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Association Between Three-Months Vitamin D Supplementation and Depressive Symptomatology incidence among Saudi Arabian Adults

By

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Dedication Page

I dedicate this achievement to my father, my guardian angel, who has always been a source of inspiration and encouragement in my life.

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Association Between Three-Months Vitamin D Supplementation and Depressive Symptomatology incidence among Saudi Arabian Adults

Rashel Khaddaj

ABSTRACT

Objective: According to the World Health Organization (WHO), depression is the main cause of disability worldwide and high risk was noticed in Saudi Arabia. The link between nutrition and mental health has been extensively studied in recent years. Recently, vitamin D has been reported an important factor that may have significant health benefits in the prevention and the treatment of many chronic illnesses including mental Illness. In fact, vitamin D levels are linked to depressive symptomatology. Since Saudi Arabia have a high prevalence of depression and vitamin D deficiency and studies assessing this effect are still scarce, the aim of this study was to explore the relationship between Vitamin D supplementation and depressive symptomatology in Saudi Arabian Population.

Methods: The present study is a 3-month randomized clinical trial of vitamin D supplementation performed in a weight loss clinic in Abha, Saudi Arabia. The study sample included 80 adults aged 18-65 years who were vitamin D deficient or insufficient. Participants were randomly allocated to receive either 50,000 IU vitamin D supplementation weekly for 3 months or to receive general dietary advice. The main outcome, depressive symptomatology was assessed using Patient Health Questionnaire-9 (PHQ-9). Serum 25(OH)D concentrations were measured in fasting venous blood samples. The analysis utilized Mann Whitney test, independent t-test, chi-square, Fisher's exact, and ANOVA.Logistic regressions were performed to assess the relationship between vitamin D deficiency and prevalence of depression while adjusting for: age, gender, Body mass Index, Mediterranean Diet Adherence, and physical activity. Lastly, repeated measures were performed to check for the interaction between time and Vitamin D.

***Results*:** The final sample size included 71 participants with an average age of 30.23 ±7.66and constituted of 59.2% females. The mean baseline 25(OH)D3 concentration was 16.92±7.23ng/ml

in the vitamin D group and 16.44±5.91 ng/ml in the control group (p =0.76). At baseline, when adjusting for age and gender only, we observed that lower vitamin D serum levels were associated with higher depression prevalence. When vitamin D was considered as continuous variable, each unit increase in vitamin D levels was associated with a lower depression prevalence (OR=0.87; 95% CI:0.79-0.95, p=0.005) and when compared to those insufficient, those deficient were 4 times more likely to suffer from depression (OR=4.47, 95% CI:1.39-14.38,p=0.012) Nevertheless, these significant results were lost with further adjustment for BMI, MeDi adherence and physical activity: continuous vitamin D: OR=0.90; 95% CI: 0.81-1.01, p=0.08, deficient versus insufficient:OR=2.18; 95% CI: 0.56-8.47,p=0.259).

After three-months supplementation of 50,000IU, vitamin D levels increased to 51.41 ±11.27ng/ml in the supplemented group and to24.95 ±6.45ng/ml in placebo group (p=0.00). PHQ-9 scores decreased from 12.53 ±5.33 to 4.92 ±2.44 in vitamin D group (p <0.001), and from 12.46 ±4.66 to 8.96±3.75in the control group (p<0.001), indicating enhancement in depressive symptomatology. Furthermore, the change between both groups was significantly different (-7.61 ±4.03 in the Vitamin D group, -3.50±1.54 in the control group; p=<0.001)

Conclusion: The present study shows thata 50.000 IU/week dose of vitamin D supplementation for 3 months was enough to increase vitamin D levels beyond sufficient and decrease depression symptoms in Saudi Arabian Adults. Nevertheless, future studies with larger sample size and longer duration are needed to determine if these benefits are long-term.

Keywords: Depressive Symptomatology, Vitamin D Supplementation, Adults, Saudi Arabia, Nutrition, Adjunct Treatment.

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List of Abbreviations

PHQ: Patient Health Questionnaire

IPAQ: International Physical Activity Questionnaire

MET: Metabolic Equivalent of Task

IQR: Interquartile

MeDi diet: Mediterranean diet

BMI: Body mass index

CI: Confidence interval

OR: Odds ratio

Chapter 1

Literature Review

1.1: Overview about Depression

Mental diseases are a major public health problem that affects hundreds of millions of people around the world (Mohsen Al Balawi et al., 2019). According to the World Health Organization (WHO), depression is a common mental disorder; sometimes known as major depressive disorder or clinical depression (World Health Organization, 2021). It creates severe symptoms that impact how a person feels, thinks, and handles day-to-day tasks including sleeping, eating, and working. It can affect both genders and all age groups including children, adolescents, adults and elderly (Depression (major depressive disorder) 2018).

Depression is a widespread condition that affects 3.8 % of the world's population. Around 322 million individuals globally suffer from depression (AlYousefi et al., 2021). According to the World Health Organization's 2011 World Health Report, 15% of those suffering from serious depression are more likely to commit suicide. Furthermore, in the United States, depression affects roughly 9% of the general population and 8.5% of the general population in Europe (Mohsen Al Balawi et al., 2019). In Saudi Arabia, the prevalence of depression is relatively high and it was noted in 2002, that depression and anxiety disorders affected roughly 18% of persons (Aljizani et al., 2020). A cross sectional study was conducted in selected primary health centers in Tabuk, Saudi Arabia between November 2018 to April 2019, with an aim to assess the prevalence of depression by the Patient Health Questionnaire-9 (PHQ-9) on 384 patients aged 20-40 years, has shown that the prevalence of depression was found to be 74%, with mild depression accounting for 37.8%, moderate for 20.8 %, and moderately severe to severe depression accounting for 15.4 %(Mohsen Al Balawi et al., 2019).Thus, reporting the prevalence of depression is important to set some prevention measures.

Depressive disorders are classified by The American Psychiatric Association’s Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and depressive disorder due to another medical condition

(Chand, 2021). The common symptoms for all depressive disorders can range from moderate to severe and include suffering from a gloomy or depressing mood, loss of interest or pleasure in previously appreciated activities, appetite changes, weight changes, sleeping difficulties or oversleeping, loss of energy and increased unproductive physical activity or slower movements or speech, feelings of worthlessness or sorrow, problems thinking, concentrating, or making decisions and suicidal or death-related thoughts(American Psychiatric Association, 2020).

Depression diagnosis requires the occurrence of five or more symptoms within a two-week period, and the symptoms must not be caused by substance misuse or any medical disease. An episode of depression can be classified as mild, moderate, or severe depending on the incidence and intensity of symptoms (AlYousefi et al., 2021). It can be diagnosed through its symptoms, clinical examination, laboratory tests and psychological measures. With minimal clinician involvement, patient self-assessment questionnaires are beneficial for screening, tracking, and recording the course of depression symptoms. The two extensively used depression screening measures are the Beck Depression Inventory-II (BDI-II) and the Patient Health Questionnaire (PHQ-9) (Schutt et al., 2015). The PHQ-9 will be described in detail in a later section of this thesis.

While the causes of depression remain not fully elucidated, several factors have been suggested to be frequently associated to its onset. Thus, a complex combination of social, psychological, and biological factors leads to depression (World Health Organization, 2021). In fact, depression is typically caused by external or internal factors; the external factors include social, financial reasons or traumaticevents such asthe death of loved one, lack or diminished social support, caregiver stress, interpersonal difficulties, and disputes. The internal factors-which can be inherited- leads to physical changes in the brain likean imbalance of neurotransmitters in the brain and spinal cord (Ministry of Health, Kingdom of Saudi Arabia, 2021). Furthermore, certain medications can lead to depression. It has been shown that acne medication, anti-obesity drugs, smoking cessation agents and corticosteroids are all drugs that can cause depression which can be referred to as drug –induced depression (DID)(Rogers & Pies, 2008). In addition, people with chronic conditions, such as diabetes, Alzheimer's disease, autoimmune illnesses (systemic lupus erythematosus, rheumatoid arthritis, and psoriasis), cancer, coronary artery disease, etc… are more likely to be depressed (National Institute of Mental Health, 2021). A common pillar to most of the aforementioned

chronic diseases is nutrition. In fact, nutrition has been closely related to depression in a bidirectional association. This association will be detailed in the next section.

1.2: Nutrition and depression

Nutrition and depression are associated in a bidirectional relation (Kris-Etherton et al., 2020). On one hand, healthy lifestyle practices are promoted by mental well-being which encourages people to do physical activity and consume healthy diets. Whileon the other hand, a lack of healthy lifestyles degrades mental health, which has a negative, cyclical impact on healthy behaviors (Kris-Etherton et al., 2021). Nevertheless, the possibility of reverse causality between nutrition and mental health, complicates the nature of these relationships (Firth et al., 2020) and raises the question of who came first, depression or poor diet? However, several recent research evaluations that looked at a variety of studies have found a link between what people eat and their risk of depression and found that diet is such a crucial part of mental health (Monique Tello, 2020).

Because of the well-established role of nutrition in the prevention and treatment of mental health issues, the International Society for Nutritional Psychiatry Research has proposed that nutritional medicine should be considered a mainstream in psychiatric practice, with research, education, legislation, and health promotion supporting this unique approach(Kris-Etherton et al., 2020).A meta-analysis of 13 observational studies has shown that a healthy diet has been linked to a decreased riskof depression(OR = 0.84; 95% CI: 0.76 - 0.92, P < 0.001)(Lai JS, 2014). Moreover, it has also been shown that people with mental illness have been found to have a poorer diet and other lifestyle behaviors that affect health (Parletta et al., 2017). As a result, it's possible to conclude that a poor diet is a preventable risk factor for depression, implying that nutrition could be used as an adjunct treatment. A well-studied food pattern that has been shown its role in depression prevention is the Mediterranean type diet (MeDi) (Oliván-Blázquez et al., 2021), defined by the daily consumption of fruits, vegetables, and grains, in addition to a weekly consumption of beans, nuts, seeds, seafood and dairies. Also, it recommends the use of olive oil, avocado, peanut butter and healthy fats, and the consumption of alcohol in a moderate amount for both men and women (Solfrizzi, et.al, 2017).

Furthermore, individual nutrients have been shown to be associated with depression (Parletta et al., 2017). In fact, B vitamins as B6, B12 and folate are all linked to depression (Sangle et al., 2020). Also, amino acids as tryptophan, phenylalanine, tyrosine, and histidine

and other components as choline and glutamic acid are all requiredfor the creation of neurotransmitters like serotonin, dopamine, and norepinephrine, which regulate mood, appetite, and cognition (Kris-Etherton et al., 2020) in addition to the decreased methionine and increased glutamate levels which it was shown to be involved in major depressive disorder (Ogawa et al., 2017). Moreover, vitamin D, omega-3, and minerals like, iron, selenium, zinc (De Mel &Suphioglu, 2014), and magnesium are essential for healthy brain structure and function, and have all been linked to the development of depression (Parletta et al., 2017). Recent studies have suggested that vitamin D may play a key role in the prevention and treatment of many chronic disorders, including mental illness (Wang et al., 2017).

