Modifiable lifestyle factor correlates of vitamin D status in United States adults.

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Abstract

Background: Maintaining sufficient serum vitamin D is fundamental to achieving optimal bone health and has widespread implications for non-skeletal health. Few studies have attempted to comprehensively examine the effects of modifiable lifestyle factors alone that may influence vitamin D status while controlling for non-modifiable factors. This initial analysis of NHANES data aims to identify modifiable factors predictive of vitamin D status in US adults.

Methods: A binary multiple logistic regression was performed on NHANES 2013–2014 data (n=3,679). The primary model used the IOM serum 25(OH)D cut point for adequacy (≥50.0 nmol/L) and the secondary model used the Endocrine Society cut point (>75.0 nmol/L). Of 24 modifiable factors tested independently in both models, each factor was entered in a hierarchical sequence and remained if the model was significantly improved by its addition.

Results: Select modifiable lifestyle factors predict vitamin D status in adults. Significant predictors of vitamin D insufficiency common to both models were use of vitamin D supplements, regular milk consumption, and total vitamin D intake. Predictors unique to the IOM model were waist circumference, daily minutes of sedentary activity, and sunscreen use. Significant predictors unique to the Endocrine Society model were sun protection via long-sleeved shirt use, lifetime cigarette consumption of ≥100, self-rated diet healthfulness, and total fat intake.

Conclusion: The present study has set a framework through which multiple lifestyle factors and their influence on serum vitamin D may be further assessed. The identification of modifiable factors which carry the greatest influence on vitamin D status can help to inform future observational studies or clinical trials, aid in the creation of screening tools, and help inform targeted interventions in at-risk populations for vitamin D insufficiency.

Résumé

Contexte: Le maintien d'un niveau adéquat de vitamine D sérique est fondamental pour atteindre une santé osseuse optimale et est aussi important pour beaucoup d'autres aspects de la santé en général. Peu d'études ont tenté d'examiner de manière exhaustive les effets des habitudes de vie modifiables sur le statut en vitamine D tout en contrôlant les interactions avec les facteurs non modifiables. Cette première analyse avec les données NHANES avait donc pour but d'identifier les facteurs modifiables qui sont des déterminants significatifs du statut en vitamine D chez les adultes vivants aux États-Unis.

Méthode: Principalement, des analyses de régressions logistiques multiples ont été effectuées à partir de la banque de données NHANES 2013–2014 (n=3,679). Une première modélisation a été effectuée avec une valeur sérique de vitamine D (25(OH)D) ($x \geq 50.0$ nmol/L) telle que suggérée par l'IOM comme variable dépendante. Une deuxième modélisation a été effectuée selon une valeur sérique de vitamine D (25(OH)D) supérieure telle que suggérée par l'Endocrine Society ($x > 75.0$ nmol/L). Chacun des 24 déterminants modifiables identifiés et disponibles dans la banque de données a été évalué pour leurs indépendances dans chacun des modèles. La construction des modèles a été effectuée selon une séquence hiérarchique et les variables ont été conservées dans le modèle statistique si celle-ci améliorait de manière significative la validité du modèle.

Résultats: Dans les deux modèles de régression logistique, l'utilisation de suppléments de vitamine D, la consommation régulière de lait et l'apport total en vitamine D ont été les déterminants significatifs d'une valeur sérique de vitamine D (25(OH)D) insuffisante. Les déterminants uniques au modèle IOM ont été la circonférence abdominale, le nombre de minutes quotidiennes de sédentarité et l'utilisation de crème solaire. Les déterminants uniques au modèle de l'Endocrine Society ont été l'utilisation de manche longue comme protection solaire, la consommation de cigarette supérieure à 100 au cours de sa vie, l'auto-évaluation de l'apport alimentaire et l'apport total en matière grasse.

Conclusion: L'identification des facteurs modifiables qui sont les plus grands déterminants du statut en vitamine D peut aider la préparation des futures études observationnelles ou des études cliniques, la création d'outils de dépistage et aider l'élaboration d'intervention ciblée dans les populations à risque d'insuffisance en vitamine D.

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Contributions

Michael Hull aided in conceiving the study concept, designed and conducted the data analysis, drafted the thesis, and had primary responsibility for the final content. Dr. Hugues Plourde aided in conceiving the study concept and provided technical oversight and input into all aspects of the study, including data analysis and thesis preparation. Dr. David Kovaz reviewed and provided input on the statistical design and methodology of the study. Michael Hull and Dr. Plourde oversaw revisions of the thesis and read and approved the final version. All authors declare no conflicts of interest related to this study.

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Abbreviations

$1,25(OH)_2D_2$	1,25-dihydroxyvitamin D_2 or ercalcitriol
$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D_3 or calcitriol
25(OH)D	25-hydroxyvitamin D, 25-hydroxycalciferol, calcidiol, or calcifediol
AA	Associate of Arts Degree
AI	Adequate Intake
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DGA	Dietary Guidelines for Americans
DRI	Dietary Reference Intake
EAR	Estimated Average Requirement
FNDDS	Food and Nutrient Database for Dietary Studies
GED	General Educational Development
HMEP	Healthy Mediterranean-Style Eating Pattern
HS	High School
IOM	Institute of Medicine
IU	International Unit
MARRS	Membrane-associated Rapid-response Steroid-binding Protein
MEC	Mobile Examination Center
MET	Metabolic Equivalent
MVMM	Multivitamin/Multimineral
N.D.	No Date
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
OSA	Obstructive Sleep Apnea
RCT	Randomized Controlled Trial

RDA	Recommended Dietary Allowance
STROBE-nut	Strengthening the Reporting of Observational Studies in Epidemiology—Nutritional Epidemiology Guidelines
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SEM	Standard Error of the Mean
SPF	Sun Protection Factor
UL	Tolerable Upper Intake Limit
US	United States
UV or UVR	Ultraviolet Radiation
UVA	Ultraviolet Alpha-rays
UVB	Ultraviolet Beta-rays
VDBP	Vitamin D Binding Protein
VDRE	Vitamin D Response Elements
VDSP	Vitamin D Standardization Program
Vitamin D_2	Ergocalciferol
Vitamin D_3	Cholecalciferol

Conversions

Serum 25(OH)D

- 1 ng/mL = 2.4959 nmol/L
- 1 nmol/L = .401 ng/mL

Vitamin D

- 1 μg = 40 International Units (IU)

INTRODUCTION

Background and Rationale

Vitamin D has been well established as a core component for attaining optimal bone health (Avenell, Mak et al., 2014; Ross, Taylor et al., 2011; Weatherall, 2000; Weaver, Alexander et al., 2016). Recently, increasing attention has been given to vitamin D's potential role in non-skeletal health factors. Vitamin D receptors (VDRs) have been found in over 35 tissues throughout the body — cardiac, muscle, intestinal, pancreatic, colon, skin, lymphocytes (B and T), kidney, lung, thyroid, prostate, and brain tissue all possess VDRs, among others (R. Bouillon, Okamura et al., 1995; Norman, 2008). The presence of VDRs across numerous tissues implies that vitamin D may play a role in many physiological functions (Christakos, Dhawan et al., 2016).

Research into vitamin Ds non-skeletal health effects have provided evidence that it may act as a mediating factor in chronic diseases such as diabetes, certain cancers, heart disease, Alzheimer's, stroke, and chronic kidney disease — all of which are leading causes of death in the United States (US), accounting for 59.0% of total deaths in 2016 (Heron, 2018; Theodoratou, Tzoulaki et al., 2014). Significant associations, with small effect sizes, have also been seen between vitamin D status and all-cause mortality (Bjelakovic, Gluud et al., 2014; Brøndum-Jacobsen, Benn et al., 2012). The sum of this research has indicated vitamin D as an important player in overall health status. Thus, maintaining adequate vitamin D levels has significant implications for public health (Palacios & Gonzalez, 2014; Roth, Abrams et al., 2018).

To this end, public guidelines have been set for adequate dietary vitamin D intake. The Dietary Reference Intakes (DRIs) for vitamin D were updated by the Food and Nutrition Board at the Institute of Medicine (IOM; presently known as the Health and Medicine Division) in 2011 (Ross et al., 2011). Under the DRIs, the Recommended Dietary Allowance (RDA) for adults aged 18–70 years is 600 IU (15 mcg) per day and 800 IU/day (20 mcg) for adults aged >70 years. These intake levels were set based on the evidence for vitamin Ds influence on bone health outcomes, as the Food and Nutrition Board concluded evidence of vitamin Ds effects on non-skeletal health outcomes were not adequate at the time. It is also important to note that, although

vitamin D can be produced through dermal synthesis via exposure to ultraviolet (UV) rays, the DRIs for vitamin D were set under the assumption of minimal endogenous vitamin D production (Ross et al., 2011).

To meet the RDA, vitamin D must be obtained via dietary intake from foods and supplements. Food sources of vitamin D can occur naturally or be fortified or enriched with it. Among adult vitamin D supplement users, daily use may increase intake by 118–309%, depending on age group, compared to those who consumed vitamin D through foods only (Blumberg, Frei et al., 2017c). Vitamin D may also be endogenously synthesized in human skin, which can contribute to overall serum vitamin D status. Yet, due to concern around widespread inadequate intake in the US, vitamin D has been deemed a nutrient of interest in public health and has been classified as a chronically underconsumed nutrient whose low intake can adversely affect health outcomes ("A Closer Look at Current Intakes and Recommended Shifts - 2015-2020 Dietary Guidelines - health.gov," n.d.).

To objectively monitor vitamin D status, serum calcidiol (25(OH)D; aka 25-hydroxyvitamin D) is the most commonly used indicator. While not the bioactive form, 25(OH)D possesses a half-life of approximately 15 days and accounts for both dietary intake and endogenous synthesis (Jones, 2008; Ross et al., 2011). The IOM recommends the following serum 25(OH)D cut points: <30 nmol/L (<12 ng/mL) for deficiency, 30–<50 nmol/L (12–<20 ng/mL) for inadequacy, and ≥50 nmol/L (≥20 ng/mL) for adequacy (Ross et al., 2011). Using these cut points, estimated prevalence of vitamin D deficiency and inadequacy, hereinafter referred to as "insufficiency", have ranged from 22–41.6% over previous NHANES cycles dating back to 1988 (Forrest & Stuhldreher, 2011; Ganji, Zhang et al., 2012; Ginde, Liu et al., 2009; Ginde, Sullivan et al., 2010; Schleicher, Sternberg et al., 2016). Data analyzed from the 1988–2010 cycles have seen the average insufficiency (<50 nmol/L) prevalence remain at a steady ~31% in the adult population from 1988–2006, with a small decrease to a prevalence of ~26% seen in 2007–2010 (Schleicher, Sternberg et al., 2016). This would place an estimated 60.99 million adults with serum vitamin D levels below 50 nmol/L, with 45.27 million in the inadequate range and 15.72 million with deficiency (Howden & Meyer, 2010). With such high occurrences of vitamin D insufficiency, it is plausible that population-wide improvements

in vitamin D status could help reduce both the incidence of chronic diseases and the economic burden associated with them (Grant, Whiting et al., 2016). To this end, there are many modifiable lifestyle factors that could be targeted to improve vitamin D status.

Among these modifiable lifestyle factors, dietary intake of vitamin D and sun exposure deliver the highest impact on improving vitamin D status. However, current dietary intakes and sun exposure are often not enough to maintain adequate serum levels year-round (Jager, Schöpe et al., 2018; Lips, van Schoor et al., 2014; Shab-Bidar, Bours et al., 2014). Additional modifiable factors can also play a role including physical activity levels, body composition, sleep duration, smoking habits, supplement use, and alcohol consumption (Beydoun, Gamaldo et al., 2014; Kühn, Kaaks et al., 2014; Liu, Baylin et al., 2018). While there have been many observational studies examining selected lifestyle determinants of vitamin D status in the US population, the majority have also included non-modifiable factors with the aim of identifying at-risk populations (Daraghmeh, Bertoia et al., 2016; Forrest & Stuhldreher, 2011; Gupta, Brashear et al., 2012; Liu et al., 2018; Nesby-O'Dell, Scanlon et al., 2002; Rajan, Weishaar et al., 2017; Weishaar, Rajan et al., 2016). Identifying these populations is a critical question to address when assessing public health. However, during the literature search no observational studies were identified that have examined the effects of modifiable lifestyle factors alone, in a comprehensive manner, in the US population. Such an analysis can help shed light on which factors carry the greatest influence on vitamin D status. These results could be used to help to inform future observational studies or clinical trials and aid in the creation of screening tools or targeted interventions in at-risk populations for vitamin D insufficiency.

Statement of Purpose and Objectives

Maintaining sufficient serum levels of vitamin D is fundamental to achieving optimal bone health and has widespread implications for non-skeletal health factors. Yet, nearly a third of US adults have insufficient levels. To date, few observational studies have attempted to comprehensively examine the effect of modifiable lifestyle factors alone, while controlling for non-modifiable lifestyle factors, that may influence vitamin D status in a US population. This

initial analysis of NHANES data will help identify which modifiable lifestyle factors contribute to predicting vitamin D status.

Research Question

The primary research question is: Do modifiable lifestyle factors predict vitamin D status in adults?

H_o: The modifiable lifestyle variables do not predict vitamin D status.

H_a: The modifiable lifestyle variables do predict vitamin D status.

The binary dependent variable was defined as "insufficient" or "sufficient" serum levels of 25(OH)D. The independent variables were modifiable lifestyle factors selected from the NHANES 2013–2014 cycle that may influence vitamin D status based on *a priori* justification from the current literature. These variables include items pertaining to diet, dietary supplement use, physical activity levels, body composition, sleep duration, smoking habits, alcohol consumption, and sun exposure. Non-modifiable lifestyle factors that could influence vitamin D serum status or intake were controlled for: age, income, day the dietary recalls were performed, education, gender, race/ethnicity, health conditions or medications affecting vitamin D absorption and/or metabolism, and the time period serum vitamin D was tested (November 1–April 30 vs. May 1–October 31).

LITERATURE REVIEW

Literature Search Strategy

The full search strategy can be seen in Appendix A. In order to identify relevant literature for this review, the following databases were searched: McGill WorldCat portal, PubMed, EMBASE, Cochrane Library, and CINAHL. All databases were searched until May 7th, 2018.

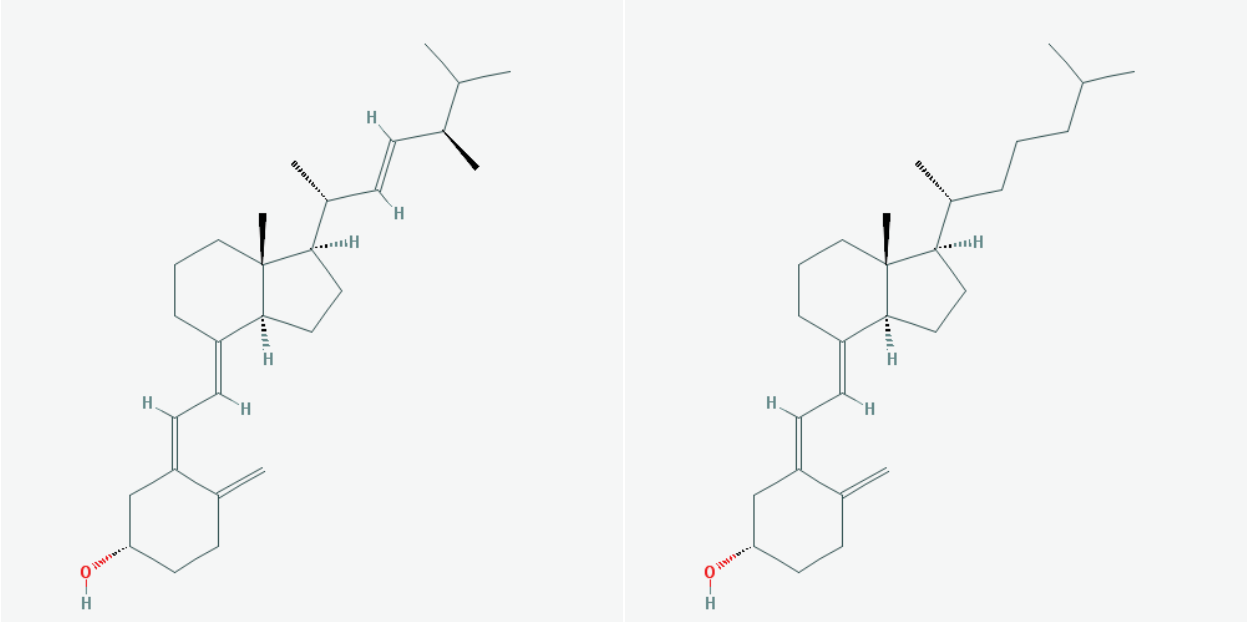
Literature Review

Sources of Vitamin D

Foods and supplements

Vitamin D, a fat-soluble vitamin, has two main dietary forms: ergocalciferol (D_2) and cholecalciferol (D_3). The differences are slight, with D_2 containing an additional side-chain double bond between C22–23 and a methyl group at C24 (Figure 1). An additional form of vitamin D, 25(OH)D, is present in select animal foods (e.g., milk, fish, egg yolks) but only appears in very low concentrations — typically .1–1 mcg/100 g (Ovesen, Brot et al., 2003). Despite its small quantity, 25(OH)D is estimated to be ~5 times more potent than vitamin D_3 in raising serum 25(OH)D levels (Cashman, Seamans et al., 2012; Ovesen et al., 2003) and has been seen to increase serum 25(OH)D more rapidly (Bischoff-Ferrari, Dawson-Hughes et al., 2012; Cashman et al., 2012; Jakobsen, Andersen et al., 2017; Jetter, Egli et al., 2014).

Figure 1. Chemical structure of vitamin D_2 and D_3



Vitamin D_2 Vitamin D_3

Source: National Center for Biotechnology Information. PubChem Compound Database; CID=5280795, CID=5280793, https://pubchem.ncbi.nlm.nih.gov/compound/5280795, https://pubchem.ncbi.nlm.nih.gov/compound/5280793 (accessed Apr. 10, 2018).

Food sources of D_2 and D_3 include those that produce them naturally or those that have had them added via fortification or enrichment. Naturally occurring sources are somewhat limited in the US food supply. For vitamin D_2, natural sources include various mushrooms such as portabella, maitake, white, chanterelle, morel, and shiitake. Milk alternatives, such as soy, coconut, and rice milk, have D_2 added to them. Similar to other fungi, mushrooms contain ergosterol which can be converted to previtamin D_2 and then to D_2 when exposed to UVB radiation (Keegan, Lu et al., 2013). This process can greatly increase the D_2 concentration (Jasinghe, Perera et al., 2005; Ko, Lee et al., 2008). In the white button mushroom, UVB exposure can increase D_2 concentrations from .2 to 26.2 mcg/100g ("USDA-FCD," n.d.-a, "USDA-FCD," n.d.-b).

For natural sources of D_3, animal-based foods such as fatty fish (e.g., halibut, mackerel, carp, salmon, trout, swordfish, sturgeon, and whitefish) and, in particular, the livers of fatty fish (e.g., anglerfish, cod, and tuna) are rich sources. Smaller amounts are found in ruminants (e.g.,

cattle, sheep, goats) as well as turkeys, chicken, cheese, and eggs yolks. The vitamin D content of these animal-based sources varies depending on living and dietary conditions of the animal (Mattila, Lehikoinen et al., 1999; Reeve, Jorgensen et al., 1982). In the US, the use of 25(OH)D_3-enriched feed can be used to increase the vitamin D content of some animal products (Food and Drug Administration, 2007). Furthermore, the US has a mandatory vitamin D fortification policy for infant formula and fluid or evaporated milk while foods that can be optionally fortified include yogurt, cheese, fruit juice, margarine, bread, and ready-to-eat cereals (Calvo & Whiting, 2013; Center for Food Safety & Nutrition, n.d.). These fortified foods contribute significantly to vitamin D intake in the US, accounting for an estimated 59.2% of dietary intake, excluding supplemental sources (Fulgoni, Keast et al., 2011).

Endogenous production

Endogenous vitamin D_3 production begins when the prohormone 7-dehydrocholesterol, primarily located in the epidermal layer of the skin, is exposed to UVB radiation. Upon exposure, the B ring of 7-dehydrocholesterol is broken, forming previtamin D_3, which is then converted to vitamin D_3 via thermal isomerization (Bikle, 2011; Holick, MacLaughlin et al., 1980; Lehmann, Genehr et al., 2001). UVB consists of the 280–320 nm wavelengths of the solar spectrum, with the most efficient range for endogenous vitamin D_3 production falling between ~293–298 nm (Kalajian, Aldoukhi et al., 2017; MacLaughlin, Anderson et al., 1982). Skin that is overexposed to UVB radiation will not result in the overproduction of vitamin D_3, as previtamin D_3 and D_3 become isomerized to biologically inactive metabolites; pre-vitamin D_3 to lumisterol and tachysterol and D_3 to suprasterols I, II, and 5,6 trans-vitamin D_3 (Holick, MacLaughlin et al., 1981; Webb, DeCosta et al., 1989). Additionally, melanin production is increased with UV exposure. This can act as additional protection against excess D_3 production as melanin can absorb UV rays.

This endogenous production cycle is prone to influence by a multitude of factors; including latitude, solar zenith angle/time of year, sunscreen use, UV index, weather conditions, clothing, skin pigmentation and pigment genes, pollution, elevation, living environment (e.g., urban, suburban, or rural), age, amount of sun-exposed skin, certain medications, and UV

exposure duration and frequency (Chen, Chimeh et al., 2007; Datta, Philipsen et al., 2019; Wacker & Holick, 2013; Webb, 2006). Interactions between these factors can lead to compounding effects on vitamin D status.

