased risk of later developing schizophrenia. Our Vital D study was not powered in regards to the 25D levels of the substudy to detect a U-shaped response to the questionnaire data.

Limitations

We acknowledge that the apparent lack of mental health benefit in the vitamin D group may be confounded by the unexpected increased rate of falls and fractures in this group compared with placebo. As previously reported the vitamin D group had a 15% higher rate of falling (incidence rate ratio (IRR) = 1.15, 95% CI 1.02–1.30, P = 0.003) and 26% higher rate of fracture (IRR = 1.26, 95% CI 1.00–1.59, P = 0.047) compared with the placebo group. Biochemistry results from our substudy suggest that only a very small proportion of participants were clearly in the vitamin D deficient range (serum 25D < 25 nmol/l) and about half of our substudy participants had baseline 25D levels above the insufficiency threshold of 50 nmol/l. Furthermore, changes in outcome measures may have occurred outside the visit schedule. Moreover, the outcome measures may not have been sufficiently sensitive to changes in mental well-being. The therapeutic response of a non-clinical sample may differ substantially from clinical effects evident in a group of individuals with depression. However, the community-based study sample provides a novel perspective of the issue. The major advantage of the Vital D study is the population-based recruitment of a large number of participants and the 3 to 5-year intervention period. The study design adequately addressed the adherence issue for vitamin D supplementation.

Implications

Whereas findings from in vitro studies suggest a plausible link between depressive mood and vitamin D insufficiency, results from observational and small intervention studies have been inconsistent and the evidence base to date is not sufficient to conclude with certainty that there is a causal connection. Results from this large randomised intervention trial do not support a therapeutic role for annual high-dose supplementation of vitamin D in older women and did not contradict a hypothesis that other compensatory neural pathways are activated in the presence of low vitamin D status. In conclusion, this study found no benefit of vitamin D supplementation for mood and general well-being in older women. The study therefore does not support the hypothesis that annual doses of the ‘sunshine’ vitamin are a practical intervention to prevent depressive symptoms in older community-dwelling women. The results of this pragmatically designed trial highlight the need for further understanding of the mechanisms and pharmacokinetics of vitamin D in relation to mental health. Clinical trials of vitamin D in clinical populations with documented insufficiency remain warranted.

References

Projective identification

Jeremy Holmes

Psychiatrists use their feelings to empathise with patients. But sometimes love, hate, fear, rage, horror overwhelm, leading to bad decisions. Projective identification helps theorise this. Babies expel difficult feelings into a ‘bad mother’, who then ‘detoxifies’ what the baby cannot tolerate. But sometimes, especially with an unresponsive caregiver, projective identification represents the child’s only means of affective communication.

Treating people with borderline personality disorder, distracted mental health workers may enact patient’s feelings rather than detoxifying them, with consequent chaos. Awareness of projective identification counters splits and boundary-breaking, helping psychiatrists see their countertransferrental feelings as manifestations of the patient’s inner world.
Annual high-dose vitamin D₃ and mental well-being: randomised controlled trial
Kerrie M. Sanders, Amanda L. Stuart, Elizabeth J. Williamson, Felice N. Jacka, Seetal Dodd, Geoff Nicholson and Michael Berk
Access the most recent version at DOI: 10.1192/bjp.bp.110.087544

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