IMPACT OF SUN EXPOSURE PROTECTIVE BEHAVIORS ON THE ASSOCIATION BETWEEN VITAMIN D AND DEPRESSION

By

Courtney E. Crawford

A THESIS

Presented to the Department of Public Health & Preventive Medicine
and the Oregon Health & Science University
School of Medicine
in partial fulfillment of
the requirements for the degree of

Master of Public Health

April 2014

Department of Public Health and Preventive Medicine

School of Medicine

Oregon Health & Science University

CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of

Courtney E. Crawford

has been approved

Jodi Lapidus, PhD

Carrie Nielson, MPH, PhD

Mary McCarthy, MD

Table of Contents

Acknowledgments

I would like to thank the three members of my committee, **Dr. Jodi Lapidus, Dr. Carrie Nielson** and **Dr. Mary McCarthy**, for putting up with several years of edits and reworks with patience and encouragement. Particularly, I would like to thank **Dr. Lapidus** for her invaluable help in shaping my questions into something manageable with the data available to me, and tolerating and aiding the long process of shaping my Monster Document into a thesis instead of a few hundred pages of disconnected rambling with some numbers thrown in.

I would also like to thank my parents … my father for providing me with much needed humor about the many things that rhyme with 'theses', and my mother for never letting me forget (in the nicest way possible) that I still had a thesis to finish! Without their love, encouragement and support through the years, I would not be where I am today.

To the Mansemallows, thank you for dealing with my late night melancholy about how I was going to be a graduate student in perpetuity and commiserating with me on the difficulties of Being A Responsible Adult.

Lastly, I would like to thank my husband for all the meals, chauffeuring, late night study sessions and chocolate that got me through graduate school.

Abstract

Depression is a serious mental illness, with an estimated prevalence of 6.7% of American adults according to the 2001-2003 National Comorbidity Survey Replication[35]. Recent studies indicate that there may be a link between insufficient vitamin D and depression. Because the primary source of vitamin D is synthesis in the skin via exposure to ultraviolet light, sun protection behaviors such as sunscreen and avoiding sun exposure may limit vitamin D synthesis. This study uses 3,367 individuals who participated in the National Health and Nutrition Examination Survey (NHANES) to explore whether compliance with recommended sun protection behaviors is associated with lower serum vitamin D, and whether lower vitamin D is associated with depression. Frequent sun exposure protective behavior, as operationalized in this study, was found to be associated with lower vitamin D (β=-0.672, p=0.044), and suboptimal vitamin D was found to be associated with clinical depression (β=0.500, p=0.003). However, there was no direct association between sun exposure protective behavior and clinical depression (β=-0.076, p=0.620). Although not significant ($F_{(4,12)} = 1.87$, p=0.180), the magnitude of the odds ratios suggests there may be an interaction. In those with optimal vitamin D, increased frequency of sun exposure protective behavior is non-significantly associated with lower risk of depression (Moderate vs. Rare OR= 0.54, 95% CI 0.27, 1.07. Frequent vs. Rare: OR=0.32, 95% CI: 0.05, 2.34), while in those with deficient vitamin D, more frequent sun exposure behavior is associated with non-significantly higher risk of depression (Moderate vs. Rare OR= 1.23, 95% CI 0.93, 1.62. Frequent vs. Rare: OR=1.52, 95% CI:

0.49, 4.66). Serum vitamin D level was no longer significantly correlated with depression after covariates were included in the model (BMI, gender, vitamin D supplementation, race/ethnicity, arthritis, smoking status and physical activity level). Overall, sun exposure protection behaviors may prevent individuals from maintaining healthy levels of vitamin D. There may or may not be a causal relationship between lower vitamin D and higher risk of depression. Attempting to evaluate the association between the two is made complicated by uncertainty about the accuracy of the current clinical cutoffs as predictors of poor health outcomes associated with insufficient vitamin D. There is not sufficient evidence to conclude an association between sun exposure behavior and depression—more detailed information about sun exposure and protective behaviors is needed.

Introduction

Depression

Depression is responsible for the fourth greatest burden of disease worldwide, according to a World Health Organization in 1990[1], and is the leading cause of disability in the United States[2]. In a 2001-2003 survey, an estimated 6.7% of American adults in the United States experienced depression, with 2% of adults experiencing depression that was categorized as 'severe'[35]. The lifetime prevalence of depression is estimated to be 16.6% in the United States[3]. These numbers include only the individuals with depression themselves, and may not reflect the true burden of the disease as experienced by family, friends and coworkers of those who suffer from this illness.

Those with depression may experience substantial disability, some of which persists even with treatment. Depression can make it difficult for individuals to work, take care of themselves, and do activities that are considered normal and essential parts of daily life. In addition, 65-71% of individuals with depression experience comorbidities, such as hypertension, diabetes, gastrointestinal disorders, arthritis, chronic back or lung problems, and other mental illnesses, which may be exacerbated by the disorder[4]. This high level of comorbidity is thought to be a partial explanation for higher prevalence in the southeastern states, which also have higher prevalence of many of these comorbid conditions[5].

In addition to its mental and physical costs, depression is also financially costly. Depression was estimated to cost 83.1 billion dollars annually in 2000[6]. This figure

includes 26.1 billion in direct cost, 5.4 billion in suicide-related mortality and 51.5 billion in workplace costs[6]. An individual with depression can expect to spend an average of $2,371 more in medical expenses in all categories of medical care every year than someone without depression[7].

The combined burdens of financial, emotional and physical distress caused by depression, in combination with its relatively high prevalence in the United States, makes depression an important target for prevention efforts. Information about depression that may lead to more effective treatment, management and prevention could have widespread benefits for the population as a whole.

Symptoms & Diagnosis

Depression is a term commonly used for several different psychiatric disorders, with differences in the pattern or expression of symptoms. Diagnosis with one of these disorders is based on the presence of the following symptoms: sadness, sleep changes, appetite changes, difficulty with mental tasks, changes in motor function, loss of interest or pleasure in things previously enjoyed, feelings of worthlessness, hopelessness, emptiness or guilt, recurring thoughts of death or suicide, or persistent physical symptoms that do not respond to treatment[8].

The most common diagnosis for those experiencing these symptoms is major depressive disorder. Diagnosis requires that at least four of these symptoms be present for at least two consecutive weeks[8]. In general, depression is an episodic disorder. Persistent mild depression is diagnosed as dysthymia. Depression with onset during a particular

season and remission the rest of the year is diagnosed as seasonal affective disorder (SAD). The depressive portion of bipolar disorder is also diagnosed based on these criteria.

A number of questionnaires have been developed to screen for depression based on this criteria. One of the most common, and the one used for this study, is the Patient Health Questionnaire (PHQ-9). The PHQ-9 is used most often in primary care settings as a quick and easy screening tool to identify patients who may have depression and need referral for treatment. It is comprised of nine questions scored on a Likert Scale (See Appendix A). The answers are summed and the score used to gauge presence and severity of depression symptoms. The PHQ-9 is a self-administered version of an earlier screener called the PRIME-MD, and was validated using two studies with sample sizes of 3,000 in a primary care and an obstetrics-gynecology setting[36,37]. It has since been used widely in primary care, and in studies to gauge depression presence and severity.

As an episodic disorder, those with depression generally experience periods of depression interspersed with periods of normal function, so a tool like the PHQ-9 will only identify depression during an episode. Some people will have only a single episode of depression, while others will have repeated episodes. Each episode experienced increases the risk of another—a single episode increases the risk of second by 50%, a second increases the risk of third by 70% and a third increases the risk of a fourth by 90%[9]. Generally, for those with multiple episodes of depression, each subsequent incident will be of increased length and severity. Over time these episodes can result in suicide attempts[2].

Those who suffer from depression often experience a great deal of impairment in function. One study of US adults receiving primary care indicated depressed patients had a mean physical function at 77.6% of normal on a validated scale, and increased difficulty in recovery from and maintenance of comorbid illnesses[10].

Populations at a higher risk of depression include women, people between the ages of 45-64, ethnic and racial minorities, individuals with low socioeconomic status, the divorced or widowed, the unemployed or unable to work, and the uninsured.

Treatment

Modern treatments for depression are varied. In particular, three types of treatment are used for depression and have substantial research indicating effectiveness: medications, psychotherapy and electroconvulsive therapy[2]. Treatments are often combined for greater effect, and life changes or practices such as peer education and support, dietary changes, exercise and smoking cessation may also help. For all forms of depression, evidence suggests that the earlier treatment begins the more effective it is[11]. An estimated 80-90% of adults with depression can be effectively treated and return to normal function[2]. Despite this, only 57% of people with depression seek treatment, most of them in a primary care setting[9]. Depression is the second most common condition in those who visit a primary care provider in the United States[12]. Despite this, the rate of missed diagnosis for depression at the primary care level is estimated to be around 50%[9].

Currently, the most effective treatment for severe depression is medication[2]. There are a wide variety and a large number of available medications on the market.

Antidepressants generally take two to four weeks to show effect, and six to twelve weeks to reach their peak effect[2].

Antidepressants often correct energy levels before stabilizing mood; as a result depression medications may temporarily increase risk of suicide, and the FDA now requires that antidepressant bear a label to warn of this potential side-effect[2]. In addition to this risk, all antidepressants have unpleasant side-effects. Some of the more common side-effects are nausea, headaches and sexual dysfunction. Proper treatment requires finding the best medication and dose that will minimize side-effects to a level that the patient finds compatible with his or her needs, and balanced with the perceived benefit. The number and severity of side-effects, the amount of time it takes for a drug to become effective, the monitoring needed in order to achieve the proper balance of side-effects to benefit, and the consequences of forgetting a dose all likely contribute to a lack of adherence. About 50% of those who are prescribed an anti-depressant discontinue use within the first 30 days[9].

Psychotherapy is often employed for the treatment of depression, and may be sufficient as a stand-alone treatment if the disorder is mild of moderate[2]. Several forms of psychotherapy can be effective for depression[2]. Potential barriers to this method of treatment include cost and locating a compatible provider. Some individuals may also fear stigma if others learn that they are seeing a therapist.

Electroconvulsive therapy (ECT) is currently the least common treatment of those known to be effective. ECT involves the use of electrical shock and is highly effective for depression when medication is either contraindicated or not working quickly enough[2].

The historical use of inhumane methods for administering ECT has led to the treatment having a bad reputation; However, the best practice involves administration under anesthesia, making it humane and relatively safe. Studies have been done in response to concerns about long term impact on brain function, and researchers have found no detrimental cognitive effects up to one year after ECT[11].

Another treatment of note is used primarily for SAD—light therapy. This involves the use of broad spectrum lights for short intervals several times a day. Although some studies have found light therapy to be effective, nearly half of those who suffer from SAD need other treatment in addition to light therapy, suggesting it should be considered an augmentation for medication or psychotherapy rather than a primary form of treatment[11]. Evidence of efficacy for SAD is tenuous, largely due to the difficulties of designing a placebo treatment for clinical trials.

In addition to proven treatment methods, many people with depression seek alternative therapies and report benefiting from them. Due to the devastating nature of depression, as well as the variation of symptoms and treatment response from person to person, it is unsurprising that sufferers take an "anything that works" approach to treatment. Ultimately, effective treatment is highly individual and may involve any mix of different therapies or approaches.

Causes and Risk Factors

The cause(s) of depression have been a matter of debate for centuries. Currently, it is believed that depression is the result of multiple contributing factors—biological,

psychological and environmental. Depression runs in families, likely due to a mix of shared environment, taught/shared life philosophy and behavior, and genetics[2]. Although some depressive episodes are at least partially generated by life events or by other illnesses or medical treatments, many have no such trigger. The increased risk experienced by minority groups, women, and the disadvantaged are likely also the result of the nuanced ways in which these groups differ in terms of environment, genetics and learned behaviors.