Metabolism and Functions

Absorption and transport

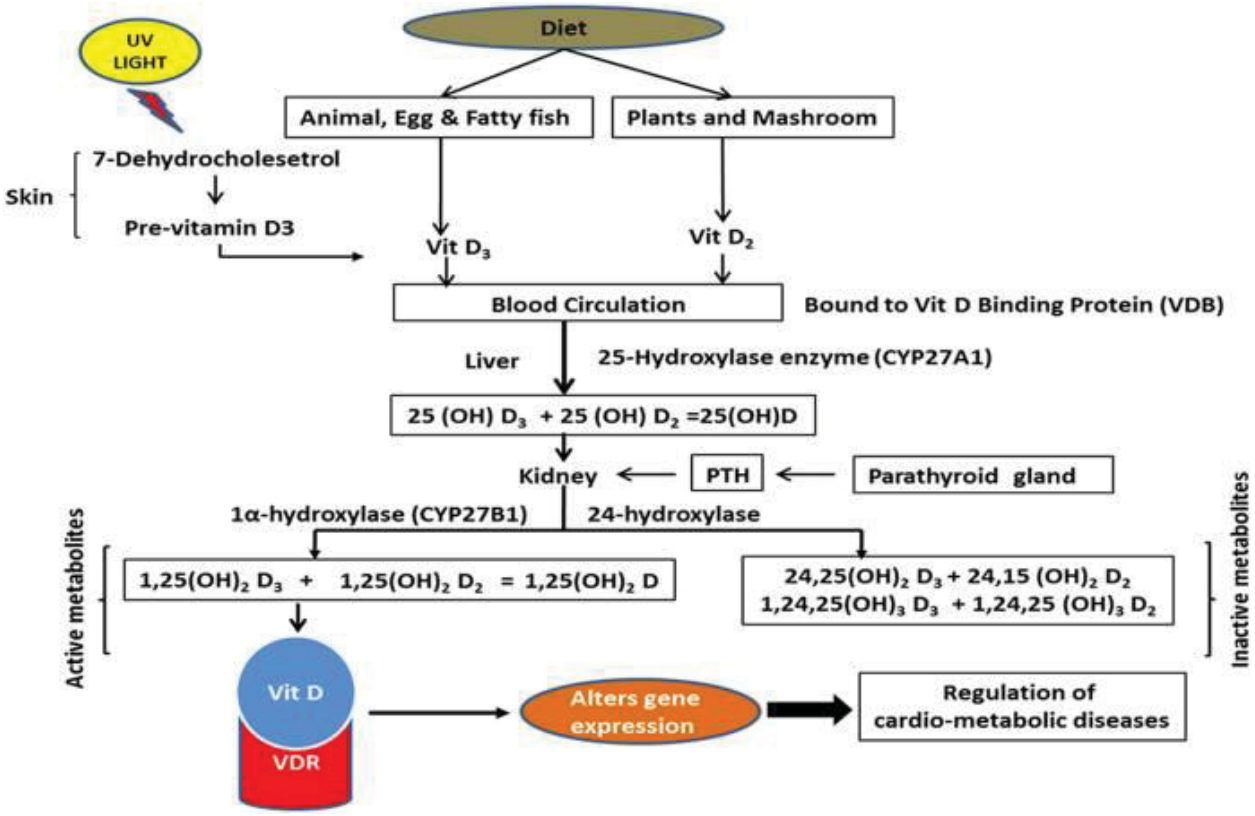
When ingested, vitamin D is transported from the lumen of the small intestine into enterocytes via bile salt micelles. Once in the enterocyte, chylomicrons then transport vitamin D metabolites into the lymphatic system where they can then be released into the bloodstream. Both 25(OH)D and 1,25$(OH)_2$D, more polar metabolites, do not require chylomicrons for transport into the lymphatic system and may be released directly into the portal vein (Maislos & Shany, 1987; Sitrin, Pollack et al., 1985). If produced endogenously, vitamin D_3 in the plasma membrane of skin cells is transported to the extracellular space where vitamin D binding protein (VDBP) aids it its entry into the capillary bed (Haddad, Matsuoka et al., 1993). Once in the bloodstream, vitamin D metabolites are mainly bound to VDBP with a lesser potion being bound to albumin (Bikle, Adams et al., 2009). A very small portion (<1%) circulates in an unbound free form (Christakos et al., 2016).

Metabolism

In order to become biologically active within the body, vitamin D_2 and D_3 must undergo enzymatic hydroxylation (Figure 2). Once transported to the liver, vitamin D_2 and D_3 are metabolized to 25(OH)D, via the enzyme 25-hydroxylase. This is the major form found circulating in serum. Once 25(OH)D is released from the liver into circulation it can then be converted to the active metabolite 1,25$(OH)_2$D via the enzyme 1α-hydroxylase. This activation step occurs mainly in the kidneys but can also take place in select extrarenal tissues such as the epithelial skin cells, lungs, prostate, and parathyroid glands (Bikle, 2014). 1,25$(OH)_2$D is the metabolically active secosteroid hormone form of vitamin D that acts upon VDRs within the body. Additionally, the kidneys can also convert 25(OH)D into the metabolites 24,25$(OH)_2$D and 1,24,25$(OH)_3$D via the 24-hydroxylase enzyme. It should be noted that, while traditionally considered an inactive

metabolite, there is some evidence that 24,25$(OH)_2$D plays a role in embryogenesis (Brandi, 2010). However, this role remains controversial. 24-hydroxylase is also the major enzyme responsible for catabolizing 1,25$(OH)_2$D. Its metabolites are mainly excreted via feces, aided by bile salts.

Figure 2. Vitamin D synthesis and metabolism



Source: Adela, R., Borkar, R. M., Bhandi, M. M., Vishwakarma, G., Reddy, P. N. C., Srinivas, R., & Banerjee, S. K. (2016). Lower Vitamin D Metabolites Levels Were Associated with Increased Coronary Artery Diseases in Type 2 Diabetes Patients in India. Scientific Reports, 6, 37593. http://doi.org/10.1038/srep37593

Mechanisms of action

Vitamin D exhibits both genomic and non-genomic actions. The genomic actions of 1,25$(OH)_2$D are mediated through the VDR. Upon reaching a target cell, 1,25$(OH)_2$D is unbound from VDBP and binds to the VDR, which aids in translocating it across the cell membrane. From there, the VDR-1,25$(OH)_2$D complex heterodimerizes to the nuclear hormone receptor retinoid

X receptor (RXR), which translocates the complex into the nucleus. Once in the nucleus, the VDR–RXR complex acts as a transcription factor, binding to vitamin D response elements (VDRE) on target genes where it can regulate gene expression. The vitamin D receptor interacting protein (DRIP) complex is translocated to the promoter gene by the VDR complex to mediate interactions between the VDR complex transcription factor and the basal transcription unit (BTU), which triggers the transcription process. Various other co-regulators can also interact with the VDR complex to activate or inhibit transcriptional activities. To date, $1,25(OH)_2D$ has been seen to trigger gene expression in over 200 genomic targets with VDREs (Pike, Meyer et al., 2010; Széles, Póliska et al., 2010).

In addition to its genomic activity, vitamin D has non-genomic actions (Hii & Ferrante, 2016). These non-genomic actions are mainly mediated via a version of the VDR receptor that can bind to non-genomic agonists and the membrane-associated rapid-response steroid-binding protein (MARRS; aka GRP58, ERp57, or ERp60) (Mizwicki & Norman, 2009; Nemere, Farach-Carson et al., 2004). $1,25(OH)_2D$ has demonstrated a non-genetically mediated ability to aid in calcium and chloride channel regulation, phospholipase C activity, and protein kinase C activity in many cells, including the intestines and muscle cells (Khare, Bolt et al., 1997; Morelli, de Boland et al., 1993).

Dietary Intake and Serum 25(OH)D Guidelines

The Institute of Medicine guidelines

In 2011, the IOM updated the DRIs for vitamin D (Ross et al., 2011). After reviewing potential health indicators to serve as the basis of the vitamin D DRIs, bone health was selected as the best candidate (Catharine Ross, Taylor et al., 2011). Other health indicators reviewed were deemed to be "not associated with evidence that could be judged either compelling or sufficient in terms of cause and effect, nor informative regarding dose-response relationships for the purposes of determining nutrient requirements" (Ross et al., 2011). Importantly, the DRIs were set assuming minimal levels of sun exposure. The EAR for vitamin D is 400 IU/d and the tolerable upper intake level (UL) is 4,000 IU/day for all adult age groups (≥19 years) and life stages. The RDA can be seen in table 1 and the RDA-like serum cut points can be seen in table 2.

Table 1. IOM RDA for Vitamin D

Age	Male	Female	Pregnancy	Lactation
0–12 months*	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

**Adequate Intake (AI)*

Table 2. IOM Serum 25(OH)D Recommendations

nmol/L	ng/mL	Health status
<30	<12	Deficiency
30 to <50	12 to <20	Inadequacy
≥50	≥20	Adequacy
>125	>50	Potential adverse effects

1 ng/mL = 2.4959 nmol/L
1 nmol/L = .401 ng/mL

Since the serum 25(OH)D cut points represent an RDA-type value, as stated by the IOM, 50 nmol/L (20 ng/mL) is the serum level that would be sufficient to meet nutrient requirements of 97.5% of the population, if otherwise healthy, and 40 nmol/L (16 ng/mL) would represent the EAR-type value, a serum cut point estimated to meet the requirement of half the healthy individuals in the population. These cut point standards have been adopted by many public health agencies in other countries, including Canada, DACH countries (Germany, Austria, and Switzerland), the European Union, the Nordic Council of Ministers countries (Denmark, Finland,

Iceland, Norway, Sweden, the Faroe Islands, Greenland, and Åland), Australia, and New Zealand (Bouillon & Rosen, 2018).

The Endocrine Society guidelines

Some have criticized the IOM's recommendations as being too low. In 2011, the Endocrine Society Task Force began disputing the IOM serum cut points and contended that serum 25(OH)D levels should exceed 75 nmol/L (30 ng/mL) for optimal bone health and muscular strength, mass, and function (Holick, Binkley et al., 2011; Vieth & Holick, 2018). Part of their critique was that, due to an error in statistical modeling (Veugelers & Ekwaru, 2014), the IOM report had underestimated the cut point for serum 25(OH)D sufficiency and thus the RDA vitamin D recommendations were too low to meet 97.5% of the population's nutrient requirements. In their clinical practice guideline, the Endocrine Society recommended a vitamin D dietary intake range of 1,500–2,000 IU/day (37.5–50 mcg/day) for adults (≥19 years) to sustain a serum 25(OH)D level that exceeds 75 nmol/L (30 ng/mL) (Holick, Binkley et al., 2011).

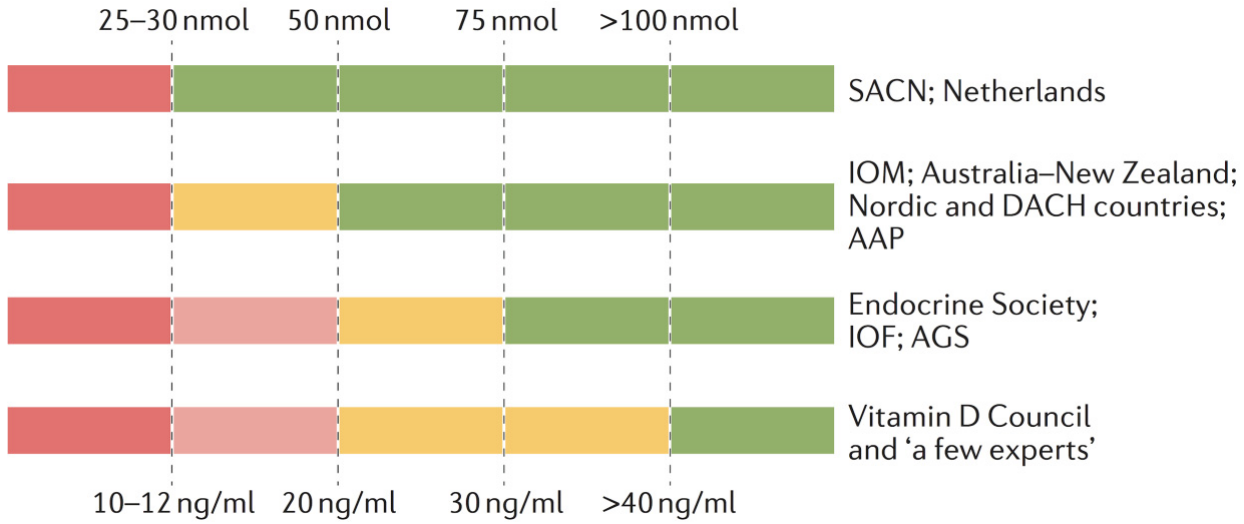
The IOM has expressed uncertainty about the quality, strength, and causal implications of the association studies used to support the Endocrine Society's higher recommendations, emphasizing that, before such firm public policy recommendations can be made, more RCTs with hard clinical endpoints are needed to confirm vitamin Ds potential extraskeletal effects (Bouillon, Van Schoor et al., 2013; Rosen, Abrams et al., 2012; Rosen, Adams et al., 2012). Additionally, those in support of the IOM recommendations stressed that some adverse effects, such as hypercalcemia, have been seen at 25(OH)D serum levels above 50 nmol/L (20 ng/mL) and, as such, caution is warranted before recommending higher levels population-wide (Bouillon & Rosen, 2018).

International guidelines summary

While the IOM and Endocrine Society guidelines are the more widely accepted and debated, a few other serum vitamin D ranges have been adopted. Two countries, the United Kingdom and the Netherlands, use a lower serum cut point for sufficiency (30 nmol/L; 10

ng/mL)(Bouillon & Rosen, 2018). The Vitamin D Council has also put forth their recommendations, although to date no country has adopted these cut points. A summary of the various recommendations for serum 25(OH)D levels among countries and organizations can be seen in figure 3.

Figure 3. Recommendations for interpreting serum levels of 25(OH)D



Red denotes a state of severe deficiency (danger) that has to be corrected without exception.
Orange denotes a state of mild deficiency (modest concern), in which intervention is desirable.
Green denotes a state of sufficient supply that does not benefit from additional supplementation.

AAP, American Academy of Pediatrics; AGS, American Geriatrics Society; DACH, Deutschland (Germany), Austria and Confoederatio Helvetica (Switzerland); IOF, International Osteoporosis Foundation; IOM, Institute of Medicine; SACN, Scientific Advisory Committee on Nutrition.

Vitamin D Status in the US

Dietary intake

Vitamin D is a nutrient of interest in public health, as it has been identified as an underconsumed nutrient whose low intake levels have been associated with poor health outcomes ("A Closer Look at Current Intakes and Recommended Shifts - 2015-2020 Dietary Guidelines - health.gov," n.d.). The NHANES surveys tracks all four major dietary sources of vitamin D (i.e., naturally occurring, via enrichment or fortification, and supplemental) allowing

for the examination of population-level intakes, subgroup intakes, and changes in intake trends. The NHANES 2003 cycle was the first to employ two 24-hour dietary recalls with the standardized Food and Nutrient Database for Dietary Studies (FNDDS; version 2) (Ahluwalia, Dwyer et al., 2016). This allowed for the collection of dietary intake measures more representative of usual intakes. In NHANES 2003–2006, adults ≥19 years had a mean dietary vitamin D intake of 180 (4 SEM) IU/day, which increased to a mean intake of 324 (8 SEM) IU/day when supplemental sources were considered (Fulgoni et al., 2011). These data indicated that a vast majority of the adult population were not achieving the recommended EAR of 400 IU/day, placing them at risk for insufficiency and deficiency.

However, including supplemental sources of vitamin D into the mean intake of a group can bias the results. It is better practice to separate out vitamin D supplement users from non-users to achieve a more accurate representation of subgroup- or population-level intakes. In 2007, NHANES expanded their interviews to include more detailed dietary supplement use questions in regard to the past 30 days and included, for the first time, a 24-hour supplement recall (Ahluwalia et al., 2016). These changes allowed for nutrient intakes from diet and supplements to be more readily split out into subgroups. The trends for vitamin D intake among supplement users and non-users for NHANES 2007–2014 can be seen in table 3 (Food Surveys Research Group, U.S. Department of Health and Human Services, et al., 2015).

Table 3. Total Vitamin D intake from food, beverages, and supplements (IU/day (SE))

	Males (≥20 years)			Females (≥20 years)		
	Supplement users		Non-Users	Supplement users		Non-Users
	% (SE)			*% (SE)*		
2007–08	*23 (1.6)*	896 (189.2)	192 (10.4)	*33 (1.6)*	904 (55.6)	136 (6.0)
2009–10	*26 (1.4)*	1,284 (156.0)	224 (8.8)	*36 (1.6)*	1,292 (109.2)	172 (5.2)
2011–12	*27 (1.7)*	1,472 (164.8)	208 (8.0)	*35 (2.0)*	1,748 (150.4)	156 (6.0)
2013–14	*23 (1.6)*	1,416 (77.2)	200 (6.4)	*25 (1.4)*	1,904 (118.0)	152 (7.2)

NHANES 2007–2014; Data are from day 1 nutrient recall intakes only for both food and dietary supplements and may not fully represent usual intakes.

Among all supplement non-users, average vitamin D intakes from food and beverage sources were insufficient to achieve the 400 IU/day EAR, indicating more than half of non-users may be potentially at risk for inadequacy and deficiency. Among users, females had a higher prevalence of use than males. Yet, supplement users of both genders were more likely to meet or exceed daily EAR and RDA requirements.

These observations have been expanded upon in further analyses of NHANES data. In an analysis of vitamin D supplement use among 10,698 adults (≥19 years) from NHANES 2009–2012, no significant differences were seen in food-only vitamin D intake between supplement users and non-users in any age group, with intakes ranging from 186.4 to 204 IU/day across all groups (Blumberg et al., 2017c). Considering only vitamin D food intake data, this placed a potential 92.8% to 96.8% of the population below the EAR. When supplemental vitamin D intake was factored into the comparison between non-users and users, users had significantly higher intakes in the age 19–50 group (193.2 IU/day for non-users; 424 IU/day for users) and the age ≥71 group (202.4 IU/day for non-users; 828 IU/day for users), but not the age 51–70 group although absolute average intakes were higher with supplement use (193.2 IU/day for non-users; 724 IU/day for users). However, in each age group, supplement users were significantly more likely to be above the EAR. It should be noted that, even among users, 73.5% in the 19–50 age group, 53.3% in the 51–70 age group, and 44.4% in the ≥71 age group still had intakes below the EAR. These findings have been echoed in an analysis of NHANES 2007–2010 data of 11,857 adults ≥19 years, which showed a similar prevalence of supplement users in the aforementioned age groups (Moore, Radcliffe et al., 2014).

Blumberg et al. (2017a,b) also investigated the effect of socioeconomic differences, using the poverty income ratio (PIR) scale, and racial or ethnic differences on the use of dietary supplements and their effects on vitamin D intake in adults (≥19 years) (Blumberg, Frei et al., 2017a, 2017b). These analyses were based on data from the NHANES 2009–2012 cycles. Blumberg et al. employed the following three PIR groups for their study: PIR < 1.35 (poor), PIR 1.35–1.85 (nearly poor), and PIR > 1.85 (not poor) (Blumberg et al., 2017b). No significant

differences (P < .01) in food-only vitamin D intake between supplement users and non-users in any PIR group were seen, both for dietary intake and percentage of group members with intakes below the EAR. Considering only vitamin D food-intake data, a potential 92.6% to 97.9% of the population was below the EAR. When supplemental vitamin D intake was factored in, supplement users had significantly higher total intakes and were significantly more likely to have intakes above the EAR in all three PIR groups. However, the prevalence of intakes below the EAR remained high in the supplement user's groups: 77.1% in the "poor" group, 70.5% in the "nearly poor" group, and 57.6% in the "not poor" group. An analysis of NHANES 2007–2010 data produced similar findings for prevalence of supplement users consuming under the EAR: 75.2% in the "poor" group, 71.2% in the "nearly poor" group, and 59.9% in the "not poor" group (Moore et al., 2014). Vitamin D intakes by racial/ethnic groups from the NHANES 2007–2010 (Moore et al., 2014) and NHANES 2009–2012 (Blumberg et al., 2017a) analyses can be seen in table 4.

Table 4. Usual intake of vitamin D among adults by race/ethnicity (IU/day ± SE)

	NH-White		NH-Black		Hispanic		NH-Asian*	
	Food Only	Total Intake	Food Only	Total Intake	Food Only	Total Intake	Food Only	Total Intake
NHANES 2009–2012	204.4 (3.2)	648 (36)	158.8 (4.8)	371.2 (14.4)	187.2 (3.6)	340 (13.6)	188.4 (12.8)	600 (40)
NHANES 2007–2010	192 (4)	424 (16)	140 (4)	284 (12)	188 (8)	324 (12)		

**NHANES 2011–2012 only. The NH-Asian category was not included in NHANES until 2011.*
Total Intake consists of food + vitamin D supplement intake among supplement users.
Food Only consists of total vitamin D intake from food sources only in both users and non-users.
Non-Hispanic whites (NH-white), non-Hispanic Blacks (NH-black), Hispanics (Mexican Americans and other Hispanics), and non-Hispanic Asians (NH-Asian)

In the NHANES 2009–2012 analysis, vitamin D intake was significantly higher (P < .01) in all race/ethnicity supplement-user subgroups compared to non-users. Users in all racial/ethnic groups were significantly more likely to have reported intakes above the EAR compared to non-users. However, for intakes below the EAR within these race/ethnicity subgroups who used supplements, there were significant between-group differences present. Supplement-using NH-

whites had a 57.9% prevalence for vitamin D intake below the EAR, NH-blacks at 77.2% , Hispanics at 80.1% , and NH-Asians at 65.7% .

When examining the effects of vitamin D supplement use or non-use, a consistent association of improved total intake is seen in adult supplement users across age, gender, racial/ethnic groups, income levels, and when examining these demographics as a whole. However, use of supplemental vitamin D at current average intakes does not appear to be sufficient to ensure adequate intakes, as vitamin D supplement use was still associated with a significant portion of the examined populations consuming vitamin D levels below the EAR. These data suggest that not using a vitamin D supplement is associated with an even greater likelihood of having a vitamin D intake below the EAR, and thus may put non-users at higher risk of insufficiency or deficiency, comparatively.

Serum 25(OH)D levels

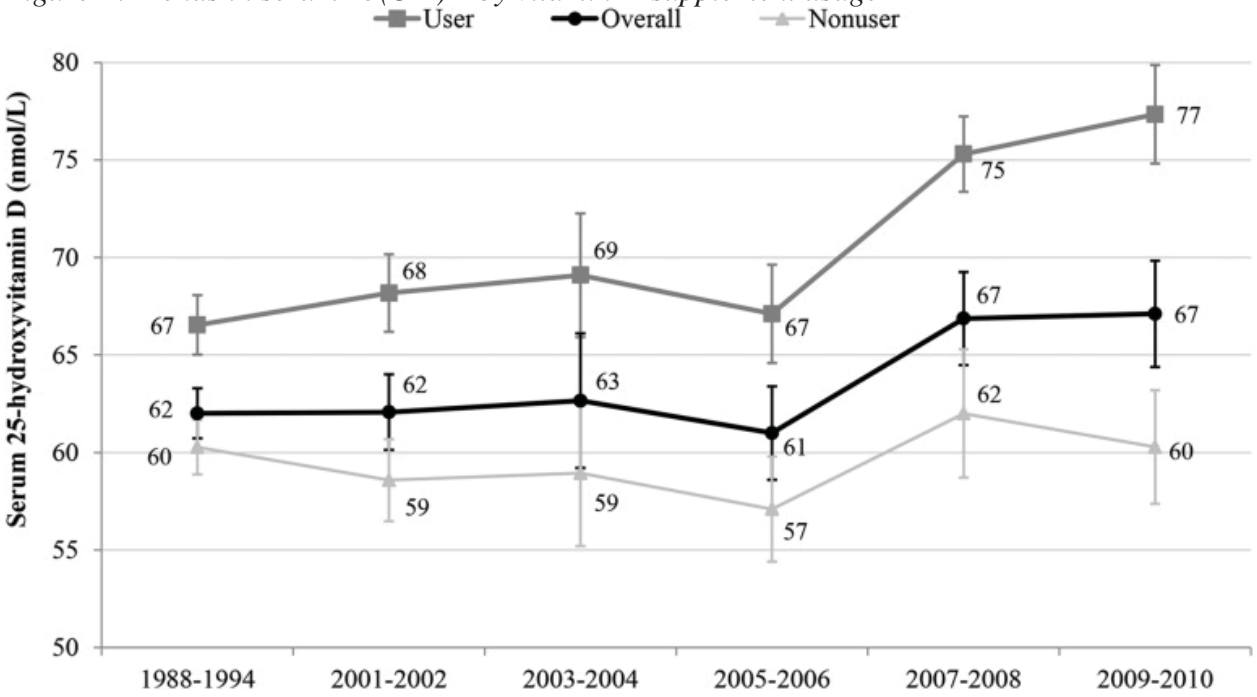
Prior to NHANES 2007, serum 25(OH)D concentrations were measured via radioimmunoassay kits susceptible to significant between- and within-assay variability (Carter, 2011; Sempos, Vesper et al., 2012). This variability was a confounding factor when attempting to pool results both within and across studies. Thus, a collaborative effort was led by the NIH Office of Dietary Supplements, the CDC National Center for Environmental Health (NCEH), the National Institute of Standards and Technology (NIST), and Ghent University to established the Vitamin D Standardization Program (VDSP), which set a gold-standard for 25(OH)D serum measurements (Sempos et al., 2012). NHANES 2007 and onward has complied with VDSP testing criteria, which employs a standardized liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for serum vitamin D measures ("NHANES - Analytical Note for 25-Hydroxyvitamin D Data Analysis," n.d.).

