

Research Article

A Chart Review Comparison of Rates of Abnormal Vitamin D Results in New Zealand and United States Mental Health Samples

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ABSTRACT

Background: Epidemiological studies have shown associations between vitamin D and its role in improving health outcomes. Vitamin D levels vary according to sun exposure and skin pigmentation. While there is little doubt that vitamin D levels effect bone health, there has been controversy and growing interest in the role of vitamin D in mental health population.

Objective: The purpose of this study was to identify and compare vitamin D levels within the mental health population using samples from a United States city, Champaign, Illinois, and a New Zealand city, Auckland.

Method: A retrospective chart review of 64 participants was conducted within two mental health clinics (Champaign, Illinois, United States: n=32; Auckland, New Zealand: n=32). 25-hydroxyvitamin D concentration was obtained through blood samples within this population.

Results: New Zealand patients had lower levels of vitamin D than United States patients ($p = .0017$), but this difference appears to be due to differences in skin pigmentation between the two samples. Within the New Zealand sample, people

with higher pigmentation had lower vitamin D levels ($p < .001$) than those with lower pigmentation. Among higher pigmented individuals, 87% (New Zealand laboratory Guidelines) and 100% (United States laboratory Guidelines) had vitamin D abnormalities. Even amongst New Zealand lower pigmented individuals, 47% (New Zealand laboratory Guidelines) or 65% (United States laboratory Guidelines) had vitamin D abnormalities.

Conclusion: High levels of vitamin D abnormalities were found in two ambulatory mental health populations in two different hemispheres, Champaign, Illinois, United States and Auckland, New Zealand. Any degree of skin pigmentation beyond Caucasian was associated with greater vitamin D deficiency. The implications of these findings for the mental and physical health of mental health patients with abnormal vitamin D levels remain unknown, but highlight a discrepancy between lab guidelines and abnormal test results.

Mesh Headings/Keywords: Vitamin D; Mental health population; Vitamin D testing guidelines

Introduction

Mental disorders including depression and anxiety are a leading cause of disability and disease burden worldwide [1]. There is a complex interplay between genetics, biological and environmental factors in the aetiology of mental disorders. Vitamin D levels fluctuate according to amount of sun exposure [2]. Due to the seasonal aspects of mood disorders [2-6], higher rates of schizophrenia have been observed for winter pregnancies [7]. Researchers have also found lower vitamin D levels in institutionalized populations [8,9]. Since many people with severe anxiety and mood disorders have decreased outdoor activity, there is a growing interest in the role of vitamin D in mental health conditions.

Vitamin D is a fat soluble nutrient that is required for absorption and utilization of calcium and phosphorous which is then absorbed in the duodenum [10-12]. It may act as a neurosteroid regulating multiple pathways for proper function of the brain and its development [13]. Not only have animal studies supported the role of vitamin D in brain function [14-17],

but a number of epidemiological studies have also examined the links with various mental health disorders and vitamin D in populations [18-23]. However, there are mixed results. For example, a correlation between low vitamin D and mood disorders has been observed [24-26] but other studies have shown no such associations [27,28]. A 2014 meta-analysis of randomized controlled trials including 4,923 subjects showed no significant reduction in depressive symptoms following vitamin D supplementation [29]. The authors of this meta-analysis noted that most of the studies focused on individuals with low levels of depression and sufficient vitamin D levels at baseline. They suggest that future RCTs be conducted with individuals with depression and low vitamin D levels. The authors also point out that there was variability in the doses of vitamin D administered. In the experience of the lead author of our paper normalizing abnormally low levels of vitamin D often requires supplementation well above the recommended daily allowances. In the support of this, a small RCT of 36 subjects, treated with 50,000 IU vitamin D per week showed a trend toward greater improvement compared to placebo ($P = .06$), but also showed improvement on a number of biomarkers of oxidative stress and insulin resistance [30].