The currently accepted physiological explanation for depression involves monoamine transmitter levels and metabolism. Early antidepressants were found to be effective and prescribed as treatment before research uncovered how they worked. The monoamine-pathway based theories of depression are largely the result of the discovery that antidepressants alter the levels or impact of neurotransmitters in the brain. These theories are based on the assertion that depression is the result of the body improperly processing dopamine, norepinephrine and/or serotonin at the synapse, either due to a lack of receptors, low production, or overactive production of the enzymes that break down these neurotransmitters[2]. Some researchers have used Magnetic Resonance Imaging (MRI) scanning technology to look at brain function in depressed subjects as compared to normal brain function. Results indicate differences in appearance between scans of individuals with and without depression. These differences are seen in the sections of the brain devoted to mood regulation, thinking, sleep, appetite and behavior, suggesting that these sections function abnormally in those with depression[11]. Most experts also agree that genetics play a role in depression. In a meta-analysis of genetic epidemiology papers

conducted in 2000, the odds ratio of depression for an individual with a depressed first degree relative was found to be 2.84 (95% CI: 2.31-3.49)[13]. This risk is likely to be more than just the result of the psychological impact of having a parent or sibling with depression, although it is difficult to measure the relative contributions. However, a recent estimate of the genetic contribution for depression is 40-50%[14].

As previously mentioned, people with depression are likely to have other comorbid conditions. Depression is associated with chronic health conditions such as obesity, cardiovascular disease, diabetes, asthma, arthritis and cancer, as well as with unhealthy behaviors like smoking, sedentary lifestyle, and binge drinking[15]. It is unclear whether depression puts one at greater risk of these chronic health conditions and unhealthy behaviors, or whether these things increase the risk of depression. The truth is probably a combination of the two, in which depression, comorbidities and behaviors influence each other in deeply interconnected ways.

Stressful life events such as unemployment, loss of close personal relationships, traumatic or adverse childhood experiences, and specific personality traits like neuroticism have also been linked to depression[16].

A number of other possible causes are under investigation. There are a handful of dietary hypotheses for causation of depression. These include insufficient vitamin levels—in particular, low vitamin D—poor dietary composition in terms of carbohydrates and proteins, and negative impacts from various artificial food additives such as dyes and preservatives.

The evidence for a connection between vitamin D and depression is still

incomplete. There have been a small number of studies on a potential link between deficiency (less than 20 ng/ml of 25(OH)D in blood serum) or insufficiency (20-32 ng/ml) of vitamin D and depression, however the results have been inconsistent. As of the publication of the Bertone-Johnson 2010 review of vitamin D/depression papers, all but one available study was cross-sectional and thus cannot speak to causation[17]. Most studies focus on a subpopulation such as the elderly, women, inpatients, or those with a specific comorbid condition, such as Alzheimers, or secondary hyperparathyroidism and thus do not represent the general population[17]. In addition, depression and vitamin D deficiency share a number of known risk factors in common, such as smoking, high BMI, and sedentary lifestyle. Many studies have presented unadjusted data, and thus associations may be confounded[17].

More evidence has been found by researchers exploring potential biological mechanisms for a link between vitamin D and depression. Although limited, there is evidence that vitamin D plays a role in monoamine regulation, as well as in the cortisol stress response in humans[17]. Researchers using rodent models have found that mice born to mothers subjected to vitamin D deficiency in pregnancy and the early post-natal period have abnormal brain development which persists into adulthood even when sufficient vitamin D is included in the diet[17]. Vitamin D receptor knockout mice and mice transiently deprived of Vitamin D also show increased anxiety as well as other behavioral differences[17]. However, mental illness is difficult to study in animal models due to the subjective nature of many of the symptoms. These biological studies suggest that a biological pathway for vitamin D and depression is plausible. However, the mechanism

of vitamin D production and the activities of vitamin D in the body are complex and still not well understood. The factors associated with both vitamin D levels and depression and thus potentially confounding are so numerous that most studies fail to or cannot control for all of them.

Depression has several different recognized and diagnosed types, with subtypes within them. The number and nature of the types of depression has been widely debated in the discipline of psychology. Diagnosis currently has more to do with labeling a system of symptoms to enable more efficient communication between providers for the purpose of treatment and management. The cause of depression is likely a web rather than a simple pathway, with each individual having a different set of contributors.

Vitamin D

Vitamin D is a nutrient that is known to be critical to bone development. Until recently, it was thought that this was the only role it had in the body. However, the discovery of vitamin D receptors in many tissues has led scientists to re-evaluate the role of vitamin D in physiology and disease processes[18].

The science of vitamin D is an emerging field, and evidence is accumulating about many potential roles for this nutrient. Areas of research include vitamin D as a contributor to muscle strength, and deficiency as a possible causal factor in cancers, autoimmune disease and cardiovascular disease, as well as depression[18].

This influx of new information about vitamin D in the body has affected our understanding of optimal vitamin D levels. Because of this, studying vitamin D is

complicated by disagreement between researchers on what optimal vitamin D levels are, and how people should attain these levels. It is likely that 'optimal' levels are different for different body uses. This is a current and ongoing area of research.

Vitamin D levels are measured using the amount of calcidiol in the blood serum. Calcidiol is a metabolite of vitamin D, produced in the liver from D3 and D2. This measure is used because calcidiol represents total vitamin D intake from both dietary sources and synthesis. It should be noted that there are multiple tests available on the market which purport to measure calcidiol levels, and there are issues of standardization for these tests. These problems are notable enough that the National Institutes of Health Office of Dietary Supplements (NIH ODS) began a project with the Centers for Disease Control and Prevention (CDC), the National Institute for Standards and Technology (NIST) and the Ghent University to standardize the available vitamin D calcidiol tests[38]. For the purpose of this study, a single assay was used for all patients, so although absolute levels of Vitamin D may be imprecise, comparisons should still be accurate.

Currently accepted clinical levels define deficiency as <20 ng/ml, insufficiency as >=20 and <32 ng/ml and optimal levels as >=32 ng/ml. These cutoffs are based on bone health and may or may not be representative of the appropriate levels for other purposes.

The major source of vitamin D for humans is through synthesis in the skin, a process that depends on exposure to UV-B radiation. UV-B radiation exposure comes from sunlight and many studies have shown that people rely on sun exposure for the vast majority of their vitamin D. Whether or not sun exposure will result in vitamin D production is dependent on multiple factors. The angle of the sun to the atmosphere and

the amount of cloud cover both impact whether or not UV-B is able to penetrate to ground level[19]. Thus, UV-B penetration is affected by latitude and season. At low latitudes, season makes little difference[20]. However, as latitude increases, the portion of the year during which UV-B radiation can penetrate the atmosphere decreases[21]. Above 37 degrees north, there are times during the year when it is not possible for UV-B to penetrate at all[22].

Once UV-B radiation reaches ground level, it must then be absorbed so that 7-dehydrocholesterol found in the skin can be converted into D3[17]. UV-B wavelengths are weak and cannot penetrate sunscreen, window glass or clothing. In addition, UV-B cannot be absorbed in the shade, and a sufficient amount of time must be spent with unprotected skin in direct sunlight in order to synthesize the needed amount of vitamin D. The amount of time in the sunlight needed is a matter of debate—particularly given the previously discussed tenuous nature of the clinically recommended vitamin D levels. The commonly repeated recommendation is 10-15 minutes of direct sunlight on the face and hands daily, however this number may be more convenient to remember then it is accurate, since effectiveness of synthesis is impacted by a variety of external factors that make such a simple recommendation dubious[19].

Factors at the individual level can also influence the ability to synthesize vitamin D. Race is one of these factors—mostly due to skin pigmentation, since darker skin tone limits the penetration of UV-B radiation[23]. Also, because the kidneys and liver are involved in metabolism of D2 and D3 into useful metabolites, anything that impacts the function of these organs (such as age or chronic illness) may also diminish processing of

vitamin D. Obesity also contributes to vitamin D deficiency since vitamin D is fat soluble and may be removed from the blood stream and sequestered into fat cells[24].

In addition to skin synthesis, some vitamin D is consumed as part of the diet. This is largely the result of fortified products such as milk and eggs, since few foods are natural sources of vitamin D. Some fatty fish, such as salmon, do contain vitamin D naturally and may help maintain serum vitamin D levels. Another potential dietary source of vitamin D is via oral supplementation. Dietary sources of vitamin D come in the form of vitamin D2 or vitamin D3[17].

The amount of supplementation necessary to maintain healthy levels of vitamin D is also a matter of debate, beyond just the questions surrounding what a 'healthy level' of vitamin D is. There is mounting evidence that supplementation recommendations are not high enough to raise blood serum levels above 32 ng/ml in those who are deficient[17].

This leaves sun exposure as the most efficient and least problematic source of vitamin D. With sufficient sun exposure the argument about what constitutes 'optimal' becomes moot, from an evolutionary perspective. Vitamin D synthesis in the skin is part of a feedback loop, wherein any synthesized D3 in the skin beyond a certain threshold is then broken down again by UV-B radiation. It is possible that this threshold represents a healthy level of vitamin D for the individual.

However, sun exposure carries its own set of risks.

Sun Exposure

Exposure to the ultraviolet wavelengths of sunlight causes damage to the skin and

eyes, and may also negatively impact the immune system[25].

In particular, sun damage to the skin can have long-lasting or even fatal effects. Ninety percent of visible changes in the appearance of skin that are commonly attributed to aging are actually the result of unprotected skin exposure[25]. Actinic keratoses are small, precancerous growths that can form on the skin as a result of exposure to ultraviolet radiation, and are a risk factor for squamous cell carcinoma[25].

Aging and keratoses are the milder risks associated with unprotected time in the sun. UV radiation has also been classified as a carcinogen by the US Department of Health & Human Services and the World Health Organization[25]. In fact, it is the most preventable risk factor for skin cancer, and most exposure comes from the sun, although tanning beds and sun lamps also emit light in the UV spectrum[25]. In addition to doing damage to the DNA of skin cells that may led to malignant growth, studies also suggest that UV radiation may interfere with the immune system's ability to halt a growth once it begins[25].

Skin cancer is the most commonly diagnosed form of cancer in the United States, and more new cases are diagnosed yearly than breast, prostate, lung and colon cancers combined[25]. One in five people will develop skin cancer at least once during his or her lifetime[25]. Skin cancer can be melanoma or non-melanoma, with melanoma being the most serious form—accounting for 3% of skin cancer cases, and 75% of skin cancer deaths[25]. Non-melanoma skin cancers include basal cell and squamous cell carcinomas, which are not often fatal but can spread if left untreated and cause disfigurement or impairment. In 2007 in America, 58,094 people were diagnosed with skin cancer, and

8,461 deaths were attributed to malignant melanoma[26].

The current recommendations of the Centers for Disease Control & Prevention are that people avoid sun exposure as much as possible. When people intend to spend time outdoors, the CDC recommends staying in the shade, covering as much of the skin in clothing as is feasible, wearing a hat that shades the face, ears, and neck, wearing UV screening sunglasses and sunscreen with a rating of SPF 15 of greater[26]. These recommendations are especially important for those with fair skin that burns easily.

These measures are important to protect the skin from damage that may lead to cancer, however, adhering to them perfectly would prevent any synthesis of vitamin D in the skin. Thus, there may need to be more careful evaluation of the risks and benefits of sunlight exposure. Total protection against the sun may lead to health problems as severe as the health risks of radiation exposure.

Study Focus and Hypotheses

My hypothesis is that engaging in sun protective behaviors leads to lower vitamin D levels, and that this increases the risk of depression.

