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SERUM VITAMIN D AND MAGNESIUM LEVELS IN A PSYCHIATRIC COHORT

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SUMMARY

Background: *Both Vitamin D deficiency and magnesium deficiency have an increased prevalence and have been associated with an increased risk of and increased severity of symptoms in both depression and schizophrenia (Boerman 2016, Tarleton & Littenberg 2015). This effect appears more pronounced in younger populations and is often apparent from the time of initial diagnosis and is present with adjustment for confounding factors. Thus, the evidence suggests that Vitamin D and magnesium deficiency reflects not only dietary or somatic aspects of health but also may have a role in the pathophysiology of depression and schizophrenia.*

Subjects and methods: *A single site audit of serum Vitamin D and magnesium levels in patients at an Acute Day Treatment Unit was carried out. Blood tests were performed on admission and analysed in house. Data were collected between April - June 2019 and was analysed subsequently, as described below (n=73).*

Results: *Our data show that our psychiatric day treatment unit cohort (n=73) had a higher proportion of vitamin D deficiency (52%) than the general population (40%), although due to the limited sample size this was not significant (p=0.22, Chi-squared test). The percentage of patients who were magnesium deficient was 78.6% (n=22/28). However, the F60 subgroup of patients with personality disorders showed a high prevalence of vit D deficiency (p=0.07), highlighting a trend towards significance despite the limited size of this subgroup.*

Conclusions: *We carried out a single-site audit of serum vitamin D and magnesium levels in a psychiatric day unit population in order to assess the extent of vitamin deficiency in such patients. These data indicate that that the proportion of patients with vitamin D deficiency is higher than in the general population. Further larger analysis is needed to establish the statistical significance of these data and whether treatment with vitamin D supplementation improves outcomes.*

Key words: *psychiatry - vitamin deficiency – audit - vitamin D - magnesium*

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INTRODUCTION

Vitamin D deficiency is widely accepted as a marker for poor somatic health status (van den Berg et al. 2016). Vitamin D plays a crucial role in neuroprotection and neurodevelopment and low levels are associated with psychiatric conditions such as depression and schizophrenia (Cieslak et al. 2014).

However, in addition to this, vitamin D level and magnesium deficiency have been explored as correlates in psychiatric subpopulations in levels above that of the average population. This is even despite a relatively high prevalence in northern European countries' general populations. Several studies show an association between schizophrenia and vitamin D deficiency (Boerman 2016, Lally et al. 2016). A Dutch single centre study (n=118) found vitamin D deficiency was 4.7 times more common among psychiatric outpatients with bipolar disorder, schizophrenia, or schizoaffective disorder than among the Dutch general population (Boerman 2016).

Both Vitamin D deficiency and magnesium deficiency have been associated with an increased risk of and increased severity of symptoms in both depression and schizophrenia (Black et al. 2014, Graham et al. 2015, Doğan Bulut et al. 2016). This effect appears more pronounced in younger populations and is often apparent from the time of initial diagnosis and is present with adjustment for confounding factors. This supports the hypothesis that Vitamin D and magnesium deficiency does not merely reflect poor somatic health status but may also has a role in the pathophysiology of depression and schizophrenia. The mechanism of which is hypothesised to be due to its beneficial effects on neurotransmitters, metabolic profiles, biomarkers of inflammation, and oxidative stress, possibly exerting an overall anti-inflammatory effect (Sepehrmanesh et al. 2016).

There is growing evidence that Vitamin D plays a key role in reducing inflammation (Zhu et al. 2015). This is potentially important as low-grade inflammation has been shown to have a contributory role in the development of depression (Yary et al. 2016). A Chinese study (n=93) found depression was inversely related to raised C-reactive protein (CRP) in a matched case-control study (Zhu et al. 2015). Also, Vitamin D deficiency may be associated with pro-inflammatory cytokines which could explain the higher incidence of comorbidities such as heart failure, hypertension and stroke seen in patients with depression or schizophrenia (Lally et al. 2016).

Magnesium also plays a key role in many pathways involved in the pathophysiology of depression and is found in several key enzymes, hormones and neurotransmitters (Tarleton & Littenberg 2015). Higher magnesium intake is also associated with lower levels of inflammation markers such as CRP.

We postulated the rates of Vitamin D and magnesium deficiency would be higher in an outpatient acute day treatment psychiatric setting in Hertfordshire. To explore this, we carried out an audit of serum Vitamin D levels and serum magnesium in patients who had a blood test as part of their admission to an Acute Day Treatment Unit, Stevenage between April - June 2019 (n=28/73).