Studies have also looked at other aspects of brain functioning beyond depression. A longitudinal study of the elderly population in Italy showed an association of low vitamin D and substantial cognitive decline [31,32], however, such associations have not been observed in other studies [33-35]. It has also been demonstrated that low vitamin D is associated with psychosis [36-39]. A recent meta-analysis observed that schizophrenia had a medium effect size for lower vitamin D than healthy controls [40] while another case control study showed vitamin D levels were lower in those with first episodes of psychosis ($p < 0.001$) than the controls [37]. Other associations were also observed for low vitamin D in adults and various indicators of cognitive function, including memory and orientation [31,32,41,42], as well as dementia and Alzheimer's disease [43]. More recently a systematic review and meta-analysis studied the location and changes in size of the brain that is linked to vitamin D depletion or repletion. They concluded that participants with vitamin D deficiency have smaller brain volume and enlarged lateral ventricles than participants without vitamin D deficiency [44]. However, the causality of this association was not confirmed.

Further evidence suggests that vitamin D is not only tissue dependent but is also disease dependent [45]. Depending on the target tissue, different levels of vitamin D may be required [46]. For example, an approximate level of 20-25 nmol/L of vitamin D is required for the prevention of rickets but for the prevention of osteoporosis it is higher (concentration of 50-60 nmol/L) [47]. For cancer prevention, a study showed that serum vitamin D levels of between 90-120 nmol/L appeared to be more desirable [48]. Whilst vitamin D has a preventive and therapeutic role in human health, there is the possibility of toxicity at much higher levels (>100 nmol/L) which can produce renal atrophy and calcification and can go unrecognised until clinical signs of renal disease appear [49,50]. There were no studies that had identified the actual dose of vitamin D for optimal brain function. Therefore understanding vitamin D levels within populations with mental health disorders becomes important so that appropriate measures can be taken at both public health and clinical levels.

Vitamin D can be in the form of D5 (sitocalciferol) which is synthetic, D2 (ergocalciferol) that comes from fungus and D3 (cholecalciferol) from animal sources synthesised by the skin under ultraviolet rays and commercially produced as a vitamin supplement by irradiating lanolin from sheep's wool with ultraviolet light [51,52]. Sun exposure is the best source of vitamin D3; however, many factors influence the absorption of vitamin D through the skin. These factors include limited exposure to sunlight which could be due to covered clothing or sunscreen [53], malabsorption due to gastrointestinal problems, or hepatic and renal diseases [52-56]. High latitude and seasons can also influence the synthesis of vitamin D [57,58]. The few food sources that naturally contain vitamin D are cod liver oil, sardines and mackerel [59]. Food items such as milk, cereals, orange juice and bread are also fortified with vitamin D in some countries [59,60]. Older people even when exposed to the sun, synthesize 75% less vitamin D than their younger counterparts [61]. Vitamin D is first converted to 25(OH)D which circulates within the body and then further converts to the active 1,25-dihydroxyvitaminD (1,25(OH)₂D) [62]. Even though 1,25-dihydroxyvitaminD (1,25(OH)₂D) is the active

form of the vitamin, it does not reflect the body's storage; instead 25(OH)D concentration is seen as the most reliable indicator of vitamin D [62]. However, measuring vitamin D can be expensive and hence guidelines are usually in place before testing for vitamin D levels in individuals. For example, strict guidelines have been implemented in New Zealand (NZ) for testing vitamin D, however the United States (US) does not have uniform guidelines regarding ordering the laboratory (lab) evaluation. The US Preventive Services Task Force (USPSTF) and Institute of Medicine (IOM) released guidelines for the US and Canada, recommending testing vitamin D in only people with bone health issues [63-65]. In NZ, unless severe deficiency is suspected, testing for vitamin D is not recommended, and even then ordering the blood test is restricted to endocrinologists unless special permission is approved [66]. But some researchers argue that these guidelines are too conservative [67,68]. Plus there is constant debate around the terminologies (sufficiency, insufficiency/deficiency, optimal range and toxicity) and serum concentrations for vitamin D [45,69]. There is variation in cut-off points for vitamin D deficiency and insufficiency between different guidelines, countries and labs, with deficiency levels defined from as low as 25 and as high as 50 nmol/L, insufficiency levels defined from as low as 25 and as high as 75 nmol/L, and normal levels being set as low as above 50 and as high as above 75 nmol/L. Also, different units of measurement are used in the international literature, some countries use ng/ml and others use nmol/L. This variation within the scientific literature makes study comparisons and interpretations difficult.