This is part of a proposed pathway from sun exposure to depression—however, at the time of this investigation, I do not have access to reliable information about sun exposure. The primary message the public is given about sun exposure is to avoid it as much as possible. Access to variables that indicate how well people adhere to guidelines on how to decrease and mitigate damaging sun exposure may give an interesting insight into unintended detrimental effects of these behaviors meant to prevent skin cancer and

other sun related conditions.

In order to address my hypothesis with the data available to me, I asked four questions.

1. Is sun protective behavior associated with lower serum vitamin D levels?
2. Is lower serum vitamin D level associated with clinical depression?
3. Is sun protective behavior associated with clinical depression?
4. Is the relationship between sun protection and depression different at differing levels of serum vitamin D?

A better understanding of how sunlight exposure protection may impact depression could lead to more effective vitamin D supplementation to alleviate the impact of sun protection, or change the recommendations in light of a balance in risk vs. benefit of unprotected sun exposure. Testing an interaction between sun protection and vitamin D as independent variables impacting depression could offer insight into the nature of the relationship—for example, if sun exposure protection is associated with higher risk of depression in the low vitamin D groups, but not in the optimal vitamin D group, this would provide further evidence of a link between vitamin D and depression—those who maintained optimal vitamin D levels despite careful mitigation of sun exposure would not experience increased depression risk.

Depression is both devastating and common, and treatment is not 100% accessible to everyone or 100% effective. The sun, however, is accessible to everyone for at least part of the year and so any mitigation or prevention of depression based on sun exposure

could have a positive impact on society as well as the individual. It is worth evaluating this potential connection between sun exposure protective behaviors and depression.

Methods

National Health and Nutrition Survey (NHANES)

This cross-sectional study uses data collected in 2005 and 2006 by the National Center for Health Statistics (NCHS) as part of the National Health and Nutrition Survey (NHANES). The National Health and Nutrition Examination Survey (NHANES) of 2005-2006 recorded scores from the PHQ-9. NHANES for these years also includes data regarding sun exposure protective measures in the dermatological portion of the survey. During the mobile examination portion, a blood sample is taken for later measurement of serum vitamin D.

This provides a unique opportunity to explore the potential relationships between serum vitamin D levels, sunlight exposure protective behaviors and depression.

NHANES is a continuous survey program that collects vital and health statistics for the population of the United States[27].

Every year, approximately 5,000 US Citizens participate in NHANES[27]. A large number of health related and demographic variables are collected based on in-home and phone interviews, and an on-site physical examination complete with blood and urine sample collection and laboratory work. The examination and most of the survey occur at one of NHANES' Mobile Examination Centers (MEC)[27].

The NHANES sampling protocol is based on a complex probability method. Each year fifteen regions (counties) are randomly selected from throughout the US. Each region is broken into segments based on location (a segment might consist of a city block, for example). A comprehensive list of addresses is made for all residential units within

that segment. A sample of these addresses is then taken, and residents of the selected addresses receive a postcard informing them that an NHANES interviewer will be visiting their home in the near future. These in-home interviewers identify eligible subjects based on a brief demographic survey[27]. As a result of this sampling strategy, subject residences are clustered and more than one subject may be chosen from a single household[28]. Inclusion is based on willingness to participate in the survey and needed demographics.

In order to determine the potentially unique health outcomes, behaviors and risk factors of minority population groups, some subpopulations are oversampled in order to guarantee sufficient statistical power for subpopulation analyses. These groups include low income Americans, Mexican Americans, African Americans, adolescents and the elderly[28]. Because of this oversampling, NHANES calculates and provides weights to allow researchers to correct the sampling to be representative of the US population as a whole.

NHANES data is released in two-year cycles. The vast majority of these data are publicly available. However, there are a number of variables for which access is restricted. Any variable that is believed to pose a privacy risk to participants or is considered particularly sensitive is restricted. This includes some variables which would have been of use for this study, such as geographical variables (e.g., latitude), the date of examination, and detailed ethnicity information.

Accessing the restricted data requires payment, as well as agreement to either travel to an NCHS location to perform analyses in a secured computer lab, or work with

an analyst who will run the needed statistical tests for the researcher. This was not feasible for this study, so restricted variables are not used. This introduces some limitations since such variables would have provided information about potential UV-B exposure in the time prior to vitamin D testing.

NHANES is a government-funded ongoing health survey. As a result of the extensive quality control procedures and experience involved in obtaining data, it is considered very reliable. The survey uses detailed protocol manuals for every step of the examination and questionnaires. Computer Assisted Personal Interviewing (CAPI) is used to collect many of the demographic variables and questionnaire responses[27,28,29]. CAPI allows skip logic to be automated and decreases the possibility that subjects or interviewers may inappropriately proceed through the questions. Examinations and questionnaires are administered by trained (and certified, where applicable) professionals under controlled conditions[27,30].

NCHS performs pilot studies and dress rehearsals to test data collection procedures on a semi-regular basis[27]. Each time a Mobile Examination Center is opened in a new area, a dry-run day is implemented to test protocols, calibrate machinery and practice data-collection procedures[29]. In addition to these formal events, interviewers are occasionally accompanied by an observer to evaluate interview technique and offer suggestions or refer interviewers for further training[27,30]. Interviewers are also instructed to look over data soon after interviews to ensure that all information was entered correctly and that hard-copy forms have been proofread for clarity[27]. Information review is also conducted again at the field office[27]. A sample of surveyed households are

revisited with a number of questions in order to validate the previous survey[27,30.]

Variables & Data Management

Because NHANES collects a vast number of variables, data is uploaded for public access in smaller datasets with a more manageable number of variables in each. In order to facilitate easy merging of these datasets, each individual is de-identified and then assigned a unique number that allows an individual's responses to be linked across multiple datasets.

This number was used to merge the following variables for use in this study:

Table 1: Primary outcome and independent variables and measurement/coding of these variables

Variable	Measurement	Notes
Depression (Yes/No)	Binary variable, 1=Yes, 0=No for clinical depression	Constructed from PHQ-9 questions.
Sun Exposure Behavior	Categorical variable: Rare, Moderate, Frequent use of sun protection	Constructed from Likert Scale questions about skin protection from the dermatology portion of the survey, based on methods used by Linos et al.[32]
Serum Vitamin D Level	Continuous, Serum 25(OH)D (ng/ml) Categorical, <20 ng/ml Deficient, >=20 and <32 Insufficient, >=32 Optimal	Test run by CASPIR (the CDC's central laboratory) on previously frozen serum.[29] Continuous measure provided by NHANES.

Depression score: The Patient-Health Questionnaire (PHQ-9) was administered to all willing NHANES participants (See Appendix A). This short Likert Scale questionnaire (nine questions) is based on the DSM-IV criteria for depression (See

Appendix C). The PHQ-9 has been validated in many studies and settings as a reliable diagnostic tool for depression[36]. The response to each question was provided in the NHANES data, and was used to calculate a depression score for each individual according to the standard guidelines for the PHQ-9. A binary variable was then constructed with a score greater than 10 as a positive for clinical depression. This is based on the accepted clinical cut-off. A score of ten of more on the PHQ-9 has a 99% sensitivity and a 91% specificity for a diagnosis of Major Depression Disorder[31]. The final question of the PHQ-9 was omitted since it is not included in the scoring. If a question was not answered, PHQ-9 was not calculated to avoid biasing the result.

Sun exposure protection: Subjects aged 20-59 were asked four questions regarding sun protection measures, 1) Staying in the shade, 2) Wearing a hat that shaded the neck and ears, 3) Wearing a long-sleeved shirt and 4) Wearing sunscreen. Initially I attempted to generate my own summary variable based on the dermatology questions. My first attempt was a binary variable based on summing the Likert scales into an overall score and then dividing the population into two groups based on cut-off at the middle of the range of scores. However, this variable proved difficult to use due to the 'coarseness' of using only two groups. In the process of working on this study, a group at Stanford published a paper looking at Vitamin D and sun exposure protection factors in NHANES[32]. This paper used a summary variable based on the same questions I wished to use for this study. I was able to apply their criteria, which used a similar sum method, and divide sun exposure protection into three categories—rare, moderate and frequent. Answers of 'never' and 'rarely' were collapsed, and answers of 'most of the time' and

'always' were also collapsed. Then the responses were summed and groups assigned based on three equal ranges for score.

Serum vitamin D level: Blood was drawn as part of the physical examinations conducted on subjects at the MEC. Venipuncture was performed by a certified phlebotomist. Blood was placed in a serum separator tube, serum separation was performed at the MEC, and then the sample was frozen and shipped in weekly batches to CASPIR for testing. The only criteria by which subjects were excluded for this test were hemophilia or chemotherapy within the prior four weeks[30]. The categorical variable for serum vitamin D level was divided as shown in Table 1, along the current clinically accepted boundaries.

As previously mentioned, the NHANES is a large survey that yields a huge number of variables in many different health related topics. In selecting potential covariates, care was taken to choose variables for which there was some rationale in the literature to justify association between both the outcome of depression and one or both of the independent variables (sun exposure protection and serum vitamin D). The one exception was milk intake, which was included because of the unique opportunity to include a dietary variable in a mental health study where diet was not the primary focus.

The selected covariates, their units/measurement and coding, and a brief explanation of the rational for their inclusion are presented in Table 2.

Table 2: Potential covariates chosen based on evidence in literature of an association with both depression and at least one of the two independent variables (sun exposure protection and serum vitamin D level).

Variable	Measurement	Rationale
Age	Ordinal, in years.	Age contributes to ability to synthesize vitamin D in the skin and convert it to active form in the kidneys. Also associated w/ depression, and possibly with sun exposure.
Gender	Categorical, male or female	Women have higher Vitamin D levels on average than men. Women are also more likely to have depression.
Race/Ethnicity	Categorical, Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black	Skin pigmentation affects ability to synthesize vitamin D in the skin, and race is also associated w/ depression.
BMI	Continuous, kg/m^2	Obesity is associated w/ decreased ability to synthesize vitamin D, and w/ depression.
Milk Intake	Categorical, yes, no, or varies over time for regular milk drinker ($\geq$ 5 times per week)	Most milk that is commercially available is Vitamin D fortified.
Smoking	Categorical, current, never or former. Current: Reported smoking some days or every day, and $\geq$100 lifetime cigarettes. Former: Reported not smoking at all, but $\geq$100 cigarettes. Never: <100 lifetime cigarettes.	Smoking is associated w/ decreased levels of vitamin D and higher levels of depression.
Physical Activity Level	Categorical: Sits during day & doesn't walk around much, stands or walks a lot but doesn't carry or lift things often, lifts light loads or climbs stairs/hills often, does heavy work or carries heavy loads	Higher physical activity levels are linked with higher serum vitamin D, lower depression scores, and may also be linked with more time spent outdoors.
Vitamin D Supplementation	Binary, yes or no to supplementing vitamin D within the last 30 days	Based on examination of labels of supplements subject reports taking on a regular basis. Should be associated with Vitamin D levels.
Marital Status	Categorical: married, widowed, single never married, living with partner, or divorced/separated	Marital status has been linked to depression and may also be linked to time spent outdoors
Education Level	Binary: < high school diploma vs. $\geq$ high school diploma	Education levels are associated w/ depression and may also be associated w/ sun exposure behaviors
Comorbid Conditions	Separate yes/no variables for: diabetes, CHD, stroke, arthritis, cancer, or current symptoms of asthma or chronic bronchitis	Comorbid conditions such as these have been linked to depression and vitamin D levels and may also be linked to sun exposure behaviors.
Parathyroid Hormone Levels	Continuous, pcg/ml	PTH has been linked to depression but may only be linked via its association with Vitamin D.
Pregnancy	Binary	Pregnancy may be linked to Vitamin D levels, as well as to a unique risk of depression.