SUBJECTS AND METHODS

A literature search was initially undertaken to identify any association of vitamin D or magnesium with mental health conditions such as depression, psychosis, anxiety and ADHD in the literature in the last 10 years. A systematic literature review was performed using PUBMED to source evidence using the following search title terms in MEDLINE summarised in Table 1.

Abstracts were screened for the following key words: vitamin D or magnesium to depression, psychosis, anxiety or schizophrenia. Examinations of vitamin D or serum magnesium in a specific subsection of the population (i.e. pregnant women) were excluded. Literature that was not a literature review or original research were also excluded comprising of 25 articles. There were 37 publications identified. The results are presented in Table 2. Most evidence that reported or studied the association of vitamin D deficiency was linked to unipolar depression followed by schizophrenia.

The audit was undertaken by reviewing the serum Vitamin D levels and serum magnesium on the patients who had a blood test as part of their admission to an Acute Day Treatment Unit,

Stevenage between April - June 2019 (n=73). This was collated with the patient's age, gender, psychiatric diagnosis and ethnic origin.

Population characteristics were characterised and analysis of variance (ANOVA) was used to assess differences was used to for all patients and each subgroup, in both serum vitamin D and magnesium level with a Type I error rate of 0.05. The vitamin D level of this population was assessed against the literature for the primary outcome. Vitamin D deficiency was defined as the threshold for treatment are based on total 25-OH Vit D i.e. 25-OH Vitamin D2 and 25-OH Vitamin D3 combined. Total 25-OH Vitamin D >50 nmol/L (≥20 ng/mL) is sufficient for almost the whole population (Cieslak et al. 2014). Secondary outcomes were assessed by categorising patients based on the following variables: World Health Organisation (WHO) International Classification of Diseases 10th edition (ICD-10) diagnosis, sex, ethnicity, age (by decade). Additionally, the Pearson correlation between serum vitamin D and magnesium was assessed.

Table 1. Summary of Search Terms used in Systematic Literature Review

Search terms	Search results
((Vitamin D[Title] OR Magnesium[Title]))	
AND	
(schizophrenia[Title] OR depression[Title] OR psychosis[Title] OR anxiety[Title])	243
AND	
"last 5 years"[PDat]	120
AND	
Humans	82
AND	
Aged 19 years old and above	
Total	*62*

Table 2. Literature search results by type of psychiatric condition

Articles	Number
Articles linked to unipolar depression	22
Articles linked to bipolar depression	2
Articles linked to schizophrenia	10
Articles linked to psychosis	6
Articles linked to Attention Deficit Hyperactivity Disorder only	0
Articles linked to anxiety only	0
Total Articles	37

RESULTS

Vitamin D levels and magnesium levels were collected for 28 patients out of the 73 who presented the acute day treatment unit (38%) of the cohort studied. The gender split of the cohort was relatively equal between males (n=35, 48%) and females (n=38, 52%) and is detailed in Figure 1. The median age of each sex was 31 (females) and 38 (males). The median age of the cohort was 34 (IQR 25-49, range 19-72). 64 participants (91.4%) were Caucasian. The most frequent diagnosis as defined by the WHO ICD-10 was personality disorders (F60, n=13), followed by schizophrenia (F32, n=9), major depressive disorder (F41, n=7), generalised anxiety disorder (F33, n=6), major depressive disorder (F32, n=9).

We show that the prevalence of vitamin D deficiency in this cohort was 52%, in comparison with the general population (40%, (Parva et al. 2018)), which are shown in Figure 2a. Although the prevalence in this cohort was higher than the population level, it was not significant (p=0.22; Chi-squared test). When considered by ICD-10 diagnosis, we identify heterogeneity in levels of vitamin D3 between disease subtypes (Figure 2b). For example, 80% of patients with specific personality disorders are vitamin D deficient, using a threshold of 50 nmol/L (F60, specific personality disorders), which shows a trend towards significance (p=0.07, Chi-squared test) despite data being available for only 5 patients.