Some authors consider vitamin D deficiency/insufficiency to be the most common nutritional deficiency and one of the most common undiagnosed medical conditions in the world [63], thus identification of vitamin D levels within the psychiatric population is relevant. Studies worldwide have identified high levels of vitamin D deficiency/insufficiency [1,12,31,50,70,71].

In a survey of 4721 adults aged 15 years and over, conducted by the Ministry of Health in NZ, about 5% of adults were vitamin D deficient and a further 27% were below the recommended blood level of vitamin D [72]. There were ethnic differences in that about 10% of Pacific people and 6% of Māori had vitamin D deficiency according to the findings from the Ministry of Health [72]. Furthermore in NZ, it was also reported that vitamin D levels were significantly lower in the obese individuals than people who were in the normal range or underweight (prevalence 0.86 (CI: 0.81-0.91)), after adjusting for age, sex and ethnic group [72]. In the US, the National Health and Nutrition Examination Survey (NHANES) carried out in 2005 to 2006, reported a mean serum levels exceeding 56 nmol/L in all the age groups [70]. Within this population, younger people had higher vitamin D levels compared to their older counterparts. The NHANES study also noted that the vitamin D levels have declined over the past 20 years [70]. There are a number of questions regarding the role of high levels of vitamin D deficiency/insufficiency world-wide, and particularly in various mental health populations, and the question of the role of vitamin D in mental health conditions. Clinicians are left in the difficult position of having conflicting testing and treatment guidelines in the context of high levels of vitamin D abnormalities in mental health populations. It is unclear whether these lab abnormalities have clinical significance for patients'

physical and mental health. This study aimed to investigate the prevalence of vitamin D abnormalities within a sample of the outpatient psychiatric population in both the US and NZ, the relationship between psychiatric diagnosis and vitamin D levels, and the relationship between vitamin D levels and skin pigmentation, and between a city in the northern and a city in the southern hemisphere.

4. Methods

This is a retrospective chart review which was conducted in the city of Champaign in the US (population of 231,000) and in the city of Auckland in NZ (population of 1.4 million) between 2008 and 2011. Champaign is located at latitude 40.12 degrees in the northern hemisphere and Auckland is located at -36.85 degrees in the southern hemisphere (with Auckland being closer to the equator). Champaign has a broader temperature range of -4.5 to 23.9 degrees Celsius, whereas Auckland's range is 11 to 19.5 degrees Celsius.

Clinical chart review centres and study population

The centres where the clinical chart reviews were conducted were in a private psychiatric practice (Champaign, Illinois, US) and in a community mental health centre (CMHC) (Auckland, NZ). The US practice was a solo "micropractice" model, providing medication management, psychotherapy, and lifestyle modification where clients were primarily self-referred. The NZ practice was at Manaaki House, one of 4 CMHCs for Auckland District Health Board. Clients are generally referred through General Practitioners, the Crisis Team, and Hospital Discharge, and many were under the Mental Health Act. For this retrospective review, 32 charts were reviewed in each of the two centres (n= 64) by the same Psychiatrist in each of the two centres. Inclusion criteria for the clinical review included adults aged 18 years and over, those with low sun exposure, higher skin pigmentation, mood disorder diagnosis and treatment resistance as well as client request.

Vitamin D measurement

25-hydroxyvitamin vitamin D concentration was obtained through blood samples and sent to lab in patients' respective cities. However, labs for US and NZ samples used different cut-offs for abnormal vitamin D. Vitamin D levels were measured in ng/ml in the US and nmol/L in NZ. US results were converted to nmol/L to allow comparison. During the course of the study in NZ, protocols for ordering vitamin D testing changed. At first there were no restrictions in ordering vitamin D levels then doctors were advised to automatically treat individuals at high risk for vitamin D deficiency ("those of Indian or African descent, or with inadequate sun exposure") without ordering the costly test, near the end of the study, testing of vitamin D levels was restricted to Endocrinologists only.