Serum 25(OH)D measures that were taken prior to NHANES 2007, specifically NHANES 1988–1994 and 2001–2006, were converted to LC-MS/MS-equivalents as to allow for more precise analyses of trends in 25(OH)D across NHANES cycles. The LC-MS/MS-equivalents were made possible by reanalyzing preserved serum samples from NHANES 1988–1994 and 2001–2006 to develop regression equations that could predict a LC-MS/MS equivalent

25(OH)D measure ("NHANES - Archived Vitamin D RIA-harmonized Data Files and Documentation," n.d.; Yetley, Pfeiffer et al., 2010). Analyses using these equivalent values have already seen significant changes in prevalence estimates for vitamin D deficiency and inadequacy compared to the original uncorrected serum measures (Cashman, Kiely et al., 2013). The adoption of the VDSP criteria has aided in improving the accuracy and precision of prevalence estimates for vitamin D status.

Using LC-MS/MS-equivalent values and direct LC-MS/MS measurements, a comprehensive analysis of NHANES data from 1988–2010 was performed to examine temporal trends in serum vitamin D status (Schleicher, Sternberg et al., 2016). Importantly, this analysis does not include data from NHANES 1995–2000, as no LC-MS/MS-equivalent values exist for these cycles. In total, serum 25(OH)D measures from 39,867 adults (≥20 years) were included in this analysis. When examining the NHANES 1988–2006 standardized data, overall mean serum 25(OH)D measures held at ~62 nmol/L for all groups which significantly ($P < .0001$) increased by ~8% in the NHANES 2007–2010 period. Note that this included both supplement and non-supplement users, which skewed the results. This ~8% increase may have been partly due to residual error rates seen in the LC-MS/MS-equivalent values and due to the growth seen in vitamin D supplement usage. Supplement users taking ≥600 IU/day increased threefold from 1988–1994 to 2007–2010 and users have also seen greater increases in average serum 25(OH)D increases compared to non-users over this same period as seen in figure 4. Over the entire 22-year period, significant serum 25(OH)D increases ($P < .0001$) were seen for those ≥40 years, females, NH-whites, and vitamin D supplement users. Additionally, NH-blacks also saw significant 25(OH)D increases ($P = .0443$). Encouragingly, no significant decreases were observed overall or for any age, gender, or racial/ethnic subgroup.

Figure 4. Trends in serum 25(OH)D by vitamin D supplement usage



Persons aged ≥12 y: NHANES 1988–2010. Values are weighted arithmetic means (95% CIs). Data were age-standardized by using the 2000 US Census as the standard population. NHANES 1988–2006 data represent predicted LC-MS/MS–equivalent concentrations; NHANES 2007–2010 data represent measured LC-MS/MS concentrations. The use of any vitamin D–containing supplements during the 30 days preceding the household interview was assessed and used to categorize participants as users or nonusers. Linear trend based on Wald F test. User, $P < 0.0001$; overall, $P < 0.0001$; nonuser, $P = 0.5615$.

When examining 25(OH)D at various cut points for the population at large, significant decreases have been seen in the prevalence of those with serum values <50 nmol/L ($P = .0315$) and <75 nmol/L ($P = .0002$), which complements the overall trend of population-level increases in 25(OH)D over this period (Schleicher, Sternberg et al., 2016). Of note is that there has been a significant increase in those with serum values >125 nmol/L ($P < .0001$), which may place some at risk of adverse events (Ross et al., 2011). This increase may be associated with the growing use of vitamin D supplements, as an estimated 1.95% to 1.99% of supplement users age 50 or older were consuming daily vitamin D intakes above the UL (Blumberg et al., 2017c). For non-users, <1% consumed above the UL daily, across all age groups (Blumberg et al., 2017c).

For serum 25(OH)D, 40 nmol/L is considered the EAR-type value and can be used as a proxy to assess vitamin D inadequacy prevalence, according to IOM cut points (Taylor, Carriquiry et al., 2013). Those with serum levels consistently at or below 40 nmol/L may be at risk for suboptimal bone health, including rickets and osteomalacia. Inadequacy estimates for age, gender, race/ethnicity, and supplement users for NHANES 1988–2010 can be seen in table 5. Over this period, serum levels <40 nmol/L significantly decreased in those ≥40 years, females, NH-whites, and vitamin D supplement users. Prevalence of serum values <40 nmol/L was very high in NH-blacks and moderately high in Hispanics and those who did not use vitamin D supplements. Overall, supplement non-users were more likely to have serum 25(OH)D levels <40 nmol/L.

Table 5. Prevalence (%) of serum 25(OH)D at various cutoffs (NHANES 1988–2010)[1]

	1988–94	2001–02	2003–04	2005–06	2007–08	2009–10	P[2]
25(OH)D cut points							
<30 nmol/L	6.0 (5.2-6.9)	5.4 (4.1-7.0)	7.5 (5.3-10)	5.2 (3.8-6.9)	6.4 (4.8-8.6)	6.7 (5.2-8.7)	.46
<40 nmol/L	16 (15-18)	17 (14-20)	17 (13-22)	18 (14-22)	14 (11-18)	15 (12-18)	.2
<50 nmol/L	30 (28-32)	29 (26-33)	30 (24-37)	32 (27-37)	26 (22-30)	26 (22-30)	.0315
<75 nmol/L	70 (68-73)	74 (70-77)	71 (66-76)	77 (73-80)	65 (62-68)	64 (60-68)	.0002
>125 nmol/L	.0 (.0-.1)	.9 (.6-1.3)	1.5 (.9-2.4)	.9 (.6-1.2)	2.4 (1.7-3.3)	2.6 (1.8-3.6)	<.001
<40 nmol/L[3]							
Age							
12–19	10 (8.9-12)	15 (11-20)	14 (10-19)	16 (12-22)	14 (9.7-20)	14 (10-18)	.34
20–39	15 (13-17)	17 (14-21)	18 (14-24)	18 (14-23)	17 (13-22)	18 (15-22)	.28
40–59	18 (16-20)	17 (14-20)	17 (12-23)	19 (15-25)	13 (10-16)	13 (10-17)	.013
≥60	19 (18-21)	18 (14-23)	15 (12-19)	17 (14-20)	13 (10-16)	13 (10-16)	<.001
Gender							

Male	11 (10-12)	14 (12-16)	14 (10-19)	16 (13-20)	12 (9.1-17)	13 (10-16)	.59
Female	21 (19-23)	20 (17-24)	20 (15-25)	20 (16-25)	16 (13-19)	17 (14-20)	.0108
Race/Ethnicity							
Hispanic	22 (19-26)	21 (17-26)	24 (18-32)	28 (20-37)	24 (17-32)	23 (19-27)	.53
NH-Black	51 (46-55)	60 (57-64)	53 (45-61)	56 (49-64)	52 (45-60)	46 (37-55)	.09
NH-White	10 (8.6-11)	9.4 (7.6-12)	9.1 (6.5-12)	9.4 (7.1-12)	6.2 (5.0-7.8)	6.6 (4.9-8.8)	.0007
Supplement use[4]							
No	19 (17-20)	23 (19-26)	22 (17-28)	24 (19-29)	19 (15-24)	20 (16-24)	.91
Yes	9.1 (7.7-11)	7.2 (5.6-9.2)	7.9 (5.6-11)	8.5 (6.3-12)	5.1 (3.7-7.0)	5.8 (4.3-7.7)	.003

1 Values are weighted proportions; % (95% CIs).

2 Linear trend based on the Wald F test.

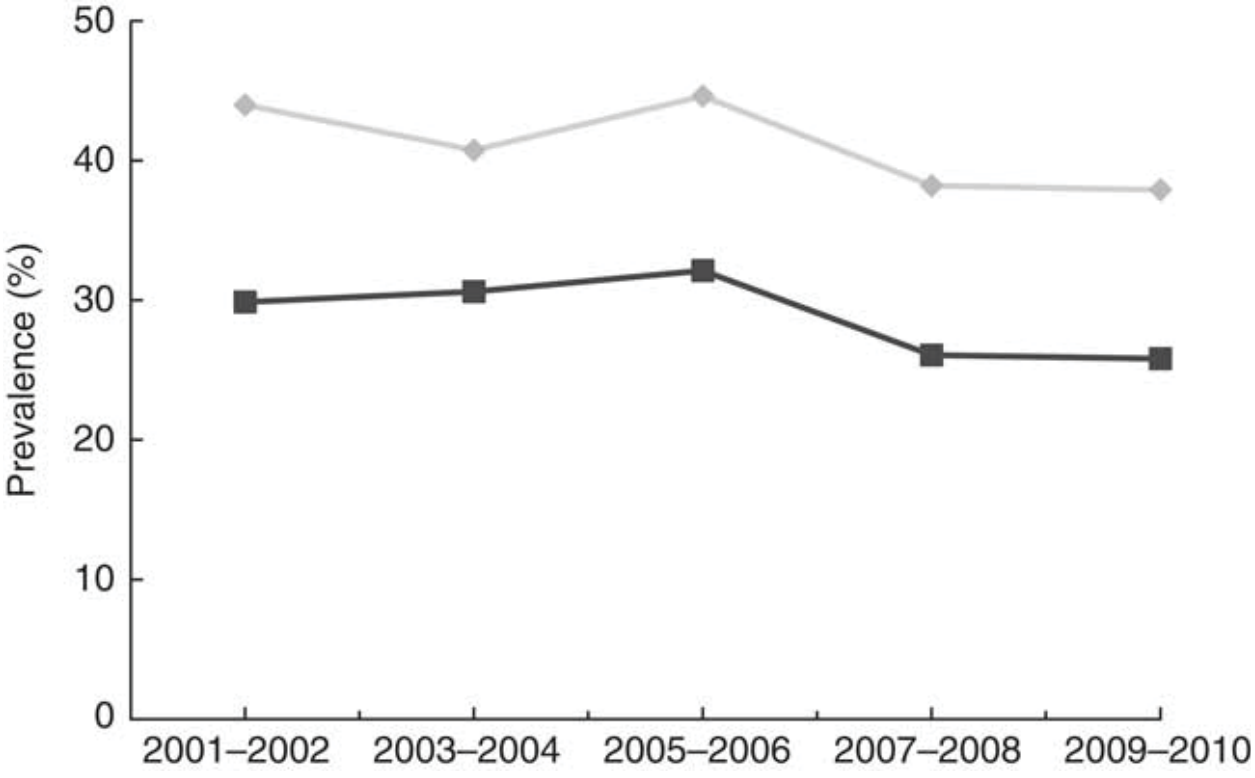
3 40 nmol/L is the cut point consistent with an intake equivalent to the EAR, which is useful for evaluating the possible adequacy of nutrient intakes of population groups.

4 The use of any vitamin D–containing supplements in the month preceding the household interview.

Of note is that, if the Endocrine Societie's cut point for insufficiency of ≤75 are used, ~65% of the population may be at risk for underconsuming vitamin D. A further analysis of NHANES 2001–2010 data with 26,010 adult participants (≥18 years) examined serum 25(OH)D status using the following Endocrine Society recommended cut points: deficiency at <50 nmol/L and insufficiency ranging from ≥50 to ≤75 nmol/L (Liu et al., 2018). Prevalence of deficiency was 28.9% (SE 1.01) and insufficiency was 41.4% (SE .63) — placing only ~29.7% of the population in a sufficient range. Neither deficiency or insufficiency prevalence estimates changed significantly over this period, although a downward trend was observed as seen in

figure 5 which coincided with the NHANES adoption of VDSP testing criteria (P = .18 deficiency linear trend; P = .15 insufficiency linear trend).

Figure 5. Trends in the prevalence of vitamin D deficiency and insufficiency among adults ≥18 years in NHANES 2001–2010



Deficiency (—■—); insufficiency (—◆—). Vitamin D deficiency was defined as 25(OH)D <50 nmol/L and vitamin D insufficiency was defined as 50≤ 25(OH)D <75 nmol/L.

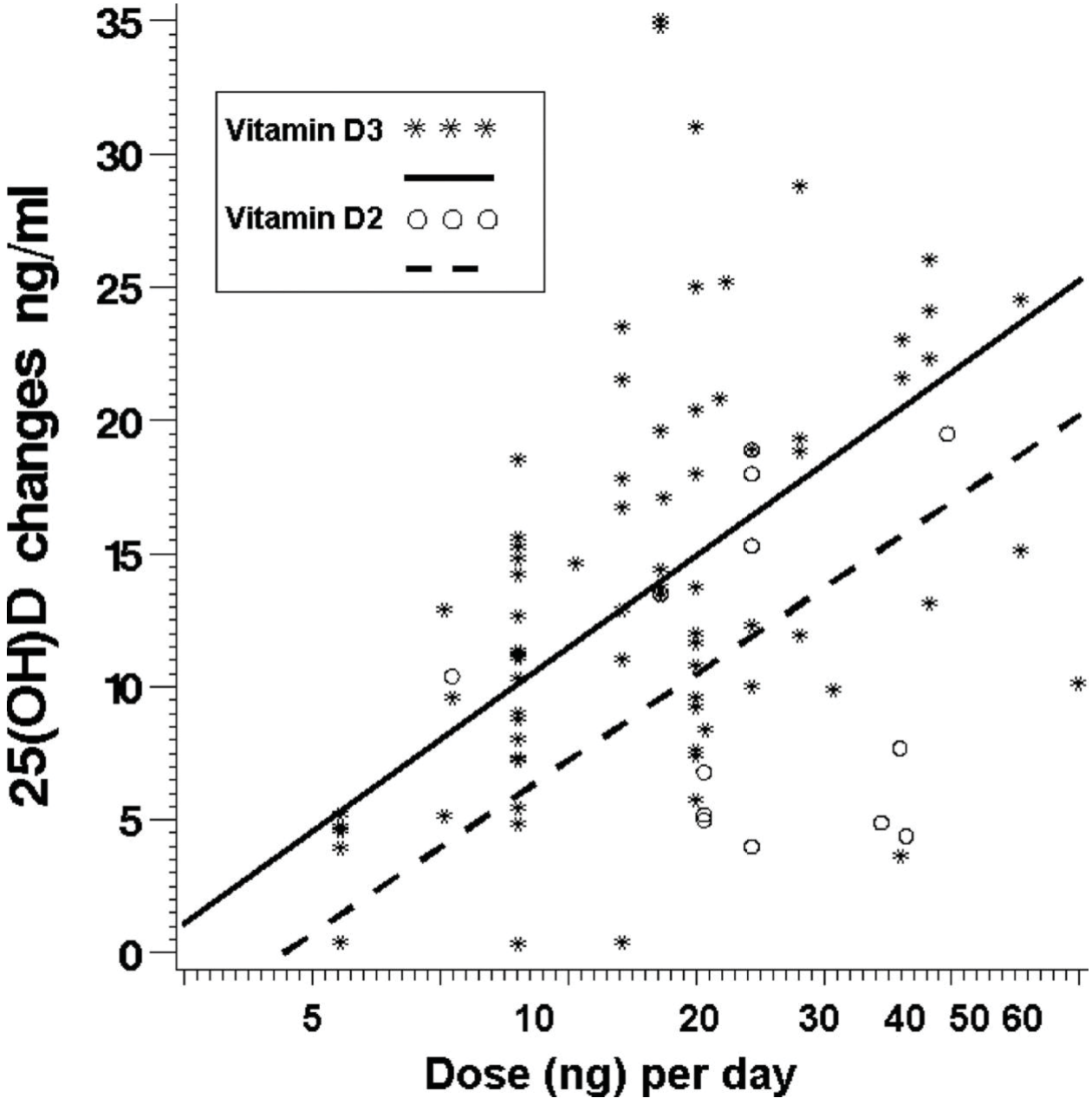
Modifiable Lifestyle Factors Affecting Vitamin D Status

Supplement use

In the US, observational data have consistently seen associations between achieving adequate serum vitamin D status and the use of supplemental vitamin D and more frequent consumption of vitamin D containing foods (Daraghmeh et al., 2016; Lips et al., 2014; Liu et al.,

2018; Schleicher, Sternberg, Looker et al., 2016; Tareen, Martins et al., 2005). These observational associations have been corroborated by clinical dose-response trials with supplemental vitamin D interventions, although the inter-individual response of serum 25(OH)D to a given vitamin D dose showed wide variation, as seen in figure 6 (Autier, Gandini et al., 2012). Body composition, race/ethnicity, type of vitamin D supplement used (D_2 or D_3), age, genetics (i.e., VDR and VDBP genotype), dietary fat intake, estrogen use, concurrent use of a calcium-containing supplement, certain diseases or medications, and baseline 25(OH)D measures can explain some of variation in serum responses to supplemental vitamin D (Mazahery & von Hurst, 2015; Zittermann, Ernst et al., 2014). Due to these variations, doses as high as 2,000 IU/day (assuming the vitamin D_3 form is used) might be needed in select cases, such as those with high amounts of body fat or with very low baseline serum levels, for individuals to meet IOM serum vitamin D targets (Weishaar & Rajan, 2015).

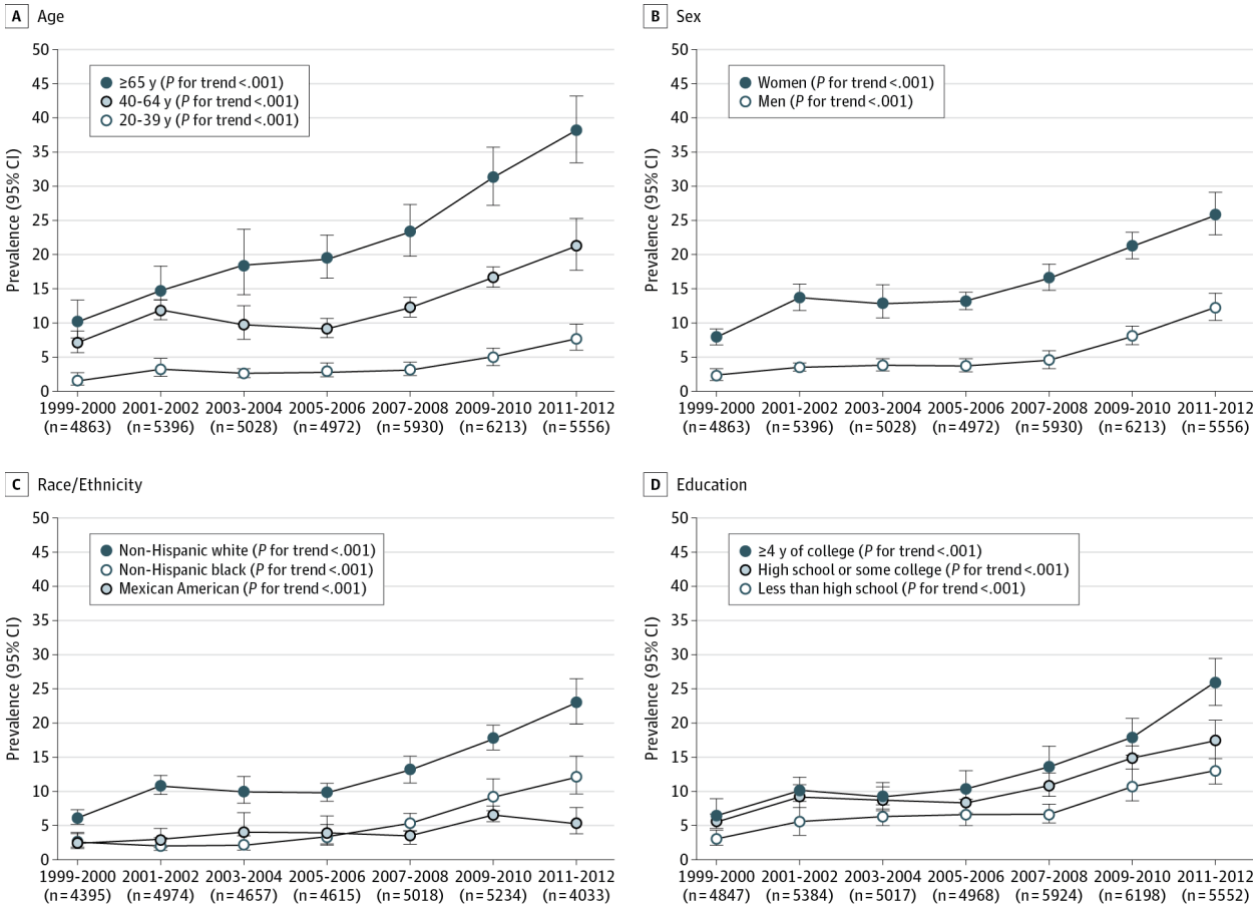
Figure 6. Summary estimates of change in serum 25(OH)D in 74 vitamin D supplement RCTs



It is worth noting the trends in use of vitamin D containing supplements, as they contribute to a significant portion of vitamin D intake among users as noted earlier. An

NHANES analysis of dietary supplement use among adults (≥20 years) from 1999–2012 showed an increase in vitamin D supplementation, excluding multivitamins/multiminerals (MVMMs; products with ≥10 vitamins and/or minerals) (Kantor, Rehm et al., 2016). From an initial 5.1% in NHANES 1999–2000, use grew to 19% by NHANES 2011–2012 (P-trend <.001). This indicates use of vitamin D specific supplements has increased over time. These data by age, gender, race/ethnicity, and education level can be seen in figure 7.

Figure 7. Trends in Use of Vitamin D, Excluding MVMMs, Among US Adults



MVMM (multivitamin/multimineral); data are weighted to be nationally representative; adults are defined as those aged ≥20 years.

Interestingly, MVMM use stayed largely flat from 1999–2012, increasing from 37% to 40% (P-trend = .14). Total vitamin D use, including MVMMs, did not increase in the 20–39 age group (30% use) or 40–64 age group (41% use) from 1999–2012, but the 65+ age group experienced a significant increase, from 42% to 61% (P-trend <.001). Similarly, while use among all adult males stayed flat at ~32.5% over this time period, female vitamin D use increased from 40% to 47% (P-trend = .02).