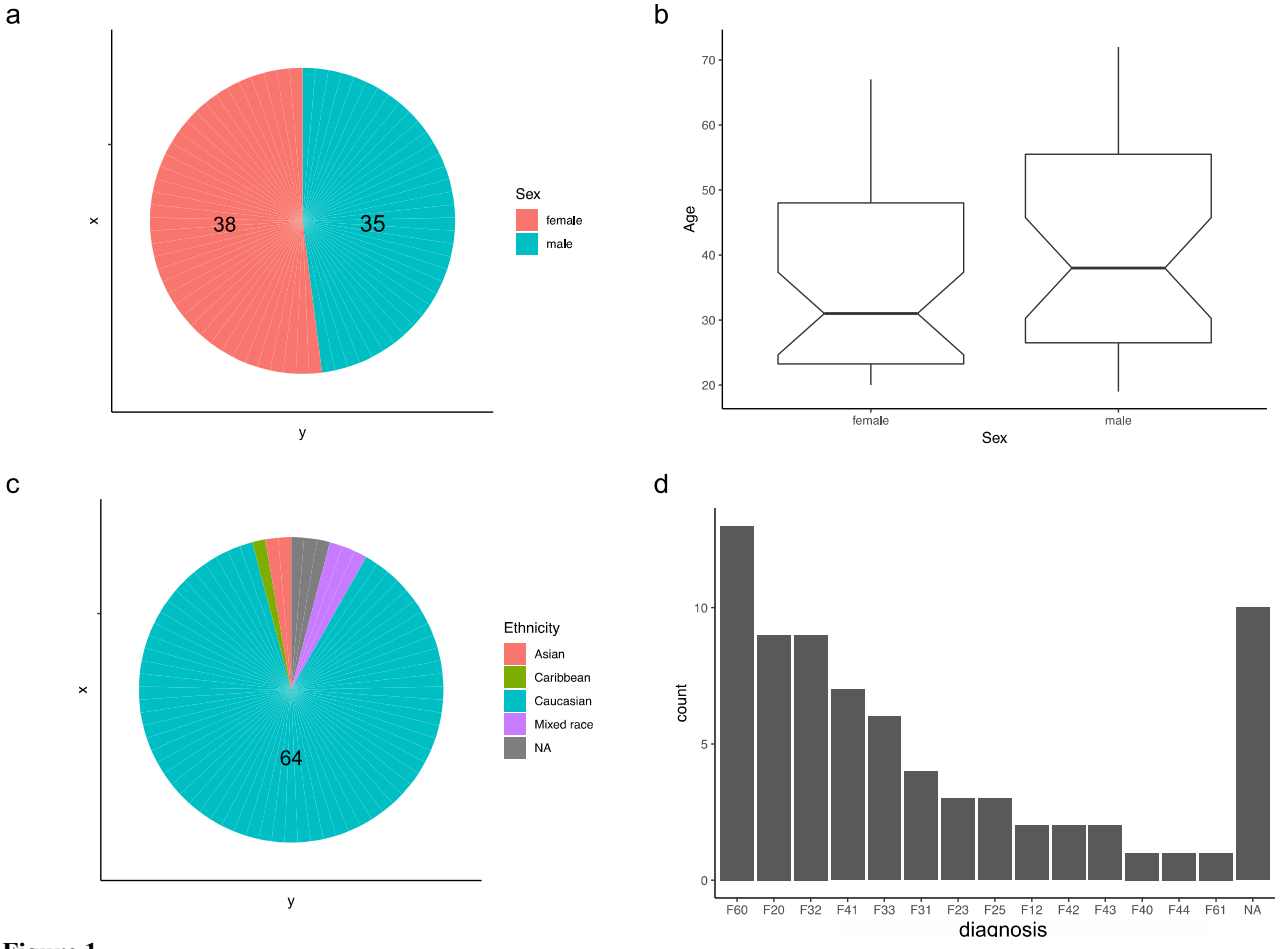

Figure 1.

a. Pie chart of sex of participants in the study. In this study, there were 35 male (48%) and 38 female (52%) participants;

b. Age distributions of each sex. The median age of each sex was 31 (females) and 38 (males). The median age of the cohort was 34 (IQR 25-49, range 19-72);

c. Pie chart of ethnicity of participants in the study. 64 participants (91.4%) were Caucasian;

d. Diagnosis breakdown by World Health Organisation International Classification of Disease, 2016. F60, personality disorders; F20, schizophrenia; F32, major depressive disorder; F41, generalised anxiety disorder; F33, major depressive disorder; F31, bipolar disorder. NA, data not collected