Once these variables had been merged into a single dataset, exclusion criteria were applied. The limiting factor for the dataset was age, since the dermatology survey was only administered to those from age 20-59. Additionally, subjects with 'Other' for race/ethnicity were excluded from analysis, since race is associated with vitamin D largely due to skin pigmentation and it would not be clear what skin pigmentation would be within this 'Other' group.

Statistical Methods

All statistical analyses and data management were performed using STATA v. 11. Multiple datafiles were downloaded from the National Center for Health Statistics (NCHS) and merged by the de-identified unique ID provided. Variables were recoded and restructured as previously mentioned.

Weights are provided by NCHS in order to allow researchers to account for the oversampling of minority groups, clustering of individuals and response rates. These weights allow the researcher to determine how many people each person in the sample represents, so that results can be calculated that are generalizable to the US population as a whole. These weights are determined using information from the Census Bureau, as well as information from NHANES about demographics and response rates.

Weights are available at a variety of levels, depending on the subpopulation in use and are provided for the in-home interview population, the MEC examination population and for a number of surveys that were conducted on smaller subsamples. NCHS recommends that researchers using the data apply the weight that is useful for the

smallest sample variables were taken from[29], in this case, the MEC examination weights were applied.

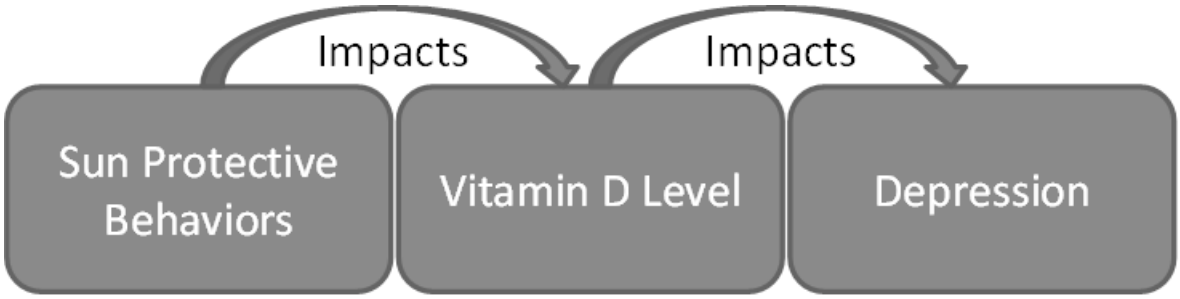
Because weighting depends on a full dataset in which weights add up to 100%, excluded individuals were not removed from the dataset—instead subgrouping was used to analyze results from only the sample population of interest.

Weighting is taken into account for all reported statistics in this study, with the exception of sample sizes which are presented unweighted.

Initial steps in the analysis process were focused on univariate measures for each variable of interest and potential confounder. Mean, range and standard deviation were calculated for each variable. Data was then examined for relationships between potential confounders, so this information could be used later to inform model building.

The analytic approach is based on the following proposed pathway:

Figure 1: Proposed pathway



To explore this pathway, I used a five step process:

1. Group population by sun protection group and compare serum vitamin D levels between groups
2. Group population by serum vitamin D level and compare clinical depression proportions between groups

3. Group population by sun protection group and compare clinical depression proportions between groups
4. Group population by both sun protection group and serum vitamin D level and compare clinical depression proportions between groups
5. Develop a logistic regression model with the outcome of clinical depression and assess the role of vitamin D level and sun protection when other covariates are included.

For steps 1, 2 and 3, two questions are of interest. Firstly, is there an association between the two categorical variables? And secondly, is there a trend between the two variables? For categorical associations, design-based F-tests—the weighted version of the chi-square—were applied. To assess trend, the grouped variable was used in a linear regression model as an independent variable with an outcome of the continuous version of the dependent variable (serum vitamin D level in ng/ml, and total PHQ-9 score).

For the fourth step, a variable was constructed to represent the interaction between sun protection group and serum vitamin D level, and logistic regression with the interaction as the independent variable and clinical depression as the dependent variable was used to calculate Odds Ratios and 95% Confidence Intervals. Overall significance of the interaction in the model was assessed using the Wald test.

Model building was based on the change-in-estimate approach[39]. Sun protection and serum vitamin D level were included in the model, and then potential confounders were added one by one, and a change of greater than 10% in the odds ratios for the primary predictors was used as the criteria for inclusion in the model. Order of addition

was at the researcher's discretion, based on the magnitude of the odds ratio changes.

The NHANES protocols and questionnaire have been reviewed and approved by the Centers for Disease Control. A request for determination for this study was submitted OHSU's Institutional Review Board and because all the data included in this study was available in public datasets, it was deemed exempt.

Results

Analytic Sample and Missing Data

Once exclusion criteria were applied the sample consisted of 3,367 NHANES respondents. There were no missing observations for sun protection—indicating that all subjects who answered at least one sun protection question answered all of them. There were 320 individuals with missing serum vitamin D levels, and 418 missing the PHQ-9 score and thus missing depression category.

Serum vitamin D level was more likely to be missing if the subject was younger (average age three years younger for those missing vitamin D level), and/or if the subject was black (8.68%) or 'Other Hispanic' (7.17%) versus Mexican (4.76%) or White (4.45%).

Depression score was more likely to be missing if the subject was younger (two years on average), of a minority race/ethnicity (Mexican: 10.63%, Other Hispanic: 12.1%, White: 5.81%, Non-Hispanic: 13.69%), had not graduated from high school (11.86% vs. 7% for graduates), and had never been married (11.37% vs. Married: 7.37%, Widowed: 7.81%, Divorced: 4.25%, and living with partner: 7.38%).

Descriptive Statistics

Descriptive statistics for the primary variables of interest are shown in Table 2. For descriptive statistics of potential confounders, refer to Supplemental Tables 1 and 2 in Appendix D.

Table 3: Descriptive statistics for depression score, sun protection and vitamin D level, n=3,667 NHANES respondents

Variable	Mean/ Proportion	Standard Error	Range
Depression Score	2.91	0.122	0-27
Clinical Depression	7.43%	-	-
Subclinical/No Depression	92.57%	-	-
Sun Exposure Protective Score	6.50	0.04	4-12
Rare Protection	54.91%	-	-
Moderate Protection	37.73%	-	-
Frequent Protection	7.36%	-	-
Serum Vitamin D Level (ng/ml)	23.61	0.576	3.00-76.00
Optimal	18.32%	-	-
Insufficient	46.93%	-	-
Deficient	34.75%	-	-

Clinical depression is estimated to occur in 7.43% of the population. 7.36% of the population met the criteria for frequent sun protection behaviors, and 37.73% reported moderate sun protection, leaving over half the population (54.91%) reporting rare sun protection. Only 18.32% of the population had optimal serum vitamin D levels. The bulk of the population were insufficient (46.93%) and 34.75% were deficient.

For a deeper understanding of sun protection and depression symptoms, I also looked at descriptive statistics for the individual dermatology and PHQ-9 questions to see what the most and least commonly reported behaviors and symptoms were. These tables can be found in Appendix D as Supplemental Tables 3 and 4. The overall practice of consistent sun exposure protection was quite low in the sample. The most commonly reported frequent protection behavior was wearing sunscreen, with approximately 25.96% of the subjects reporting always using sunscreen when in the sun. The least common behavior was wearing a long sleeved shirt in the sun, which was reported by

only 7.32% of the population. For all behaviors but staying in the shade, a higher percentage reported 'never' engaging in the behavior than reported any other level of frequency. Only 12% reported never staying in the shade. No one in the sample reported never spending time in the sun. For depression symptoms, the most commonly reported symptom was feeling tired or lacking energy (50.85%), followed by hypersomnia or insomnia (35.27%). The least commonly reported symptom was thinking oneself better off dead, with only 3.11% reporting experiencing the symptom.

Sun Protection and Vitamin D

The first research question regards what relationship, if any, exists between sun protection and vitamin D levels. Results are given in Table 4.

Table 4: Association between sun protection and serum vitamin D, categorical association by design-based F-test, trend by linear regression

Sun Protection	Optimal n (%)	Insufficient n (%)	Deficient n (%)	Cat. Assoc. p-value	Mean Vit. D (ng/ml)	Trend Assoc. p-value
Rare	266 (20.4%)	685 (46.1%)	753 (33.5%)		23.92	
Moderate	161 (16.1%)	476 (48.0%)	505 (35.9%)	0.145	23.07	0.044
Frequent	25 (14.0%)	90 (47.9%)	86 (38.1%)		22.88	

There was no categorical association between sun protection frequency and serum vitamin D level. However, there is a trend, indicating that as sun protection increases, vitamin D decreases by -0.67 ng/ml per increase in sun group level (p=0.044). Notably, the proportion of deficient individuals does increase with increased sun protection, and the proportion optimal decreases.

For further exploration, I also evaluated the relationship between vitamin D level and each individual behavior. The trend was significant for all sun protection behaviors, indicating that increased sun protection is associated with lower vitamin D levels. Results are shown in Table 5. The trend indicated decreased vitamin D with increased levels of sun protection for all behaviors except for sunscreen use, which showed the reverse trend.

Table 5: Mean serum vitamin D by sun protection question and trend by linear regression

	Always	Most of the Time	Sometimes	Rarely	Never	Trend
	Mean Vit. D (ng/ml)	Mean Vit. D (ng/ml)	Mean Vit. D (ng/ml)	Mean Vit. D (ng/ml)	Mean Vit. D (ng/ml)	
Stay in the shade?	18.34	20.99	23.90	26.27	23.85	<0.001
Wear a protective hat?	22.27	22.31	23.47	23.71	23.90	0.030
Wear a long-sleeved shirt?	20.57	19.89	22.76	23.95	24.04	<0.001
Use sunscreen?	25.28	25.90	24.69	23.92	21.00	<0.001

Vitamin D and Depression

The second research question regards what relationship, if any, exists between vitamin D levels and depression. Results are given in Table 6.

Table 6: Association between serum vitamin D and depression, categorical association by design-based F-test, trend by linear regression

Vitamin D Level	No Depression n (%)	Depression n (%)	Cat. Assoc. p-value	Mean PHQ-9	Trend Assoc. p-value
Optimal	403 (95.05%)	24 (4.95%)	0.030	2.45	0.003
Insufficient	1,076 (93.06%)	96 (6.94%)		2.76	
Deficient	1,094 (90.77%)	123 (9.23%)		3.40	

At higher levels of vitamin D, the proportion of clinically depressed individuals

decreases. The proportion clinically depressed in the optimal vitamin D group is half the proportion depressed in the deficient group. The odds of depression in the insufficient vitamin D group is 1.43 (95% CI: 0.92-2.22) times greater than in the optimal group, and the odds of depression in the deficient vitamin D group is 1.95 (95% CI: 1.17-3.26) times greater than in the optimal group. The percent clinically depressed is less than 10% in all groups.

Looking at individual symptoms, associations with serum vitamin D level were found for all PHQ-9 questions except for "hypersomnia or insomnia" and "overeating or loss of appetite" (Table 7).

Table 7: Mean serum vitamin D by PHQ-9 Question and trend by linear regression, asterisks indicate statistical significance at the 0.05 level

Question	Not at All Mean Vitamin D (ng/ml)	Several days Mean Vitamin D (ng/ml)	More than half of days Mean Vitamin D (ng/ml)	Nearly every day Mean Vitamin D (ng/ml)	Trend (p-value)
Little interest in doing things	23.82	23.21	21.04	21.81	0.021*
Feeling depressed or down	24.09	21.93	20.87	22.10	<0.001*
Hypersomnia or insomnia	23.52	23.89	23.81	23.11	0.648
Feeling tired/lacking energy	24.14	23.46	21.87	22.28	0.003*
Poor appetite/overeating	23.87	22.93	21.05	22.99	0.073
Feeling bad about self	23.86	22.69	19.87	21.26	0.022*
Trouble concentrating	23.76	22.88	23.42	20.88	0.050*
Moving/talking fast/slow	23.79	22.30	21.05	18.19	0.005*
Thoughts of dying/death	23.67	22.33	18.69	19.75	0.020*

Sun Protection and Depression

The third research question regards what relationship, if any, exists between sun

protection and depression.