Among adult vitamin D supplement users (≥19 years), supplementation may account for 54.43% to 75.70% of total vitamin D intake (Blumberg et al., 2017c). Supplement use significantly increases vitamin D intake and significantly decreases the odds of consuming vitamin D at levels below the EAR compared to non-users (Blumberg et al., 2017c). These associations are consistently seen across various subgroups, including age, gender, racial/ethnic, and income levels (Blumberg et al., 2017a, 2017b, 2017c; Moore et al., 2014). Many observational studies have seen inadequate vitamin D intakes in US adults when dietary intake comes from foods alone (Blumberg et al., 2017b; Fulgoni et al., 2011; Moore et al., 2014). Thus, supplemental vitamin D may be a useful tool in improving serum vitamin D status. However, as vitamin D is a fat-soluble vitamin, it can be absorbed and stored above physiological needs. As such, some caution is warranted. Excessive intake may lead to hypercalcemia, a calcification of soft tissues (Tebben, Singh et al., 2016). Those using vitamin D supplements have a significant but small absolute increased prevalence of consuming daily doses above the UL. For non-users, <1% exceed the UL while 1.95–1.99% of users may exceed the UL, depending on age group (Blumberg et al., 2017c). Additionally, mutations in CYP24A1, which encodes the 1,25$(OH)_2$D degrading enzyme 24-hydroxylase, can cause the inability to metabolize vitamin D into inert compounds. This mutation can lead to vitamin D toxicity at intake levels as low as 500 IU/day (Schlingmann, Kaufmann et al., 2011).

Diet

In addition to supplementation, dietary patterns may also be altered to improve vitamin D intake from food sources. A NHANES 2003–2006 analysis indicated vitamin D consumption from fortified or enriched foods provided a larger portion of dietary vitamin D than from

naturally occurring food sources (Fulgoni et al., 2011). When examining intakes from those aged ≥2, food products with added vitamin D accounted for 59.2% of intake from all food sources. Total mean intake from natural sources was 80 IU/day while foods with added vitamin D provided a mean intake of 116 IU/day, providing a 196 IU/day total intake from all food sources on average. Major food and food group contributors to vitamin D intake are milk, fish and shellfish, eggs, ready-to-eat cereals, and fruit juices as seen in table 6 (O'Neil, Keast et al., 2012).

Table 6. Food sources of vitamin D among US adults

	All adults (19+)		19–50 years		51+ years	
Food group	Ranking	% Total	Ranking	% Total	Ranking	% Total
Milk	1	45.1	1	45.8	1	43.9
Fish and shellfish	2	14.4	2	12.9	2	16.8
Eggs	3	5.4	4	5.1	3	6
Ready-to-eat cereal	4	5.4	3	5.3	4	5.6
Fruit juice	5	3.6	7	3.6	5	3.6
Pork, ham, bacon	6	3.6	6	3.7	6	3.4
Milk drinks	7	3.1	5	3.7	10	2.2
Frankfurters, sausages, lunch meats	8	3.1	9	3.2	7	3
Cheese	9	2.9	8	3.4	9	2.2
Margarine and butter	10	2.2	11	1.9	8	2.7
Meal replacements/supplements	11	2	10	2.2	11	1.6

Data are Day 1 intakes by adults aged 19+ years from NHANES 2003–2006 (n = 18,980)

Source: O'Neil, C. E., Keast, D. R., Fulgoni, V. L., & Nicklas, T. A. (2012). Food sources of energy and nutrients among adults in the US: NHANES 2003–2006. Nutrients, 4(12), 2097–2120.

Milk and fish have consistently remained in first and second place for food-source contributors of vitamin D over the past two decades, with some variability in placement seen between eggs, ready-to-eat cereals, and fruit juices (O'Neil et al., 2012). Of note is that milk and milk-based product consumption has increased by 9% between 1970 and 2014, from 255.8 kg (563.9 lb.) per person per year to 278.7 kg (614.3 lb.) (Bentley & Others, 2017). However, while overall dairy-product consumption increased over this period, fluid milk consumption decreased by 35% from 118.1 liters (31.2 gallons) per person per year to 76.1 liters (20.1 gallons) over this

same time period. By these estimates, Americans were consuming 1.5 cup-equivalents of milk and milk products per day in 2014, half of the recommended 3 servings advised by the 2015 Dietary Guidelines for Americans (DGA) based on a 2,000 calorie/day diet for adults ("2015-2020 Dietary Guidelines - health.gov," n.d.). Analysis of NHANES 2007–2010 data have indicated that among all US adults, between 88.8% and 99.6% are not meeting total daily dairy intake recommendations which may partially contribute to inadequate vitamin D intake (Quann, Fulgoni et al., 2015).

Diet modeling studies have examined various simulations of what would happen to vitamin D intake under conditions of improved adherence to the DGA recommendations. Using 2-day dietary recall data from NHANES 2007–2010, one model examined the prevalence of adults who would have vitamin D intakes below the EAR if recommended dairy intake targets were met (Quann et al., 2015). Under these assumptions, no significant improvements were seen in the prevalence of vitamin D intake below the EAR. The greatest improvement was seen in males aged 71 or older, who saw an absolute prevalence reduction of 2.6%. A second modeling study examined what would happen to daily vitamin D intake if one or one-half serving of dairy were added to the Healthy Mediterranean-Style Eating Pattern (HMEP) recommended in the 2015 DGA. Three scenarios were run at the 1,600, 2,000, and 2,400 kcal per day levels. Model 1 added one serving of dairy, model 2 added one serving of dairy and removed one serving of refined grains, and model 3 added one half serving of dairy and removed one half serving of refined grains. Model 3 was only run for the 2,400 kcal HMEP scenario. The results, as seen in table 7, do yield an improvement in overall daily vitamin D intake under these scenarios. It should be noted that even under these idealized conditions, with the assumption of excellent adherence to the HMEP and increased dairy intake, the model results only see vitamin D intake exceeding the EAR at the 2,400 kcal level for model 1 and 2.

Table 7. Impact of modifying dairy servings of the HMEP on vitamin D intake (IU/day)

	Baseline	Model 1	*% Change*	Model 2	*% Change*	Model 3	*% Change*
1,600 kcal	273	333	*21.7*	332	*21.32*	—	—
2,000 kcal	300	359	*19.8*	359	*19.45*	—	—
2,400 kcal	361	420	*16.4*	419	*16.1*	390	*8.03*

HMEP; Healthy Mediterranean-Style Eating Pattern

The high prevalence of inadequate dietary vitamin D intake observed in NHANES data, as well as the results from dietary pattern modeling studies, indicate that while dietary patterns can be modified to improve vitamin D intake from food sources such modifications may be insufficient to reach EAR or RDA targets for many populations.

Sun exposure

A potential primary source of vitamin D is through dermal synthesis via exposure to UVB rays. The skin has a large vitamin D producing capacity (Holick, 2006). This capacity is often quantified in terms of circulating vitamin D levels given a certain erythemal dose. A minimal erythema dose (MED) is the "smallest UV dose that produces perceptible redness of the skin (erythema) with clearly defined borders at 16 to 24 hours after UV exposure" ("CFR-code of federal regulations title 21," 2017). The MED for a given individual will be greatly influenced by skin pigmentation. Exposure to 0.75 MEDs, thrice weekly, may be sufficient for keeping blood levels of 25(OH)D >40 nmol/L (Holick, Chen et al., 2007). A sub-erythemal UV exposure is preferred in order to keep the risk of developing skin cancer low.

UVB-induced endogenous vitamin D production can be influenced by a multitude of factors: age, amount of sun-exposed skin, certain medications, clothing type, elevation, latitude, living environment (e.g., urban, suburban, or rural), air pollution, skin pigmentation and pigment genes, solar zenith angle, sun exposure duration and frequency, sunscreen use, time of year, and weather conditions can all mediate dermal vitamin D synthesis (Calbó, 2005; Datta et al., 2019; Grosick & Tanner, 2004; Wacker & Holick, 2013). Of particular interest has been the effects of sunscreen use on vitamin D status. As some sunscreen agents can block UVB rays, it was suspected they may also reduce the amount of endogenously produced vitamin D. In tightly controlled lab experiments, sunscreen was shown to cause a decrease in skin vitamin D production that may contribute to inadequate serum 25(OH)D levels (Faurschou, Beyer et al., 2012; Grigalavicius, Iani et al., 2016). However, these lab experiments were conducted under conditions assuming optimal sunscreen use, with the correct application amount and type of sunscreen tested (i.e., broad-spectrum with an appropriate sun protection factor (SPF)) and a

consistent exposure to UV rays. When prospectively studied in free-living populations, sunscreen use was found to be frequently not optimal and thus decreases in vitamin D production were not as readily observed (Libon, Courtois et al., 2017; Petersen & Wulf, 2014).

Due to the risks of developing skin cancer, it is not advisable to forgo sunscreen in order to increase vitamin D levels or to rely on sun exposure as a main source of vitamin D (Schalka, Steiner et al., 2014). While only accounting for 5% of UV rays reaching Earth's surface, UVB rays are the main cause of sunburn and DNA damage, both of which increase skin cancer risk (Kennedy, Bajdik et al., 2003). This risk is mediated by skin pigmentation, and those with Fitzpatrick skin types 1–3 are at an increased lifetime risk of developing skin cancer compared to those with Fitzpatrick skin types 4–6 ("Figure 16.2 SEER Incidence and US Death Rates, Melanoma of the Skin, Both Sexes," n.d.). The Fitzpatrick scale descriptions can be seen in table 8 and are correlated with melanin pigmentation amount in the skin (Webb, 2006).

Table 8. Fitzpatrick Skin Phototypes

Phototype	Sunburn and tanning history	Immediate pigment darkening	Delayed tanning
I	Burns easily, never tans	None	None
II	Burns easily, tans minimally with difficulty	Weak	Minimal to weak
III	Burns moderately, tans moderately and uniformly	Definite	Low
IV	Burns minimally, tans moderately and easily	Moderate	Moderate
V	Rarely burns, tans profusely	Intense (brown)	Strong, intense brown
VI	Never burns, tans profusely	Intense (dark brown)	Strong, intense brown

Adapted from Fitzpatrick's Dermatology in General Medicine. McGraw-Hill Education; 8th edition.

At present, recommendations for unprotected skin sun exposure range from 5 to 15 minutes to the hands, face, and arms two to three times a week between the hours of 10 am and 3 pm ("WHO | The known health effects of UV," 2017a). These recommendations are thought to be sufficient for most people to keep serum vitamin D levels above the deficient range (<30 nmol/L; <12 ng/mL) (Ross et al., 2011; Shih, Farrar et al., 2018; "WHO | The known health effects of UV," 2017). However, these are general recommendations that can be modulated by

proximity to the equator, where less exposure time may be needed due to higher UV levels, time of day, season, weather conditions, and skin pigmentation.

Attempts have been made to quantify the minimum sun exposure requirement needed to meet vitamin D targets year-round. In one study, a model was built based on real-world UVR climatology data and UVR intervention studies in Caucasian adults (Fitzpatrick type I or II) (Webb, Kazantzidis et al., 2018b). The model assumed outdoor sun exposure during the hours of 12–2 pm nearly every day, no sunscreen use, not under shade, that arms and lower legs would be exposed during June–August, that hands and face were exposed during September–May, and at UK latitudes (between 49°N and 59°N). The theoretical exposure time projected was 9 minutes from March–September and 13 minutes from June–August for optimizing vitamin D production while minimizing cancer risk. These projections do not apply to those with greater skin pigmentation, particularly skin types V and VI, as vitamin D photosynthesis is reduced in these skin types due to their UVB-absorbing properties (Xiang, Lucas et al., 2015). Following the same methodology, a second study from the same research group was conducted using data from UVR intervention studies in adults with Fitzpatrick skin type V. It found that these skin types may need 25–40 minutes of sun exposure to prevent deficiency (Webb, Kazantzidis et al., 2018a).

Sun exposure can be a potent intervention to aid in sustaining adequate serum 25(OH)D levels. However, caution should be taken to prevent adverse effects of excessive UV exposure. Sun exposure that results in skin erythema or sunburns should be avoided to reduce the risk of skin cancer. Unprotected and direct sun exposure to the face, arms, and hands for 10–15 minutes a day up to thrice weekly has been given as a broad recommendation to prevent vitamin D deficiency. Yet, with many moderating factors influencing endogenous production, broad sun exposure recommendations may better be tailored on the regional level while also considering age, season, and skin type. Lastly, as dietary vitamin D does not increase skin cancer risk and higher serum levels have been associated with some skin cancer protective effects (Caini, Boniol et al., 2014), interventions around increasing dietary intakes are preferred.

Body weight

Adipose tissue acts as a major storage site for vitamin D, with approximately 75% of vitamin D_3 and 34% of 25(OH)D being stored in subcutaneous and visceral adipose tissues (Heaney, Horst et al., 2009; Mawer, Backhouse et al., 1972; Rosenstreich, Rich et al., 1971). Circulating 25(OH)D levels have been shown to have a negative linear association with adipose tissue volume, with decreasing adiposity resulting in increased circulating 25(OH)D (Gangloff, Bergeron et al., 2015; Rafiq & Jeppesen, 2018). This relationship has been seen across different populations in observational studies and has been demonstrated in clinical trials (Gangloff et al., 2015; Pereira-Santos, Costa et al., 2015; Saneei, Salehi-Abargouei et al., 2013; Vimaleswaran, Berry et al., 2013; Zittermann et al., 2014). As such, a higher prevalence of vitamin D deficiency is seen in those classified as obese (BMI ≥30 kg/m^2) compared to those classified as normal weight (BMI 18.5–24.9 kg/m^2) (Pereira-Santos et al., 2015). This association also holds when examining waist circumference, with higher measures of circumference being correlated with lower serum 25(OH)D (Cheng, Millen et al., 2014; Santos, Amaral et al., 2017; Vogt, Baumert et al., 2017).

Volumetric dilution and sequestration have both been proposed as potential mechanisms as to why increased adiposity leads to decreases in serum 25(OH)D (Drincic, Armas et al., 2012; Wortsman, Matsuoka et al., 2000). Volumetric dilution posits that, due to the greater volume of adipose tissue available in those with overweight or obesity, greater amounts of vitamin D become deposited in these tissues which causes less vitamin D to be available in serum (Drincic et al., 2012). Sequestration refers to the concept that, once absorbed into adipose tissue, vitamin D may become unavailable for further metabolism due to the lack of regular adipose tissue breakdown in the overweight or obese, essentially "trapping" vitamin D in the adipocyte (Wortsman et al., 2000).

It has been questioned whether low serum 25(OH)D reflects a true state of insufficiency in those who are overweight or obese. Measures of unbound free 25(OH)D have been studied to help determine if they may better reflect vitamin D activity or sufficiency in those with high BMIs. In one cross-sectional observational study of 223 normal-to-obese men and women, total 25(OH)D, free 25(OH)D, and 1,25$(OH)_2$D were all significantly lower in obese participants

(Walsh, Evans et al., 2016). This difference was not explained by DBP or DBP genotype, as they did not significantly differ between BMI groups. Furthermore, in a 12-week randomized double-blinded clinical trial in young obese or normal-weight adults saw similar changes between groups in free 25(OH)D after supplementing with 2,000 IU of D_3 daily (Holmlund-Suila, Pekkinen et al., 2016). These differences were also not explained by DBP. No consistent association between BMI and DBP has been seen in the literature (Bolland, Grey et al., 2007; Karlsson, Osmancevic et al., 2014; Winters, Chennubhatla et al., 2009). Given the high correlation between free and total 25(OH)D concentrations and lack of a consistent association between BMI and DBP, measuring free 25(OH)D may not yield any additional clinically relevant information on vitamin D status in the obese above that provided by measures of total serum 25(OH)D.

As adiposity reduction in the overweight or obese is a significant driver of increasing circulating 25(OH)D levels, such reductions in adipose tissue may help to ensure adequate serum 25(OH)D. However, long-term weight maintenance after a period of weight loss has proven challenging, with many regaining all or a portion of initially lost weight (Anderson, Konz et al., 2001; Loveman, Frampton et al., 2011). Supplementation with vitamin D may also aid in bringing serum 25(OH)D levels into the adequate range, but obese and overweight individuals may require higher doses of vitamin D compared to those classified as normal weight (Zittermann et al., 2014). Zitterman et al., (2014) conducted a systematic review and meta-analysis of 94 vitamin D supplementation trials, combining data from these trials to estimate the average intake needed to reach a target of 50 nmol/L or 75 nmol/L based on body weight and age as seen in table 9. Depending on baseline serum 25(OH)D concentrations, target 25(OH)D concentration, and age the required daily vitamin D dose can be double in those with obesity compared to normal weight individuals.

Table 9. Calculated daily vitamin D_3 dose for achieving adequate serum 25(OH)D levels

	30-year-old person	70-year-old person
Baseline 25(OH)D 25 nmol/l; target 50 nmol/L		
50 kg body weight	360 IU (9 mcg)	200 IU (5 mcg)
75 kg body weight	540 IU (13.5 mcg)	308 IU (7.7 mcg)
100 kg body weight	720 IU (18 mcg)	400 IU (10 mcg)
Baseline 25(OH)D 25 nmol/l; target 75 nmol/L		
50 kg body weight	1,680 IU (42 mcg)	960 IU (24 mcg)
75 kg body weight	2,520 IU (63 mcg)	1,460 IU (36.5 mcg)
100 kg body weight	3,360 IU (84 mcg)	1,960 IU (49 mcg)

IU; international unit

Physical activity

A number of studies have documented associations between Vitamin D levels, physical fitness activities, and exercise capacity (Afzal, Bojesen et al., 2013; Al-Othman, Al-Musharaf et al., 2012; Grimaldi, Parker et al., 2013; Klenk, Rapp et al., 2015; Romme, Rutten et al., 2013; Valtueña, González-Gross et al., 2013). In general, higher volumes of physical activity correlate with having adequate serum vitamin D levels which may be explained, in part, by increased sun exposure via outdoor activities (Grandner, Kripke et al., 2006; Willett, 2013). Exercise type and energy expenditure may also influence serum 25(OH)D. Undertaking regular vigorous activities (gardening, cycling, etc.) have been associated with modestly higher serum vitamin D levels (~5 nmol/L higher) compared to those who undertake low (walking, standing, etc.) or no vigorous exercise (Brock, Cant et al., 2007; Orces, 2018; van den Heuvel, van Schoor et al., 2013; Wanner, Richard et al., 2015).

Part of the association between physical activity and higher serum vitamin D levels may be attributed to when physical activities are undertaken outdoors — therefore increasing sun exposure. However, in studies examining indoor versus outdoor physical activity time, the

results have been inconsistent. Some have noted no significant difference (van den Heuvel et al., 2013) while other have seen small differences (Al-Othman et al., 2012; Scragg & Camargo, 2008). These differences may be attributed to disparate observational study designs, as there is no uniform method of determining what qualifies as an outdoor activity. Additionally, sun protection methods employed, time of day of the outdoor activity, and duration were not evenly assessed between studies, limiting the ability to make comparisons.

The relationship between physical activity and vitamin D is a synergistic one. As physical activity may aid in maintaining adequate serum vitamin D levels, vitamin D can aid in repairing muscle tissue. Data from observational studies have seen a consistent association between low serum vitamin D levels and poor muscle function outcomes, particularly in the elderly (Bischoff-Ferrari, Dietrich et al., 2004; von Hurst, Conlon et al., 2013; Wicherts, van Schoor et al., 2007). Evidence from human muscle cell lines (Garcia, Ferrini et al., 2013; Garcia, King et al., 2011), rat models (Stratos, Li et al., 2013), and human *in vitro* and *in vivo* studies have shown a consistent ability of vitamin D to improve the migration speed and distance covered of cells involved in the muscle repair process (Barker, Schneider et al., 2013; Owens, Sharples et al., 2015).

The vitamin D-physical activity relationship is of particular importance for the elderly and institutionalized, who are at increased risk of vitamin D insufficiency and often have low levels of physical activity. Insufficient vitamin D in the elderly is predictive of physical performance decline and skeletal muscle atrophy, particularly of type 2 muscle fibers (Girgis, Clifton-Bligh et al., 2013; E. Sohl, van Schoor et al., 2013; Wicherts et al., 2007). Additionally, age-related decreases in levels of skeletal muscle VDRs can compound the negative effects of low serum vitamin D levels (Bischoff, Borchers et al., 2000). However, supplementation with vitamin D in this population can help to increase muscle fiber density and upregulate skeletal muscle VDRs (Ceglia, Niramitmahapanya et al., 2013). Vitamin D mediated improvements in skeletal muscle mass, repair, and function may aid in the reduction of falls in the elderly. Current evidence indicates that an 800–1,000 IU/day dose may reduce falls if baseline serum 25(OH)D levels are ≤40 nmol/L (Bischoff-Ferrari, Dawson-Hughes et al., 2009; Wu & Pang, 2017). Yet, the specific role of vitamin D in the prevention of falls is presently debated.

Alcohol consumption

High chronic, but not acute, alcohol intake has been shown to influence vitamin D metabolism. Among those who consume high levels of alcohol chronically, serum 25(OH)D levels may fall in the adequate range, as reported in some studies (Barragry, Long et al., 1979; Laitinen, Lamberg-Allardt et al., 1991), although most report inadequate levels in this population (Bjørneboe, Johnsen et al., 1987; Bjørneboe, Johnsen et al., 1986; Feitelberg, Epstein et al., 1987; Pepersack, Fuss et al., 1992; Peris, Parés et al., 1994; Santori, Ceccanti et al., 2008). Additionally, 1,25$(OH)_2$D serum levels appear depressed in studies of those with high chronic alcohol intakes (Bjørneboe, Bjørneboe et al., 1988; Lindholm, Steiniche et al., 1991; Verbanck, Verbanck et al., 1976) but not all (Laitinen et al., 1991).

The cases of observed lower serum vitamin D levels in this population are multifactorial. As with healthy individuals, inadequate dietary intake of vitamin D, as well as low sun exposure, may be compounded by the effects of alcohol on vitamin D metabolism. Data from animal models indicate possible malabsorption in some chronic alcohol users and an increase of 25(OH)D biliary excretion, which may also contribute to vitamin D insufficiency (Gascon-Barré & Joly, 1981). It should be noted that, in some human trials, normal vitamin D intestinal absorption has been observed in alcoholics (Barragry et al., 1979; Lundy, Sørensen et al., 2009).

Elucidating the specific contributions of alcohol intake to serum vitamin D levels remains challenging due to the myriad of other comorbidities associated with chronic alcohol use and from other general factors known to influence vitamin D status (e.g., dietary intake, supplement use, sun exposure, age, etc.). A particular issue arises in the inconsistencies in assessing alcohol intake over time, particularly in epidemiological studies, which use disparate cut points to define intake categories. Furthermore, the definition of levels of alcohol intake (i.e., low, moderate, high) differs between countries, making comparisons challenging (Jugdaohsingh, O'Connell et al., 2006). Drinking patterns over time, age, and genetic differences affecting the metabolism of alcohol are further potential confounders (Edenberg, 2007).

Serum vitamin D status in alcoholism is likely to be predominantly affected by overall vitamin D intake, endogenous production capacity, and frequency and amount of alcohol

consumption. Those categorized as “non-functioning” alcoholics may be at higher risk for insufficiency due to poor nutrition, liver dysfunction, and potentially decreased sun exposure (Gascon-Barré, 1985). Other than the cessation of high chronic alcohol intakes, supplementation with vitamin D may aid in preserving serum vitamin D status in those who consume high levels of alcohol.