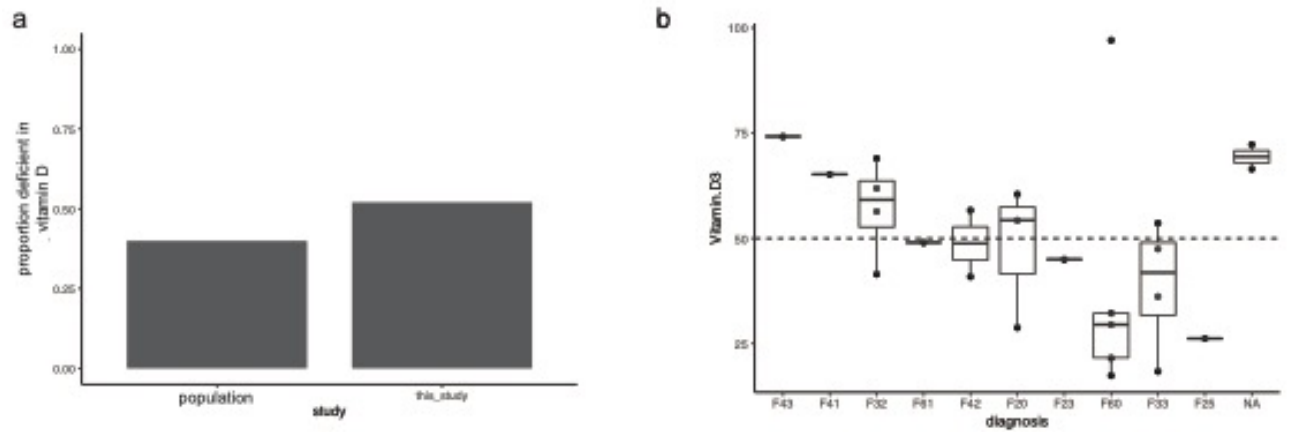

Figure 1. Prevalence of vitamin D deficiency identified in this cohort (52%) in comparison to the general population (40%). Although the prevalence in this cohort was higher than the population level, it was not significant (p=0.22; Chi-squared test);

Box plots of vitamin D level across the cohort, stratified by diagnosis. The threshold for vitamin D deficiency is shown as a horizontal line at 50 nmol/L. The vitamin D3 level for individuals with an F60 diagnosis (personality disorder) had a trend towards being lower (p=0.07, Chi-square test, n=5)