Table 8: Association between sun protection and clinical depression, categorical association by design-based F-test, trend by linear regression

Sun Behavior Group	No Depression n (%)	Depression n (%)	Cat. Assoc. p-value	Mean PHQ-9	Trend Assoc. p-value
Rare	1,501 (92.66%)	137 (7.34%)		3.00	
Moderate	1,015 (92.54%)	101 (7.46%)	0.944	2.80	0.620
Frequent	178 (92.06%)	17 (7.94%)		3.05	

No statistically significant trend or association was found between sun protection and depression, and percentages of clinical depression were almost identical across sun behavior groups.

Depression and Sun Protection within Levels of Vitamin D

The fourth research question addresses the possibility of an interaction between sun protection and vitamin D level in association with depression.

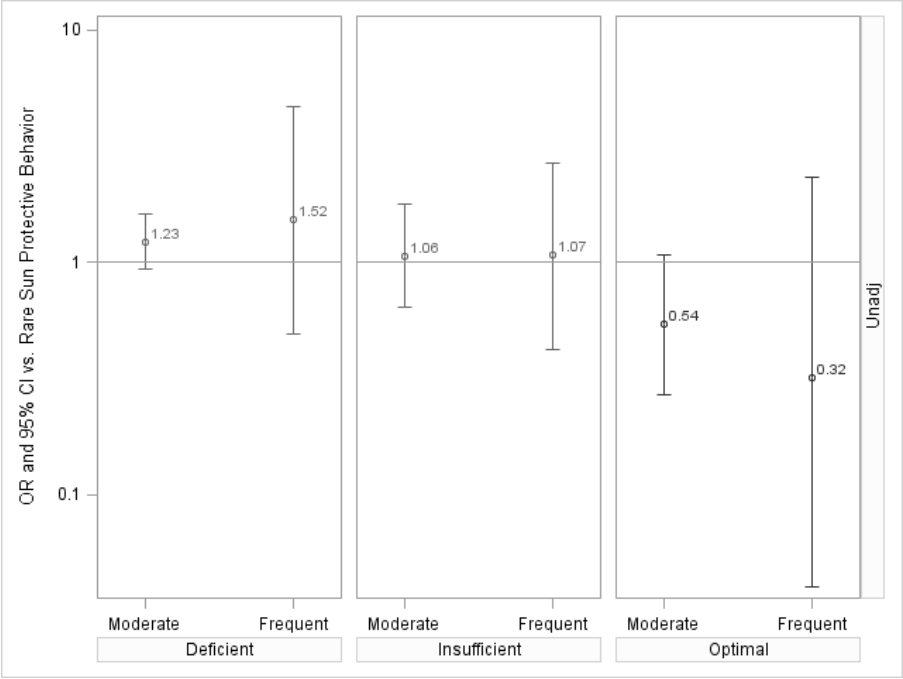
Table 9: Clinical depression and odds ratios for clinical depression within serum vitamin D levels by sun protection group

	Rare Protection	Moderate Protection	Frequent Protection
Optimal Vitamin D			
n depressed (n Total)	18 (249)	5 (153)	1 (25)
% clinically depressed	6.09%	3.36%	2.04%
OR for clinical dep.	***1.00 (Ref)***	***0.54 (95% CI: 0.27-1.07)***	***0.32 (95% CI: 0.04-2.34)***
Insufficient Vitamin D			
n depressed (n Total)	47 (637)	42 (455)	7 (80)
% clinically depressed	6.75%	7.16%	7.19%
OR for clinical dep.	***1.00 (Ref)***	***1.06 (95% CI: 0.64-1.78)***	***1.07 (0.42-2.69)***
Deficient Vitamin D			
n depressed (n Total)	63 (682)	52 (460)	8 (75)
% clinically depressed	8.28%	9.98%	12.05%
OR for clinical dep.	***1.00 (Ref)***	***1.23 (95% CI: 0.93-1.62)***	***1.52 (95% CI: 0.49-4.66)***

Table 9 gives the proportion clinically depressed in each subgroup by serum vitamin D level and sun protection, as well as the sample size for each group. Odds ratios are presented within each level of vitamin D, with the reference the rare sun protection behavior.

Sample sizes are very small in the frequent sun protection groups. None of the odds ratios are significant; however, an interesting pattern emerges. The odds of depression trend downward with increased sun protection in the optimal vitamin D group, but trend upward with increased sun protection in the deficient group (See Figure 2).

Figure 2: Odds ratios for clinical depression by sun protection groups within serum vitamin D levels



The interaction is not significant (p=0.18), however the pattern in odds ratios is worth noting. Due to the small group of people with optimum vitamin D, power

calculations suggest that—if the distribution of vitamin D in the population is correct, a sample size of roughly 64,000 people would be needed to detect the odds ratios in the optimal vitamin D group at statistically significant levels.

Logistic Regression

Prior analysis was based only on the variables of interest, and did not account for the potential impact of confounding. In order to adjust for potential confounders, logistic regression was used to model the outcome of clinical depression

First, logistic regression was performed using only vitamin D level and then only sun protection as independent variables (Table 10). The second step was to include both of these primary variables in the model together (Table 11).

Table 10: Logistic regression results, outcome of depression with sun protection group and vitamin D group individually as independent variables

Variable	Odds Ratio (95% CI)	P-value
Sun Group		
Rare Protection	Ref.	-
Moderate Protection	1.02 (95% CI: 0.74-1.39)	0.903
Frequent Protection	1.09 (95% CI: 0.57-2.09)	0.786
Vitamin D Group		
Optimal	Ref.	-
Insufficient	1.43 (95% CI: 0.93-2.22)	0.099
Deficient	1.95 (95% CI: 1.17-3.26)	0.014*

When serum vitamin D level is used as a predictor of clinical depression, there is a significantly increased odds of depression in the deficient group as compared to the optimal group. The odds are also increased for the insufficient, though the odds ratio is not statistically significant (p=0.099). Neither moderate nor frequent sun protection is associated with a statistically significant increased risk of depression.

Table 11: Logistic regression results, depression as outcome, sun protection group and serum vitamin D level as independent variables, unadjusted model

Variable	Unadjusted Model Odds Ratio (95% CI)	P-value
Sun Group		
Rare Protection	Ref.	-
Moderate Protection	1.04 (95% CI: 0.73-1.48)	0.800
Frequent Protection	1.13 (95% CI: 0.57-2.25)	0.706
Vitamin D Group		
Optimal	Ref.	-
Insufficient	1.43 (95% CI: 0.92-2.22)	0.105
Deficient	1.94 (95% CI: 1.17-3.24)	0.014*

In this unadjusted model, sun protection was not significant, and effect size was small. The odds of depression in the moderate sun protection group were 1.04 times the odds in the rare protection group, and in the frequent protection group the odds were only 1.13 times the odds in the rare protection group. Vitamin D deficiency was statistically significant, with deficient individuals having nearly double the odds of depression as those in the optimal group (OR: 1.94). Although the odds of depression in the vitamin D insufficient were not significantly different from the odds in the optimal group, the odds ratio estimate was 1.43.

Variables entered the model in the following order, based on largest impact on odds ratios: body mass index, gender, self-reported vitamin D supplementation in the prior month, race/ethnicity, arthritis, smoking status, and physical activity level. Tables with odds ratios and p-values for each added variable are provided in Appendix E. While variables did significantly impact the coefficients for the sun protection groups, the odds ratios for these sun exposure groups never deviated far from 1.00, and were never significant.

Results for the final model are shown in Table 12.

Table 12: Logistic regression results, final model, depression as an outcome with sun protection and serum vitamin D level as independent variables, adjusted for BMI, gender, vitamin D supplementation, race/ethnicity, arthritis, smoking status and physical activity level

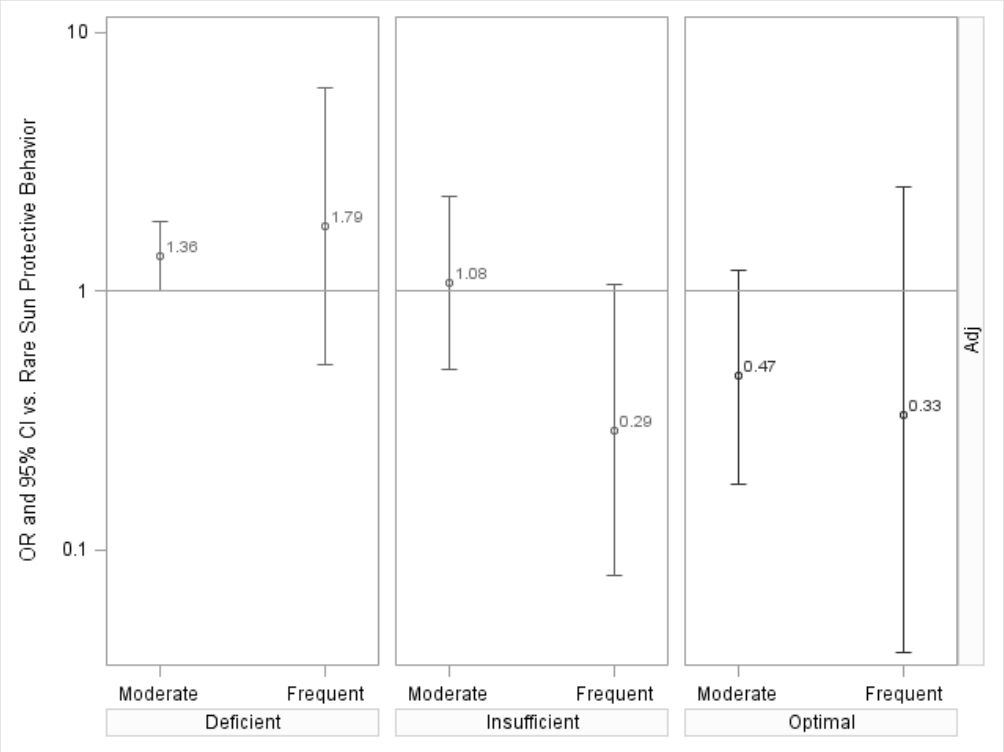
	Adjusted Model	
Variable	**Odds Ratio (95% CI)**	**P-value**
Sun Group		
Rare Protection	Ref.	Ref.
Moderate Protection	0.94 (95% CI: 0.47-1.88)	0.857
Frequent Protection	0.83 (95% CI: 0.32-2.11)	0.678
Vitamin D Group		
Optimal	Ref.	Ref.
Insufficient	1.30 (95% CI: 0.65-2.52)	0.446
Deficient	1.71 (95% CI: 0.68-4.30)	0.232

Body mass index, gender, and vitamin D supplementation all had a confounding effect on both the relationship between vitamin D and depression, and the relationship between sun group and depression. Race/ethnicity, arthritis, smoking status and physical activity had confounding effects on the relationship between sun group and depression. When only the first three variables were present, vitamin D deficiency still conferred a statistically significant increased odds of depression as compared to those with optimal vitamin D (OR: 1.77, 95% CI: 1.01-3.09). Confounders of the relationship between sun group and depression were included per my a priori protocol. However, the sun group variable never gained significance. Although Vitamin D deficiency is no longer significant in the final model, the point estimate for the Odds Ratio only dropped from 1.94 to 1.71, and the odds ratio for insufficiency dropped from 1.43 to 1.30, and did not lose significance until I attempted to control for confounding of the sun group/depression relationship. The Odds Ratios for sun protection groups remain near the null for the full

model building process.