Smoking habits

Significant associations have consistently been seen between current smokers and low serum levels of 25(OH)D and 1,25$(OH)_2$D (Brot, Rye Jørgensen et al., 1999; Cutillas-Marco, Fuertes-Prosper et al., 2012; Kassi, Stavropoulos et al., 2015; McKibben, Zhao et al., 2016; Melamed, Michos et al., 2008; Sebekova, Krivosikova et al., 2016; Shinkov, Borissova et al., 2015; Skaaby, Husemoen et al., 2016; Evelien Sohl, Heymans et al., 2014; Supervía, Nogués et al., 2006; Tønnesen, Hovind et al., 2016). A negative correlation has been observed between decreasing serum vitamin D levels and an increasing number of cigarettes smoked per day, duration of smoking, and a higher number of cigarette packs smoked per year (Jiang, Chan et al., 2016). Maternal exposure to smoking, via first or second-hand exposure, during pregnancy may reduce vitamin D levels in both mothers and infants (Banihosseini, Baheiraei et al., 2013; Díaz-Gómez, Mendoza et al., 2007; Khuri-Bulos, Lang et al., 2013; Lawlor, Wills et al., 2013). Furthermore, current smokers with deficient levels of vitamin D might experience a more rapid decline in lung function over time, if smoking is not ceased (Lange, Sparrow et al., 2012; Larose, Brumpton et al., 2015). Earlier observational studies may have been limited by the use of some 25(OH)D assays which may have overestimated 25(OH)D levels in smokers (Grimnes, Almaas et al., 2010). However, more recent studies obtaining 25(OH)D levels using LC-MS/MS have corroborated the association between smoking and increased odds of low serum vitamin D (Kassi et al., 2015).

Smoking has also been associated with lower levels of parathyroid hormone (PTH), which is involved in the regulation and activation of vitamin D (Brot et al., 1999; Cutillas-Marco et al., 2012; Supervía et al., 2006). Dysfunction caused in the vitamin D-PTH axis, via smoking, may contribute to lower serum vitamin D levels. More frequent smoking has also been

associated with decreased dietary intake of vitamin D, which may further contribute to low serum levels (Morabia, Bernstein et al., 2000). Additionally, smoking may impair the cutaneous production of vitamin D as well via premature aging of the skin.

Many of the limitations seen in epidemiological studies of alcohol consumption and serum vitamin D status also arise in epidemiological studies examining smoking and vitamin D status. Chiefly, the definitions pertaining to the extent of smoking is variable. Grouping respondents into current, never, and former or ex-smokers is one of the more commonly used categorizations, but no standardized definitions have been set for these. Definitions of "never" smoked have ranged from 0 to <100 cigarettes over the course of a participant's lifetime. The definition for "former" smokes is variable as well, with anywhere from 1 month to 5 years of smoking cessation being used as cutoff points for inclusion. The category of "current" smoker is also ill-defined, as those in this category may be infrequent smokers (e.g., 1 cigarette a day) to heavy users (e.g., 1 pack or more a day). Such variability limits the ability to compare studies and to determine the nature of the relationship between smoking habits and serum vitamin D status.

Serum cotinine levels may be used as a more objective assessment of the smoking status of an individual. Cotinine is the major metabolite of nicotine and possesses a half-life of approximately 20 hours (Ahijevych, Tyndale et al., 2002). Interestingly, when cotinine levels were used to assess the influence of smoking on serum 25(OH)D in individuals aged 10-18 years who participated in the Korean National Health and Nutrition Examination Survey (n=2,515), no significant difference in serum vitamin D was observed between current and non-smokers (Byun, Heo et al., 2017). However, an analysis of NHANES 2001–2006 data (n=22,196) found inconsistent associations between cotinine and serum vitamin D by gender and race/ethnicity (Manavi, Alston-Mills et al., 2015). Given the variable nature of these study results, the use and utility of cotinine as a factor to be quantified in vitamin D status research is still yet to be determined.

The precise mechanisms by which smoking may decrease serum vitamin D levels are still a matter of scientific debate (Mousavi, Amini et al., 2019). As cigarette smoke is comprised of numerous compounds, including tar, nicotine, and various heavy metals, it is difficult to

determine if one or many of these compounds, or behaviors correlated with smoking, are resulting in lower serum vitamin D. However, smoking cessation may contribute to improved serum vitamin D status.

Sleep habits

The National Sleep Foundation recommends that adults between the ages of 18–64 get 7 to 9 hours of sleep per night and those >64 get 7 to 8 hours per night (Hirshkowitz, Whiton et al., 2015). Present estimates from NHANES 2005–2012 indicate that 36.82% of US adult get ≤6 hours of sleep on an average weeknight night (Cepeda, Stang et al., 2016). Among observational studies examining the sleep-vitamin D connection, many have identified a correlation between insufficient serum vitamin D levels and inadequate sleep duration, poor quality sleep, increased time to fall asleep, and a higher risk for sleep disorders (Beydoun et al., 2014; Doo, 2018; Gong, Li et al., 2018; Grandner, Jackson et al., 2014; Pazarli, Ekiz et al., 2018; Shiue, 2013). What role vitamin D may play in sleep regulation is possibly due to the influence of vitamin D in certain regions of the brain. Tracer studies in various animal models, using radiolabeled $1,25(OH)_2D_3$, have shown high concentrations of VDRs in parts of the hypothalamus and brainstem known to be involved in sleep regulation (Musiol, Stumpf et al., 1992; Stumpf, Bidmon et al., 1992; Stumpf & O'Brien, 1987). However, precise mechanisms underlying this association are still unclear.

A 2018 systematic review and meta-analysis by Gao et al. explored the connections between vitamin D deficiency and sleep disorder risk (Gao, Kou et al., 2018). Nine studies with a total of 9,397 participants were included. Six were cross-sectional, two were case-control, and one was a prospective cohort. The most commonly used serum 25(OH)D cutoff values among these studies were <50 nmol/L, although <75 and <25 nmol/L were used in a few. In total, those with vitamin D deficiency were at significantly increased risk of sleep disorders (OR: 1.50, 95% CI: 1.31–1.72) compared to those with adequate serum vitamin D. Subgroup analyses indicated that those with serum 25(OH)D levels ≤50 nmol/L were at the highest risk (OR: 1.59, 95% CI: 1.31–1.94). When poor sleep quality, short sleep duration, and sleepiness were analyzed as 3 separate outcomes, all were significantly associated with vitamin D insufficiency.

A second 2018 meta-analysis by Neighbors et al. examined the relationship between 25(OH)D levels and patients with obstructive sleep apnea (OSA) (Neighbors, Noller et al., 2018). The analysis included 14 retrospective case-control studies with 4,937 patients; 1,513 controls and 3,424 OSA patients. Subgroups were those with mild, moderate, or severe OSA. OSA severity was inversely related to 25(OH)D status compared to controls. The mean difference in serum 25(OH)D compared to controls was −2.7% for mild, −10.1% for moderate, and −17.4% for severe OSA.

To date, only one RCT has been conducted with a primary outcome of investigating vitamin D supplementation for its effects on sleep disorders. Majid et al. conducted a double-blind randomized clinical trial on 89 people with sleep disorders who received 50,000 IU of vitamin D every two weeks for eight weeks or placebo (Majid, Ahmad et al., 2018). The intervention saw significant improvements in sleep score, latency, duration, efficiency, disturbances, and quality at the study's end.

For some sleep disorders, the causal direction may be more that low vitamin D leads to poorer sleep but, due to the present literature gaps, it is possible that poor sleep may be also be contributing to lower vitamin D levels in some capacity. Further studies will be needed to elucidate the nature of this relationship.

Both insufficient serum vitamin D and unhealthy sleep have been associated with an increased risk of developing adverse health outcomes, including early death, diabetes, cardiovascular disease, stroke, coronary heart disease, obesity, and hypertension among others (Itani, Jike et al., 2017; Jike, Itani et al., 2018; Theodoratou et al., 2014). Attaining adequate vitamin D status on a population level could serve a complementary function by potentially improving sleep quality, which in turn may aid to decrease the health and economic burden associated with inadequate vitamin D and sleep.

Summary

From reviewing the literature, there have been a substantial number of studies previously conducted which examined the nature of relationships between a single or a few modifiable lifestyle factors and their possible effects on serum vitamin D status. Data from these studies are

suggestive of potentially causal associations between many of these factors and vitamin D insufficiency. However, the presence of studies in the literature attempting to quantify how the intersection of these individual lifestyle factors may predict vitamin D status when examined comprehensively is currently lacking. Given the importance of vitamin D in overall health and the high number of adults with insufficient dietary intake and serum levels, understanding which factors are more predictive in determining vitamin D status may focus the efforts of future studies and potentially yield actionable information to at-risk populations. The study conducted for this thesis will attempt to fill a portion of this gap in the literature.

RESEARCH METHODS

Research Question

The primary research question is: Do modifiable lifestyle factors predict vitamin D status in adults? Such factors that may exert influence on vitamin D status include diet, dietary supplement use, physical activity levels, body composition, sleep duration, smoking habits, alcohol consumption, and sun exposure.

H_o: The modifiable lifestyle variables do not predict vitamin D status.

H_a: The modifiable lifestyle variables do predict vitamin D status.

Research Design

This is a retrospective initial analysis using cross-sectional public-use data from the NHANES 2013–2014 cycle. NHANES is an annual survey, released in 2-year cycles, conducted by the Centers for Disease Control and Prevention (CDC) in the US. The primary stated objective of the NHANES survey is to produce a "broad range of descriptive health and nutrition statistics … of the U.S. population [that] can then be used to measure and monitor the health and nutritional status of the civilian noninstitutionalized population" (Johnson, Dohrmann et al., 2014).

To test our question, a binary multiple logistic regression was performed to assess which modifiable lifestyle factors could aid in predicting vitamin D status. This type of regression is an appropriate analysis for this dataset as the dependent variable is dichotomous (sufficient vs insufficient serum vitamin D) and the independent variables are continuous or categorical (Pituch & Stevens, 2015).

Methodology

Population

The study subsample was taken from an initial sample of 14,332 NHANES participants representative of civilians in the US over the period of 2013–2014. The sample excludes

civilians residing in nursing homes, those in the armed forces, institutionalized persons, or U.S. nationals living abroad ("NHANES: Survey Design," n.d.).

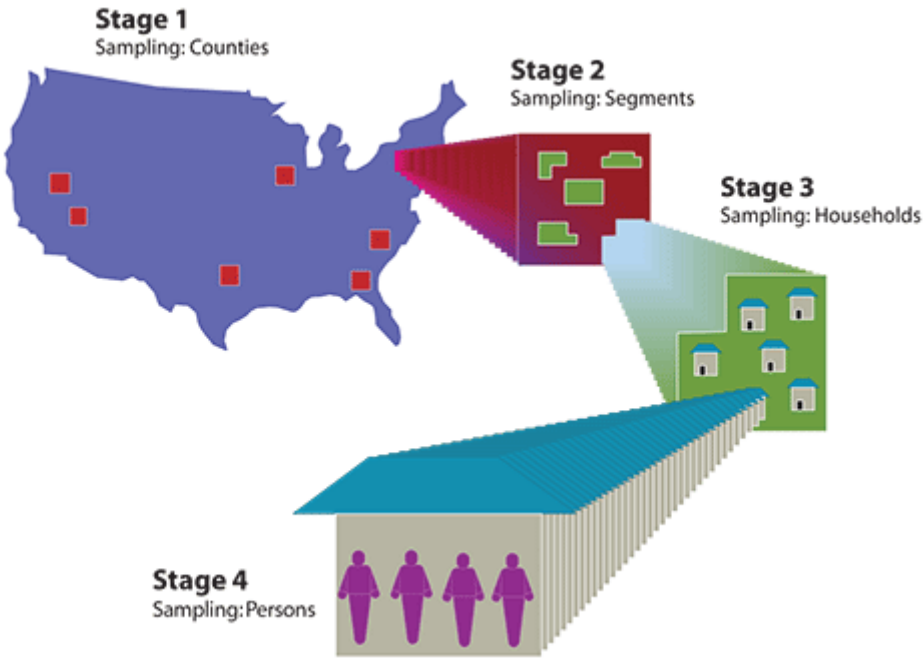
Sampling

Comprehensive sample design procedures for NHANES have been previously published (Johnson et al., 2014). Briefly, NHANES obtains data, not from a simple random sample, but from a complex, multistage, probability sampling design. This is used to collect a sample representative of the US civilian population. The sampling procedure consists of four main stages, as shown in figure 8.

- Stage 1: Primary sampling units (PSUs) are selected from an initial pool of all US counties.
- Stage 2: A sample comprised of single census blocks or combinations of them are taken. Samples are designed to be of approximately equal sizes.
- Stage 3: This stage collects a sample of dwelling units or households. A subsample of these units is taken to produce a national, approximately equal probability sample of households.
- Stage 4: A subsample of eligible individuals within the dwelling units or households are selected to participate in the NHANES survey.

Oversampling was carried out in the 2013–2014 cycle to increase the precision of estimates of select population domains, including Hispanic, non-Hispanic black, Asian, those at or below 130% of the federal poverty level, and for white and other persons 80 years old and above (Johnson et al., 2014).

Figure 8. Overview of NHANES sampling design



Source: US, Centers for Disease Control and Prevention, National Center for Health Statistics. (2018, October 19). NHANES - Survey Participants. Retrieved November 13, 2018, from https://www.cdc.gov/nchs/nhanes/participant/participant-selected.htm

Of 14,332 participants initially screened for the NHANES 2013–2014 cycle, 10,175 completed the interview and 9,813 were physically examined ("NHANES response rates and population totals," 2013). Of those, 3,679 participants met this study's inclusion criteria. Our inclusion criteria were as follows:

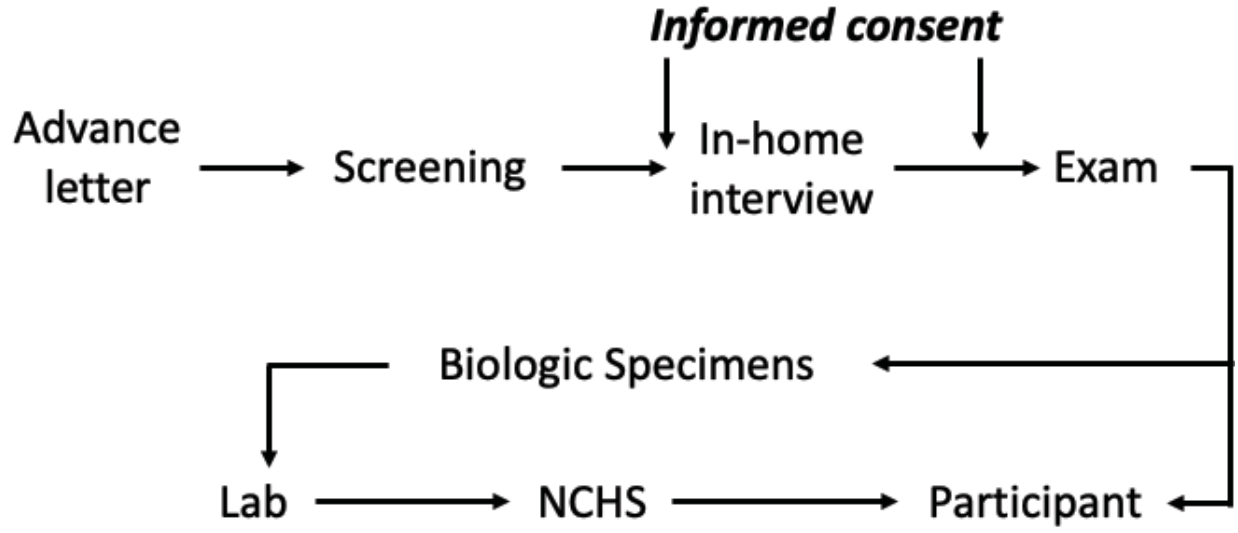
- Valid serum 25(OH)D measure
- Aged 20 years or older
- Day 1 24-hour dietary recall is reliable and met minimum criteria
- Day 2 24-hour dietary recall is reliable and met minimum criteria
- Day 1 and 2 24-hour dietary recalls both completed
- Household interviewed and Mobile Examination Center (MEC) examined
- Not currently pregnant
- No health conditions that may interfere with vitamin D absorption or metabolism (e.g., kidney/liver/intestinal diseases, celiac disease, IBD, Crohn's, etc.)

- Not currently taking medications that may interfere with vitamin D absorption or metabolism (e.g., systemic steroid users, anticonvulsants, corticosteroids, PTH, PTHrP, thyroid hormone, etc.)

Data Collection

Detailed procedures for NHANES data collection have been previously published and are briefly described herein ("NHANES Questionnaires, Datasets, and Related Documentation," n.d.). An overview of the data collection process can be seen in figure 9. The NHANES survey is comprised of two major data collection components: a questionnaire component and an examination component. The questionnaire component includes a household interview and an interview at the MEC. The household interview collects data on participant eligibility, relationships of household members, information about health insurance coverage, housing characteristics, food security status, and family income. Additionally, individual-level data is collected for eligible participants for demographics, socioeconomic status, dietary behaviors, and health and medical history. The second interview is conducted at the MEC in a private setting. This questionnaire covers more sensitive topics such as sexual health and habits and alcohol and drug use.

Figure 9. NHANES information flow



Source: Porter, K. S. (2015, August 24). National Health and Nutrition Examination Survey (NHANES) (US, Centers for Disease Control and Prevention, National Center for Health Statistics). Retrieved November 13, 2018, from https://www.cdc.gov/nchs/ppt/nchs2015/Porter_Monday_SalonE_A6.pdf

During the examination component physical and laboratory measures are taken. Physical measures can include body anthropometry measures, grip strength tests, taste and smell evaluations, and dual-energy x-ray absorptiometry scans. Post-MEC data collection activities may include a second 24-hour dietary recall interview and a 24-hour urine collection. Biological specimens are also collected at the MEC for analysis to provide information about the health status of the participant (blood, urine, and mucosal swabs). Such measures include tests of kidney function, cholesterol levels, screening for STDs, blood glucose, and tests of nutrition status (e.g., copper, selenium, zinc, vitamin B12, and vitamin D).

Important to our study is the method of serum vitamin D measurement. As discussed previously, serum 25(OH)D concentrations prior to NHANES 2007 were measured via assay kits susceptible to significant between- and within-assay variability (Carter, 2011; Sempos et al., 2012). After 2006, all NHANES cycles complied with VDSP testing criteria, employing an LC-MS/MS method for serum vitamin D measures ("NHANES - Analytical Note for 25-Hydroxyvitamin D Data Analysis," n.d.). The 25(OH)D measures in the present study were quantified via ultra-high performance liquid chromatography-tandem mass spectrometry

(UHPLC-MS/MS). Full 25(OH)D laboratory testing procedures have been documented elsewhere (Encisco S, 2010).

Funding and Ethical Procedures

The NHANES survey is primarily funded by the US Centers for Disease Control and Prevention and from various collaborative institutes and centers within the US National Institutes of Health. No funding was used for this thesis. Approval for NHANES 2013–2014 was granted by the National Health and Nutrition Examination Survey Research Ethics Review Board (continuation of Protocol #2011-17) ("NHANES - NCHS Research Ethics Review Board Approval," 2017). As this study is a secondary analysis of public access anonymized observational data that comply with US federal data use restriction policies ("CDC - Assurances of Confidentiality," 2018; Lim, Ha et al., 2019), no further ethical approval was required.

Data Analysis

Data Analysis Plan

Preliminary analysis

Variables of interest were selected from the NHANES 2013–2014 cycle. These data were cleaned and re-coded in accordance with NHANES guidelines ("NHANES - Clean & Recode Data," n.d.). For example, questions where the participant answered "Don't know" or refused were re-coded as missing, the continuous serum 25(OH)D measure was dichotomized into insufficient and sufficient vitamin D status, and questions regarding physical activity were combined to form a continuous MET (metabolic equivalent) hours per week variable.

All analyses were performed using IBM SPSS Statistics version 25 with the R Project for Statistical Computing 3.3.3 plugin extension. Recommended sample size requirements were ascertained using the methodology defined in the NHANES analytic guidelines (Johnson, Paulose-Ram et al., 2013). Collinearity diagnostics (tolerance and variance inflation factor values) were used to identify the presence of multicollinearity. As deemed necessary, multiple imputations were performed using the Markov Chain Monte Carlo simulation method after assessment of the missing data mechanism. For all tests, $P < .05$ was considered significant.

A residuals check was performed to identify observations poorly fit by the model. Outliers were assessed via standardized residuals examining variables with standard deviations ±2.5. Influential cases were assessed via Cook's distance values. As needed, cases identified as outliers or highly influential were removed from the final analysis.

Finally, the Box-Tidwell procedure was performed to determine if the continuous independent variables were linearly related to the logit of the dependent variable. As needed, data transformations were performed on continuous independent variables that violated this assumption.

Final analysis

A binary multiple logistic regression was performed to assess which modifiable lifestyle factors could aid in predicting vitamin D status. Two dependent variables were selected for separate testing in this analysis. The primary analysis used the more widely accepted serum vitamin D cut points proposed by the IOM (Ross et al., 2011). However, there is debate over which serum vitamin D levels reflect an optimal range for health. Thus, a secondary analysis was conducted using the serum vitamin D cut points proposed by the Endocrine Society (Holick et al., 2011). The dependent variable was the only factor that differed between models. Values for the dependent variables were as follows:

- Primary Analysis: Serum vitamin D (IOM vitamin D cut points)
    - Vitamin D deficient or insufficient (<50.0 nmol/L)
    - Vitamin D sufficient (≥50.0 nmol/L)
- Secondary Analysis: Serum vitamin D levels (Endocrine Society vitamin D cut points)
    - Vitamin D deficient or insufficient (≤75.0 nmol/L)
    - Vitamin D sufficient (>75.0 nmol/L)

Independent variables were selected based on their documented potential influence on serum vitamin D levels, quality of the variable data collection method, because they are modifiable lifestyle factors, and because they had sufficient response rates.

- Alcohol consumption
    - Average number of alcoholic drinks/day over past 12 months on the days the participant drank
    - How frequently the participant had 4/5 drinks per day over the past 12 months
    - How often the participant drank alcohol over past 12 months (average drinks per week)
- Diet
    - Average energy intake (kcal)

    - Average fat intake (g)
    - Self-assessed overall health of their diet
    - Frequency of milk consumption in the past 30 days
    - How regularly the participant uses any type of milk at least 5 times a week
    - Total daily vitamin D (D2 + D3) (mcg) intake
    - Takes vitamin D containing supplement?
    - Total daily calcium (mg) intake
    - Takes calcium-containing supplement?
- Physical activity and body composition
    - Body Mass Index (kg/m^2)
    - Waist circumference (cm)
    - Combined hand grip strength (kg)
    - Self-Assessed general health condition
    - Average physical activity in MET-hours per week
    - Average minutes of sedentary activity per day
- Sleep habits
    - How many hours of sleep the participant usually gets at night on weekdays or workdays
- Smoking habits
    - Smoked at least 100 cigarettes in their lifetime?
- Sun exposure
    - Minutes outdoors 9am–5pm, weekly average
    - Stay in the shade?
    - Sunscreen use?
    - Wear a long-sleeved shirt on sunny days?

Control variable's were selected due to their documented potential influence on serum vitamin D levels and/or because they are non-modifiable lifestyle factors.

- Age in years at screening
- Annual household income
- Compare food consumed to usual (for 24-hour recall)
- Education level
- Gender
- Household food security
- Race/Ethnicity
- The time period of vitamin D blood draw (summer and spring versus fall and winter)

One of the questions asked during the 24-hr recalls is whether the amount of food consumed was usual, much more than usual, or much less than usual. This is not strictly a "non-modifiable" factor, but still needs to be controlled for as it may affect reported dietary vitamin D intake.