Treatments for depression (both pharmacological and psychotherapy) have been relatively effective up to this point, however a subset of individuals does not totally improve their symptoms. As a result, in these people, a nutritional strategy would be a good choice especially that currently there is a scientific data that supports the use of some nutritional supplements (nutraceutics) as a depression coadjuvant therapy (A; & M., 2017).

1.3: Vitamin D

Researchers recently discovered a modest correlation between vitamin D and depression; however, the link is not fully understood (Menon et al., 2020). This association does not establish the temporal association between vitamin and depression. More research is needed to determine whether a lack of vitamin D is the reason for depression or whether depression causes a lack of vitamin D, since a depressed person usually tend to eat less healthy foods and avoid engaging in outdoor activities (GengC; 2019). Nevertheless, there is strong evidence showing that low serum vitamin D levels may raise the risk of depression (Wang et al., 2017).

Vitamin D is a fat-soluble vitamin known as the “sunshine” vitamin. It is naturally found in few foods like oily fish such as sardines, herring, tuna, mackerel, salmon, and cod liver oil, egg yolks, shiitake mushrooms, liver or organ meats. Nevertheless, dermal synthesis after ultraviolet radiation (UVB) remains the primary route for vitamin D replenishment, accounting for 90% of vitamin D (Nair & Maseeh, 2012).

Vitamin D status can be checked indirectlythrough assessment of the diet and the exposure to the sunlight or directly bymeasuring the circulating form of vitamin D in serum (GengC; 2019). Vitamin D level is considered sufficient if itis greater than 30 ng/mL,

deficient if less than 20 ng/mL, and insufficient if it is between 20 ng/ml and 30 ng/ml(Sizar, 2021). However, there is a lack of international consensus regarding the criteria of what is considered vitamin D deficiency and insufficiency and the recommendations differ in many countries. A safe and commonly available dose is 1000 IU which raises vitamin D serum level by 15-25 nmol/L over months/weeks (Amrein et al., 2020).

1.4: Vitamin D Deficiency

Vitamin D deficiency is the most common medical issue affecting people of all ages all over the world, including those who live in low-latitude areas where UV light was thought to be sufficient to avoid deficiency, and those who live in industrialized countries where vitamin D fortification has been in place for years(Palacios & Gonzalez, 2014).Nonetheless, there was consistent evidence that vitamin D deficiency is more common in Asia, the Middle East, and Africa, as well as among immigrants from these regions who live in nations with higher latitudes(Roth et al., 2018).According to the existing literature on the Saudi Arabian population, roughly 60% of the population is Vitamin D deficient(Al-Alyani et al., 2018). This was also shown in cross-sectional series that was conducted in the central region of Saudi Arabia between 2008-2017 which included 7360 participants of all ages to check the wide spread vitamin D deficiency (<20 ng/ml) in Saudi Arabia and found that the incidence of vitamin D deficiency in Saudi Arabia is 73.2% over a 10-year period (Al-Daghri et al., 2021). A billion people worldwide are believed to be vitamin D deficient or insufficient (Hovsepian et al., 2011). Because vitamin D deficiency is so widely prevalent in many countries, a number of dietary fortification and supplementing policies and programs have been developed and implemented to reduce the burden of vitamin D deficiency (Roth et al., 2018).

Vitamin D Deficiency can result from several causes. Although UVB radiation is the primary source of vitamin D in humans, which is estimated to provide 80–100% of the body's vitamin D requirements, however, environmental factors such as season, latitude, and prevailing weather conditions, as well as personal factors such as skin pigmentation, age, clothes, sunscreen use, working environment, outdoor physical activity, and sun exposure behavior, can all hinder or impede vitamin D production. (Cashman, 2019). Also, certain malabsorption syndromes like celiac disease, short or inflammatory bowel syndrome, and gastric bypass and chronic liver diseases like cirrhosis that may lead to vitamin D deficiency.

In addition to some medications that induce hepatic p450 enzymes which activates the degradation of vitamin D (Sizar O et al., 2021).

In order to overcome vitamin D deficiency, the two main methods for raising serum 25(OH)D concentration are sun exposure and oral supplementation (Cho SH;YunJM;LeeJE;LeeH;JohHK;Cho B;, 2021). Nevertheless, in the absence of sufficient UVB availability/exposure to permit skin synthesis, dietary vitamin D supplyboth naturally as a fortification ingredient, or as nutritional supplementsis essential for satisfying population needs and preventing vitamin D deficiency (Cashman, 2019).

As a result, various agencies and scientific organizations have established vitamin D supplementation guidelines for optimal serum 25(OH)D levels (Pludowski et al., 2017).

The Institute of Medicine suggests taking 200 IU of vitamin D daily from birth to the age of 50, 400 IU daily from the age of 51 to the age of 70, and 600 IU daily from the age of 70 or later (Khan & Fabian, 2010). However, these recommendations are insufficient to cure vitamin D deficiency because it assumes some sun exposure and vitamin D intake from food. Thus, a higher basal intake of vitamin D from supplements are recommended to avoid vitamin D deficiency(Khan & Fabian, 2010) as it was shown that vitamin D supplementation raises 25(OH)D levels in the blood, potentially reversing the consequences of vitamin D deficiency(Li et al., 2013).As a result, vitamin D recommendations propose a target 25(OH)D concentration of 30ng/mL (75nmol/L) and vitamin D supplementation dosages ranging from 400 to 2000IU/day depending on age, body weight, illness state, and ethnicity (Pludowski et al., 2017).

When taking vitamin D supplements, timing and dosage are very important, so vitamin D supplementation can be taken daily, weekly or monthly and it comes with different doses: 1,000 IU, 5,000 IU, 10,000 IU and 50,000 IU, however, there isn't currently a consensus regarding the dose or the D2/D3 of vitamin D supplementation to reach the target level.Although daily administration is thought to be the most physiological way to treat vitamin D deficiency; however, less frequent administration is expected to increase patient compliance and help achieve a higher mean vitamin D level(DalleCarbonare et al., 2017).

1.5: Vitamin D Functions

Vitamin D is known to be vital in the development, function, and maintenance of healthy bones throughout life through regulating calcium homeostasis. It is involved in the formation of bone and its deficiency can lead to rickets in infants (Sahay & Sahay. 2012), osteoporosis and osteomalacia in adults (Nasr et al,. 2019). In addition to its classical role in bone metabolism, vitamin D has been shown to affect other bodily functions, such as reducing inflammation and modulating cell proliferation, neuromuscular and immunological function, and glucose metabolism (Umar et al., 2018). VitaminD influences the expression of several genes that code for proteins that control cell proliferation, differentiation, and death (O'Mahony et al., 2011).

Lastly, there is growing evidence that vitamin D plays a role in the etiology and treatment of depression (Menon et al., 2020). Vitamin D roles in depression areexpanding as the research in this field accumulates.

1.6: Vitamin D Deficiency and Depression

Vitamin D levels are strongly linked to depression, according to researchas shown from different study types (cross-sectional, randomized controlled trials, longitudinal and case-control studies).

A huge population-based cohort study was conducted in 5607 older adults “54.9% females” - aged 50 years and over- from the English Longitudinal Study of Ageing to examine the cross-sectional relationship between 25-hydroxyvitamin D (25OHD) levels and depressive symptoms using the 8-item Center for Epidemiological Studies-Depression scale (de Oliveira et al., 2018). Vitamin D levels were measured using the Diasorin Liaison immunoassay, which can identify both vitamin D2 and D3. Vitamin D values were separated into four quartiles because there was no universal 25OHD values: the lowest (30 nmol/L), the 2^{nd} (30.01 - 46.00 nmol/L), the 3^{rd} (46.01 - 64.00 nmol/L), and the highest (>64.01 nmol/L; reference category). They additionally classified 25 OHD levels using the US Institute of Medicine (IOM)cut-off points: 30 nmol/L, 30 to 50 nmol/L, and more than 50 nmol/L.This study found that there is a link between low vitamin D levels and increased depressed symptomsafter adjusting for a large number of clinically significant covariates, the lowest quartiles (OR = 1.58; 95% CI = 1.20-2.07); the 30 nmol/L cut-off (OR = 1.45; 95 % CI = 1.15-1.83) and for the 50 nmol/L cut-off (OR = 1.34; 95% CI = 1.10-1.62).Fully adjusted

models (adjusted for age, sex , season, wealth, smoking, physical activity, number of cardiovascular conditions, non-cardiovascular conditions, difficulty with daily living activities, difficulty with instrumental daily tasks, overall memory score, and waist circumference)found that women with levels of 30 nmol/L (OR = 1.40, 95 % CI = 1.06–1.86) and 50 nmol/L (OR = 1.35, 95 % CI = 1.07–1.72),lowest quartiles of vitamin D (OR =1.67, 95% CI = 1.20–2.34)and second-lowest quartiles of vitamin D (OR = 1.68, 95% CI = 1.20–2.35) were more likely to suffer severe depression symptoms.However, only men with vitamin D levels of 30 nmol/L continued to show a significant association (OR=1.60; 95 % CI=1.06-2.42) in this connection. Accordingly, this independent, inverse association raises the possibility that low vitamin D levels, particularly in women, may be a significant risk factor for late-life depression.

The results of this cohort study were consistent with a meta-analysis which analyzed 31,424 participants from one case–control study, ten cross-sectional studies and three cohort studies to determine if there is a relationship between low levels of vitamin D and depression(Anglin et al., 2018).All studies included adults (over the age of 18) and reported depression as the primary outcome and vitamin D as a risk factor or intervention.Depression outcomes for participants with vitamin D deficiency compared to those with normal vitamin D levels were needed to be reported in cross-sectional and cohort studies. As for the RCTs that enrolled depressed participants, the secondary outcome was the change in the depressive symptoms. Depression for all studies was diagnosed using a standardized psychiatric interview for the DSM diagnoses of depressive disordersor clinical diagnosis of depression or using a validated rating scale with a set cut-off point, such as a score of ≥16 on the Center for Epidemiological Studies – Depression scale or ≥8 on the Geriatric Depression Scale. For case control studies, the standardized mean difference (SMD) in vitamin D levels between depressed patients and healthy controls was calculated and it was considered small if it is <0.4, moderate if it's between 0.4-0.7, and high if it's>0.7. This single case–control study showed a moderate difference (SMD=0.60, 95%CI: 0.23-0.97) in vitamin D levels between women with depression and healthy controls. For the cross-sectional studies, they used the adjusted OR of depression for the lowest versus highest vitamin D categories since the cross-sectional studies used different vitamin D concentration reference categories (either 550 nmol/l or the lowest and highest category) and presented data in different quartiles, tertiles, or categories. A meta-analysis of these studies found a borderline significant increased risk of depression for the lowest versus highest vitamin D categories (OR=1.31; 95%CI:1.00–1.71,

P= 0.05). Nevertheless, the cohort studies revealed a significantly higher risk of depression for the lowest vs. highest vitamin D categories (HR = 2.21; 95 % CI: 1.40–3.49). The findings of this meta-analysis showed that vitamin D Deficiency is linked to depression.