Lastly, I added the interaction between sun protection and vitamin D group to the model to generate an adjust Forest Plot. In order to do this, supplementation was removed from the model, since its inclusion reduced one of the cell sizes to zero. Results are shown in Figure 3.

Figure 3: Odds Ratios for depression by sun protection group within vitamin D level, adjusted for BMI, gender, race/ethnicity, arthritis, smoking status and physical activity level



The odds ratio for moderate vs. rare sun protection in the deficient group gained significance, indicating an increased odds of depression in those with deficient vitamin D and moderate sun protection as compared to those with rare sun protection. All other odds ratios were not significant in the model. However, results seem to indicate that there

may still be a pattern present in which increasing sun protection increases the odds for depression in the vitamin D deficient group, but decreases them in the insufficient and optimal group.

Discussion

Sun Protection & Vitamin D

There was a statistically significant trend between sun protection and vitamin D level (p=0.021) despite the lack of categorical association. However, when looking at individual sun protection behaviors and vitamin D, the p-values for both categorical association and trend are all significant. This indicates that for all sun protection behaviors, increased frequency of behavior is associated with decreases in serum vitamin D. This supports my hypothesis that engaging in sun protection measures meant to prevent skin damage and decrease risk of skin cancer has the unfortunate side effect of blocking ultraviolet radiation from triggering vitamin D synthesis.

These results also support the idea that the overall sun protection behavior measure should be used with care, because people who engage frequently in one or two behaviors seem to neglect the others to the extent that they will appear to be 'moderate' or 'rare' protection users when—in fact—they are perhaps using one method at a time, or exclusively using one method even though they use it every time they go outdoors.

In addition, the pattern noted in the interaction between sun protection and vitamin D levels suggests that those in the frequent sun protection category may also be individuals who spend more time in the sun in general. These individuals may be able to synthesize sufficient vitamin D despite their protection measures due to the level of sun exposure. Without information on how much sun exposure each individual had, this possibility cannot be adequately explored and controlled for.

Overall, I believe my results are sufficient to say that there is an association

between sun protection and vitamin D level that deserves further consideration.

Vitamin D and Depression

In line with prior studies, before adjusting for any confounders, there is an association between vitamin D level and depression—specifically, a trend relationship in which those with higher levels of vitamin D report fewer symptoms of depression and are less likely to score in the Clinical Depression range on the PHQ-9. The difference is such that the proportion of depressed individuals in the optimal vitamin D group is half the proportion in the deficient group.

All individual symptoms of depression are associated with vitamin D level as well, with the exception of two questions. It is interesting that both questions involve two ends of a spectrum. The first question asks about hypersomnia or insomnia, while the second asks about overeating or loss of appetite. It is possible that if each question was broken into two questions, so that it would be possible to discern which of the two symptoms the participant was experiencing, there may be an association between vitamin D level and one end of the symptom spectrum. Asking about two related symptoms in a single question is useful for a screening tool, but is not so helpful for research purposes.

Either way, the result is certainly convincing that there is an association between vitamin D and depression. Graphing raw PHQ-9 scores against vitamin D levels for this study shows that the maximum PHQ-9 score falls rapidly with rising vitamin D level—however, so does the number of individuals. Because this study is cross-sectional, I do not have information on the temporality of this association. It is possible that vitamin D

deficiency/insufficiency does not come before depression, but after it—people with depression may be less likely to supplement vitamin D, and less likely to spend sufficient time in the sun to synthesize adequate vitamin D.

Sun Protection and Depression

If there were a strong enough association between sun protection and depression, and a strong enough association between vitamin D and depression, then I would expect a relationship between sun protection and depression. Essentially, this is a question of a causal pathway between sun exposure, vitamin D and depression, with sun protection interfering with the generation of vitamin D from sun exposure. Because I do not have a variable for sun exposure, I could only look at the relationship with sun protection. Overall, despite results that suggest that the link between sun protection and lower vitamin D is there, and that the link between vitamin D and depression is there, I was unable to find a significant relationship between sun protection and depression.

This is likely due to the previously discussed difficulties with attempting to summarize the individual protection behaviors into a single variable, as well as inability to adjust for sun exposure. If those who use frequent sun protection are spending more time in the sun, and those with depression spend less time in the sun, then any association may be obscured without information about exposure time.

Depression and Sun Protection within Levels of Serum Vitamin D

Although power was insufficient for statistically significant results, there is an interesting pattern in the odds of depression within each level of vitamin D. The results of my exploration of interaction lend support to my theory that those who reported using enough sun protection to fall into the 'frequent' category are also those that spend the most time in the sun. Someone who spends extensive time in the sun may be more likely to use multiple methods of sun protection—even if they are not all used at the same time—and may also be more likely to get enough vitamin D via skin synthesis to reach optimal levels despite using protective measures. For example, missing a spot with sunscreen, or not applying it quickly enough to keep UV-B from penetrating for the full duration of sun exposure.

Someone who is very active outdoors also logically seems less likely to be depressed. Individuals with depression experience difficulty with self-motivation, and loss of interest in previously enjoyed activities—such as outdoor recreation. Thus, it is sensible that someone who spends a lot of time outdoors would be less likely to have depression and more likely to have optimal vitamin D. Conversely, someone who is not spending much time outdoors may be staying in because they are depressed, resulting in low vitamin D which is worsened if they are using sun protection when they do go outdoors.

In the absence of sun exposure information, I believe that the sun protection score may actually be serving as a 'messy' proxy for sun exposure, rather than as a true measure of how carefully someone is protecting themselves against the sun.

This interesting interaction pattern persists even when a fully adjusted model is used.

Adjusted Associations of Sun Protection and Serum Vitamin D with Depression

In an unadjusted model containing only vitamin D level and sun protection level as independent variables with an outcome of clinical depression, sun exposure protection level was not significant and odds ratios were near the null of one. Those with deficient vitamin D had 1.94 times the odds of depression than those with optimal vitamin D, (95% CI: 1.17-3.24). Insufficient vitamin D had an odds of 1.42 times the odds in those with optimal vitamin D, but it was not statistically significant (95% CI: 0.92-2.22). Modeling depression is complicated by the vast number of things associated with depression status, especially given how many things are known to be associated with both vitamin D and depression (race, age, obesity, etc.)

Using a change-in-estimate method, there were many variables that influenced the odds ratios for vitamin D and sun exposure score. Addition of these variables never altered sun protection to the point of significance, nor to the point of clinical relevance.

Vitamin D levels were a different matter. Vitamin D level lost significance initially when the educational status variable entered the model, then regained it with the vitamin D supplementation variable. Once all variables had been added, vitamin D level had lost significance. However, the odds ratios were still in the clinically relevant range. I believe that my study suffers from the same limitation as many other studies of the relationship between vitamin D and depression—inadequate power. There are so many

potential covariates that it would take a very large sample indeed to sufficiently control for all of them without 'controlling away' the association to a point of clinical but not statistical significance.

Inclusion of the supplementation variable may seem questionable, since it would be expected to be collinear with vitamin D level. However, I chose to include this variable anyway. The question asked was very broad—participants were asked if they had supplemented vitamin D in the last thirty days. Either because of this, or because subjects were not taking an adequate dose, there was not a statistically significant association between reporting supplementation and vitamin D level.

Other Potential Mechanisms

In addition to Vitamin D, Circadian rhythm regulation has been suggested in the literature as an explanation for seasonal depression or seasonally increased severity of depression. The most commonly reported symptoms of depression were feeling tired or lacking energy, and then sleep disturbances. Light is an important part of maintaining circadian rhythms and melatonin levels—two factors that govern sleep patterns[33]. It is light exposure of the eyes rather than UV-B exposure of the skin that is required for entrainment, and therefore sun protection behaviors would be less likely to interfere. This is in line with one of the most common theories regarding why light therapy is an effective treatment for Seasonal Affective Disorder. Sun exposure may have multiple roles in depression management and prevention.

Strengths

The NHANES survey yields a massive dataset for public use. The sampling strategy results in a large sample, with adequate power to explore minority subpopulations, and apply weights to give results representative of the United States population as a whole. The variety of questions asked allowed me to include many variables for modeling purposes which are rarely collected together in a secondary data source.

A strength of the NHANES data on depression is that these participants may not have known they had depression. Everyone was asked to participate in this portion of the survey, regardless of perceived need. However, it is also possible that depressed individuals are less likely to participate in such an involved survey, since people with depression often have difficulty with self-motivation. Because of this, the sample may not adequately capture the most depressed individuals.

Likewise, dermatological questions were asked of everyone within a broad age range, rather than only being asked of those with skin conditions that might otherwise warrant such questions.

Limitations

Although there were no missing values for the sun protection variables, there were missing variables for vitamin D and for PHQ-9 score. Vitamin D level was more likely to be missing if the subject was younger, black or "Other Hispanic". Age difference was only three years between the two groups, which seems unlikely to

introduce undue bias to serum vitamin D level distribution. Missing values by race may artificially inflate vitamin D level estimates for the population, since darker skin pigmentation is associated with lower levels of vitamin D synthesis.

The missing PHQ-9 scores are slightly more problematic. The two year age difference is unlikely to impact depression scores. However, minorities are generally found to have higher rates of depression, as are those who did not finish high school. This would serve to underestimate the level of depression in the population as a whole. This could explain why the estimated population prevalence of depression (7.43%) is lower than the CDC's 2006-2008 estimate for the US population (9.1%)[5].

Overall, categorizing sun protection meaningfully was a difficult prospect. My first attempt to do so proved difficult to work with and interpret. Some of this was due to my use of a binary breakpoint. This made results very 'coarse'. Applying the three-level categorical approach used by Linos et al[32] proved more useful. However, only 7.36% of the population met the criteria for frequent sun protection, while over half (54.91%) reported rare sun protection. Looking at individual behaviors, it appears that most people may engage in one or two behaviors, but not the others. This makes sense, since someone who always wears sunscreen may see no need to wear a long-sleeved shirt or stay in the shade, while someone who intends to stay in the shade may not put on sunscreen. Combining multiple behaviors into one score neglects to recognize the ways in which people actually think about and engage in sun protection—they may use one or two methods and see no need for more than that.

Optimal serum vitamin D levels are estimated to occur in only 18.32% of the U.S.

population. Keeping in mind that missing values were more likely in African Americans and non-Mexican Hispanics, this is likely an overestimate. 34.75% of the population were deficient—a likely underestimate. The mean vitamin D level in the population is in the insufficient range. This is in line with many studies showing that Vitamin D insufficiency and deficiency are still widespread in the U.S. population despite supplementation of foods. However, I do not have access to the date on which blood samples were collected. This would have been useful information to control for the general decline in vitamin D that most people experience during the winter months.

Conclusion

Sun protection serves an important purpose—decreasing the risk of skin cancer, which can be disfiguring, disabling and even fatal. However, in the effort to encourage people to take steps to protect themselves from the damage caused by UV light, we have neglected to recognize that there are also health benefits to this exposure. Vitamin D is known to be important to bone health and development, and over time researchers are finding more and more ways in which the body may be dependent on vitamin D—possible roles such as maintaining muscle strength, boosting the immune system, and preventing/assuaging the symptoms of depression. Pamphlets abound, recommending that people stay out of the sun when possible, and wear sunscreen and protective hats and clothing when sun exposure cannot be prevented. None of these pamphlets mention that these protective measures may prevent the synthesis of vitamin D, and result in vitamin D deficiency.