The day of the week (weekend vs weekday) in which a dietary recall is taken may bias the results of this study, as eating patterns can substantially differ between these periods. The proportion of 24-hour dietary recall responses on a weekend versus a weekday were adjusted for in the dietary two-day sample weight, which is used in this analysis. A complete list of each variables operational definition and how it was measured or scored can be seen in Appendix B.

The use of recommended sampling weights and sample design variables was used to account for the complex sampling design of the NHANES survey. The masked variance unit pseudo-stratum variable (SDMVSTRA) was used to account for design effects of stratification. The masked variance unit pseudo-PSU variable (SDMVPSU) was used to account for the design effects of clustering. The dietary two-day sample weight (WTDR2D) was used as dietary data taken from participants completing both 24-hour dietary recalls was used in the analysis.

Due to the large body of preexisting knowledge of factors that influence vitamin D status, and due to the documented concerns with regression models employing stepwise algorithms delivering potentially biased results (Harrell, 2015), the order of independent variable entry

into the model was determined using justification from the current literature and the response rate for the variable. After entering all control variables into the model, the independent variables were entered in the following hierarchical sequence.

1. Total vitamin D (D2 + D3) (mcg) intake
2. Takes vitamin D containing supplement?
3. Frequency of milk consumption in the past 30 days
4. How regularly the participant uses any type of milk at least 5 times a week
5. Average fat intake (g)
6. Average energy intake (kcal)
7. Minutes outdoors 9am–5pm, weekly average
8. Stay in the shade?
9. Sunscreen use?
10. Wear a long-sleeved shirt on sunny days?
11. Waist circumference (cm)
12. Body Mass Index (kg/m^2)
13. Total calcium (mg) intake
14. Takes calcium-containing supplement?
15. Smoked at least 100 cigarettes in their lifetime?
16. Average number of alcoholic drinks/day over past 12 months on the days the participant drank
17. How frequently the participant had 4/5 drinks per day over the past 12 months
18. How often the participant drank alcohol over past 12 months (average drinks per week)
19. Average physical activity in MET-hours per week
20. Average minutes of sedentary activity per day
21. How many hours of sleep the participant usually gets at night on weekdays or workdays
22. Self-assessed health of the diet
23. Self-assessed general health condition
24. Combined hand grip strength (kg)

Each independent variable was entered into the model one at a time. At each step, if the calculated right-tailed probability of the chi-squared distribution values was significant, indicating the model was significantly improved by the addition of a given variable, it was included in the model. Otherwise, it was removed. Model evaluations reported tests of model effects (df, Wald Chi-Square, significance, Bonferroni significance), variance (Nagelkerke, Cox & Snell), parameter estimates (B, SE, Exp(B) with 95% CI), classification, and the receiver operating characteristic curve (ROC) with Youden's Index (J). Lastly, this thesis followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology—Nutritional Epidemiology (STROBE-nut) guidelines, which are intended to improve reporting for nutritional epidemiology and dietary assessment research (Lachat, Hawwash et al., 2016).

RESULTS

Preliminary Data Management

In total, 3,679 participants met this study's inclusion criteria from those included in the NHANES 2013–2014 cycle, providing a weighted sample of 188,368,464 participants. Descriptive statistics of the subsample are presented in table 10.

Table 10. Descriptive Statistics of Included Participants, Weighted and Unweighted

	Weighted	%	Unweighted	%
Age *(n=3,679)*				
Mean (SD)	45.61 (17.08)		47.22 (17.64)	
Gender				
Male	98,073,403.10	52.1	1,842	50.1
Female	90,295,061.89	47.9	1,837	49.9
Total	188,368,464.99	100.0	3,679	100.0
Race/Ethnicity				
Mexican American	19,736,000.53	10.5	529	14.4
Other Hispanic	10,106,182.97	5.4	317	8.6
Non-Hispanic Black	21,853,943.38	11.6	761	20.7
Non-Hispanic Asian	10,442,041.88	5.5	385	10.5

Other Race - Including Multi-Racial	5,974,468.91	3.2	117	3.2
Non-Hispanic White	120,255,827.33	63.8	1,570	42.7
Total	188,368,464.99	100.0	3,679	100.0
Education level				
1st–8th grade	7,540,616.11	4.0	230	6.3
9–11th grade & 12th w/ no diploma	19,055,251.62	10.1	487	13.2
HS graduate/GED or equivalent	40,084,345.14	21.3	856	23.3
Some college or AA degree	61,658,546.00	32.8	1,139	31.0
College graduate or above	59,906,900.77	31.8	964	26.2
Total	188,245,659.64	100.0	3,676	100.0
Annual household income				
$0 to $4,999	2,455,702.79	1.4	64	1.9
$5,000 to $9,999	4,988,646.73	2.8	132	3.9
$10,000 to $14,999	7,543,408.15	4.3	197	5.9
$15,000 to $19,999	8,427,446.84	4.8	205	6.1
$20,000 to $24,999	13,130,669.72	7.5	288	8.6
$25,000 to $34,999	15,896,581.95	9.1	410	12.2
$35,000 to $44,999	17,884,077.83	10.2	346	10.3
$45,000 to $54,999	14,726,651.43	8.4	291	8.7
$55,000 to $64,999	11,599,005.57	6.6	215	6.4
$65,000 to $74,999	8,814,001.35	5.0	160	4.8
$75,000 to $99,999	19,499,593.95	11.1	330	9.8
$100,000 and Over	50,537,969.65	28.8	726	21.6
Total	175,503,755.96	100.0	3,364	100.0
Season of vitamin D blood draw				
November 1 through April 30	85,791,664.60	45.5	1,818	49.4
May 1 through October 31	102,576,800.39	54.5	1,861	50.6
Total	188,368,464.99	100.0	3,679	100.0
Amount of food consumed (24-hr recall)				
Much more than usual	2,698,296.72	1.4	58	1.6
A little more than usual	21,785,970.81	11.6	404	11.0
Usual	119,493,322.43	63.7	2,247	61.4
A little less than usual	36,670,055.23	19.5	777	21.2

Much less than usual	7,074,055.65	3.8	174	4.8
Total	187,721,700.85	100.0	3,660	100.0
Household food security category				
HH full food security	143,430,724.23	76.8	2,593	71.1
HH marginal food security	15,839,954.81	8.5	373	10.2
HH low food security	16,682,124.44	8.9	417	11.4
HH very low food security	10,835,940.85	5.8	264	7.2
Total	186,788,744.33	100.0	3,647	100.0
Serum 25(OH)D (IOM cut points)				
Vitamin D insufficient (<50 nmol/L)	46,486,336.85	24.7	1,130	30.7
Vitamin D sufficient (≥50 nmol/L)	141,882,128.14	75.3	2,549	69.3
Total	188,368,464.99	100.0	3,679	100.0
Serum 25(OH)D (Endocrine Society cut points)				
Vitamin D insufficient (≤75 nmol/L)	123,747,072.47	65.7	2,590	70.4
Vitamin D sufficient (>75 nmol/L)	64,621,392.52	34.3	1,089	29.6
Total	188,368,464.99	100.0	3,679	100.0

The subsample exceeded the minimum sample size requirements recommended by the NHANES analytic guidelines (Johnson et al., 2013). The design effects were comprised of 15 strata, 30 primary sampling units, and 15 sampling design degrees of freedom. The reference group in the dependent variable for both analyses were those with sufficient levels of serum vitamin D.

The linearity of continuous variables with regard to the logit of the dependent variable was assessed via the Box-Tidwell procedure. All continuous independent variables were linearly related to the logit of the dependent variable for both the primary IOM and secondary Endocrine Society analysis. Additionally, there was no evidence of collinearity (all tolerance values >.650; all VIFs <1.6) and no influential cases were identified via Cook's distance (all <1). Outliers were assessed via standardized residuals examining variables with standard deviations ±2.50. There were 48 cases in the IOM analysis and 54 in the Endocrine Society analysis with standardized residual values exceeding ±2.50 standard deviations. Upon reanalysis after removing these cases,

both models were significantly improved (P < .001) and these cases remained excluded from the final models. No imputation methods were used for any variable.

Results

IOM Analysis

Of the 24 independent variables tested, six significantly improved the overall IOM model as seen in table 11. In total, 2,605 valid cases were included in the final regression model (model 1) yielding a weighted subsample size of 125,768,999.45. The unweighted subsample is above the minimum sample size requirements recommended by the NHANES analytic guidelines (Johnson et al., 2013). The regression model was statistically significant (P <.001) and remained significant when a Bonferroni correction was applied (P <.001). The model explained 31.07% (Cox & Snell R^2) to 44.65% (Nagelkerke R^2) of the variance in the dependent variable. The overall accuracy in classification was 79.68%, sensitivity was 50.26%, specificity was 91.24%, the positive predictive value was 69.26%, and the negative predictive value was 82.36%.

Table 11. IOM Analysis Model Results

Source	df	Wald Chi-Square	Sig.	Bonferroni Sig.
(Corrected Model)	15.00	3,066.505	<.001	<.001
(Intercept)	1.00	11.122	<.001	<.001
Control variables				
Age	1.00	9.481	.002	.002
Gender	1.00	.278	.598	.598
Race/Ethnicity	5.00	166.490	<.001	<.001
Education level	4.00	1.301	.861	1.000
Annual household income	11.00	75.905	<.001	.051
Season of vitamin D blood draw	1.00	15.927	<.001	<.001
Amount of food consumed (24-hr recall)	4.00	6.976	.137	.162
Household food security category	3.00	3.353	.340	.281

Independent variables				
Vitamin D (D2 + D3) intake (mcg)	1.00	25.648	<.001	<.001
Vitamin D dietary supplement use	1.00	16.294	<.001	<.001
Regular milk use 5 times per week?	2.00	3.007	.222	.385
Sunscreen use	4.00	1.726	.786	.974
Waist Circumference (cm)	1.00	42.204	<.001	<.001
Minutes sedentary activity per day	1.00	2.231	.135	.135

The area under the ROC curve (AU-ROC) for predicted vitamin D insufficient values was .826 (.803–.848 95% CI), which is an excellent level of discrimination (Royston & Altman, 2010). Discrimination in the ROC curve is the ability of the regression model to discern between participants with and without insufficient levels of serum vitamin D. The AUC discrimination classification scale by Hosmer et al. proposed the following cut points (Hosmer, Lemeshow et al., 2013).

- ≤ .5 - No discrimination
- <.5 – < .7 - Poor discrimination
- .7 – < .8 - Acceptable discrimination
- .8 – < .9 - Excellent discrimination
- ≥ .9 - Outstanding discrimination

The optimal cut point threshold for Youden's Index was .49. The Youden Index is a test of overall diagnostic effectiveness and is a reflection of the intention to maximize the rate of correct classification (Perkins & Schisterman, 2005; Youden, 1950).

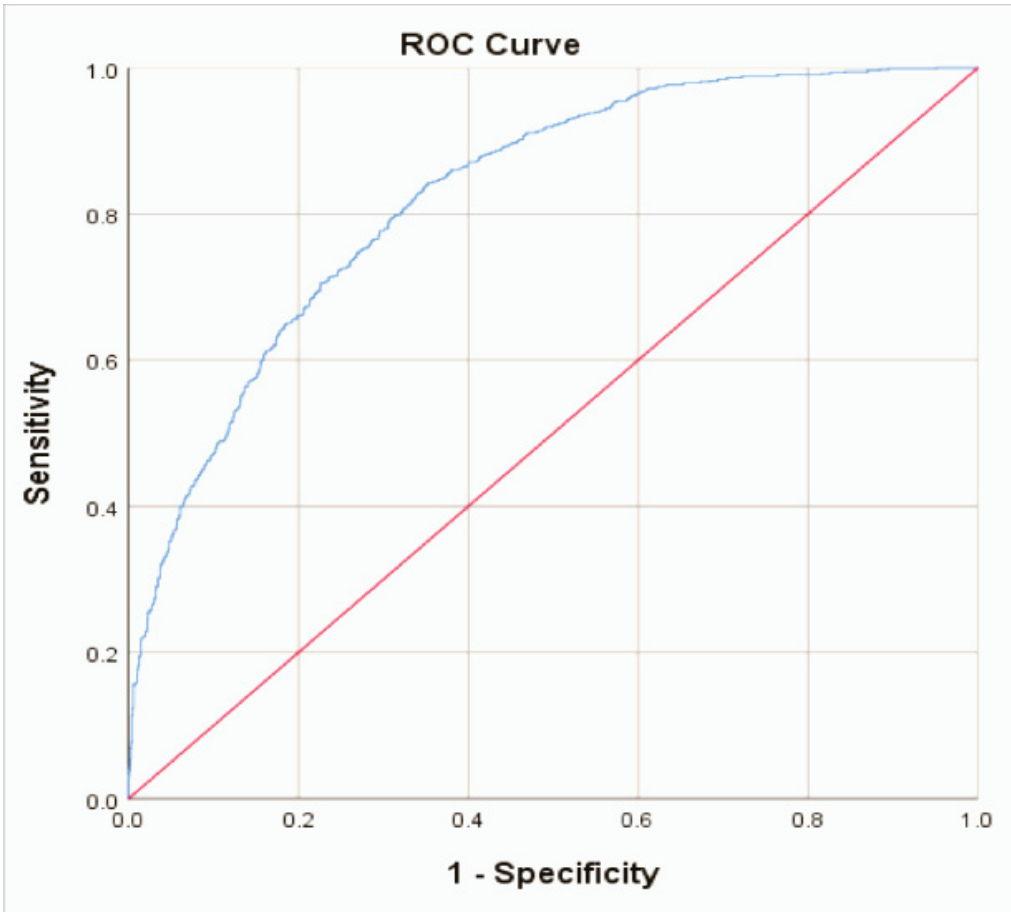
Table 12. IOM Analysis AU-ROC curve for predicted Vitamin D insufficient

			Asymptotic 95% CI	
Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
.826	.009	<.001	.803	.848

a. Under the nonparametric assumption

b. Null hypothesis: true area = .5

Figure 10. IOM AU-ROC curve for predicted Vitamin D insufficient



B coefficients, standard error, and odds ratios with 95% CIs for all variables can be seen below in table 13. Compared to vitamin D supplement users, non-use was associated with a 4.414 (95% CI: 2.015–9.669) times greater increase for insufficiency. Odds of insufficiency was 1.431 (0.921–2.225) and 1.299 (0.847–1.994) for those who have never been a regular milk drinker or whose milk drinking has varied over their life, respectively, compared to lifetime regular milk consumers. The reported odds ratios for the variable "sunscreen use" are inverted. Thus, the odds of insufficiency for each unit reduction in the variable were calculated (e.g., 1 / 1.046 = 0.956, for sunscreen use: never). Compared to those who answered always use sunscreen, the odds of insufficient vitamin D is 0.956 (0.547–1.672) for those answering never use, 1.094 (0.605–1.980) for rarely use, 1.275 (0.712–2.283) for sometimes use, and 1.156 (0.644–2.075) for uses most of the time. Higher dietary vitamin D intake is associated with decreased odds of insufficiency by 0.925 (0.895–0.956). Lastly, increases in waist circumference and minutes of self-reported sedentary activity per day are both associated with slightly increased odds of insufficiency, by 1.024 (1.016–1.032) and 1.001 (1.000–1.001), respectively.

Table 13. IOM Analysis Parameter Estimates

				95% CI	
Vitamin D insufficient (<50 nmol/L)	B	Std. Error	Exp(B)	Lower	Upper
(Intercept)	-5.452	.857	.004	.001	.027
Age	-.024	.008	.977	.955	.999
Gender					
Male	.090	.171	1.095	.760	1.577
Female	.000[a]		1.000		
Race/Ethnicity					
Mexican American	1.134	.287	3.107	1.684	5.730
Other Hispanic	.239	.256	1.270	.737	2.191
Non-Hispanic Black	2.374	.186	1.736	7.216	15.973

Non-Hispanic Asian	1.769	.281	5.868	3.224	1.679
Other Race - Including Multi-Racial	.601	.274	1.824	1.018	3.270
Non-Hispanic White	.000[a]		1.000		
Education level					
1st–8th grade	-.138	.243	.871	.519	1.460
9–11th grade & 12th w/ no diploma	.062	.257	1.063	.615	1.840
High school graduate/GED or equivalent	-.073	.291	.930	.501	1.728
Some college or AA degree	.017	.251	1.017	.595	1.737
College graduate or above	.000[a]		1.000		
Annual household income					
$0 to $4,999	.429	.515	1.536	.512	4.605
$5,000 to $9,999	.586	.477	1.797	.650	4.968
$10,000 to $14,999	1.277	.530	3.585	1.159	11.090
$15,000 to $19,999	.935	.474	2.548	.927	7.000
$20,000 to $24,999	1.088	.437	2.970	1.171	7.534
$25,000 to $34,999	.185	.349	1.204	.571	2.535
$35,000 to $44,999	1.181	.520	3.258	1.076	9.863
$45,000 to $54,999	.819	.289	2.269	1.224	4.203
$55,000 to $64,999	.471	.405	1.602	.676	3.800
$65,000 to $74,999	.003	.365	1.003	.461	2.183
$75,000 to $99,999	.515	.318	1.673	.849	3.298
$100,000 and Over	.000[a]		1.000		
Season of vitamin D blood draw					
November 1 through April 30	.958	.240	2.607	1.563	4.350
May 1 through October 31	.000[a]		1.000		
Amount of food consumed (24-hr recall)					
Much more than usual	.441	.503	1.555	.533	4.538
A little more than usual	.370	.247	1.448	.855	2.453
A little less than usual	.229	.168	1.257	.878	1.799
Much less than usual	-.105	.315	.900	.460	1.762

Usual	.000[a]		1.000		
Household food security category					
HH very low food security	.247	.140	.801	.595	1.080
HH low food security	.142	.170	1.153	.802	1.657
HH marginal food security	-.221	.208	1.280	.822	1.993
HH full food security	.000[a]		1.000		
Vitamin D dietary supplement use					
Does not use vitamin D containing supplement	1.485	.368	4.414	2.015	9.669
Uses vitamin D containing supplement	.000[a]		1.000		
Regular milk use 5 times per week?					
Never been a regular milk drinker	.358	.207	1.431	.921	2.225
Milk drinking has varied over their life	.262	.201	1.299	.847	1.994
Been a regular milk drinker for most or all their life	.000[a]		1.000		
Sunscreen use					
Never	.045	.262	.956	.547	1.672
Rarely	-.090	.278	1.094	.605	1.980
Sometimes	-.243	.274	1.276	.712	2.283
Most of the time	-.145	.274	1.156	.644	2.075
Always	.000[a]		1.000		
Vitamin D (D2 + D3) intake (mcg)	-.078	.015	.925	.895	.956
Waist Circumference (cm)	.024	.004	1.024	1.016	1.032
Minutes sedentary activity per day	.001	.000	1.001	1.000	1.001

a. Set to zero because this parameter is the reference variable.

A comparison of variance, classification, and ROC values between the baseline IOM model, which only contains the control variables, and the final model, which contains all control and the six independent variables noted above, can be seen below in table 14.

Table 14. Change Between Baseline and Final IOM Models

	Baseline	Final	Difference
Variance (%)			
Cox & Snell R^2	21.10	31.07	+9.97
Nagelkerke R^2	31.36	44.65	+13.29
Classification (%)			
Overall Accuracy	80.13	79.68	−0.45
Sensitivity	41.05	50.26	+9.21
Specificity	92.89	91.24	−1.65
Positive Predictive Value	65.35	69.26	+3.91
Negative Predictive Value	82.84	82.36	−0.48
ROC	.770	.826	+.056

Endocrine Society Analysis

Of the 24 independent variables tested, seven significantly improved the overall Endocrine Society model as seen below in table 15. In total, 2,655 valid cases were included in the final regression model (model 1) yielding a weighted subsample size of 128,098,654.73. The unweighted subsample is above the minimum sample size requirements recommended by the NHANES analytic guidelines (Johnson et al., 2013). The model was statistically significant ($P < .001$) and remained significant when a Bonferroni correction was applied ($P < .001$). The model explained 21.20% (Cox & Snell R^2) to 30.40% (Nagelkerke R^2) of the variance in the dependent variable. The overall accuracy in classification was 78.13%, sensitivity was 93.18%, specificity was 40.21%, the positive predictive value was 79.69%, and the negative predictive value was 70.08%.