Furthermore, in order to determine the temporal association between vitamin D and depression, a meta-analysis of four randomized controlled trials (RCTs) was conducted – three were double blinded and one was non-blinded- to assess the effect of vitamin D supplementation on depression symptoms scores in people who had been diagnosed with major depression. Three of the trials were done in Iran while one was done in Southeast China. The number of participants in each trial ranged from 40 to 746 and the pooled sample size was 942 participants. The primary outcome was expressed as the depression symptoms scores and the interventional group was vitamin D supplementation in any dosage with a follow-up ranging from 8 to 52 weeks. The results showed that vitamin D supplementation had a pooled mean effect size of 0.58 (95 %; CI: 0.45–0.72) on depressive symptom ratings in major depression and there was low heterogeneity among studies, $I^2 = 0$. Thus, this meta-analysis showed that with a moderate effect size, vitamin D supplementation improved depression scores in major depression patients. However, due to the small number of trials available and methodological bias detected in a few of them, these conclusions must be viewed with caution.

Moreover, a randomized clinical trial (VITAL) aimed to examine the effect of vitamin D supplementation on late-life depression risk and mood scores for a period of 5.3 years (Okereke et al., 2020). The study comprised 18,353 adults aged 50 and up who were free of depression (16,657 participants with no depression history) or clinically relevant depressive symptoms (1,696 participants without treatment for depression for two years) at baseline. Randomization was assigned in to two-two factorial design, where 9,181 participants has received 2000 IU of vitamin D_3supplementation and 9,172 has received fish oil or placebo. The primary outcome was depression and the mean difference in mood scores using PHQ-8 with 0 points as the least symptoms to 24 points as the most symptoms, and the minimal clinically important difference for change in scores was 0.5 points. Vitamin D_3 supplementation compared with placebo did not result in statistically significant differences in the depression incidence and recurrence, as well as clinically relevant depressive symptoms (HR= 0.97; 95% CI: 0.87-1.09, $P = 0.62$) for the change in mood scores (mean difference for change in mood scores, 0.01 points [95% CI: −0.04 - 0.05 points])

throughout the course of a 5-year treatment period. Thus, these findings contradict the use of vitamin D to reduce depression in adults.

Another randomized clinical trial was carried out in China between November 2015 and March 2019 to investigate the impact of vitamin D supplementation on the symptoms of depression and anxiety in vitamin D deficient patients.106 participants were randomly assigned to the control group, who continued to consume their regular diet, which contained fish oil(n=44) or vitamin D supplementation group (n=62) of 1,600 IU and both were followed up for a period of 6 months. Vitamin D levels were measured using commercial kits and it was considered to be deficient it it's ≤75 nmol/L. Psychological symptoms were measured using the Hamilton Anxiety Rating Scale (HAMA-14), the Revised Social Anhedonia Scale (RSAS), and the Revised Physical Anhedonia Scale (RPAS).The scores of RPAS, RSAS, and HAMD17 did not differ substantially between the two groups from baseline to endpoint ($p>0.5$) and this study found no significant difference in depression symptoms between the vitamin D group and the control group.However, the two groups' total HAMA-14 scores had statistically different temporal effects(β= - 2.235; 95%Cl:3.818, 0.653,p =.006). Thus, this study demonstrated that among depressed people with low vitamin D levels, vitamin D treatment may lessen anxiety symptoms but not depression.

So, based on those results, thereare still conflicting results and more research should be done to determine the temporal association between Vit D and depressive symptomatology among Vitamin D deficient people.

Chapter 2

Aims and Hypothesis

2.1: Problematic

As previously presented, vitamin D deficiency/insufficiency is a rapidly growing condition in Saudi Arabia, and a recent published data has revealed that in the Saudi Arabian population vitamin D deficiency is as high as 100%. (F. Bokhari &Albaik, 2020). In fact, several studies have examined vitamin D deficiency in Saudi Arabia. According to these reports, it was observed that Saudi women have a significantly higher prevalence of vitamin D deficiency (41.2–100%) than Saudi men (32.5–92.6%). Furthermore, vitamin D deficiency was not only found in adults, but also in newborns (88–90 %), infants, and teenagers (40.6–97.8%) (F. Bokhari &Albaik, 2020).

Furthermore, vitamin D deficiency has been linked to a variety of mental and physical illnesses (Al Hariri, 2016). Particularly in Saudi Arabia, depression is a common condition and the prevalence of both anxiety and depressive disorders was found to be around 18% of the population in 2002. In fact, Saudi Arabia is known by its hot weather and high temperatures reaching 50 degrees which maybe a barrier for most people to get exposed to the sunlight. Nevertheless, Abha, called “the capital of clouds”, is situated at high altitude of 2,270 meters above the sea level and has a pleasant weather all year round. Surprisingly, people living in this region still suffer from insufficient/deficient levels of vitamin D and approximately 27% of its population had prevalent depression in 2008 (Anglin et al., 2018). This deficiency in vitamin D may be due to social, cultural, and religious factors, which substantially reduces the rate of exposure to sunlight. Moreover, sedentary and indoor lifestyle, fear of the adverse effects of prolonged sunlight exposure, full body coverage, obesity, poor diet and chronic diseases all limit the amount of sunlight available for vitamin D synthesis (Al-Atram, Ragunath, & Kannan, 2020). This also can be due to the increasein risk factors that might worsen depression, such as stress, chronic diseases, sedentary lifestyle, social isolation, and social stigmas associated with psychiatric illnesses (Mohsen Al Balawi et al., 2019). In addition to the genetics which may also be a risk factor for depression (Kris-Etherton et al., 2020).

Thus, despite the high prevalence of depression in Saudi Arabia and the high vitamin D deficiency, there are several debates about the causality of this relation and if correction of vitamin D by supplementation is efficient to treat or prevent depression among Saudi Arabia Adults. Furthermore, to our knowledge, there are no studies that tried to determine the role of vitamin D supplementation in depressive symptomatology.

2.2: Objectives and hypothesis

Several studies have highlighted Saudi Arabia's low vitamin D levels and its link to depression in a cross-sectional way. However, the majority of studiesare observational studies only, which produce lower-quality evidence than RCTs. The cross-sectional studies cannot exclude the possibility of reverse causality, in which people with depression have less sun exposure and a poor diet with low vitamin D levels. In light of this, it is essential to conduct randomized controlled studies of vitamin D for the treatment and prevention of depressionto discover whether this link is causal. Therefore, we designed this randomized controlled trial in order to assess the role of vitamin D supplementation on depressive symptomatology among Saudi Arabian population.

Hence the present study aimed to:

1. Explore the relationship between 3-month Vitamin D supplementation and depressive symptomatology in Saudi Arabian Population.

We hypothesized that:

1. Vitamin D deficiency is linked to a higher prevalence of depressive symptomatology among Saudi Arabian Population.
2. Vitamin D Supplementation for 3-month at 50,000 IU might be associated with an improved depressive status.

Thus, this study would add value to the actions taken to treat vitamin D deficiency in Saudi Arabian adults in particular. This might also assist in approaching new recommendations related to preventing or treating depression via vitamin D supplementation.

Chapter 3

Methods

3.1: Participants and study design

This study was a randomized controlled trial (RCT) done on Saudi Arabian adults to investigate the impact of vitamin D supplementation on depression symptomatology. The study was conducted between September 2021 and March 2022. All the participants were patients– who were doing regular medical check-ups – at Al Themal Medical Center which is located in Abha, Saudi Arabia. Briefly, 80 male and female Saudi adults were recruited over a period of six months. When patients came to Al Themal Medical Center, they were requested to do a general blood test to check for any vitamins and minerals deficiencies as part of the routine clinical procedure. This procedure did not incur any additional costs on the behalf of the participants. The participants who were identified to have any deficiencies were recommended to take supplements, also as part of the routine clinical procedure. Therefore, participants identified to be deficient or insufficient Vitamin D levels were screened and recruited to participate in the current study. Based on the calibrations of the kits used in Al-Themal Medical center, participants were considered deficient if their Vitamin D level was <20 ng/ml; insufficient if vitamin D was between 20.1-30 ng/ml, sufficient if Vitamin D was between 30-100 ng/ml and toxic if its more than 100 ng/ml. Once they agreed on participating, those participants were divided into two groups, the control group, and the interventional group.

Based on earlier 2-arm RCT trials conducted on the same topic, 60 subjects were chosen. Thus 30 participants were recruited for each group. Additionally, we accounted for 30% of missing data (n=18), therefore the final sample size that was included in the study was 80 participants.

The inclusion criteria were: Vitamin D deficient/Insufficient, between 18 and 65 years old, 17kg/m2≤BMI <55 kg/m2, able to understand Arabic and able to provide written consent; whereas the exclusion criteria were: participants already taking Vitamin D supplements or Anti-depressants, having normal vitamin D levels, reporting other mental health diseases, and pregnant or lactating women.

Before the initiation of the study, all participants signed a written informed consent form. For participants who are unable to read, the dietitian read the consent for them and helpsthem to fill out the questionnaire. The trial was approved by the management of Al Themal Medical Center in Saudi Arabia and by the Lebanese American University, Institutional Review Board (Protocol Number: LAU.SAS.BR2.12/Sep/2021).

3.2: Intervention and Randomization

The trial was randomized control with participants randomly assigned to either an interventional (vitamin D) or placebo group (control). The interventional group received vitamin D supplementation of 50.000IU/week for 3 months and the placebo group received dietary advice and education on food sources of vitamin D for the same period. Both Groups received a weight gain or a weight loss diet as per their case. As previously mentioned, as part of the routine clinical procedure, deficient/insufficient participants were recommended a supplementation form. Therefore, in this study, we did not endorse nor tested any specific form/brand of vitamin D supplementation. We only recommended a specific weekly dosage of 50.000 IU of vitamin D in which the participants were the ones who supplied the supplements for themselves. The 50.000 IU dose was chosen since it is easier for the participants to remember taking their supplementations once per week rather than daily which will be harder to follow. Also, 50.000 IU has been used in the literature (Penckofer et al., 2010) (Menon et al., 2020).

A computerized random sequence generator program was used to perform the randomization for age, and to establish a gender balance, participants were randomized by sex.

Compliance with the intervention was assessed by follow-up visits every 2 weeks. We depended on the center's system which has a policy of sending messages to the patients one day before their appointments to remind them of their follow-up visit and thus on their follow-up appointment it was our job to remind the participants of their vitamin D supplementation dose.

3.3: Data collection and Analysis

Data were collected at baseline and during a 3-month follow-up. After signing the consent form, participants who were eligible for the study filled socio-demographic and lifestyle questionnaire, and they were screened for medical history, anthropometric measurements, physical activity assessment, Mediterranean diet adherence, assessment of

symptoms of depression using the Patient Health Questionnaire (PHQ-9) and measurement of serum Vitamin D concentrations to document vitamin D status. Exposure to sunshine, work type, and the sleeping pattern were also assessed to have an idea about Vitamin D taken from the sun.

3.4: Measurement of serum 25(OH)D concentration

Vitamin D levels were assessed in fasting venous blood samples obtained at the beginning of the study and three months afterwards. Vitamin D level was measured by Al Themal Medical Center's Laboratory which is an accredited laboratory. Participants were considered deficient if their Vitamin D level was 20 ng/ml or less, insufficient if its level ranges between 20.1 ng/ml to 30 ng/ml, and sufficient if their Vitamin D level is more than 30ng/ml (WMA - The World Medical Association-WMA statement on Vitamin D insufficiency).