Although I cannot conclude from my findings that sun protection results in an increased risk of depression, I can conclude that the potential negative impacts of sun protection remain under-explored. From a biological perspective, it is plausible and even obvious that extensive sun protection measures would result in insufficient vitamin D in the absence of extra dietary or supplementary measures. Recommendations for sun protection should be given in conjunction with information on vitamin D synthesis, and possibly even regular serum vitamin D testing to ensure that vitamin D levels are not in the deficient or insufficient range. This is particularly important in parts of the world where the latitude prevents UV-B penetration during parts of the year.

The most obvious way to deal with decreased vitamin D is supplementation. Taking a vitamin D supplement on a daily basis does not require potentially damaging sun exposure, and thus avoids the increased risk of skin cancer. However, in order to appropriately supplement vitamin D, more information is needed in two areas 1) what level of vitamin D is needed for health? And 2) how much supplementation is needed to attain this level of vitamin D in the blood serum?

Current recommended vitamin D levels are based on optimal bone health and development, and may not reflect how much is needed for other functions. Recent studies indicate that levels in excess of 40 ng/ml in the blood serum are necessary in order to obtain anti-cancer effects[34]. Although the dosage for over-the-counter supplements varies, the recommendation has commonly been 200 IU supplements for young adults, and 600 IU for older adults. A 2006 study by Bischoff-Ferrari et al found that this dose is not sufficient to bring most insufficient/deficient individuals into the optimal range. Dosages of 1000-2000 IUs seem the best method for maintaining optimal vitamin D levels. In order for supplementation to effectively maintain vitamin D levels, supplementation recommendations need to be updated and carefully researched for effectiveness.

In the United States, there is the added problem of supplement accessibility. Vitamin D supplements are available by prescription, but not all citizens have easy access to prescription medications. Over-the-counter supplements are not under FDA oversight, and may not be of consistent dosage or have accurate labeling. Food supplementation of milk and eggs has been going on in the United States for years, but is clearly not

sufficient to keep even most of the population at optimal vitamin D levels. Fortification levels are simply not high enough to be expected to prevent vitamin D deficiency or insufficiency.

The same problem of accessibility exists for the idea of routine vitamin D level testing for everyone. Those without insurance may not be seen regularly, and for those who do have insurance, coverage may not cover a new routine test without an associated diagnosis or symptom.

This is not the first study to look at vitamin D and depression, and as previously mentioned, results have been inconsistent. I believe a large part of it has to do with the fact that vitamin D deficiency and depression share many common risk factors, and thus controlling for confounding is both necessary and difficult. If there is an association between vitamin D deficiency, then a much larger sample is needed, so that there is adequate power to detect a true association once all necessary covariates are included in the model.

Perhaps more importantly, longitudinal studies are needed to determine if low vitamin D causes or exacerbates depression, or if depression causes people to spend less time outdoors and thus leads to lower vitamin D. Without establishing directionality, there can be no clear case made for causation.

A few longitudinal studies are in the planning phase—most of them involving clinical trials supplementing vitamin D with multiple health measures for outcome. Some of these studies include depression as a possible outcome. While these studies may provide good results, they may also suffer from insufficient dosing of vitamin D

supplements due to the current recommended supplementation level being lower than needed.

Using the PHQ-9 for this study presented its own set of problems. While the PHQ-9 is an excellent screening tool, it was not designed for use in research. Its usefulness is limited by the presence of the two questions that ask about two opposite symptoms (insomnia/hypersomnia and undereating/overeating).

It is also important to keep in mind that—just as the PHQ-9 was not designed for research purposes—the diagnosis of depression was also not designed for research purposes. Rather, it is meant to help inform treatment. As such, a diagnosis of depression indicates that someone experiences certain symptoms, and can likely be helped by certain treatments. There is no biological diagnostic test for depression, and no reason to expect that any time a diagnosis of depression is given, the individual suffers from the same system of symptoms and the same web of biological, environmental and experiential causes as all other sufferers of depression. This is true of most mental illnesses and makes them difficult to research.

It is possible—even likely—that what we call depression is actually a large number of different illnesses stemming from different causes with similar symptoms. Vitamin D deficiency may play a role in the cause or exacerbation of some, but not all of them. As depression research progresses, it is important that weak or 'disproven' associations are not discarded prematurely. Mental illness research requires a great deal of backtracking and rechecking as new knowledge comes to light. The best way to research depression may be by looking at individual symptoms or closely associated

constellations of symptoms, rather than attempting to look at ‘depression’ as a single illness.

Another consideration is the role that vitamin D may play in brain development, as suggested by research done on mouse models. If vitamin D is critical to brain development, it is possible that the vitamin D level of an adult may not matter as much as the vitamin D level during a certain life stage.

As always, further research is needed. With respect to the particular set of research questions I asked, the next step would be to gain access to the restricted NHANES variables. This would allow coding of proxy variables for sun exposure, as well as better information on season of blood draw and latitude as they might impact serum vitamin D. In order to get at the true impact of sun protection on vitamin D levels, questions that will ascertain the difference between someone who uses multiple methods but does not use them frequently, and someone who uses only one method but does so constantly may be needed. With the summary sun score method I used, someone who wears sunscreen every time they go outdoors, but does not wear a hat, wear long-sleeved shirt, or stay in the shade would still be considered a ‘rare’ sun protection individual.

In order to better assess depression, a larger sample size is needed to allow for better power when modeling with covariates. It may be wise to limit initial studies to a single race/ethnicity, or otherwise restrict the sample to decrease the number of possible covariates that need to be assessed in modeling.

Overall, health care providers should be more diligent in reminding people to supplement vitamin D and protect themselves from UV exposure. Clearer, evidence-

based guidelines are needed for 1) necessary levels of vitamin D for health and 2) required dosage of vitamin D supplements in order to maintain the recommended vitamin D level. Primary care providers should diligently screen for depression. Vitamin D supplementation should be recommended for everyone, particularly during the winter months in northern latitudes. Even if low vitamin D does not cause or exacerbate depression, it certainly has other negative health impacts, and should be treated.

References

1. Murray, Christopher J.L. & Lopez, Alan D. "Evidence-Based Health Policy—Lessons from the Global Burden of Disease Study" *Science* 274.5288 (1996): 740-743.
2. Duckworth, Ken. "Major Depression Fact Sheet" *nami.org.* September 2009. Web. 3 Jul 2011.
3. Kessler, Ronald C. et al. "Prevalence, Severity and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication." *Archives of General Psychiatry* 62 (2005): 617-709.
4. Wells et al. "How the Medical Comorbidity of Depressed Patients Differs Across Health Care Settings: Results From the Medical Outcomes Study" *American Journal of Psychiatry* 148 (1991): 1688-1696).
5. "An Estimated 1 in 10 U.S. Adults Report Depression" *cdc.gov.* Centers for Disease Control, 2010. Web. 3 July 2011.
6. Greenberg et al. "The Economic Burden of Depression in the United States: How Did It Change Between 1990 and 2000?" *Journal of Clinical Psychiatry* 64:12 (2003): 1465-1475.
7. Simon et al. "Health Care Costs of Primary Care Patients with Recognized Depression" *Archives of General Psychiatry* 52.10 (1995): 850-856.
8. "Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.)" *American Psychiatric Association* Washington, D.C. (2000).
9. Casano, Paola & Fava, Maurizio. "Depression and public health, An overview" *Journal of Psychosomatic Research* 53.4 (2002): 849-857.

10. Wells et al. “The Functioning and Well-being of Depressed Patients: Results From the Medical Outcomes Study” *Journal of the American Medical Association* 7.62 (1989): 914-919.

11. “Depression.” *Nimh.nih.gov.* National Institute of Mental Health, 2008. Web. 7 July 2011.

12. Wells et al. “Caring for Depression.” *Harvard University Press* Cambridge, MA. (1996).

13. Sullivan et al. “Genetic Epidemiology of Major Depression: Review and Meta-Analysis” *American Journal of Psychiatry* 157 (2000): 1552-1562.

14. Lee et al. “Depression research: where are we now?” *Molecular Brain* 3.8 (2010): 1-10.

15. “Current Depression Among Adults—United States, 2006 and 2008.” *Cdc.gov.* Morbidity and Mortality Weeky Report, 1 October 2010. Web. 3 July 2011.

16. Fava, Maurizio & Kendler, Kenneth S. “Major Depressive Disorder.” *Neuron* 28 (2000): 335-341.

17. Bertone-Johnson, Elizabeth R. “Vitamin D and the Occurrence of Depression: Causal association or circumstantial evidence?” *Nutrition Review* 67.8 (2009): 481-492.

18. Borradale, David & Kimlin, Michael. “Vitamin D in health and disease: an insight into traditional functions and new roles for this ‘sunshine vitamin’.” *Nutrition Research Reviews* 22 (2009): 118-136.

19. Engelsen et al. “Daily Duration of Vitamin D Synthesis in Human Skin with Relation to Latitude, Total Ozone, Altitude, Ground Cover, Aerosols and Cloud

Thickness." *Photochemistry and Photobiology* 81.6 (2005): 1287-1290.

20. Kimlin et al. "Location and Vitamin D synthesis: Is the hypothesis validated by geophysical data?" *Journal of Photochemistry and Photobiology* 86 (2007): 235-239.

21. Holick, Michael F. "Environmental factors that influence the cutaneous production of vitamin D." *American Journal of Clinical Nutrition* 61 (1995): 638S-645S.

22. Stewart, Robert & Hirani, Visant. "Relationship Between Vitamin D Levels and Depressive Symptoms in Older Residents From a National Survey Population." *Psychosomatic Medicine* 72.7 (2010): 608-612.

23. Matsuoka, Lois Y., et al. "Racial pigmentation and the cutaneous synthesis of vitamin D." *Archives of Dermatology* 127.4 (1991): 536.

24. Wortsman et al. "Decreased bioavailability of vitamin D in obesity." *American Journal of Clinical Nutrition* 72.3 (2000): 690-693.

25. "Health Effects of Overexposure to the Sun." *United States Environmental Protection Agency.* June 2010.

26. "Skin Cancer." *Centers for Disease Control and Prevention website*, Centers for Disease Control and Prevention Division of Cancer Prevention and Control, 28 April 2011. Web. 2 August 2011.

27. Centers for Disease Control. *National Health and Nutrition Examination Survey: Interviewer Procedures Manual.* Hyattsville, MD: National Center for Health Statistics, 2005. PDF.

28. Centers for Disease Control. *Documentation, Codebook and Frequencies: Depression*

Screener Questionnaire, Survey Years 2005-2006. Hyattsville, MD: National Center for Health Statistics, 2008. PDF.

29. Centers for Disease Control. *Analytic and Reporting Guidelines: The National Health and Nutrition Examination Survey (NHANES).* Hyattsville, MD: National Center for Health Statistics, 2006. PDF.

30. Centers for Disease Control. *National Health and Nutrition Examination Survey (NHANES): MEC In-Person Dietary Interviewers Procedures Manual.* Hyattsville, MD: National Center for Health Statistics, 2006. PDF.

31. Kroenke, Kurt & Spitzer, Robert L. "The PHQ-9: A New Depression Diagnostic And Severity Measure." *Psychiatric Annals* 32.9 (2002): 1-7.

32. Linos et al. "Sun protective behaviors and vitamin D levels in the US population: NHANES 2003-2006." *Cancer Causes Control* 23 (2012): 133-140.

33. Roenneberg, Till & Foster, Russel G. "Twilight Times: Light and the Circadian System." *Photochemistry and Photobiology* 66.5 (1997): 549-561.

34. Bischoff-Ferrari et al. "Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes." *American Journal of Clinical Nutrition* 84 (2006): 18-28.

35. Kessler, Ronald C. et al. "Prevalence, Severity and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication." *Archives of General Psychiatry* 62 (2005): 617-709.

36. Spitzer, R.L. et al. "Patient Health Questionnaire Study Group. Validity and utility of a self-report version of PRIME-MD: The PHQ Primary Care Study." *Journal of*

the American Medical Assocation 282 (1999): 1737-1744.