Table 15. Endocrine Society Analysis Model Results

Source	df	Wald Chi-Square	Sig.	Bonferroni Sig.
(Corrected Model)	15.000	622.652	<.001	<.001
(Intercept)	1.000	66.611	<.001	<.001
Control variables				
Age	1.000	3.173	.075	.075
Gender	1.000	7.409	.006	.006
Race/Ethnicity	5.000	101.009	<.001	<.001
Education level	4.000	1.478	.831	1.000
Annual household income	11.000	22.139	.023	.117
Season of vitamin D blood draw	1.000	4.816	.028	.028
Amount of food consumed (24-hr recall)	4.000	6.213	.184	.248
Household food security category	3.000	1.325	.723	.825
Independent variables				
Vitamin D (D2 + D3) intake (mcg)	1.000	10.835	.001	.001
Vitamin D dietary supplement use	1.000	8.910	.003	.003
Regular milk use 5 times per week?	2.000	.759	.684	.794
Fat intake (g)	1.000	.605	.437	.437
Wear a long-sleeved shirt?	4.000	13.491	.009	.279
Smoked at least 100 cigarettes in lifetime?	1.000	3.362	.067	.067
How healthy is the diet	4.000	6.815	.146	.115

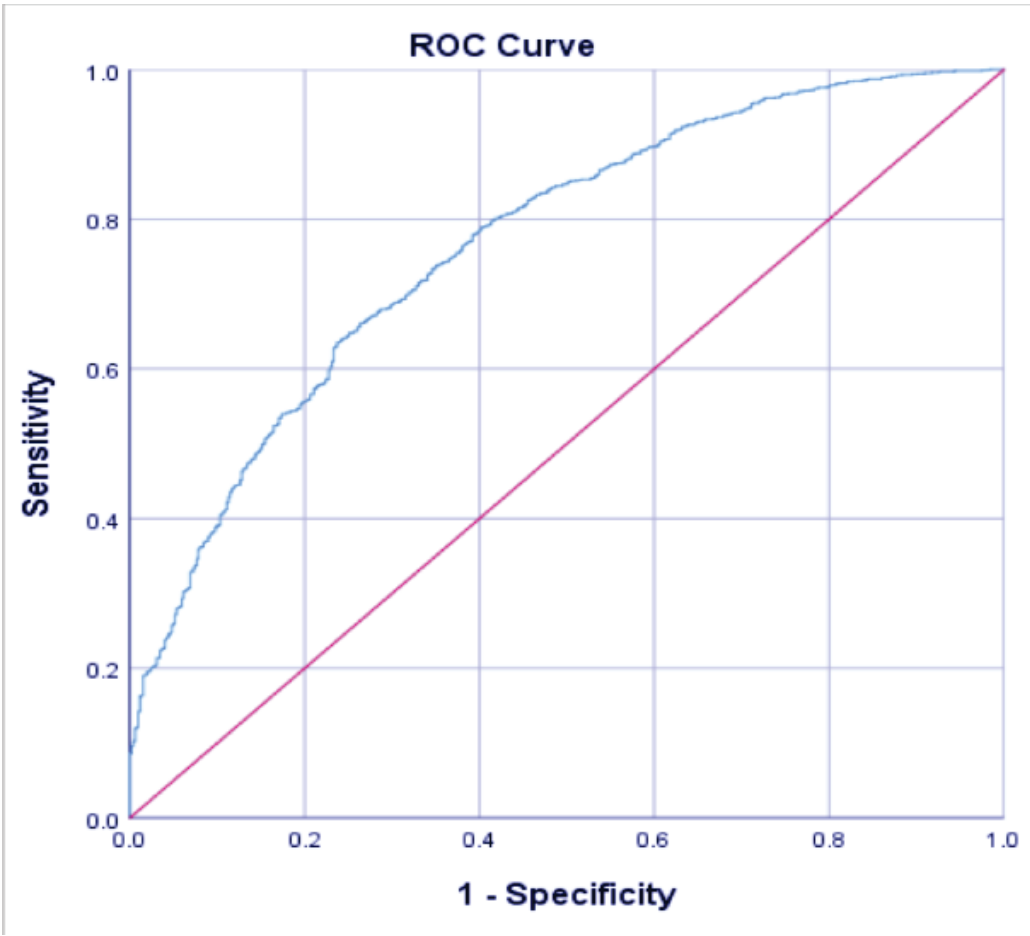
The area under the ROC curve for predicted vitamin D insufficient values was .768 (95% CI: .738–.798), which is an acceptable level of discrimination (Royston & Altman, 2010). The optimal cut point threshold for Youden's Index was .40

Table 16. Endocrine Society AU-ROC curve for predicted Vitamin D insufficient

			Asymptotic 95% CI	
Area	Std. Error[a]	Asymptotic Sig.[b]	Lower Bound	Upper Bound
.768	.012	<.001	.738	.798

a. Under the nonparametric assumption
b. Null hypothesis: true area = .5

Figure 11. Endocrine Society AU-ROC curve for predicted Vitamin D insufficient



B coefficients, standard error, and odds ratios with 95% CIs for all variables can be seen below in table 17. Odds of being vitamin D insufficient is associated with a 2.030 (95% CI: 1.224–3.367) times greater increase for those who do not take a vitamin D containing supplement as compared to those who do. Compared to those who have been regular milk

drinkers for most or all their life, odds of insufficiency is 1.234 (0.727–2.095) and 1.080 (0.771–1.513) for those who have never been a regular milk drinker or whose milk drinking has varied over their life, respectively. Compared to those who answered always to wearing a long-sleeved shirt outside on sunny days, the odds of insufficient vitamin D were 0.464 (.188–1.144) for those answering never, 0.651 (0.236–1.797) for rarely, .790 (0.304–2.050) for sometimes, and 0.811 (0.264–2.491) for most of the time. Higher dietary vitamin D intake is associated with decreased odds of insufficiency by 0.976 (0.961–0.991). Increases in dietary fat intake were associated with decreased odds of insufficiency, by 0.998 (0.993–1.003). Compared to those who had not smoked at least 100 cigarettes in their lifetime, odds of insufficiency were 1.425 (0.944–2.15) for those who had. Lastly, when participants were asked to give a self-rated score on the overall healthfulness of their diet the associated odds of insufficient vitamin D status were 1.880 (0.787–4.490) for those answering poor, 1.602 (0.910–2.821) for fair, 1.545 (1.011–2.360) for good, and 1.376 (0.783–2.419) for very good, compared to those answering excellent.

Table 17. Endocrine Society Analysis Parameter Estimates

				95% CI	
Vitamin D insufficient (≤75 nmol/L)	B	Std. Error	Exp(B)	Lower	Upper
(Intercept)	.183	.557	1.201	.367	3.937
Age	-.011	.006	.989	.976	1.002
Gender					
Male	.498	.183	1.645	1.114	2.429
Female	.000[a]		1.000		
Race/Ethnicity					
Mexican American	1.298	.263	3.663	2.090	6.418
Other Hispanic	.643	.363	1.902	.877	4.125
Non-Hispanic Black	2.106	.301	8.214	4.324	15.602
Non-Hispanic Asian	1.107	.307	3.024	1.573	5.814
Other Race - Including Multi-Racial	.927	.333	2.527	1.243	5.136

Non-Hispanic White	.000[a]		1.000		
Education level					
1st–8th grade	-.230	.295	.794	.423	1.491
9–11th grade & 12th w/ no diploma	.052	.345	1.053	.505	2.195
High school graduate/GED or equivalent	-.188	.203	.829	.538	1.278
Some college or AA degree	-.134	.193	.875	.580	1.320
College graduate or above	.000[a]		1.000		
Annual household income					
$0 to $4,999	-.001	.748	.999	.203	4.920
$5,000 to $9,999	-.555	.425	.574	.232	1.421
$10,000 to $14,999	-.132	.440	.876	.343	2.240
$15,000 to $19,999	.239	.381	1.270	.564	2.857
$20,000 to $24,999	.566	.357	1.761	.823	3.768
$25,000 to $34,999	.077	.384	1.080	.477	2.448
$35,000 to $44,999	.990	.388	2.691	1.178	6.151
$45,000 to $54,999	.499	.462	1.647	.616	4.406
$55,000 to $64,999	.253	.346	1.288	.616	2.693
$65,000 to $74,999	-.356	.484	.700	.250	1.964
$75,000 to $99,999	.476	.299	1.610	.851	3.046
$100,000 and Over	.000[a]		1.000		
Season of vitamin D blood draw					
November 1 through April 30	.473	.215	1.604	1.014	2.538
May 1 through October 31	.000[a]		1.000		
Amount of food consumed (24-hr recall)					
Much more than usual	.182	.720	1.199	.259	5.558
A little more than usual	.000	.266	1.000	.567	1.764
A little less than usual	-.163	.188	.849	.569	1.267
Much less than usual	.807	.432	2.241	.892	5.632
Usual	.000[a]		1.000		
Household food security category					

HH very low food security	.147	.317	1.096	.517	2.323
HH low food security	.366	.336	1.443	.705	2.950
HH marginal food security	.092	.352	1.158	.589	2.275
HH full food security	.000[a]		1.000		
Vitamin D dietary supplement use					
Does not use vitamin D containing supplement	.708	.237	2.030	1.224	3.367
Uses vitamin D containing supplement	.000[a]		1.000		
Regular milk use 5 times per week?					
Never been a regular milk drinker	.210	.248	1.234	.727	2.095
Milk drinking has varied over their life	.077	.158	1.080	.771	1.513
Been a regular milk drinker for most or all their life	.000[a]		1.000		
Wear a long-sleeved shirt on sunny days?					
Never	-.769	.424	.464	.188	1.144
Rarely	-.430	.477	.651	.236	1.797
Sometimes	-.236	.448	.790	.304	2.050
Most of the time	-.210	.527	.811	.264	2.491
Always	.000[a]		1.000		
Smoked at least 100 cigarettes in lifetime?					
Yes	.354	.193	1.425	.944	2.150
No	.000[a]		1.000		
How healthy is the diet?					
Poor	.631	.408	1.880	.787	4.490
Fair	.471	.265	1.602	.910	2.821
Good	.435	.199	1.545	1.011	2.360
Very good	.319	.265	1.376	.783	2.419
Excellent	.000[a]		1.000		

Vitamin D (D2 + D3) intake (mcg)	-.024	.007	.976	.961	.991
Fat intake (g)	-.002	.002	.998	.993	1.003

a. Set to zero because this parameter is the reference variable.

A comparison of variance, classification, and ROC values between the baseline Endocrine Society model, which only contains the control variables, and the final model, which contains all control and the seven independent variables noted above, can be seen below in table 18.

Table 18. Change Between Baseline and Final Endocrine Society Model

	Model 0	Model 1	Difference
Variance (%)			
Cox & Snell R^2	17.46	21.20	+3.74
Nagelkerke R^2	24.11	30.40	+12.94
Classification (%)			
Overall Accuracy	71.39	78.13	+6.74
Sensitivity	85.44	93.18	+7.74
Specificity	44.63	40.21	−4.42
Positive Predictive Value	74.60	79.69	+5.09
Negative Predictive Value	61.69	70.08	+8.39
ROC	.740	.768	+.028

DISCUSSION

Summary and Interpretation of Findings

The primary objective of this study was to determine the ability of modifiable lifestyle factors to predict vitamin D status in adults. In both models, lifestyle factor predictors of vitamin D insufficiency were total dietary vitamin D intake, use of a vitamin D containing supplement, and regular milk consumption at least 5 times a week for most or all their life, including childhood. Predictors unique to the IOM model were waist circumference, daily minutes of sedentary activity, and sunscreen use. Predictors unique to the Endocrine Society model were sun protection via long-sleeved shirt use, lifetime cigarette consumption of ≥100, self-rated diet healthfulness, and total fat intake. With these results, we can accept our hypothesis that modifiable lifestyle variables do predict vitamin D status. A comparison of model predictors are summarized in table 19.

Table 19. Comparison of model predictors

IOM Model	Endocrine Society Model
Common predictors	
Total vitamin D (D2 + D3) intake	
Vitamin D dietary supplement use	
Regular milk use 5 times per week for most of your life?	
Unique predictors	
Waist circumference	Wear a long-sleeved shirt for sun protection?
Minutes sedentary activity per day	Smoked at least 100 cigarettes in lifetime?
Sunscreen use	How healthy is your diet (self-rated)
	Total fat intake

The present study focused on modifiable lifestyle predictors which have been previously associated with vitamin D status. Of the three predictors common to both models, each has been well-established in the literature as having a large potential effect on modulating serum vitamin D status. Our findings support the results of these prior studies. Persons with higher total dietary vitamin D intakes show significantly higher serum 25(OH)D levels when compared to those with

low consumption, on average (Schleicher, Sternberg et al., 2016; Webb, Pilbeam et al., 1990). However, total vitamin D intake is greatly influenced by vitamin D supplement use and dietary patterns, particularly the consumption of fortified milk. Both of these variables also significantly improved each model. According to multiple dietary surveys, the largest at-risk group for having vitamin D intakes or serum levels at or below the EAR are those not taking a vitamin D containing supplement — an effect seen across different age, gender, income, education, and ethnic/racial demographics (Blumberg et al., 2017a, 2017b, 2017c; Moore et al., 2014). These non-supplement users are at a near 4-fold increase in risk for having serum 25(OH)D levels <40 nmol/L, the EAR-type serum 25(OH)D value (Schleicher, Sternberg et al., 2016).

Evidence for the predictive ability of fortified milk consumption on vitamin D status is bolstered by surveys that have seen fortified milk consumption contribute to a significant portion of daily vitamin D intake from food sources — an estimated 45.1% of total intake from food among all adults (O'Neil et al., 2012). Numerous observational across multiple countries studies have also consistently seen low fortified milk intake to be predictive of low serum vitamin D levels (Itkonen, Erkkola et al., 2018). While milk remains the top contributor of food-source vitamin D, consumption in the US has dropped by 35% over the past three decades (Bentley & Others, 2017), with Americans' daily intake currently at half the recommended levels. However, increasing use of vitamin D supplements over the past two decades may have partially offset the decrease of vitamin D intake from lower milk consumption (Schleicher, Sternberg et al., 2016).

There were a number of predictor variables unique to each model. The differences seen in these predictors between models may have been due in part to the sample sizes of the reference group. For both models, those who had sufficient vitamin D levels acted as the reference group. In the IOM model, the reference group accounted for 75.3% of the sample size while in the Endocrine Society model the reference group accounted for 34.3% of the sample size.

It is important to acknowledge a number of independent variable predictors that, while not individually significant, did significantly improve the model fit when added given the other variables in the model. The significant model-fit improvements seen with the addition of

these variables were retained when a Bonferroni correction was applied. These variables were included in the final model for the following reasons. First, the primary aim of the study was to build a predictive model as opposed to an explanatory one. Second, the model fit becomes significantly worse with their removal, which can indicate their inclusion may be providing a critical adjustment or mediation for one or more of the other variables in the model. Third, previous literature on these variables suggests they may have larger effects on vitamin D status than were seen in our model. Thus, their non-significance may be due to the limitations of the dataset tested. The exception to this is the variable regarding self-rated general healthfulness of the diet in the Endocrine Society model, which was retained out of exploratory interest. We acknowledge that the predictive capability of these variables may be considered preliminary in nature and that their inclusion may cause some overfitting of the models. Their validity will need to be further tested using a different dataset and/or using different statistical approaches, such as ridge regression, which may be better suited to aid in evaluation of these variables.

IOM Model

Waist circumference, daily minutes of sedentary activity, and sunscreen use variables all significantly improved the IOM model. Waist circumference is a measure of abdominal obesity that has been inversely associated with higher odds of vitamin D deficiency, which in agreement with our results (Cheng, Massaro et al., 2010; Cheng et al., 2014; Santos et al., 2017; Vogt et al., 2017). Cheng et al. (2014) showed a significant inverse association between waist circumference and serum 25(OH)D in subset of participants from the Women's Health Initiative Observational Study. The study found that a one-centimeter increase in waist circumference was associated with a 0.26 nmol/L drop in serum 25(OH)D concentrations. Santos et al. (2017) similarly found that having a waist circumference >88 cm for females and >102 cm for males was significantly associated with higher odds of 25(OH)D deficiency. This inverse association was also seen to be significant in a Framingham Heart Study cohort and within an NHANES 2001–2006 data analysis (Cheng et al., 2010; Vogt et al., 2017).

Time spent sedentary in a typical day also significantly improved the IOM model, with an increase in minutes of self-reported sedentary activity per day being associated with a very

small increase in odds of insufficiency (OR: 1.001, 95% CI: 1.000–1.001). The small odds increase seen here are not unusual, given the variability in the strength of associations between vitamin D and physical activity levels reported in the literature also using self-report measures (Fernandes & Barreto, 2017). Studies using objectively measured physical activity levels have also reported variable results. In a south German cohort of 1,193 community-dwelling participants aged ≥65 years, physical activity was collected via uniaxial accelerometer (Klenk et al., 2015). A dose-response relationship was seen between walking duration and serum vitamin D, with lower amounts of walk time seeing statistically significant lower 25(OH)D serum levels in the winter, spring, and fall but not during the summer. However, in an adolescent cohort of 1,006 participants in the cross-sectional Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study, vitamin D was weakly correlated to physical activity levels measured via accelerometers and was not a significant predictor of vitamin D status (Valtueña et al., 2013). To better test the effects sedentary time may or may not be having on vitamin D status, future regression studies could include variables related to sedentary time and time spent active, as well as their interaction terms. This could help to elucidate the relationship of physical activity and inactivity on vitamin D status.

More frequent use of sunscreen for sun protection also significantly improved the IOM model. A dose-response relationship was seen between increased frequency of sunscreen use and having higher odds of insufficient serum vitamin D. These results confirm the work of prior studies which have also seen lower serum vitamin D with increased sunscreen use. When applied in the correct concentrations, sunscreens with an SPF as low as 8 can nearly abolish endogenous vitamin D production (Faurschou et al., 2012; Grigalavicius et al., 2016; Matsuoka, Ide et al., 1987). While increased sunscreen use can decrease serum levels of vitamin D, it may not do so to a clinically relevant degree depending on the concentration of sunscreen applied and how often it is reapplied when subject to sun exposure (Libon et al., 2017; Petersen & Wulf, 2014).

The full IOM model was able to explain 9.97% (Cox & Snell R^2) to 13.29% (Nagelkerke R^2) more of the variation in serum 25(OH)D above the base model, which only included the control variables. The ROC curve indicated the full IOM model had an excellent overall capacity to discriminate between vitamin D sufficient and insufficient subjects. However, to maximize the

rate of correct classification an optimal threshold value of .49 should be used. This threshold would provide the best diagnostic balance between the true positive rate (sensitivity) and the false positive rate (1 – specificity), given the model. However, if the desire was to maximize the true positive rate and minimize the number of cases in which insufficiency was not detected, the classification threshold would need to be set at a lower value.

While the final IOM model did not improve overall accuracy in classification compared to the base model, improvements in sensitivity (+9.21%) and the positive predictive value (+3.91) were seen while small decreases were seen in specify (−1.65%) and the negative predictive value (−.48%). Overall, the model saw better performance in correctly classifying participants with sufficient serum vitamin D. When a participant was vitamin D insufficient the model returned a correct classification 50.26% of the time and, when the model predicted a participant as being insufficient, the probability of the participant actually being insufficient was 69.26%. When a participant was vitamin D sufficient the model returned a correct classification 91.24% of the time and, when the model predicted a participant as being sufficient, the probability of the participant actually being sufficient was 82.36%.

Note that the model results presented here are not intended to be used for diagnostic purposes in a clinical setting. Such a use would be inappropriate, given the limitations of the present study. Rather, the information presented is a demonstration of how the current model might perform in a real-world setting.

Endocrine Society Model

Sun protection via long-sleeved shirt use, lifetime cigarette consumption of ≥100, self-rated diet healthfulness, and total fat intake variables all significantly improved the Endocrine Society model. It is unsurprising to see greater skin coverage lead to higher odds of vitamin D insufficiency, as this has been well-established in previous studies (Buyukuslu, Esin et al., 2014; Farahati, Nagarajah et al., 2015; Granlund, Ramnemark et al., 2016; Matsuoka, Wortsman et al., 1992). The effects of clothing type on serum vitamin D levels are clearly demonstrated in studies of populations where traditional clothing can greatly limit sun exposure. In Saudi Arabia, where many women follow the cultural practices of wearing niqabs or abayas that offer near full

coverage of the skin, the rates of vitamin D insufficiency in this population are some of the highest reported in the world (Fuleihan, 2009; Elsammak, Al-Wossaibi et al., 2011). Similarly, a study of Turkish adults saw 86% of women who wore traditional clothes covering the head, legs, and arms with vitamin D insufficiency (Farahati et al., 2015). An additional study of 100 female students at Istanbul Medipol University saw 55% with vitamin D deficiency in those who typically wore Muslim-style clothing (Buyukuslu et al., 2014). While there is still debate surrounding the appropriate use of sun exposure for increasing vitamin D level, the WHO currently recommends unprotected skin sun exposure range from 5 to 15 minutes to the hands, face, and arms two to three times a week when the UV index is 3 or higher to keep serum vitamin D levels above the deficient range ("WHO | The known health effects of UV," 2017).

There have been many studies examining the contributions of foods, food groups, or dietary patterns to vitamin D status, but none to our knowledge have tested self-rated general healthfulness of the diet as a predictor for vitamin D status. Similarly, many studies have used validated food recall or history of sun exposure questionnaires to screen for vitamin D insufficiency but none have used the aforementioned variable either. The closest approximation in the literature was from the 16-item Vitamin D Status Predictor questionnaire, which asks "Do you feel malnourished? Yes or No?" (Annweiler, Kabeshova et al., 2017). Because this is the first time a self-rated question of this nature has been associated with predicting vitamin D status, caution is warranted over its validity. Future trials are needed to explore this variable.

Smoking at ≥100 cigarettes in a participants' lifetime was also predictive of vitamin D status, in line with previously published research showing increased amounts of smoking associating with lower vitamin D levels (Brot et al., 1999; Cutillas-Marco et al., 2012; Kassi et al., 2015; McKibben et al., 2016; Melamed et al., 2008; Sebekova et al., 2016; Shinkov et al., 2015; Skaaby et al., 2016; Evelien Sohl et al., 2014; Supervía et al., 2006; Tønnesen et al., 2016). Five additional variables related to smoking habits were explored for inclusion: current smoking status, amount of time since quit smoking cigarettes, number of days cigarettes were smoked in the past 30 days, average number of cigarettes smoked per day during past 30 days, and estimated number of cigarettes smoked in the participant's entire life. However, their response rates ranged from 14.0 to 35.9% which was too low to be included in our study models or for

subgroup analyses. Future NHANES studies combining many data cycles may yield a large enough response rate to conduct further analyses.

Total fat intake was also predictive of vitamin D status. Clinical trials investigating the effect of dietary fat amount in a meal on vitamin D absorption and serum 25(OH)D circulation have seen higher fat intake produce significantly higher absorption and serum 25(OH)D increases in some (Dawson-Hughes, Harris et al., 2015; Raimundo, Faulhaber et al., 2011) but not all (Dawson-Hughes, Harris et al., 2013) trials. Dawson-Hughes et al. (2015) conducted a 1-day trial in 50 healthy senior males and females who were randomly assigned to consume one of three meals: fat-free, a 30% fat meal with a low MUFA:PUFA ratio, or a 30% fat meal with a high MUFA:PUFA ratio. Each participant consumed a single 50,000 IU dose of supplemental D_3 with the meal. Peak serum 25(OH)D at 12-hours post-meal consumption was significantly higher in those who consumed the fat-containing meals. Raimundo et al. (2011) conducted a clinical trial with 32 healthy physicians who consumed a 50,000 IU dose of supplemental D_3 with either a meal containing 25.6 g or 1.7 g of fat. The group consuming 25.6 g of fat saw significantly higher serum 25(OH)D when measured at both 7 and 14 days after baseline. In both studies, though the results were significant, the 95% confidence intervals were very wide, indicating a highly variable response to the 50,000 IU doses. These results are in contrast to Dawson-Hughes et al. (2013) who tested a once-monthly 50,000 IU dose of supplemental D_3 for three months with a meal containing 35.2 g or 11.1 g of fat or with no meal (fasted). When serum 25(OH)D when measured at 30 and 90 days, no significant differences were seen between groups. It is possible that dietary fat type may have influence over vitamin D absorption,(Niramitmahapanya, Harris et al., 2011) but here too studies present conflicting results (Dawson-Hughes et al., 2015).

The full Endocrine Society model was able to explain 3.74% (Cox & Snell R^2) to 12.94% (Nagelkerke R^2) more of the variation in serum 25(OH)D above the base model. The ROC curve indicated the full Endocrine Society model had an acceptable overall capacity to discriminate between vitamin D sufficient and insufficient subjects. To maximize the rate of correct classification, an optimal threshold value of .40 should be used. Like the IOM model, if the desire was to maximize the true positive rate and minimizes the number of cases in which

insufficiency was not detected, the classification threshold would likewise need to be set at a lower value.

The final Endocrine Society model was able to improve, above the base model, overall accuracy in classification (+6.74%), sensitivity (+7.74%), positive predictive value (+5.09%), and negative predictive value (+8.39), but not specificity (−4.42). Overall, the model saw a somewhat comparable performance in correctly classifying participants with sufficient and insufficient serum vitamin D. When a participant was vitamin D insufficient the model returned a correct classification 93.18% of the time and, when the model predicted a participant as being insufficient, the probability of the participant actually being insufficient was 79.69%. When a participant was vitamin D sufficient the model returned a correct classification 40.21% of the time and, when the model predicted a participant as being sufficient, the probability of the participant actually being sufficient was 70.08%.

Additional Covariates

Several tested variables failed to significantly improve either model as seen in table 20. A few of the more notable variables are discussed herein.

Table 20. Variables not included in final models

Diet	Fitness, Activity, & Body Composition	Alcohol Use	Sun Exposure	Sleep
30-day milk consumption frequency	Self-assessed general health condition	When drinking, average consumption	Average weekly minutes outdoors	Average hours of sleep a night
Total dietary calcium intake	Average MET-hours per week	Average consumption over 12 months	Seeks shade for sun protection?	
Uses calcium supplement	Hand grip strength	Binge-drinking frequency		
Average energy intake	BMI			

Variables that did not significantly improve either model.