3.5: Assessment of depressive symptomatology

Depressive symptomatology was assessed using the Patient Health Questionnaire (PHQ) (Kroenke et al., 2001). It is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders and it has been approved for usage in primary care settings. Nevertheless, this questionnaire was shown to be a valid measure to evaluate depression (Vaughan et al., 2019). The Arabic version of the PHQ is a valid and reliable tool to screen for depression, anxiety, somatic, and panic disorders and its validity and reliability were demonstrated in Saudi Arabia (AlHadi et al., 2017). The Questionnaire assessed depression by asking nine questions about the loss of interest, feeling depressed, trouble sleeping, feeling tired, poor appetite or overeating, feeling bad about yourself, low levels of concentration, moving or speaking slowly, and suicidal ideation (Al-Qadhi et al., 2014). Participants stated how often they experienced each of nine depression symptoms in the previous two weeks on a 0 "not at all" to 3 "nearly every day" scale, resulting in composite scores ranging from 0 to 27(Vaughan et al., 2019). The participants were asked to select one statement that most accurately described their condition. The scores of the PHQ questionnaire were interpreted as follows: 0-4 Minimal depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression, 20-27 severe depression (Vaughan et al., 2019).

3.6: Confounding Variables

3.6.1: Sociodemographic, anthropometric and lifestyle assessment

Moreover, general questions regarding sociodemographic and clinical characteristics were asked. Data about age, gender, marital status (Single, Married, Divorced), and level of education (Primary, secondary, and college) was collected. There was only one divorced participant and therefore decided to consider them single. Clinical characteristics included the number of chronic diseases 'anemia, hypertension, hypothyroidism, and diabetes mellitus', intake of any medications 'for diabetes, hypertension, and thyroid' dichotomized into yes/no, and BMI and supplement use 'Iron, B complex vitamins". As described earlier, because of the nature of life in Saudi Arabia, information about the work type (office-based, vs field-based) and sleeping pattern (day vs night) were collected as this would have an effect on sun exposure. We did not ask about smoking since it is not culturally acceptable for women to smoke in Saudi Arabia.

Weight and Body mass index (BMI) were assessed using the Tanita Body Composition Analyzer (DC-430MA).

3.6.2: Physical Activity assessment

Participants filled out validated questionnaires about their physical activity using the International Physical Activity Questionnaire (IPAQ)(M,Hagströmer, 2006).

IPAQ is a validated questionnaire that provides information on the time spent walking, in vigorous- and moderate-intensity activity, and sedentary activity for the past seven days on weekdays and weekends (Maddison et al., 2007). There are two versions of the questionnaire, the long and the short form. The short version is a cost-effective way to assess physical activity and is suitable for use in national and regional surveillance systems, while the long version contains more detailed information that is typically required in research and evaluation (Craig et al., 2015). The short version is easy to administer, and there was no difference in the short and long IPAQ forms' reliability and validity (Bauman et al., 2009). As a result, we employed the IPAQ short form in the Arabic Language since it's the native language of the Saudi participants.

Participants were asked about how many times per week they do vigorous, moderate or light activities and for how many minutes per day. The results might be provided in

categories (low, moderate, or high activity levels) or as a continuous variable (MET minutes a week). The quantity of energy expended during physical activity is represented as MET minutes.

So, the MET values can be computed according to the following equations:

- Low MET-minutes/week = 3.3 * minutes the activity was carried out* the number of days that activity was undertaken.
- Moderate MET-minutes/week = 4.0 * minutes the activity was carried out *the number of days that activity was undertaken
- Vigorous MET-minutes/week = 8.0 * minutes the activity was carried out * the number of days that activity was undertaken.

3.6.3: Diet assessment

The Mediterranean Diet (MeDi) dietary pattern is characterized by a moderate intake of lean fresh meat and dairy products, as well as a daily intake of extra-virgin or virgin olive oil as the main source of fat, whole grains, fruits, and vegetables, as well as legumes, nuts, fish, and wine on a weekly basis (Martínez-González et al., 2012). The MeDi is advocated internationally as one of the healthiest eating patterns because of its frequently credited benefits against chronic diseases and its link with longevity (García-Conesa et al., 2020). Furthermore, the MeDi is associated with depression (Sánchez-Villegas et al., 2006). Therefore, diet quality was assessed using the 14-item Mediterranean diet adherence Screener (MEDAS) (García-Conesa et al., 2020). The MEDAS consists of 12 questions about the frequency of food consumption and 2 questions about food intake patterns. Each question received a score of 0 or 1. One point was awarded for using olive oil as the primary source of fat in cooking, choosing white meat over red meat, or consuming: 4 tablespoons (13.5 g) or more of olive oil every day (including that used in frying, salads, and meals eaten away from home); 2 or more vegetable servings every day; 3 or more pieces of fruit per day; 1 serving of red meat or sausages per day; 1 serving of animal fat per day; 1 cup of sugar-sweetened beverages per day;7 or more servings of red wine per week; 3 or more servings of pulses per week; 3 or more servings of fish per week; no more than two commercial pastries per week; three or more servings of nuts per week; or two or more dishes per week seasoned with a typical tomato, garlic, onion, or leek sauce sautéed in olive oil(Gil Á;Martinez de Victoria E;Olza J;, 2015).

Nevertheless, Saudi Arabia is a Muslim country, and alcohol consumption is culturally and religiously prohibited. Therefore, the question related to wine consumption was eliminated from the questionnaire and it was assumed to be 0 for everyone.

All these questions were translated into the Arabic language since it's the native language of all the participants.

The 14-item Mediterranean diet adherenceScreener questionnaire was found to be a valid and reliable instrument for estimating MeDi adherence in a short amount of time and it could range anywhere from 0 to 14. The following criteria were used to categorize the adherence to the MeDi: weak adherence if it is less than or equal to 5; moderate to fair adherence if it ranges between 6 and 9; good or very strong adherence if it is equal or more than 10(García-Conesa et al., 2020).

Moreover, the consumption of calcium and vitamin D fortified foods was also assessed. We created a food list of the most consumable calcium and vitamin D fortified products in Saudi Arabia and the patients were asked to check the most consumed foods.

Questions	Criteria for 1 point
1. Do you use olive oil as main culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥4 tbsp
3. How many vegetable servings do you consume per day? (1 serving : 200 g [consider side dishes as half a serving])	≥2 (≥1 portion raw or as a salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥3
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	<1
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	<1
7. How many sweet or carbonated beverages do you drink per day?	<1
8. How much wine do you drink per week?	≥7 glasses
9. How many servings of legumes do you consume per week? (1 serving : 150 g)	≥3
10. How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	<3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g)	≥3
13. Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic and simmered with olive oil)?	≥2

3.7: Statistical Analysis

Descriptive statistics were assigned using the mean for continuous variables, percentage frequencies for categorical variables, and cross-tabulations. The dependent variable is the depression status assessed by the PHQ-9and the independent variables are Vitamin D levels, BMI, Mediterranean diet adherence, and physical activity. The dependent variable was dichotomized into no depression (Minimal and Mild depression) and yes (Moderate- Moderately Severe and severe depression) for the PHQ-9.

We used several tests to assess the demographic, clinical, and lifestyle characteristics and depression of the participants; for the categorical variables we used the chi-square test and for the continuous variables, we ran the independent t-test for the normally distributed variables and the non-parametric test Mann-Whitney for the variables that have a skewed distribution.

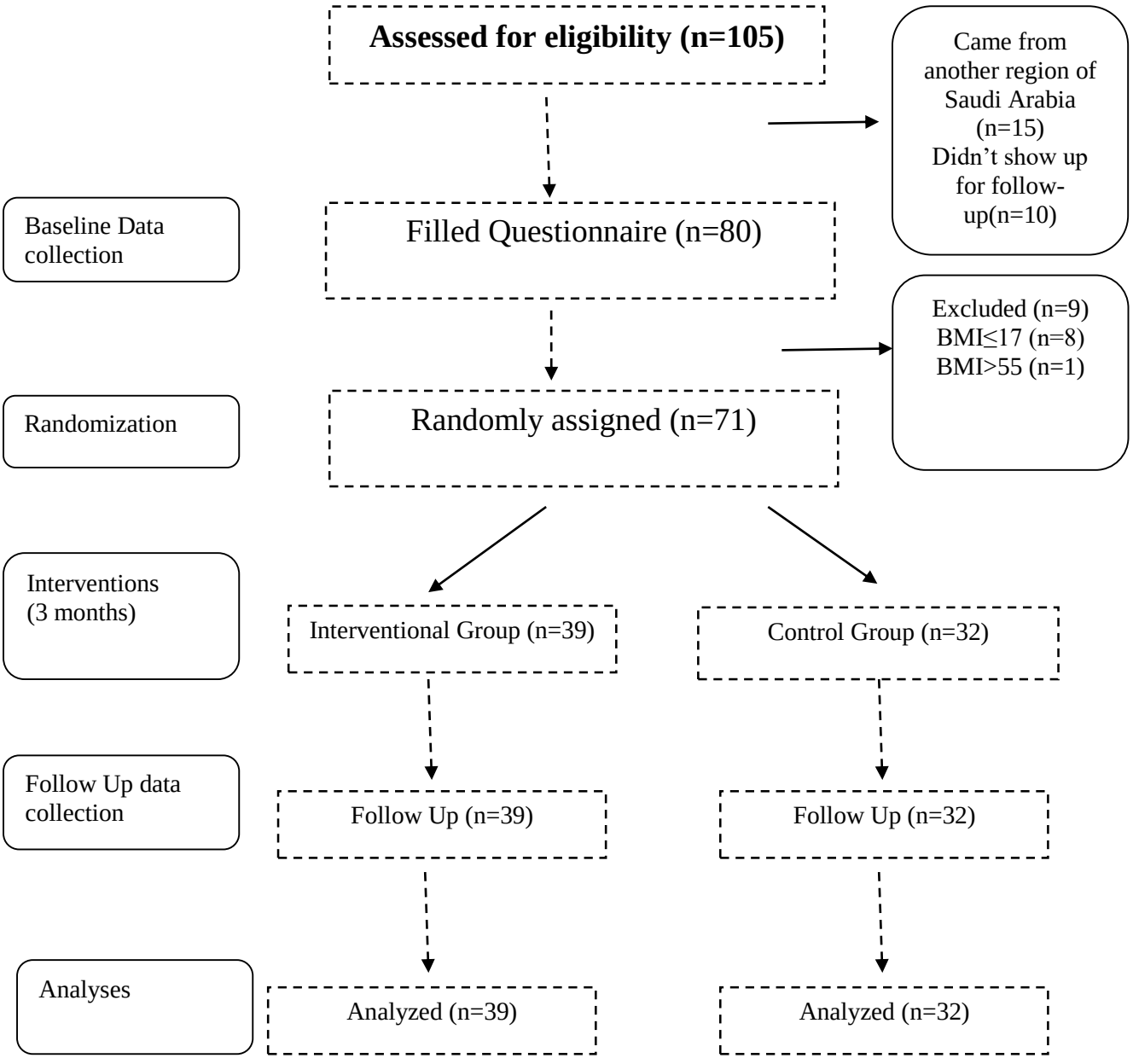
We did the independent t-test to compare changes between placebos versus the control group. In addition, we did a paired t-test to compare the change within both groups. Anova test was used to compare the change between groups. Moreover, logistic regressions were performed to assess the association between vitamin D and depression and w the adjustment variables were treated as continuous and categorical while controlling for other confounders. These variables were chosen based on the literature using two models. Model 1 was adjusted for gender, and age, and model 2 was additionally adjusted for physical activity, BMI, and Mediterranean diet adherence. Lastly, repeated measures were done to check for the effect of time on vitamin D levels. SPSS software version 22 was used for statistical analysis with a confidence interval of 95% and a significance level of $p<0.05$.