37. Spitzer R.L. et al. "Validity and utility of the Patient Health Questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study." *American Journal of Obstetrics & Gynecology* 183 (2001): 759-769.
38. Freeman, James and Wilson, Kimberly. "Vitamin D." *Clinical Laboratory News.* August 2013. Web 7 Apr 2014.
39. Hosmer, David W. and Lemeshow, Stanley. "Applied Logistic Regression." *Wiley-Interscience Publication.* New York, 2000. Print.

APPENDIX A

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Results are then summed to give the PHQ-9 Score.

APPENDIX B

DEQ034A: When you go outside on a very sunny day, for more than one hour, how often do you stay in the shade? Would you say …

1: Always
2: Most of the time
3: Sometimes
4: Rarely
5: Never
6: Don't go out in the sun

DEQ034B: When you go outside on a very sunny day, for more than one hour, how often do you wear a hat that shades your face, ears and neck? Would you say …

1: Always
2: Most of the time
3: Sometimes
4: Rarely
5: Never

Include any wide-brimmed hat that shades your face, ears and neck from the sun. Do NOT include visors, baseball caps, or hats that do not shade the ears and neck.

DEQ034C: When you go outside on a very sunny day, for more than one hour, how often do you wear a long-sleeved shirt? Would you say …

1: Always
2: Most of the time
3: Sometimes
4: Rarely
5: Never

DEQ034D: When you go outside on a very sunny day, for more than one hour, how often do you wear sunscreen? Would you say …

1: Always
2: Most of the time
3: Sometimes
4: Rarely
5: Never

APPENDIX C

Criteria for Major Depressive Episode: Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. , feels sad or empty) or observation made by others (e.g., appears tearful). **Note:** in children and adolescents, can be irritable mood.
- Markedly diminished interest or pleasure in all, or almost all, activities most or the day, nearly every day (as indicated by either subjective account or observation made by others)
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gain.
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt to specific plan for committing suicide
- The symptoms do not meet the criteria for a Mixed Episode
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation psychotic symptoms, or psychomotor retardation.
- Diagnostic criteria for 296.2x Major Depressive Disorder, Single Episode
- Presence of single Major Depressive Episode
- The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder,

Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

- There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects or a general medical condition.

If the full criteria are currently met for a Major Depressive Episode, specify its current clinical status and/or features:

Mild, Moderate, Severe Without Psychotic Features/Severe with Psychotic Features
Chronic
With Catatonic Features
With Melancholic Features
With Atypical Features
With Postpartum Onset

If the full criteria are not currently met for a Major Depressive Episode, *specify* the current clinical status of the Major Depressive Disorder or features of the most recent episode.

In Partial Remission, In Full Remission
Chronic
With Catatonic Features
With Melancholic Features
With Atypical Features
With Postpartum Onset
Diagnostic Criteria for 296.3x Major Depressive Disorder, Recurrent
Presence of two or more Major Depressive Episodes

Note: To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a Major Depressive Episode.

The Major Depressive Episodes are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects or a general medical condition.

If the full criteria are currently met for a Major Depressive Episode, specify its current clinical status and/or features:

Mild, Moderate, Severe Without Psychotic Features/Severe with Psychotic Features
Chronic
With Catatonic Features
With Melancholic Features
With Atypical Features
With Postpartum Onset

If the full criteria are not currently met for a Major Depressive Episode, *specify* the current clinical status of the Major Depressive Disorder or features of the most recent episode.

In Partial Remission, In Full Remission
Chronic
With Catatonic Features
With Melancholic Features
With Atypical Features
With Postpartum Onset

Specify:
Longitudinal Course Specifiers (With and Without Interepisode Recovery)
With Seasonal Pattern

APPENDIX D

Supplemental Table 1: Distribution for categorical covariates

Variable	Percent
Supplementation	
Yes	29.64%
No	70.36%
Gender	
Male	49.68%
Female	50.32%
Pregnant	5.58%
Not Pregnant	94.42%
Race	
Non-Hispanic White	72.88%
Non-Hispanic Black	13.08%
Mexican American	9.81%
Other Hispanic	4.23%
Milk Intake	
Regular Milk Drinker	41.25%
Not Regular Milk Drinker	20.67%
Milk Drinking Varied Over Lifetime	38.08%
Smoking Status	
Current	27.10%
Former	19.95%
Never	52.95%
Average Physical Activity Level	
Sits, rarely stands/walks	22.37%
Stands/walks, no lifting	47.24%
Light loads, stairs/hills often	19.85%
Heavy work, heavy lifting	10.53%
Marital Status	
Married	57.38%
Widowed	1.07%
Single, Never Married	18.88%
Living With Partner	10.25%
Divorced/Separated	12.42%
Education Level	
Less Than High School Diploma	15.31%
High School Diploma or More	84.69%
Diabetes	
Yes	5.08%
No	93.66%
Borderline	1.27%

Variable	Percent
Coronary Heart Disease	
Yes	1.12%
No	98.88%
Stroke	
Yes	1.06%
No	98.94%
Arthritis	
Yes	16.26%
No	83.74%
Cancer	
Yes	4.52%
No	95.48%
Current Asthma	
Yes	8. 35%
No	91.65%
Current Bronchitis	
Yes	2.78%
No	97.22%

Supplemental Table 2: Mean and standard error for continuous covariates

Variable	Mean	Standard Error
Body Mass Index	28.65	0.3226
Age	39.42	0.3104
Parathyroid Hormone Level	40.49	0.4970

Supplemental Table 3: Distribution of responses by question for sun protection

Question How often do you …	Rarely/Never n (%)	Sometimes n (%)	Always/Most of the Time n (%)
… stay in the shade?	1,069 (34.63%)	1,294 (39.39%)	1,004 (25.98%)
… wear a protective hat?	2,182 (65.23%)	597 (17.66%)	588 (17.10%)
… wear a long-sleeved shirt?	2,486 (75.72%)	593 (16.96%)	288 (7.32%)
… use sunscreen?	2,014 (50.42%)	643 (23.62%)	710 (25.96%)

Supplemental Table 4: Frequency of reported symptoms on PHQ-9, never vs. ever

Question Over the last two weeks, how often have you …	Not at All n (%)	Ever n (%)
… felt little interest or pleasure in doing things?	2,326 (80.31%)	621 (19.69%)
… felt down, depressed or hopeless?	2,262 (78.67%)	687 (21.33%)
… had trouble falling or staying asleep, or sleeping too much?	1,889 (65.27%)	1,057 (35.27%)
… felt tired or had little energy?	1,409 (49.15%)	1,540 (50.85%)
… had poor appetite or overeating?	2,252 (77.92%)	695 (22.08%)
… felt bad about yourself?	2,484 (84.82%)	465 (15.18%)
… had trouble concentrating on things?	2,438 (83.51%)	510 (16.49%)
… moved or spoke slowly or been fidgety or restless?	2,631 (90.46%)	316 (9.54)
… Thought you would be better off dead/hurting yourself?	2,841 (96.89%)	107 (3.11%)

APPENDIX E

Step by step model building:

	Unadjusted Model		**Model + BMI=Model 1**	
Variable	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Sun Group				
Rare Protection	Ref.	Ref.	Ref.	Ref.
Moderate Protection	1.04 (0.73-1.48)	0.800	1.05 (0.71-1.54)	0.807
Frequent Protection	1.13 (0.57-2.25)	0.706	1.01 (0.50-2.05)	0.973
Vitamin D Group				
Optimal	Ref.	Ref.	Ref.	Ref.
Insufficient	1.43 (0.92-2.22)	0.105	1.30 (0.85-1.98)	0.208
Deficient	1.94 (1.17-3.24)	**0.014**	1.71 (1.01-2.91)	**0.046**

	Model 1		**Model 1+ Gender=Model 2**	
Variable	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Sun Group				
Rare Protection	Ref.	Ref.	Ref.	Ref.
Moderate Protection	1.05 (0.71-1.54)	0.807	1.02 (0.69-1.49)	0.935
Frequent Protection	1.01 (0.50-2.05)	0.973	0.91 (0.44-1.88)	0.784
Vitamin D Group				
Optimal	Ref.	Ref.	Ref.	Ref.
Insufficient	1.30 (0.85-1.98)	0.208	1.37 (0.88-2.11)	0.143
Deficient	1.71 (1.01-2.91)	**0.046**	1.77 (1.01-3.09)	**0.045**

	Model 2		**Model 2+ Supplement=Model 3**	
Variable	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Sun Group				
Rare Protection	Ref.	Ref.	Ref.	Ref.
Moderate Protection	1.02 (0.69-1.49)	0.935	0.94 (0.55-1.60)	0.798
Frequent Protection	0.91 (0.44-1.88)	0.784	1.03 (0.48-2.20)	0.943
Vitamin D Group				
Optimal	Ref.	Ref.	Ref.	Ref.
Insufficient	1.37 (0.88-2.11)	0.143	1.37 (0.79-2.37)	0.232
Deficient	1.77 (1.01-3.09)	0.045	2.21 (1.21-4.02)	**0.013**

	Model 3		Model 3+ Race=Model 4	
Variable	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Sun Group				
Rare Protection	Ref.	Ref.	Ref.	Ref.
Moderate Protection	0.94 (0.55-1.60)	0.798	0.92 (0.50-1.68)	0.769
Frequent Protection	1.03 (0.48-2.20)	0.943	0.81 (0.35-1.84)	0.597
Vitamin D Group				
Optimal	Ref.	Ref.	Ref.	Ref.
Insufficient	1.37 (0.79-2.37)	0.232	1.41 (0.78-2.55)	0.230
Deficient	1.66 (0.94-2.90)	0.073	2.24 (0.97-5.16)	0.057

	Model 4		Model 4+ Arthritis=Model 5	
Variable	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Sun Group				
Rare Protection	Ref.	Ref.	Ref.	Ref.
Moderate Protection	0.92 (0.50-1.68)	0.769	0.89 (0.45-1.75)	0.948
Frequent Protection	0.81 (0.35-1.84)	0.597	0.82 (0.33-2.00)	0.991
Vitamin D Group				
Optimal	Ref.	Ref.	Ref.	Ref.
Insufficient	1.41 (0.78-2.55)	0.230	1.34 (0.68-2.62)	0.367
Deficient	2.24 (0.97-5.16)	0.057	2.00 (0.82-4.84)	0.115

	Model 5		Model 5+ Smoking Status=Model 6	
Variable	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Sun Group				
Rare Protection	Ref.	Ref.	Ref.	Ref.
Moderate Protection	0.89 (0.45-1.75)	0.948	0.93 (0.46-1.87)	0.834
Frequent Protection	0.82 (0.33-2.00)	0.991	0.93 (0.37-2.33)	0.865
Vitamin D Group				
Optimal	Ref.	Ref.	Ref.	Ref.
Insufficient	1.34 (0.68-2.62)	0.367	1.34 (0.67-2.65)	0.376
Deficient	2.00 (0.82-4.84)	0.115	1.86 (0.74-4.66)	0.167

	Model 6		**Model 6+ Phys. Activity=Final Model**	
Variable	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Sun Group				
Rare Protection	Ref.	Ref.	Ref.	Ref.
Moderate Protection	0.93 (0.46-1.87)	0.834	0.94 (0.47-1.88)	0.857
Frequent Protection	0.93 (0.37-2.33)	0.865	0.83 (0.32-2.11)	0.678
Vitamin D Group				
Optimal	Ref.	Ref.	Ref.	Ref.
Insufficient	1.34 (0.67-2.65)	0.376	1.30 (0.65-2.52)	0.446
Deficient	1.86 (0.74-4.66)	0.167	1.71 (0.68-4.30)	0.232