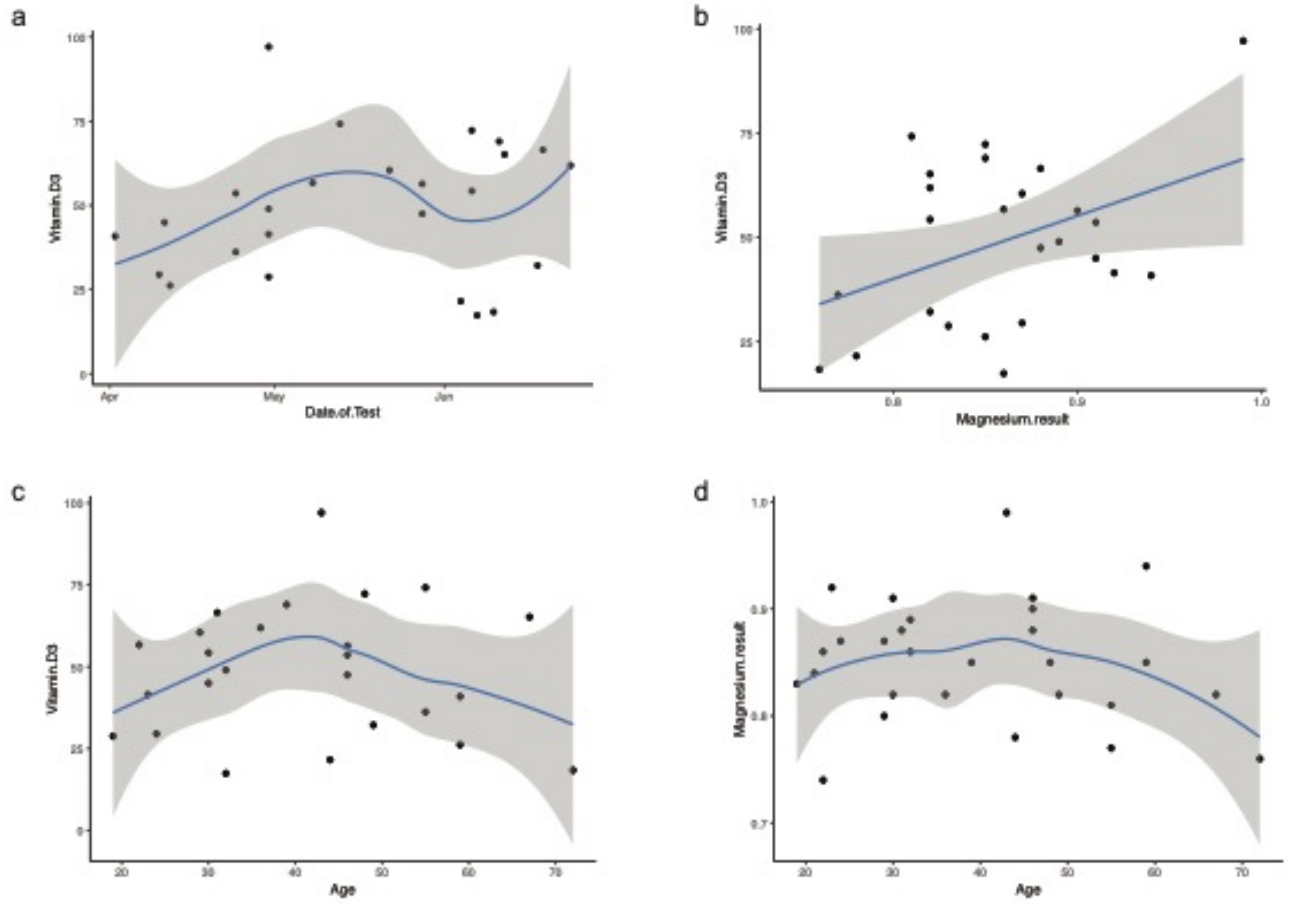

Figure 3.
a. Vitamin D3 levels over time between April and June. There was no significant correlation between the date of sampling and the vitamin D3 level (p=0.16, Pearson correlation). The blue line indicates a smoothed line of best fit, and the grey area indicates the standard error of the fit;
b. Comparison of magnesium and vitamin D3 levels. There was a significant correlation between magnesium and vitamin D3 levels (p=0.04, Pearson correlation);
c. Vitamin D3 levels of patients of varying age. We observe highest levels of serum vitamin D3 in patients aged 40 years old, with lower levels in both younger and older patients;
d. Magnesium levels of patients of varying age. We observe a similar trend as in vitamin D3, i.e. levels peak at 40 years of age

We observe a seasonal variation in vitamin D levels which was identified when visualising levels by month (Figure 3). We observe median vitamin D3 levels rising from 41.2 nmol/L in April, to 56.7 nmol/L in May then 58.1 nmol/L in June, suggesting a seasonal effect on vitamin D. We show a significant positive correlation between Vitamin D deficiency and serum magnesium levels (p=0.04, Pearson correlation), consistent with food sources of vitamin D also containing magnesium or indicating shared metabolic pathways between these nutrients. We studied the distributions of vitamin D and magnesium by age, which showed peak levels of both nutrients at the age of 40, with lower levels in both young and older patients. Overall, 78.6% (n=22/28) of patients were magnesium deficient (<0.9 mmol/L) as defined by serum magnesium. The median serum magnesium level was 0.85 mmol/L.

DISCUSSION

Our audit has identified a higher prevalence of vitamin D deficiency than the general population consistent with previous research (Boerman 2016). Both lifestyle and physical health factors associated with low vitamin D such as smoking, high body mass index and social withdrawal precipitating or exacerbating lack of sun exposure are all found more frequently in people with psychosis (Lally et al. 2016). It is also known that individuals who suffer from heart failure, hypertension, stroke and other cardiovascular diseases tend to have lower vitamin D levels (Lally et al. 2016). Discerning whether vitamin D deficiency is a causative or contributory factor or merely an association is challenging however it is clear from the literature vitamin D deficiency identified in this cohort has associated negative outcomes so treatment and patient care should be optimised to account for this.

Reduced levels are strongly associated with increased symptoms of depression in young adult males (Black et al. 2014). Our audit indeed identifies that younger patients (those below 40) have lower serum vitamin D levels. This consistent with a previous study in England in community psychiatric patients (n=324) (Lally et al. 2016). Potential vitamin D supplementation, particularly in this young cohort, could reduce the severity of their symptoms of depression as well as potentially have an anti-inflammatory effect and reduce the likelihood of complications from other comorbidities.

Our study identifies a clear increased risk of vitamin D deficiency in our psychiatric population which could potentially be treated with vitamin supplementation. Vitamin D treatment has been identified to be beneficial in a large Australian study of young adults with depression (n=1565) with 78% (n=1220) completing a Depression Anxiety Stress Scales (DASS-21). After adjustment for confounding factors, an increase in serum 25(OH)D concentrations of 10 nmol/L decreased total DASS-21 scores in males by 9% (rate ratio (RR) 0.91; 95% CI 0.87, 0.95; $p<0.001$) but no association was seen with anxiety or stress levels. Supplementation may, therefore, be a pertinent approach in the younger patient to potentially reduce the severity of depression symptoms.