Statistical analysis

All statistical analysis were performed in SPSS. The total number and percentages of the study population was provided. Summary statistics for vitamin D levels was calculated which included the mean and range, measured in nmol/L, rates were also calculated of vitamin D abnormality. A significance level of $p > .001$ was applied where required.

Ethical approval was sought from the Auckland District Ethics Board to conduct the clinical audit.

Results

There were 64 participants whose charts were reviewed in both Champaign and Auckland. The Champaign participants were of European-American ancestry. NZ participants were a range of ethnic groups (Table 1). Majority of the participants were between 36-59 year brackets (53%). No significant differences were found with regards to age and gender (p value of >0.001).

Distribution of Vitamin D levels

The US population had higher vitamin D levels compared to NZ as shown in Figure 1. The range for vitamin D for the US population was between 17.5 nmol/L and 152.5 nmol/L. And the range for NZ population was between <10 nmol/L and 128 nmol/L. The overall mean vitamin D levels within the US sample was 72 nmol/L (SD: 31) while for NZ it was 48 nmol/L (SD: 32). From Figure 1, the US sample is normally distributed while the NZ sample distribution is skewed.

Vitamin D status by lab guidelines

This study compares the cut-offs for differentiating levels of vitamin D based on the NZ lab values used by Auckland District Health Board and those from a region in central Illinois, which is located in the "Midwest" of the US. The Table 2 also includes the guidelines recommended in 2010 by the Institute of Medicine, which as can be seen represent yet a third set of criteria for determining abnormal vitamin D levels. Table 2 shows the discrepancies in determining what is a normal and abnormal vitamin D level based on the labs used in the US and NZ samples, as well as through the Institute of Medicine. The US lab used for this sample had higher requirements for "normal" vitamin D levels.

As can be seen in Table 3, dramatically different results are obtained using the more stringent US guidelines compared to the NZ guidelines. By US lab values, 81% of the NZ sample would have abnormal vitamin levels, for the US population 59% had abnormal levels. Even using the less stringent NZ lab

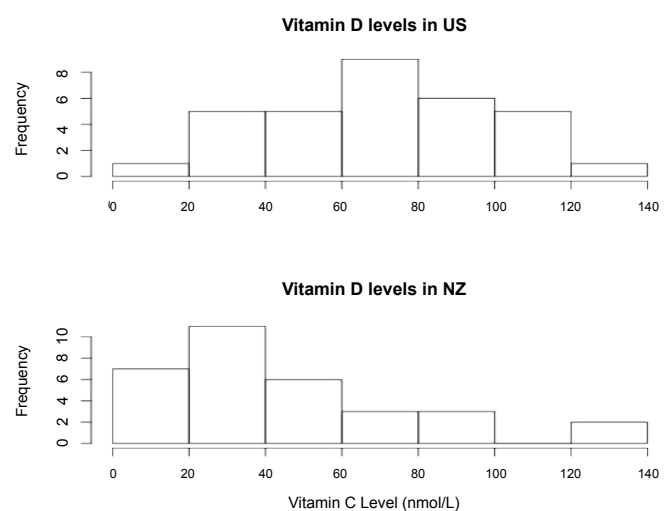


Figure 1: The distribution of vitamin D levels in the US and NZ samples.

Table 1: Description of all participants (n=64).

	Number (%)
Place	
<i>Champaign</i>	32 (100)
European American	
<i>Auckland</i>	
European	17 (53)
Maori	5 (16)
Pacific	3 (9)
Asian	6 (19)
African	1 (3)
Age range	
18-35	12 (19)
36-59	34 (53)
≥ 60	18 (28)
Gender	
Female	43 (67)
Male	21 (33)

Table 2: Cut-offs of abnormal vitamin D levels per different labs and guidelines (nmol/L).