Chapter 5

Results

5.1: Sample Size

We approached 105 participants but a total of 80 participants agreed to participate in the study and completed data collection. Among those, nine participants were excluded from this study because they were outliers for BMI: eight had a BMI ≤17 kg/m^2 and one had a BMI > 55kg/m^2. Therefore, the final sample size was 71 adults.



5.2: Participant's Characteristics based on Gender

5.2.1: Socio-demographic characteristics

The socio-demographic characteristics of the participants are shown in **table 1**. Among the 71 participants, 59.2%(n=42) were females and the mean ageof the whole sample was 30.23 ±7.66years with no significant difference between groups (*P=0.344*). More than half of the participants were married 59.2% (n=42) and had a college degree66.2% (n=47). Nevertheless, there was no significant difference in these characteristics between the interventional group and the control group.

Table 1: Participants' baseline characteristics in the study

Covariates	Whole Sample (N=71)	Interventional group (n=39)	Control Group (n=32)	P-value[c]
Age (years) Mean (±SD)[a]	30.23 ±7.66	31.02 ±8.06	29.28 ±7.17	**0.344**
Gender, n(%)[b]				**0.467**
Female	42 (59.2)	25 (64.1)	17 (53.1)	
Male	29 (40.8)	14 (35.9)	15 (46.9)	
Educational Leveln(%) [b]				**0.802**
Primary and Secondary	24 (33.8)	14 (35.9)	10 (31.3)	
College	47 (66.2)	25 (64.1)	22 (68.8)	
Marital Status n(%) [b]				**0.225**
Single	29 (40.8)	13 (33.3)	16 (50)	
Married	42 (59.2)	26 (66.7)	16 (50)	

*All data are presented as n (%) except for age where mean (±SD) was presented.
Differences between the Control group and intervention group tested by:

[a] Independent-test;[b]Chi-square; [c] significance level at <0.05

5.2.2: Lifestyle characteristics

Lifestyle characteristics are presented in **Table 2**. More than half of the participants (n=43, 60.6%) were employed and the majority (n=68, 95.8%,) have office-based employment. Furthermore, the majority (n=65, 91.5 %) of the participants stated that their daily sun exposure is less than 15 minutes and there was no significant difference between both groups (p=0.084). When asked if the participants' mood affects their appetite, 85.9% answered positively, while no significant difference was observed between the control and the intervention groups. The number of participants who were diagnosed with chronic disease in the control group (n=5, 15.6%) was approximately the same as the intervention group (n=7, 17.9%). The most common chronic diseases that the participants suffered from were anemia,

hypertension, hypothyroidism, and diabetes mellitus. There was no significant difference in the number of chronic diseases between both groups.

Moreover, at baseline, a high percentage of participants were taking any supplements (n=21, 29.6%) or medications (n=8, 11.3%) and this percentage increased for the supplement use to reach 54.9 % and slightly decreased for the medications to 8.5% at the three-month follow-up. There was no significant difference in supplement use between both groups at baseline (p=0.116), however, a significant difference between both groups was noticed at follow-up (p=0.00) since vitamin D supplementation was prescribed for the interventional group.

In addition, a high percentage of participants were consuming enough amount of calcium and vitamin D fortified foods (93%) which further increased after the intervention to reach 97.2% which is also part of the intervention for the control group.

Table 2: Lifestyle characteristics of study participants at baseline and follow-up

	T1				T2			
Covariates	**Whole Sample (N=71)**	Interventional group (n=39)	Control Group (n=32)	P-value[e]	**Whole Sample N=71**	Interventional group (n=39)	Control Group (n=32)	P-value[e]
Employed n(%) [d]				**0.143**				**0.143**
Yes	43 (60.6)	27 (69.2)	16 (50)		43 (60.6)	27 (69.2)	16 (50)	
No	28 (39.4)	12 (30.8)	16 (50)		28 (39.4)	12 (30.8)	16 (50)	
Work Type n(%)[c]				**1.000**				**1.000**
Office-Based	68 (95.8)	37 (94.9)	31 (96.9)		68 (95.8)	37 (94.9)	31 (96.9)	
Field-Based	3 (4.2)	2 (5.1)	1 (3.1)		3 (4.2)	2 (5.1)	1 (3.1)	
Daily Sun Exposure n(%) [c]				**0.084**				**0.084**
> 15 minutes	6 (8.5)	1 (2.6)	5 (15.6)		6 (8.5)	1 (2.6)	5 (15.6)	
< 15 minutes	65 (91.5)	38 (97.4)	27 (84.8)		65 (91.5)	38 (97.4)	27 (84.8)	
Sleep Pattern n(%) [d]				**0.463**				**0.463**
During the Day	27 (38)	13 (33.3)	14 (43.8)		27 (38)	13 (33.3)	14 (43.8)	
During the night	44 (62)	26 (66.7)	18 (56.3)		44 (62)	26 (66.7)	18 (56.3)	
Does the mood affect the Appetite n(%) [c]				**0.495**				**0.204**
Yes	61 (85.9)	35 (89.7)	26 (81.3)		60 (84.5)	35 (89.7)	25 (78.1)	
No	10 (14.1)	4 (10.3)	6 (18.8)		11 (15.5)	4 (10.3)	7(21.9)	
Sleeping Hours Mean (SD)[a]	6.68±2.33	6.55±2.07	6.84±2.64	**0.603**	6.29 ±2.116	6.89 ±1.72	6.93±2.53	**0.94**
Are you taking any				**0.116**				**0.00**

Supplements n(%) [d]								
Yes	21 (29.6)	15 (38.5)	6 (18.8)		39 (54.9)	39 (100)	0	
No	50 (70.4)	24 (61.5)	26 (81.3)		32 (45.1)	0	32 (100)	
Are you taking any Medications n(%)[c]				**0.065**				**0.0213**
Yes	8 (11.3)	7 (17.9)	1 (3.2)		6 (8.5)	5 (12.8)	1 (3.1)	
No	63 (88.7)	32 (82.1)	31 (96.9)		65 (91.5)	34 (87.2)	31 (96.9)	
Are you consuming Vitamin D fortified foods n(%)[c]				**0.167**				**1.000**
No	5 (7)	1 (2.6)	4(12.5)		0		0	
50 IU/100 ml<VitD<100 IU/100 ml	66 (93)	38(97.4)	28 (87.5)		68 (95.8)	37 (94.9)	31 (96.9)	
>100 IU/100ml	0	0	0		3 (4.2)	2 (5.1)	1 (3.1)	
Are you consuming calcium-fortified foods n(%) [c]				**0.105**				**0.183**
No	5 (7)	1 (2.6)	4 (12.5)		2 (2.8)	0	2 (6.3)	
<500mg/100ml	35 (49.3)	23 (59)	12 (37.5)		37 (52.1)	23 (59)	14 (43.8)	
>500mg/100ml	31 (43.7)	15 (38.5)	16 (50)		32 (45.1)	16 (41)	16 (50)	
Presence of chronic diseases n(%) [d]				**0.203**				**0.452**
Yes	12 (16.9)	7 (17.9)	5 (15.6)		7 (9.9)	5 (12.8)	2 (6.3)	
No	59 (83.1)	32 (82.1)	27 (84.4)		64 (90.1)	34 (87.2)	30 (93.8)	

All data are presented as n (%) and mean (±SD) except for sleeping hours presented as mean (± SD). Physical activity is presented as n(%) and median (IQR).
[a]Independent-test;[b] Mann-Whitney test, [c] Fisher's exact;[d]Chisquare; [e] significance level at <0.05

5.2.3: Clinical and dietary characteristics

The clinical and dietary characteristics of our sample at baseline and 3-month follow-up are shown in **Table 3**. At baseline, the mean BMI of the participants was 30.2 ±9.30, with more than half of the participants considered obese 52.1%(*n=37*), while 15.5% (*n=11*) were considered underweight. At the 3-month follow-up, the mean BMI decreased to 27.29 ±6.63 with only 32.4 % (*n=23*) obese while none was underweighted.

Moreover, 42.3 % (*n=30*) of participants had a moderate MeDi adherence while this improved to 71.8% (*n=51*) following the intervention. Regarding physical activity, 71.8 % (*n=51*) of the participants had low levels of physical activity as indicated by the IPAQ, which did not alter significantly following the intervention (n=46, 64.8 %). There was no significant difference between both groups among these 3 covariates (physical activity, BMI, and MeDi Adherence) at baseline and at 3-month follow-up(P>0.005).

Table 3: Clinical &Dietary Patterns characteristics for the whole sample and stratified by groups

	T_1				T_2			
Covariates	**Whole Sample (N=71)**	Interventional group (n=39)	Control Group (n=32)	P-value[e]	**All Sample (N=71)**	Interventional group (n=39)	Control Group (n=32)	P-value[e]
BMI (kg/m2) Mean ±SD[a]	30.2±9.30	30.71 ±8.79	29.61 ±9.98	**0.62**	27.29 ±6.63	27.61 ±5.98	26.90±7.42	**0.65**
BMI categories				**0.56**				**0.77**
Underweight n(%) Mean ± SD	11 (15.5)17.9±0.36	6 (15.4) 18.04±0.35	5 (15.6) 17.83±0.38		0	0	0	
Normal n(%) Mean ± SD	11 (15.5) 20.8±1.79	5 (12.8) 21.36±2.04	6(18.8) 20.43±1.62		33 (46.5) 21.62±1.91	17 (43.6) 21.86±1.86	16 (50) 21.36±1.99	
Overweight n(%) Mean ± SD	12 (16.9) 27.2±1.32	5 (12.8) 27.23±1.45	7 (21.9) 27.33±1.34		15 (21.1) 27.71±1.5	8 (20.5) 28.44±1.12	9 (28) 26.88±1.67	
Obesity n(%) Mean ± SD	37 (52.1) 37.6±5.9	23 (59) 36.81±5.22	14 (43.8) 38.90±6.9		23 (32.4) 35.1±4.45	14 (35.9) 34.12±3.21	7 (21.9) 36.7±5.7	
MeDi Adherence Mean ±SD[a]	5.86 ±2.07	5.84 ±2.084	5.87±2.10	**0.95**	8.08 ±1.68	8.48 ±1.21	7.59±2.04	**0.03**
MeDi Categories				**0.92**				**0.03**
Lown(%) Mean ± SD	35 (49.3) 4.22±0.84	20 (51.3) 4.25±0.85	15 (46.9) 4.20±0.86		5 (7) 4.40±0.54	0	5 (15.6) 4.40±0.54	
Mediumn(%) Mean ± SD	30 (42.3) 6.68±1.07	16 (41) 7.00±1.09	14 (43.8) 6.71±1.06		51 (71.8) 7.82±1.07	31 (79.5) 8.06±0.96	20 (62.5) 7.45±1.14	
Highn(%) Mean ± SD	6 (8.5) 10.33±0.51	3 (7.7) 10.3±0.57	3 (9.4) 10.33±0.57		15 (21.1) 10.2±0.41	8 (20.5) 10.21±0.35	7 (21.9) 10.2±0.48	
Physical Activity (MET) Mdn (IQR) [b]	297 (198, 693)	297 (99, 593)	307.50 (198, 857.25)	**0.47**	396 (476.4, 802.1)	396 (198, 876)	505.5 (297, 855)	**0.37**
MET Categories				**0.37**				**0.42**
Lown(%) Mean ± SD	51(71.8) 240.41±188.0	30 (76.9) 249.6±197.20	21(65.6) 227.28±177.9		46 (64.8) 258.71±187.8	27(69.2) 249.3±176.6	19(59.4) 272.05±206.9	
Moderaten(%)Mean ± SD	20 (28.2) 1331.8±745.46	9(23.1) 1167.6±385.7	11(34.4) 1466.18±944.8		25(35.2) 1339.4±725.4	12(30.8) 1277.5±479.8	13(40.6) 1396.6±913.2	