Curiously, while separate questions about lifetime and past 30-day milk consumption frequency were asked of all participants, only the lifetime milk consumption variable significantly improved both models. These results may have been an effect of the question wording, as the 30-day milk consumption was prompting consumption frequency over the past month while the lifetime question asked if the participant had been regularly consuming milk at least 5 times a week for most or all their life.

BMI and waist circumference have also been seen to be predictive of vitamin D status in a number of studies (Cheng et al., 2014; Pereira-Santos et al., 2015; Vogt et al., 2017). In the IOM model, when the "waist circumference" variable was already entered in the model, the inclusion of BMI added no further predictive benefit. However, in the Endocrine Society model neither variable significantly improved the model. This is surprising, given the clinical data linking BMI to lower serum vitamin D. The inability of BMI to add predictive ability to the Endocrine Society model may have been due to the limited reference group size, which only accounted for 34.3% of the included participants.

Average MET-hours per week was also removed from the models. However, there were a number of confounding effects in relation to the physical activity variable that were unable to be controlled for. Exercise volume, type, and location (indoors vs outdoors) can influence the vitamin D-physical activity relationship and were not accounted for in this study, which may have biased the results. Interaction testing between reported physical activity and reported sun exposure may warrant testing in additional studies.

Two variables related to sun exposure were not included in either model: average weekly minutes outdoors and use of shade for sun protection. It should be noted that all four sun exposure variables included for testing had somewhat high non-response rates (~35%). Of the two sun protection variables included in the final models, each reduced the testable sample size due to this high non-response. A higher response from combined NHANES cycles rate may yield different results.

Lastly, two variables related to alcohol consumption habits were seen to significantly improve the regression models. A variable related to alcohol consumption over the past 12 months produced significant improvements in both the IOM and Endocrine Society models,

while a variable related to binge drinking habits produced significant improvement in the Endocrine Society model. However, due to the very low response rates for these variables in our subsample, their inclusion drastically decreased the sample size by ~64% for both models. This produced a low total *n* that threatened the validity of the model and its results. Given the high amount of missing responses for the variables and the use of a single NHANES data cycle in the present study, imputation was decided against. Thus, these variables were removed from the final model in order to preserve model integrity. The influence of these variables should be followed up in studies with a more adequate sample size and higher response rates to further elucidate the nature of the relationship between alcohol consumption habits and vitamin D status.

Strengths and Limitations

This thesis has a number of strengths. It had a relatively large sample size, controlled for numerous potential confounders, used two automated multi-pass 24 hour recalls for both dietary and supplement intake per participant, used gold-standard LC-MS/MS measures of serum 25O(H)D, used a representative sample of adults residing in the US, employed standardized questionnaires and lab assessment practices, corrected for multiple comparisons within the models, and comprehensively assessed lifestyle variables, in the models, that have been shown to affect vitamin D status. Additionally, this thesis followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology—Nutritional Epidemiology (STROBE-nut) guidelines for reporting nutritional epidemiology and dietary assessment research (Lachat et al., 2016).

This thesis also has several limitations. Chiefly, the data sources analyzed herein are cross-sectional in nature and thus the results cannot be used to infer causality nor reverse causality, as data on the direction of the effect and temporal trends are not quantified. NHANES guidelines recommend combining two or more data cycles to produce results with greater external validity. As this study uses a single data cycle, it should be considered as an initial analysis and extrapolation of the results to the general US public should be done with caution. Additionally, not all factors that can affect endogenous production of vitamin D were accounted for. Skin pigmentation and related genes, latitude, altitude, weather conditions, living

environment (e.g., urban, suburban, or rural), and pollution can all moderate cutaneous vitamin D production. While NHANES does collect the approximate latitude and longitude of participants, as well as information about living environment, these data are not publicly available and were not incorporated into this study. Future researchers may wish to petition for access to these data and incorporate them as control variables to aid in reducing confounders.

While steps were taken to reduce confounding from variables used in this study that rely on subjective memory-based recall, such as the dietary intake and physical activity reports, omissions, inaccurate, or false reporting may remain as a residual confounder. With regard to the dietary recalls, while the automated multiple-pass method to collect 24-hour dietary recalls used in NHANES has been validated for energy intake,(Moshfegh, Rhodes et al., 2008) similar types of recalls have been shown to underestimate dietary fat intake (Lafay, Mennen et al., 2000). This in turn may lead to an underestimation of dietary vitamin D intake.

NHANES relies on the Food and Nutrient Database for Dietary Studies (FNDDS) which bases its food composition data on the USDA National Nutrient Database for Standard Reference ("FNDDS : USDA ARS," n.d.). This database does not currently account for the 25(OH)D content in foods, which may contribute to part of the discrepancies seen between reported dietary vitamin D intake and serum 25(OH)D measures (Taylor, Patterson et al., 2014; Taylor, Roseland et al., 2016). Inclusion of more food 25(OH)D content may increase reported daily vitamin D intakes by 1.73 mcg (69 IU) – 2.91 mcg (116 IU), depending on gender and eating habits of a given individual (Taylor et al., 2014).

Serum 25(OH)D concentrations are known to be affected by genetic variations. At present, NHANES does not collect the genetic information necessary to control for these variables. Adipose tissue volume can also affect serum 25(OH)D. While the measures tested in this study (BMI, waist circumference) can approximate adiposity, they are not direct measures. What's more, the use of a single 25(OH)D serum measure per participant may have led to a certain degree of inadvertent misclassification of vitamin D status, as serum 25(OH)D levels can fluctuate seasonaly and are particularly influenced by levels of PTH. Further, while total dietary vitamin D intake was assessed, type of vitamin D (D_2 and D_3) may affect serum 25(OH)D and was not separately accounted for. Indoor tanning habits were also not assessed. Lastly, it is important to

acknowledge that serum 25(OH)D is a marker of vitamin D exposure that correlate with serum measures of $1,25(OH)_2D$, the bioactive vitamin D form. This may intruduce further clasification error.

Recommendations for Further Research

The present study has set a foundation which lends itself to a natural research progression. As the external validity of the present studies results are limited by the use of a single NHANES data cycle, an expanded analysis using a similar framework could be conducted by combining multiple NHANES data cycles. The results of such a study would have greatly enhanced external application, comparatively, and allow for appropriately powered subgroup analyses that were not viable in the present study. In the opinion of the author, combining data cycles going back no further than 2007 would provide a dataset with more consistent variables across the included cycles, allowing for a greater "apples-to-apples" comparison. At present, following this recommendation would produce a dataset spanning 8 years (NHANES 2007–2014) with an estimated sample size of 12,000–16,000 participants meeting the inclusion criteria set in the present study. This recommendation is made for the following reasons.

1. In 2007, the NHANES program expanded their interview portion to include two 24-hour supplement recalls as well as a much more detailed questionnaire regarding dietary supplement use and intake in the past 30 days. This allows for more granular analysis regarding vitamin D form and dose from dietary supplement sources.
2. The Vitamin D Standardization Program guidelines were adopted by NHANES in 2007, which was the first cycle to use the gold-standard LC-MS/MS method for 25(OH)D serum measurements. While serum 25(OH)D measures taken via assay kits pre-2007 were converted to LC-MS/MS-equivalents to reduce measurement bias, residual confounding may still exist in these measures.
3. The NHANES survey began using the Global Physical Activity Questionnaire in 2007 to assess physical activity level. This questionnaire provides greater detail about recreational activity, work and school transportation methods, and measures of duration, frequency, and intensity of work that allow for the calculation of MET hours or minutes

done per week. Such details are advantageous when accounting for the effects of physical activity on serum 25(OH)D.

There were a few variables of potential interest whose response rates were too low within our sample to be included in the analysis, but that that may be of interest to explore in a future analysis with a larger dataset. As noted earlier, the variables related to alcohol consumption for NHANES 2013–2014 possessed high non-response rates within our subsample preventing their inclusion in the final models. Other variables to examine would be those regarding diet type or pattern of the participant such as low-carb, low-fat, high fiber, avoidance of certain foods, or habits around the use of nutrition information labels. Skin reaction to the sun after non-exposure is another variable of interest, as skin pigmentation can modulate endogenous vitamin D production. Skin sun reaction is an approximation of the Fitzpatrick scale, which classifies skin pigmentation on into one of six categories (from I, those who become sunburned very easily, to VI, those who never burn and tan heavily) (Astner & Anderson, 2004). However, there is a risk of collinearity with race/ethnicity, a variable which is very likely to be included as a control variable. Thus, particular attention should be given to screen the nature of the relationship between these two variables as collinearity may threaten the validity of an analysis. Lastly, drug use (cocaine, methamphetamines, marijuana) and history of sleep disorders may also be assessed, as both topics in relation to vitamin D have not been as well researched.

Some of these above variables have not been previously well-studied in regard to serum vitamin D status or only shown weak associations. Their inclusion in a model may be better suited for exploratory subgroup analyses. By combining multiple NHANES cycles, an adequate sample size from which the variables included in the present analysis and discussed in this section could be tested or re-tested may yield further insight into the influence of modifiable lifestyle factors on vitamin D status.

CONCLUSIONS

In summary, the present study explored the link between modifiable lifestyle factors and their ability to predict vitamin D status in a large, heterogeneous population taken from a representative sample of US adult residents. The results of this study have replicated some of the

findings of previous works on lifestyle predictors of vitamin D status, adding additional confirmation of their validity, and given further insight into potential, less-studied predictors which may warrant further investigation.

It is apparent from a large body of evidence that a considerable portion of US adults are not meeting recommended daily vitamin D intakes nor achieving adequate serum 25(OH)D status. An estimated 60.99 million adults in the US have serum vitamin D levels below 50 nmol/L, with 45.27 million in the inadequate range and 15.72 million with deficiency. The identification of valid modifiable lifestyle predictors of vitamin D status is a key step towards mitigating this public health issue.

The present study has set a framework through which multiple lifestyle factors and their influence on serum vitamin D may further be assessed. A follow-up study combining multiple NHANES cycles is needed to confirm the results seen here and to provide greater external validity. The identification of modifiable factors which carry the greatest influence on vitamin D status may help to inform future observational studies or clinical trials, aid in the creation of screening tools, help in the development of targeted and strategic interventions within at-risk populations for vitamin D insufficiency, and could help inform healthcare practitioners approach to promoting lifestyle interventions for their patients.

APPENDICES

Appendix A: Literature review search strategy

WorldCat

McGill Portal

Databases Searched

- Academic Search Complete
- AccessMedicine
- AgeLine
- Annual Reviews
- BioMed Central
- BioOne
- InfoSci-Books
- JAMAevidence
- JSTOR Arts & Sciences X
- JSTOR Life Sciences Collection
- MEDLINE
- OAIster
- OECD iLibrary
- OmniFile Full Text Mega
- Oxford Scholarship Online
- ProQuest
- ProQuest Dissertations & Theses
- ScienceDirect
- SPORTDiscus
- Taylor and Francis Journals
- Wiley Online Library
- WorldCat
- WorldCat.org

Limit To

- Libraries Worldwide

Formats

- Peer-reviewed
- Thesis/dissertation

- Print book
- eBook

Queries

1. kw:united states ti:vitamin d
2. kw:united states of america ti:vitamin d
3. kw:US ti:vitamin d
4. kw:USA ti:vitamin d
5. kw:america ti:vitamin d
6. kw:american ti:vitamin d
7. kw:americans ti:vitamin d
8. ti:vitamin d (Limited to January 1, 1998 – April 1, 2018)
9. kw:vitamin d (Limited to January 1, 1998 – April 1, 2018)

PubMed, EMBASE, Cochrane Library, and CINAHL

The above were searched with the following queries.

Query 1

(Vitamin D[mh] OR Vitamin D deficiency[mh] OR "vitamin d" OR "vitamin d3" OR "vitamin d2" OR cholecalciferol OR ergocalciferol OR calcitriol OR dihydrotachysterol OR hydroxycholecalciferols OR 25-hydroxyvitamin OR calciferol OR cholecalciferol OR alfacalcidol OR alphacalcidol OR "25-hydroxyvitamin D" OR "25(OH)D" OR "25OHD" OR "1,25-dihydroxyvitamin D" OR "1,25(OH)2D" OR "1-25-dihydroxyvitamin D" OR "1-25(OH)2D")
AND
(america OR american OR americans OR US OR USA OR "united states" OR "united states of america")

Query 2

(Vitamin D[mh] OR Vitamin D deficiency[mh] OR "vitamin d" OR "vitamin d3" OR "vitamin d2" OR cholecalciferol OR ergocalciferol OR calcitriol OR dihydrotachysterol OR hydroxycholecalciferols OR 25-hydroxyvitamin OR calciferol OR cholecalciferol OR

alfacalcidol OR alphacalcidol OR "25-hydroxyvitamin D" OR "25(OH)D" OR "25OHD" OR "1,25-dihydroxyvitamin D" OR "1,25(OH)2D" OR "1-25-dihydroxyvitamin D" OR "1-25(OH)2D")
AND
(NHANES OR "national health and nutrition examination" OR Nutrition Surveys[mh])

Query 3
(Vitamin D[mh] OR Vitamin D deficiency[mh] OR "vitamin d" OR "vitamin d3" OR "vitamin d2" OR cholecalciferol OR ergocalciferol OR calcitriol OR dihydrotachysterol OR hydroxycholecalciferols OR 25-hydroxyvitamin OR calciferol OR cholecalciferol OR alfacalcidol OR alphacalcidol OR "25-hydroxyvitamin D" OR "25(OH)D" OR "25OHD" OR "1,25-dihydroxyvitamin D" OR "1,25(OH)2D" OR "1-25-dihydroxyvitamin D" OR "1-25(OH)2D")
AND
(correlates OR correlate OR correlated OR determinants OR determinant OR determinants OR determinate OR determinated OR associations OR association OR associated OR predict OR predicts OR predictors OR status OR modifiable OR lifestyle)

Appendix B: Operational definitions of included study variables

Variable Name	Variable Label	Prompt	Value/Measure
Dependent Variable			
LBXVIDMS	25-hydroxyvitamin D2 + D3		25OHD2+25OHD3 (nmol/L)
Control Variables			
RIDAGEYR	Age in years at screening	Age in years of the participant at the time of screening. Individuals 80 and over are top-coded at 80 years of age.	0 to 79 80 years of age and over
FSDHH	Household food security category	Household food security category for last 12 months	HH full food security: 0 HH marginal food security: 1-2 HH low food security: 3-5 (HH w/o child) / 3-7 (HH w/ child) HH very low food security: 6-10 (HH w/o child) / 8-18 (HH w/ child)
DMDEDUC2	Education level - Adults 20+	What is the highest grade or level of school {you have/SP has} completed or the highest degree {you have/s/he has} received?	Less than 9th grade 9-11th grade (Includes 12th grade with no diploma) High school graduate/GED or equivalent Some college or AA degree College graduate or above
RIAGENDR	Gender	Gender of the participant.	Male Female
INDHHIN2	Annual household income	Total household income (reported as a range value in dollars)	$ 0 to $ 4,999 $ 5,000 to $ 9,999 $10,000 to $14,999 $15,000 to $19,999 $20,000 to $24,999 $25,000 to $34,999 $35,000 to $44,999 $45,000 to $54,999 $55,000 to $64,999 $65,000 to $74,999 $20,000 and Over Under $20,000 $75,000 to $99,999 $100,000 and Over

RIDRETH3	Race/Hispanic origin w/ NH Asian	Recode of reported race and Hispanic origin information, with Non-Hispanic Asian Category	Mexican American Other Hispanic Non-Hispanic White Non-Hispanic Black Non-Hispanic Asian Other Race - Including Multi-Racial
RIDEXMON	Six month time period	Six month time period when the examination was performed	November 1 through April 30 May 1 through October 31
DR1_300 & DR2_300	Compare food consumed yesterday to usual	Was the amount of food that {you/NAME} ate yesterday much more than usual, usual, or much less than usual?	Much more than usual Usual Much less than usual

Independent Variables

DR1TVD & DR2TVD	Vitamin D (D2 + D3)	Taken from 24-hour dietary recall	mcg
DS1TVD & DS2TVD	Vitamin D (D2 + D3)	Taken from 24-hour supplement dietary recall	mcg
DR1TTFAT & DR2TTFAT	Total fat	Taken from 24-hour dietary recall	g
DR1TKCAL & DR2TKCAL	Energy	Taken from 24-hour dietary recall	kcal
DBQ197	Past 30-day milk product consumption	Now I'm going to ask a few questions about milk products. Do not include their use in cooking. In the past 30 days, how often did {you/SP} have milk to drink or on {your/his/her} cereal? Please include chocolate and other flavored milks as well as hot cocoa made with milk. Do not count small amounts of milk added to coffee or tea. Would you say...	Never Rarely-less than once a week Sometimes-once a week or more, but less than once a day, or Often-once a day or more? Varied
DBQ229	Regular milk use 5 times per week	The next question is about regular milk use. A regular milk drinker is someone who uses any type of milk at least 5 times a week. Using this definition, which statement best describes {you/SP}?...	{I've/He's/She's} been a regular milk drinker for most or all of {my/his/her} life, including {my/his/her} childhood {I've/He's/She's} never been a regular milk drinker; {My/His/Her} milk drinking has varied over {my/his/her} life-sometimes {I've/he's/she's} been a regular milk drinker

DED120	Minutes outdoors 9am - 5pm work day	The next questions ask about the time you spent outdoors during the past 30 days. By outdoors, I mean outside and not under any shade. How much time did you usually spend outdoors between 9 in the morning and 5 in the afternoon on the days that you worked or went to school?	No time spent outdoors 1-14 minutes 15 to 480 Does not work or go to school
DED125	Minutes outdoors 9am - 5pm not work day	During the past 30 days, how much time did you usually spend outdoors between 9 in the morning and 5 in the afternoon on the days when you were not working or going to school?	No time spent outdoors 1-14 minutes 15 to 480 At work or at school 9 to 5 seven days a week
DEQ034C	Wear a long-sleeved shirt	Wear a long-sleeved shirt? Would you say . . .	Always Most of the time Sometimes Rarely Never
DEQ034A	Stay in the shade?	When {you go/SP goes} outside on a very sunny day, for more than one hour, how often {do you/does SP} Stay in the shade?	Always Most of the time Sometimes Rarely Never Don't go out in the sun
DEQ034D	Use sunscreen?	Use sunscreen? Would you say . . .	Always Most of the time Sometimes Rarely Never
DBQ700	How healthy is the diet	Next I have some questions about {your/SP?s} eating habits. In general, how healthy is {your/his/her} overall diet? Would you say . . .	Excellent Very good Good Fair Poor
BMXBMI	Body Mass Index	n/a	kg/m^2
BMXWAIST	Waist Circumference	n/a	cm
ALQ130	Avg # alcoholic drinks/day - past 12 mos	In the past 12 months, on those days that {you/SP} drank alcoholic beverages, on the average, how many drinks did {you/he/she} have?	Number
ALQ141Q	# days have 4/5 drinks - past 12 mos	In the past 12 months, on how many days did {you/SP} have {DISPLAY NUMBER} or more drinks of any alcoholic beverage? PROBE: How many days per week, per month, or per year did {you/SP} have {DISPLAY NUMBER} or more drinks in a single day?	Number
ALQ141U	# days per week, month, year?	Unit of measure	Number per week, month, year

ALQ120Q	How often drink alcohol over past 12 mos	In the past 12 months, how often did {you/SP} drink any type of alcoholic beverage? PROBE: How many days per week, per month, or per year did {you/SP} drink?	0 to 366
ALQ120U	# days drink alcohol per wk, mo, yr	Unit of measure	Number per week, month, year
HSD010	General health condition	Next I have some general questions about {your/SP's} health. Would you say {your/SP's} health in general is . . .	Excellent Very good Good Fair Poor
MGDCGSZ	Combined grip strength	Combined grip strength (kg): the sum of the largest reading from each hand.	kg/m^2
SLD010H	How much sleep do you get (hours)?	The next set of questions is about your sleeping habits. How much sleep {do you/does SP} usually get at night on weekdays or workdays?	0-11 12 hours or more
SMQ020	Smoked at least 100 cigarettes in life	These next questions are about cigarette smoking and other tobacco use. {Have you/Has SP} smoked at least 100 cigarettes in {your/his/her} entire life?	Yes No
PAD680	Minutes sedentary activity	The following question is about sitting at school, at home, getting to and from places, or with friends including time spent sitting at a desk, traveling in a car or bus, reading, playing cards, watching television, or using a computer. Do not include time spent sleeping. How much time {do you/does SP} usually spend sitting on a typical day?	Minutes
PAQ605	Vigorous work activity	Next I am going to ask you about the time {you spend/SP spends} doing different types of physical activity in a typical week. Think first about the time {you spend/he spends/she spends} doing work. Think of work as the things that {you have/he has/she has} to do such as paid or unpaid work, household chores, and yard work. Does {your/SP's} work involve vigorous-intensity activity that causes large increases in breathing or heart rate like carrying or lifting heavy loads, digging or construction work for at least 10 minutes continuously?	Yes No

PAQ610	Number of days vigorous work	In a typical week, on how many days {do you/does SP} do vigorous-intensity activities as part of {your/his/her} work?	Number of days
PAD615	Minutes vigorous-intensity work	How much time {do you/does SP} spend doing vigorous-intensity activities at work on a typical day?	Minutes
PAQ620	Moderate work activity	Does {your/SP's} work involve moderate-intensity activity that causes small increases in breathing or heart rate such as brisk walking or carrying light loads for at least 10 minutes continuously?	Yes No
PAQ625	Number of days moderate work	In a typical week, on how many days {do you/does SP} do moderate-intensity activities as part of {your/his/her} work?	Number of days
PAD630	Minutes moderate-intensity work	How much time {do you/does SP} spend doing moderate-intensity activities at work on a typical day?	Minutes
PAQ635	Walk or bicycle	The next questions exclude the physical activity at work that you have already mentioned. Now I would like to ask you about the usual way {you travel/SP travels} to and from places. For example to school, for shopping, to work. In a typical week {do you/does SP} walk or use a bicycle for at least 10 minutes continuously to get to and from places?	Yes No
PAQ640	Number of days walk or bicycle	In a typical week, on how many days {do you/does SP} walk or bicycle for at least 10 minutes continuously to get to and from places?	Number of days
PAD645	Minutes walk/bicycle for transportation	How much time {do you/does SP} spend walking or bicycling for travel on a typical day?	Minutes
PAQ650	Vigorous recreational activities	The next questions exclude the work and transport activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities. In a typical week {do you/does SP} do any vigorous-intensity sports, fitness, or recreational activities that cause large increases in breathing or heart rate like running or basketball for at least 10 minutes continuously?	Yes No

PAQ655	Days vigorous recreational activities	In a typical week, on how many days {do you/does SP} do vigorous-intensity sports, fitness or recreational activities?	Number of days
PAD660	Minutes vigorous recreational activities	How much time {do you/does SP} spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?	Minutes
PAQ665	Moderate recreational activities	In a typical week {do you/does SP} do any moderate-intensity sports, fitness, or recreational activities that cause a small increase in breathing or heart rate such as brisk walking, bicycling, swimming, or volleyball for at least 10 minutes continuously?	Yes No
PAQ670	Days moderate recreational activities	In a typical week, on how many days {do you/does SP} do moderate-intensity sports, fitness or recreational activities?	Number of days
PAD675	Minutes moderate recreational activities	How much time {do you/does SP} spend doing moderate-intensity sports, fitness or recreational activities on a typical day?	Minutes

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