	NZ Lab	US Lab*	IOM 2010 Guidelines*
Deficient	<25	<50	<30
Insufficiency	25-50	50-75	30-50
Normal	>50	>75	>50

*Note that units the figures for the US lab and IOM are converted from ng/ml to nmol/L by multiplying by 2.5

Table 3: Vitamin D lab results for each sample using US and NZ lab cut-offs.

Sample Country	NZ Lab Guidelines		US Lab Guidelines	
	US	NZ	US	NZ
Deficiency	9%	22%	22%	66%
Insufficiency	13%	44%	37%	15%
Normal	78%	34%	41%	19%

guidelines, still 66% of the NZ sample had abnormal vitamin D levels, and the US population has 22% abnormal levels.

The US private practice population included only Caucasian individuals. The NZ community mental health population had n=17 Caucasian and n=15 non-Caucasian. Based on levels of skin pigmentation (with the Caucasian population being considered low and all other populations considered higher), under the US lab guidelines, 100% of higher pigmented New Zealanders would be found to have abnormal vitamin D levels, whereas the combined NZ and US low pigmented group had 65% abnormal levels. Under the NZ guidelines, 87% of higher pigmented individuals had abnormal vitamin D levels and the low pigmentation group had 47% abnormal levels (Table 4).

Discussion

This retrospective chart review highlights many of the controversies around testing for and treating vitamin D

Table 4: Rates of vitamin D abnormality based on higher/low* pigmentation comparing NZ and US lab guidelines.

Level of Pigmentation	NZ Lab Guidelines		US Lab Guidelines	
	Higher	Low	Higher	Low
Deficiency	33%	12%	87%	47%
Insufficiency	54%	35%	13%	18%
Normal	13%	53%	0%	35%

*Higher vs. low pigmentation was based on a crude distinction of Caucasian vs. non-Caucasian. Given the small sample size, the decision to lump all higher pigmented individuals into one group for comparison was made. Pigmentation is a factor in how readily an individual creates vitamin D following sun exposure, as skin pigmentation blocks harmful sun rays as well as those involved in vitamin D synthesis.

insufficiency and deficiency. On the one hand, testing in mental health populations reveals high levels of abnormal vitamin D levels. This study supports the findings of previous research on mental health populations, revealing high levels of abnormal vitamin D levels. Depending on the cut-off criteria used by the lab, the majority of those sampled were found to have abnormal vitamin D (using US lab cut-offs, 59% of the US and 81% of the NZ samples; using NZ lab cut-offs, 22% of the US and 66% of the NZ samples). On the other hand, the Institute of Medicine and NZ lab ordering protocols discourage the testing of vitamin D levels in the mental health population and focus primarily on bone health. The vitamin D testing protocols advocated by these bodies indicate that they believe that vitamin D levels have little or no relevance in the treatment of psychiatric disorders.

Before we can even begin a discussion about whether vitamin D levels should be tested in a mental health population, there are a number of complicating factors. First of all is the use of different units of measurement in different studies, with US studies seeming to use ng/ml and other studies using nmol/L. Additionally, different countries and even different laboratories within countries may have different cut-offs for differentiating vitamin D deficiency, insufficiency, and normal levels. These two factors are crucial to consider when evaluating the research data. Further, in an era of cost-containment, many organizations are limiting the ability of clinicians to measure vitamin D levels. It was partly this very limitation that led to this audit being done. It is safe to say that testing vitamin D levels has the highest yield of abnormal test results of any screening laboratory test done in mental health. The question remains of whether diagnosing and treating abnormal vitamin D levels improve the physical and mental health of our patients.

Arguments for testing vitamin D in the mental health population include the high rates of social isolation (and subsequent decreased exposure to sunlight) and also periods of institutionalization that may also limit sun exposure. Preliminary data support at least the possibility that vitamin D levels may play a role in the course of mood disorders. Vitamin D also has a suggested role in pain levels. A last argument is that mental health is integrally linked to physical health and vice versa. Possible roles of vitamin D in hypertension and diabetes are relevant to the medical management of mental health patients.