* All data are presented as n (%) and mean (±SD) except for sleeping hours presented as mean (± SD). Physical activity is presented as n (%) and median (IQR).
[a]Independent-test;[b] Mann-Whitney test, [c] Fisher's exact; [d] Chisquare; [e] significance level at <0.05

5.2.4: Association between vitamin D and depression based on categories

Vitamin D and Depression status are shown in **table 4**. At baseline, vitamin D levels were 16.71±6.63 ng/ml and there was a significant increase after the intervention to reach 39.49 ±16.22 ng/ml (p=0.00). In addition to that, more than half of the participants were vitamin D deficient 64.8 % (*n=46*) and 35.2 % (*n=25*) were vitamin D insufficient; however, after the intervention, the percentage of the participants that were vitamin D deficient and insufficient decreased to reach 8.5% and 28.2 % respectively and the percentage of participants who are vitamin D sufficient reached 63.4%, being 100% in the intervention group and 18.8% in the control group. There was a significant difference between the groups in the vitamin D levels after the intervention P=0.000 with no significant difference at baseline p= 0.76.

However, the PHQ-9 score decreased from 12.50±5.01 at baseline to 6.75±3.68 after the intervention. This decrease is as follows: the percentage of the severely depressed participants has decreased from 8.5% to zero%, the moderately severe from 22.5% to 2.8%, the moderately depressed participants from 39.4% to 21.1%; whereas the percentage of the mildly and minimally depressed participants has increased from 22.5% to 46.5% and 7% to 29.6% respectively. There was no significant difference at baseline between the groups p=0.880, while a significant difference has been shown after the intervention p=0.000.

Table 4: Vitamin D levels and depression status for the whole sample of Saudi Adults and stratified by groups.

	T_1				**T_2**			
Covariates	**Whole Sample (N=71)**	Interventional group (n=39)	Control Group (n=32)	P-value[e]	**Whole Sample N=71**	Interventional group (39)	Control Group (32)	P-value[e]
Vitamin D Level Mean ± SD [a]	16.71±6.63	16.92±7.23	16.44±5.91	**0.76**	39.49 ±16.22	51.41 ±11.27	24.95 ±6.45	**0.000**
Vitamin D Categorical				**0.25**				**0.000**
Deficientn(%) Mean ± SD	46 (64.8) 12.50±3.61	23 (59) 11.53±3.23	23 (71.9) 13.47±3.7		6 (8.5) 17.80±2.20	0	6 (18.8) 17.80±2.20	
Insufficientn(%) Mean ± SD	25 (35.2) 24.4±2.7	16 (41) 24.6±2.96	9 (28.1) 24.03±2.45		20 (28.2) 25.87±2.94	0	20 (62.5) 25.94±2.94	
Sufficient n(%) Mean ± SD	0	0	0		45 (63.4) 49.14±12.05	39 (100) 51.4±11.27	6 (18.8) 34.4±3.38	
PHQ-9 Mean (SD)[a]	12.50 ± 5.01	12.53 ±5.33	12.46 ± 4.66	**0.95**	6.75 ±3.687	4.92 ±2.44	8.96 ±3.75	**0.000**
PHQ-9 categorical				**0.88**				**0.000**
MinimalDepressionn(%) Mean ± SD	5 (7) 3.80±0.44	3 (7.7) 4.0±0.0	2 (6.3) 3.50±0.70		21 (29.6) 2.71±0.9	17 (43.6) 2.70±0.8	4 (12.5) 2.75±1.2	
Mild Depression n(%) Mean ± SD	16 (22.5) 7.37±1.40	10 (25.6) 7.40±1.42	6 (18.8) 7.30±1.50		33 (46.5) 6.66±1.40	20 (51.3) 6.25±1.3	13 (40.6) 7.30±1.31	
Moderate depression n(%) Mean ± SD	28 (39.4) 12.93±1.19	14 (35.9) 12.7±1.06	14 (43.8) 12.07±1.21		15 (21.1) 11.26±1.43	2 (5.1) 10.50±0.70	13 (40.6) 11.38±1.5	
Moderately Severe Depressionn(%)Mean ± SD	16 (22.5) 17.06±1.23	8 (20.5) 16.8±1.35	8 (25) 17.25±1.1		2 (2.8) 16.5±2.12	0	2 (6.3) 16.5±2.12	
Severe Depressionn(%)Mean ± SD	6 (8.5) 21.8±1.47	4 (10.3) 22.5±1.29	2 (6.3) 20.5±0.70		0	0	0	

* All data are presented as n (%) and mean (±SD) except for sleeping hours presented as mean (± SD). Physical activity is presented as n (%) and median (IQR).

[a]Independent-test;[b] Mann-Whitney test, [c] Fisher's exact; [d] Chisquare; [e] significance level at <0.05

5.2.5: Association between vitamin D, depression, MeDi Adherence, BMI, and physical activity.

After 3 months of intervention, vitamin D level has increased significantly in both the intervention group (16.92 ±7.23 to 51.41 ±11.27; p<0.001) and in the control group (16.44 ±5.91 to 24.95±6.45; p<0.001). However, a greater change has been observed in the intervention group compared to the control group (34.48 ±6.56 vs 8.50 ±2.13, respectively; p<0.001) (Table 5). A significant difference in vitamin D levels between both groups has been seen (p<0.001).

A significant change was also noticed in BMI in both groups. This change was statistically significant (-3.10±3.22 in the intervention group vs -2.71±3.17in the control group; p<0.001) however, it is clinically small and both groups have lost approximately the same weight; however, the difference in the BMI between both groups was insignificant (p=0.60)**.**

There was a significant decrease in the PHQ-9 score in both groups with a double decrease in the interventional group vs control group (-7.61 ±4.03, p <0.001 vs -3.50±1.54; p<0.001). Furthermore, there was an improvement in MeDi adherence in the interventional (2.64 ±1.75, P<0.001) and the control group (1.71 ±1.65; P<0.001); however, there was no difference in change in the MeDi adherence between both groups (P=0.27).

Last but not least, no significant difference has been observed in the intervention and control groups in the physical activity level between baseline and at the 3-month follow-up (p=0.19, p=0.51 respectively).

Table 5: Paired T-test to compare the change between baseline and the 3-month follow-up within the control and the intervention groups

Outcome Variable	Interventional Group (n=39)				Control Group (n=32)				Difference between Control Group &Interventional group
	T1	T2	P_1Value	Change	T1	T2	P_2Value	Change	P_3 Value
Vitamin D level	16.92 ±7.23	51.41 ±11.27	**<0.001**	34.48 ±6.56	16.44 ±5.91	24.95±6.45	**<0.001**	8.50 ±2.13	**<0.001**
BMI	30.71 ±8.79	27.61 ±5.98	**<0.001**	-3.10±3.22	29.61 ±9.98	26.90±7.42	**<0.001**	-2.71±3.17	**0.60**
PHQ-9	12.53 ±5.33	4.92 ±2.44	**<0.001**	-7.61 ±4.03	12.46 ±4.66	8.96±3.75	**<0.001**	-3.50±1.54	**<0.001**
MeDi	5.84 ±2.04	8.48 ±1.21	**<0.001**	2.64 ±1.75	5.87 ±2.10	7.59 ±2.04	**<0.001**	1.71 ±1.65	**0.27**
P.A (MET)	297 (99, 593)	396 (198, 876)	**0.19**	0±1923	307.50 (198, 857.25)	505.5 (297, 855)	**0.51**	0±198	**0.66**

* All data are presented as mean (±SD) or median (Interquartile range)
Abbreviations: T1: Baseline; T2: Follow up; BMI: Body mass index; PHQ-9: Patient health questionnaire-9; MeDi: Mediterranean Diet Adherence; MET: the metabolic equivalent of task.
P_1: Paired t-test to check the difference between baseline and follow-up in the interventional group.
P_2: Paired t-test to check the difference between baseline and follow-up in the control group.
P_3: Anova for the difference at baseline between Control Group & Interventional group

5.2.6: Association between vitamin D levels and prevalence of depressive symptoms

Association of depression with vitamin D levels at baseline is shown in **table 6**. A logistic regression analysis was conducted to predict the association between vitamin D levels and the prevalence of depression while considering vitamin D as both continuous and categorical variables. Two models were employed with model 1 adjusting for age and gender, and model 2 additionally adjusted for the continuous variables, physical activity (MET), BMI, and MeDi adherence. When vitamin D was considered as a continuous variable, we observed that for each unit increase in vitamin D levels was associated with a lower depression prevalence (OR=0.87; 95% CI: 0.79-0.95, p=0.005). Nevertheless, this significance was lost with further adjustment in model 2 (OR=0.90; 95% CI: 0.81-1.01, p=0.08).

When vitamin D levels were dichotomized, we observed that deficient patients more likely to suffer from depression compared to those who were insufficient (OR= 4.47; 95% CI:1.39-14.38, P=0.012) after adjustment for age and gender. Nevertheless, this significance was lost with further adjustment in model 2(OR= 2.18; 95% CI: 0.56-8.47, P=0.259).

Table 6: Association of Depression with baseline Vitamin D levels.