Our study also identified a clear drop off in vitamin D levels in patients over 50 indicating deficiency. This may be for dietary or social reasons; elderly patients are less likely to be as active outdoors and more likely to spend time indoors. However, the association of severity of depression and reduced serum vitamin D levels is less strong in elderly cohorts in which most research on vitamin D levels has been performed making it more uncertain there is a benefit in treatment in the elderly (Black et al. 2014).

Research shows that lower vitamin D levels in schizophrenia are also associated with more severe symptoms. Lower vitamin D levels are associated with increased negative symptoms and overall cognitive deficits (Graham et al. 2015, Doğan Bulut et al. 2016). Unlike in depression and schizophrenia, no evidence of Vitamin D supplementation improving mood or anxiety in bipolar however was seen in studies identified (Boerman 2016), suggesting that vitamin D is unlikely to be involved in the pathogenesis of bipolar disorder.

Seasonal variation in vitamin D levels was identified in our UK study which is relevant to other Northern European countries. This is consistent with previous studies (Lally et al. 2016). Our study identified a higher incidence of vitamin D deficiency despite taking place during spring-summer. Despite only studying a 3-month, seasonal effects were observed with vitamin D levels lower in those tested during April compared to June (Figure 2). This may be due to levels of sunlight or diet during the transition from winter to summer. Repeating our analysis to look at patients presenting during the winter months may show an increased incidence of vitamin D deficiency compared to the current study.

The association of magnesium levels and vitamin D deficiency in our study may be linked to poor dietary or physical status. However further research concerning patient's magnesium intake is likely to be a more reliable indicator of magnesium status (Tarleton & Littenberg 2015). Poor magnesium intake has also been linked to worsening depressive symptoms in a Finnish cohort study of patients with depression (n=2320) (Yary et al. 2016). Patients who were in the middle tertile of dietary magnesium intake had a statistically significant decreased risk of getting a hospital discharge diagnosis of depression compared to participants in the lowest tertile of magnesium intake (HR 0.49, CI 0.25-0.95, $p=0.035$) in the prospective setting after multivariable adjustments. In addition, an inverse association between magnesium intake and the risk of depression was found when the combined middle and highest tertiles of magnesium intake were compared with the lowest tertile (HR 0.53, CI 0.29-0.95, $p=0.033$) (Yary et al. 2016).

Younger patients identified in the cohort had lower levels of serum magnesium than those of middle age which is consistent with the literature identified. Magnesium deficiency is associated with depression particularly in younger adults; these form a significant proportion of an acute day treatment units demographic (Tarleton & Littenberg 2015).

This may offer treatment benefit in an ADTU setting as an adjunct for patients for which supplementation could be continued within primary care to reduce the risk of relapse. Vitamin D and magnesium supplementation could be an additional intervention to recommend in order to optimise care. Deficiency could potentially be identified in this setting and supplementation could be continued in primary care to form a targeted intervention to help patients ensure they are getting both pharmacological and psychological support. There is good evidence to suggest patients respond well to vitamin supplementation. Magnesium supplementation is well accepted and adherence is high in psychiatric populations where it is identified and is also effective (Tarleton et al. 2017, Tarleton & Littenberg 2015, Rajizadeh et al. 2017, Mehdi et al. 2017).

CONCLUSIONS

Our audit population shows higher prevalence of vitamin D deficiency compared to the general population, however, given the limited sample, it does not reach the level of statistical significance. When comparing various diagnostic groups, we found strong association between Vitamin D deficiency in patients with personality disorders.

Additionally, we have shown a significant positive correlation between Vitamin D deficiency and serum magnesium levels.

We recommend larger studies to gain better understanding of numerous factors that interact (from the molecular to clinical level) to show somewhat consistent link between low Vitamin D and magnesium levels

and various psychiatric disorders. Our own study points to further exploration of relationship between Vitamin D and magnesium and personality disorder.

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Conflict of interest: *None to declare.*

Contribution of individual authors:

Rashid Zaman conceived and designed the study and revised the manuscript.

Kiran Viswanath collected samples and data.

George Woodward & Jonathan C. M. Wan wrote the manuscript and analysed the data.

George Woodward performed the literature review.

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