Even using the most stringent criteria of testing vitamin D levels in regard to bone health, this study shows that screening vitamin D levels reveals troubling rates of vitamin D deficiency, which could be silently leading to bone health issues (using US lab guidelines 22% of the US and 66% of the NZ samples have deficiency; using the NZ lab guidelines 9% of the US and 22% of the NZ samples had vitamin D deficiency).

If it were considered worthwhile to measure vitamin D levels as part of mental health treatment or as part of general health screening, it would be useful to know if a sub-population of people receiving mental health treatment were at higher risk. Given the primary source of vitamin D is through sun exposure, sub-populations who had limited sun exposure are at increased risk of abnormal vitamin D levels. The current study was done on ambulatory outpatients and did not include institutionalized patients. Also, no difference was found between vitamin D levels and psychiatric diagnoses. Further, no difference was found based on the number of psychiatric medications an individual was taking (an indirect measure of severity of condition). Although other studies have shown advancing age as a risk factor, the current study did not show this relationship. Gender in this study was also not a significant factor.

The primary significant variable in this study that was linked to abnormal vitamin D levels was skin pigmentation. As a retrospective study with a small sample size, ethnicity was used as an indirect estimator of skin pigmentation. The sample was divided into two groups, with Caucasian (NZ Europeans) being considered low skin pigmentation, and all other ethnicities being considered high skin pigmentation (in this sample this included Māori, Polynesian, Asian, Indian sub-continent, and Africans). The US sample was very homogenous, with an all-Caucasian population. The NZ population was much more heterogeneous, with roughly half of the sample having higher pigmentation. The NZ low skin pigmentation group had vitamin D levels that were twice those of the NZ high skin pigmentation group. Looking at abnormal vitamin D levels in the high pigmentation group, using the US lab guidelines 100% of this group had abnormal vitamin D levels; using the NZ lab guidelines 87% of the high pigmentation group had abnormal vitamin D levels. These are astounding figures.

This study has a number of limitations. It is a retrospective chart review and should not be considered in any way a random or blinded study. It grows out of the intersection of research and clinical practice, and in fact the NZ portion of the study was done as part of a clinical audit, a practice review that is one of the requirements of certification through the Royal Australian and New Zealand College of Psychiatrists. The value of research is not research as an end, but as it can be used to inform clinical practice. The sample chosen by the first author from his clinical practice should be taken to represent those individuals suspected of being at risk for abnormal vitamin D levels. This decision included a number of factors: treatment resistance, avoidance of social/sun exposure, seasonal mood disorder and also patient request. If these clinical factors play a role in selecting individuals with higher risk for abnormal levels of vitamin D, then this study represents not a general sample, but a testing of individuals clinically suspected to be at higher risk.

The most helpful future research would be a large, prospective study that included testing of all patients entering treatment for

mental health conditions, randomization with some subjects receiving vitamin D replacement therapy and others not, with the treatment being double-blinded. An estimate of sun exposure would be a useful variable, as would be an estimate of severity of disorder, treatment resistance, diagnostic classification (anxiety, mood, psychotic disorder), perhaps physical health disorders. According to the current study, the degree of skin pigmentation is another variable that would be important to measure. As always, although evidence continues to mount about the importance of vitamin D for optimal performance of the brain and body, further research is required into this.

Conclusion

High levels of vitamin D abnormalities were found in two ambulatory mental health populations in two different hemispheres, Champaign, Illinois, US and Auckland, NZ. Any degree of skin pigmentation beyond Caucasian was associated with higher levels of abnormal vitamin D. The implications of these findings for the mental and physical health of mental health patients with abnormal vitamin D levels remain unknown, but highlight a discrepancy between lab guidelines and abnormal test results. From a public health perspective, there could be considered to be an epidemic of abnormal vitamin D levels in international mental health populations, particularly for those individuals with higher levels of skin pigmentation. Clarification and standardization of testing and treatment guidelines would be helpful for clinicians when working to optimize physical and mental health of patients.

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