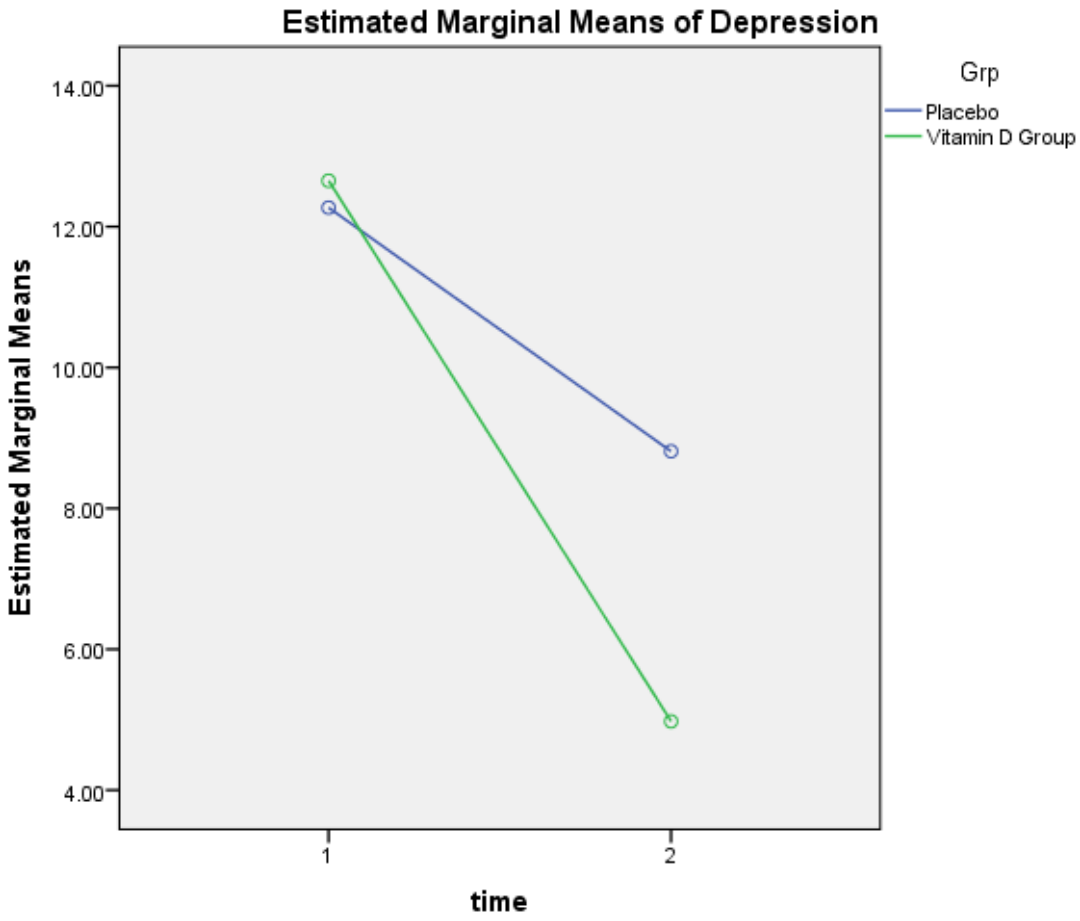
	VIT D (Continuous)			**VIT D categorical (Insufficient-Deficient)**		
				Insufficient	**Deficient**	
		OR 95% CI	**P-value**		**OR 95% CI**	**P-value**
n Depression (depressed/total)	**N= 50/71**			**N= 12/25**	**N= 38/46**	
Model 1		0.87 (0.79-0.95)	0.005	Ref	**4.47 (1.39-14.38)**	**0.012**
Model 2		0.90 (0.81-1.01)	0.084	Ref	**2.18 (0.56-8.47)**	**0.259**

* OR: Odds ratio, CI: Confidence Intervals, Ref: Reference, n Depression: Number of participants with depression
Model 1: Adjusted for age and Gender
Model 2: Model 1 + Further adjustment for the continuous variables: P.A (MET), BMI, and MeDi diet Adherence

5.2.7: Repeated analysis

Repeated measures were done to check forthe effect of time on vitamin D and the graph is shown in figure 1. The repeated measures showed that there was a time interaction with vitamin D. Thus, the duration of 3 months' intervention helped to have an effect on the increase of vitamin D.

Figure 1: Repeated measures for the interaction between time and vitamin D.



Chapter 6

Discussion

In this randomized single-blind clinical trial, we evaluated the association between vitamin D supplementation and the incidence of depressive symptomatology at three-month follow-up among Saudi Arabian adults aged between 18 and 65 years old. We observed that a three-month vitamin D supplementation at a dose of 50.000 IU was associated with lower depression symptoms, implying that Vitamin D supplementation was effective in improving depression.

The prevalence of depression in Saudi Arabia is high and it was noted in 2002 to be around 18% (Aljizani et al., 2020). Furthermore, in another Saudi Arabian region, Tabuk, it was observed that 20.8 % of the participants were moderately depressed, and 15.4 % were suffering from moderately severe to severe depression in a cross-sectional study conducted between November 2018 to April 2019 on participants aged 20-40 years (Mohsen Al Balawi et al., 2019). This prevalence is lower than what we observed in the current study where 39.4% were moderately depressed, 22.5% were moderately severely depressed and 8.5 % were severely depressed as shown by PHQ-9.

Obesity may be one of the factors for this high prevalence in our study since obesity was shown to be a risk factor for depression by impairing the neurotransmitter activity in the brain via neuroinflammation induced by pro-inflammatory cytokines (Almarhoon et al., 2021). Our participants had a high BMI (30.2±9.30) and the majority visited the clinic to lose weight.

Another reason for the observed higher prevalence of depression might be the broader age range in our study (18-65) compared to the Al Balawi study where they had a narrower and younger age range (20-40years old) (Mohsen Al Balawi et al., 2019). In fact, older age has been shown to be another consistent and significant risk factor for depression as demonstrated in a longitudinal cohort study which aimed to examine whether older age (70 years or older) was linked to worse MDD course than that of younger age (18-29 years) (Schaakxs et al., 2018). Between 2004 and 2012, 1042 participants from the Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Study of Depression in Older Persons (NESDO) cohorts provided baseline and two-year follow-up data.Four indicators were used to assess the primary outcome: the time to remission, the change in

depression severity, attaining a depression diagnosis after 2 years, and the presence of depressed symptoms for at least 80% of the two-year follow-up period. Results revealed that the severity of MDD worsened linearly with age, with people 70 years or older showing the worst outcomes when compared to the reference group of those between the ages of 18 and 29(Depression severity change: -12.64 (SD 10 85) in those aged 18 to 29 years and -5.57 (11.14) in those aged 70 years or more; MDD diagnosis: OR=2.02; 95% CI:1.18-3.45; chronic symptom course: OR= 3.19; 95% CI:1.74-5.84; duration to remission: HR= 0.60; 95%CI:0.44-0.83).

Furthermore, the current study demonstrated that vitamin D levels were associated with depressive symptomatology in the cross-sectional analyses performed at baseline when adjusting for age and gender in model 1. In fact, when vitamin D was considered as a continuous variable or categorical, by comparing those deficient to those insufficient, we observed a significant association between higher vitamin D levels and lower depressive symptomatology when adjusting for age, and gender. Nevertheless, this significance was lost in model 2 after additional adjustment for MeDi Adherence, physical activity and BMI.

This finding is similar to a cross- sectional study conducted in Riyadh, Saudi Arabia to check if vitamin D deficient participants had different levels of anxiety and depression than vitamin D insufficient participants (Al Hariri, 2016). This study included 246 participants(44.1%females) aged between 14-80 years old previously diagnosed with vitamin D deficiency (50.8%) or insufficiency (49.2%). Participants were considered vitamin D deficient or insufficient if their vitamin D levels were ≤ 10ng/ml or between 10.1 ng/ml to 30 ng/ml, respectively. Depression level was assessed by an experienced psychotherapist, International Classification of Diseases 10th (ICD-10) and diagnostic and Statistical Manual of Mental Disorders-4 (DSM-4) and DSM-5 using a structured questionnaire developed by the researcher. This study found that although there was no significant difference between depression and anxiety scores for clients with vitamin D deficiency and vitamin D insufficiency, the means for depression (M=2.59) and anxiety levels (M=2.67) were higher in clients with vitamin D deficiency. Thus, these results are in line with the results of this study showing that people with lower vitamin Dare more likely to experience depression.

Moreover, a comparative observational study was conducted in Iran University of Medical Sciences to investigate the relationship between depression and blood vitamin D levels in patients with obesity aged 18 to 60 who were seen at an outpatient obesity clinic

(Kamalzadehet al., 2021). The vitamin D levels of obese people with depression (n = 174) and those without depression (n = 173) were compared. Depression was assessed by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. It was shown that 78% and 67%, respectively, of the depressed and non-depressed groups had vitamin D deficiency/insufficiency(p=0.03) which shows the link between depression and low vitamin D levels in obese persons. These results are in line with our descriptive and model 1 logistic regression, especially that both studies had overweight/obese participants.

The results showed that after 3 months of intervention, vitamin D level has increased significantly in both the intervention group and the control group. This increase reflects a high adherence meaning that the 50.000 IU/week dose of vitamin D supplementation was effective in rising vitamin D level more than the dietary recommendations that were given. On the other side, there was a significant decrease in the PHQ-9 score in both groups with a double decrease in the interventional group vs control group (-7.61 ±4.03, p <0.001 vs-3.50±1.54, p<0.001). So, there was a positive change in the mood in both groups however a better enhancement was seen in the interventional group. In the Vitamin D group, the score has changed by 7 points which is almost double the range of each depression category allowing the participants to move down by one to two categories on the PHQ-9 scale. As an example, this change was enough to move a participant from being moderately severely depressed (15-19 points) to being mildly depressed (5-9 points). On the other hand, although the change was also significant in the control group, the magnitude of change was smaller (-3.5 points) which is smaller than the range of the categories. Therefore, this change was either a jump in one category in the depression scale or was not enough to change the depression category of the participant.

After supplementing with vitamin D at 50,000 IU/week for three months, we also observed that the participants in the intervention group had lower scores on the PHQ9, indicating an improvement in the depressive symptomatology. In fact, the supplementation increased vitamin D levels enough that at three months' follow-up, very few participants remained deficient and lots of participants were mostly insufficient or deficient at baseline.

This is in line with a double blind RCT conducted by Kaviani et al. on 56 subjects with a mean age of 43 ± 1.15 years for 8 weeks to examine the effects of vitamin D supplementation on patients with mild to moderate depression, serum vitamin D levels, and specific neurotransmitters (Kaviani et al., 2020). The intervention group took 50.000 IU

vitamin D dose every 2 weeks and the control group took a placebo pill similar in appearance and packaging to vitamin D pills. Depression severity was measured by the Beck Depression Inventory-II. Similar to our study, when participants with mild to moderate depression received vitamin D supplements, their serum vitamin D concentration increased and their vitamin D status was upgraded to an acceptable level. When compared to the control group, this was accompanied by a considerable improvement in the severity of the depression. (-11.75±6.40 vs. -3.61±10.40; P = 0.003) in addition to the significant increase in serum vitamin D in the interventional group vs the control group (+40.83±28.57 vs. +5.14±23.44 nmol/L; P<0.001).

Lastly, the VITAL study, one of the largest randomized clinical trials done so far aimed to determine how vitamin D supplementation will affect mood scores and risk for late-life depression for a period of 5.3 years among 18353 participants aged 67.5±7.1(Okereke et al., 2020). In this RCT, 9181 participants have received 2000 IU of vitamin D3supplementation and 9,172 has received fish oil or placebo. Vitamin D3 supplementation compared with placebo did not result in statistically significant differences in the depression incidence and recurrence or change in mood scores. Thus, the use of vitamin D in adults to prevent depression is not supported by these findings. These results are not in line with ours. Nevertheless, this study is worth mentioning since it included a large sample size and a long follow-up period. This opens the discussion to the efficacy of supplementation versus food intake, especially that in our study participants who had dietary advice were also able to have increase their vitamin D serum and levels and have better PHQ-9 scores. Furthermore, this effect maybe due to the intake of vitamin D fortified food in which we observed that 93% of our participants consumed calcium and vitamin D fortified foods. So, there is still controversy about the efficacy of supplementation and more studies are still needed to determine the preventive effects of supplementation in general.

As previously described, obesity can be a risk factor for depression and our results may be due to the weight loss we observed in both groups. This was in line with what Jorde et al observed. Their trial showed a slight but statistically significant reduction in depression symptoms with vitamin D treatment in a trial with overweight and obese subjects.

Furthermore, due to the frequent coexistence of vitamin D deficiency and obesity, several studies have questioned whether the relationship is causal. Therefore, a systematic review and meta-analysis of 4 randomized (n=2554) and 11 nonrandomized controlled studies (n=917) with participants of any age were conducted to determine whether weight loss compared to weight maintenance results in an increase in blood 25-hydroxyvitamin

D(Mallard et al., 2016). Changes in adiposity and blood 25 hydroxyvitamin D were taken as the primary or secondary outcomes. The results showed a greater increase in serum vitamin D levels in groups that were randomly assigned to weight loss as opposed to weight maintenance, with a mean difference between groups of 3.11 nmol/L (95% CI: 1.38, 4.84 nmol/L), as compared to nonrandomized trials, which showed a mean difference of 4.85 nmol/L (95 %CI: 2.59, 7.12 nmol/L).However, there was no proof that weight loss had a dose-response impact on the change in blood 25-hydroxyvitamin D. Therefore, the results imply that weight loss may lead to a slight improvement in vitamin D status when compared to weight maintenance under conditions of supplemented vitamin D intake. This is noteworthy to mention as we speculate that the beneficial effects, we observed might also be associated to the weight loss observed in both groups and particularly the placebo group. This might lead to a liberation of vitamin D from adipose tissue to the blood and therefore an increase in vitamin D serum levels.

Moreover, a review of the most recent data from meta-analyses examining vitamin D status in obesity proposed the underlying pathogenetic mechanism linking low vitamin D to obesity (Karampela et al., 2021).In fact, adipose tissue is the most significant quantitative vitamin D storage organ, so in individuals who have an excessive buildup of adipose tissue, vitamin D as a fat-soluble vitamin, may become stored and sequestered in adipose tissue, preventing it from entering the bloodstream to synthesize 25(OH)D in the liver which may result in reduced plasma levels of vitamin D. Moreover, vitamin D is transported, possibly by simple diffusion, in fat, muscle, liver, and serum but because of obesity, all of these compartments have an increased volume which will result in decreased serum vitamin D concentrations compared to lean persons. Furthermore, obesity is linked to decreased expression of particular genes that control vitamin D metabolism -in adipose tissue, the liver, and possibly other tissues- by coding the synthesis of the enzymes 25- hydroxylase and 1-hydroxylase; so, a diminished production of these enzymes in patients with obesity will lead to a low levels of vitamin D in the blood. This may explain the high rate of hypovitaminosis D in our study at baseline despite the plentiful sunshine in the study's region, since a high percentage of the participants were overweight/obese and may also explain the observed significant effect in the placebo group.

Moreover, 42.3% of our participants had a low adherence to the MeDi while 57.8% had a moderate or high adherence at baseline. This is noteworthy to mention as MeDi adherence has been shown to be protective against decreasing the risk of depression (Adjibade et al., 2017) (Molendijk et al., 2018). This can be due to the fact that the hallmark

of the MeDi is the extensive use of olive oil which is high in monounsaturated fatty acids (MUFA) that has a favorable effect on depression because it improves the binding of serotonin to its receptors (Sánchez-Villegas et al., 2009). Therefore, the observed minimal adherence to the MeDi in the current study may explain the reason behind the high depression prevalence at baseline. Nevertheless, since more than half of the participants had moderate (49.3%) and high adherence (8.5%), this helps explain the lost significance in model 2 when adjusting for this variable. Furthermore, the observed increase in the MeDi score in both groups (+ 2.64 ±1.75 in Vitamin D group, p=<0.001; +1.71 ±1.65 in the control group, p<0.001; with no significant difference between the groups p=0.27) may also help explain the improvement in the PHQ-9 scores. This was shown in the Australian Longitudinal Study on Women's Health that women in the highest quartile of adherence to a 'Mediterranean-style' diet were found to be 37% less likelyto have depressive symptoms than those in the lowest quintile after 3 years of follow-up (Sánchez-Villegas et al., 2013). Therefore, future studies should take into consideration the role of diet in general and MeDi in particular when determining the role of vitamin D in the prevention of depression.

Another factor to consider when examining our results is physical activity. The majority of the participants (71.8%) had low physical activity level. This may additionally explain the high prevalence of depressive symptomatology at recruitment. In fact, physical activity has been demonstrated to minimize anxiety and depression symptoms while also improving physical and psychological well-being (Sander et al., 2017). Nevertheless, one of the symptoms of depression is fatigue and loss of energy, and these symptoms will lead individuals to engage less in physical activity thus facilitating obesity. Therefore, whether depression leads to low physical activity and obesity, or obesity causes depression is unclear yet and needs more research.

The exact biological pathways that relate vitamin D to depression are unknown however several mechanisms have been proposed (Jorde et al., 2008). In fact, it was suggested that vitamin D Deficiency increases the symptoms of depression by negatively affecting the cerebral process (Anglin et al., 2018) and by affecting the central nervous system through the vitamin D receptor (VDR) (Kris-Etherton et al., 2021). In fact, it has been found that the hypothalamus has vitamin D receptors, which may be involved in neuroendocrine function. (Penckofer et al., 2010). Moreover, by controlling intracellular calcium storage and cellular signaling, vitamin D may help to correct the calcium and

neurotransmitter imbalance, as well as having a positive impact on the beginning of depression (Menon et al., 2020). In addition to protecting against dopamine and serotonin depletion, which are critical for mood regulation, vitamin D controls the supply of the monoamine neurotransmitters adrenaline, norepinephrine, and dopamine in the adrenal cortex(GengC; 2019). Lastly, it was observed in that in animal models of multiple sclerosis, vitamin D treatment controls inflammatory cytokine levels. This is noteworthy since evidence links depression to high levels of systemic inflammation. (Menon et al., 2020).

Some limitations to the current study should be considered before drawing firm conclusions. First, some of the data were self-reported (Diseases, MeDi, and IPAQ) so there might be an underestimation due to either recall bias or social desirability since most participants were overweight and obese. Furthermore, depressive symptomatology was assessed using the PHQ-9 questionnaire and not through a clinician. Nevertheless, this questionnaire was shown to be a valid measure to evaluate depression (Sun Y;FuZ;BoQ;MaoZ;MaX;Wang C;, 2020)(Vaughan et al., 2019)and its validity and reliability were demonstrated in Saudi Arabia (AlHadi et al., 2017). Second, the study took place in a weight management clinic which means that the participants are already at the change stage and are seeking help to manage their weight and start a new healthy lifestyle. This will skew the results because the recruited sample is very motivated and might have affected their adherence to both the supplementation and the dietary advice. Also, since weight loss was observed at the 3-months follow-up, this might have also affected our results since obesity is a risk factor for depression. Thus, we are not sure if losing weight was behind improving the depressive symptoms or the combination between vitamin D supplementation and maintaining a healthy weight. Third, this study assessed only participants coming to the Al Themal Medical Center in Saudi Arabia for a medical check-up which are from a medium to high socioeconomic levels that makes them able to afford the costs of the visit to a private medical center. Also a high percentage (66%) of the participants were of high educational level and thus they were aware of the benefits of having a healthy weight and lifestyle; consequently, the sample may not be representative, thus limiting the generalizability; Fourth, only vitamin D deficient/insufficient and not sufficient participants were recruited in this study and this had limited our ability to strengthen our conclusion by further comparing the participants to a sufficient group. Nevertheless, vitamin D deficiency/insufficiency in addition to depression are very high is Saudi Arabia, which made us choose the vitamin D deficient/insufficient participants and intervene to improve their depression status. Fifth, the

Saudi Arabian community is a restrictive community and some of the questions were eliminated from the MeDi questionnaire like drinking wine, and smoking in the lifestyle assessment questionnaire, which might affect our results due to the health benefits of wine and the drawbacks of smoking on the health. Lastly, despite taking into consideration several factors, some residual confounding cannot be eliminated as depression has several factors other than dietary ones.

Despite those limitations, our study has several strengths. To our knowledge, this is the first study in Saudi Arabia to assess the relation between vitamin D supplements and its effect on depression symptoms. This is noteworthy as a high prevalence of depressive symptomatology was observed in Saudi Arabia. In Addition, while most of the previous studies were observational, the study design (RCT) allows us to determine a temporal association and observes that a weekly 50.000 IU vitamin D supplementation can enhance the depressive symptomatology among adults. Moreover, this study included both genders and had a wide age range, reinforcing the observation that vitamin D supplementation is beneficial among different stages of adulthood and for both genders. Furthermore, the use of international instruments that are translated to Arabic and validated in Arab countries (PHQ9, IPAQ) increases the generalizability of our results. Additionally, vitamin D levels were determined using the gold standard method which is measuring serum vitamin D levels. In addition, we used the World Medicalassociation (WMA) classification for vitamin D levels to denote deficiency and insufficiency which is internationally recognized and approved, although the lack of an international consensus on one classification. Besides, based on the repeated measures done to check the effect of time on vitamin D, the 3 months period was enough as we noticed an interaction between time and vitamin D; however longer durations are needed to check if this effect is maintained beyond the 3 months period. Last but not least, the high adherence of vitamin D supplementation intake was remarkable as observed by the increased levels in the intervention group. This shows that a weekly supplementation is easier to follow than a daily one and that the system followed at the center is an effective way to remind participants to take their supplements.

Chapter 7

Conclusion

As a conclusion, this study showed that a 50.000 IU/week dose of vitamin D supplementation for 3 months was enough to increase vitamin D levels beyond sufficient and decrease depression symptoms in Saudi Arabian Adults; however, the exact mechanism is still unclear and needs more investigation. Furthermore, having low physical activity levels, not adhering to a MeDi, being obese, and not being sufficiently exposed to the sun might also be modifiable risk factors for depression. These results were consistent with previous studies, but a non-significant result was shown in our study after adjusting for BMI, physical activity and MeDi Adherence.

As a summary, sunlight exposure or food alone may not be enough to provide enough amounts of vitamin D for many people. So, it would be an easy and affordable solution for many people who are at risk of depression and other mental illnesses to exercise in the sun, eat foods high in vitamin D, and/or use dietary supplements in order to treat vitamin D deficiency to improve their mental health.

In fact, future studies should be done in Saudi Arabia regarding supplementing vitamin D deficient/insufficient people with vitamin D to treat or prevent depression. However, all the identified limitations should be taken into consideration to support these results in order to initiate recommendations for non-therapeutic interventions and avoid the several negative consequences of depression. Knowing that Saudi Arabia is one of the countries that ranks high in vitamin D deficiency, this study might be one of the steps that will shed lights on the importance of maintain good vitamin D levels and thus, as a future step, the focus should be on decreasing the prevalence of this depression.

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