University of Cincinnati

Date: 4/4/2022

I, Maxwell J Tallman, hereby submit this original work as part of the requirements for the degree of Master of Public Health in Epidemiology.

It is entitled:

Vitamin D Insufficiency and its Association with Risk for Dementia

Student's name: **Maxwell J Tallman**

This work and its defense approved by:

Committee chair: Kelly Brunst, Ph.D.

Committee member: Robert Krikorian, Ph.D.

Committee member: Jeffrey Welge, Ph.D.

UNIVERSITY OF Cincinnati

41858

Vitamin D Insufficiency and its Association with Risk for Dementia

A thesis project submitted to the Department of Environmental and Public Health Sciences of the University of Cincinnati College of Medicine in partial fulfillment of the requirements

for the degree of

Master of Public Health

in

Epidemiology

by

Maxwell Tallman

BS, University of Cincinnati, 2015

Approved by Committee Members:

Kelly Brunst, PhD

Jeffrey Welge, PhD

Robert Krikorian, PhD

Abstract

Background. Vitamin D is commonly understood to be involved in the regulation of bone density and calcium homeostasis which also regulate parathyroid hormone activity. Many studies also discuss the impact of vitamin D deficiency on neuropsychological conditions such as depression, multiple sclerosis, and dementia. This study seeks to examine the relationship between age, serum vitamin D levels, and risk for dementia.

Methods. This study was a retrospective cohort study of patients seen at the University of Cincinnati Academic Health Center. 21264 subjects contributed to 50268 total observations. Observations were included if they contained serum vitamin D levels, as well as values for predictors of interest such as dementia status, age, race, gender, and UV status at the time of the visit. A mixed methods approach was used to conduct multiple linear regression using vitamin D level as the primary outcome variable, dementia status, age, race, gender, UV status, and an interaction term between dementia status and age.

Results and Conclusions. Patients who eventually develop dementia were shown to have reduced vitamin D values compared to their counterparts in the never dementia group. Race, gender, and UV status of the visit were all statistically significant. Belonging to black or African American race, and male gender patient groups contributes to having lower serum vitamin D levels. Age alone was not statistically significant; however, the interaction term between age and dementia group was ($t= 3.99$, $F=15.94$, $p<0.0001$). This supports the hypothesis that the rate of change in serum

vitamin D values would be different between patients who go on to develop dementia and those who do not. Of specific interest, mean serum vitamin D values in each group were relatively close to 32 ng/ml of vitamin D which has been reported to be a threshold about which parathyroid hormone activity is modulated. Further research to better understand the role of parathyroid hormone in risk for dementia and other neuropsychiatric illnesses is warranted.

Acknowledgements

I would like to take this opportunity to acknowledge the efforts my committee members have put in to helping me produce this thesis project and the role they have played in my education.

To my committee chair, Dr. Kelly Brunst, thank you for leading this committee and providing your perspective in the presentation and interpretation of this work. I would also like to thank you for the time and effort that went into three years of academic and career advising you have provided me with.

To Dr. Jeffrey Welge, thank you for serving as my primary advisor on this project. I could not have completed this project without your guidance in determining an appropriate strategy for preparing the data and implementing the statistical analysis methods.

To Dr. Robert Krikorian, thank you for allowing me the opportunity to analyze the data you collected from the University of Cincinnati Academic Health Center's electronic medical record system. Your input in and assistance with my interpretation of results and your command of the literature proved invaluable in completing this project.

To Thomas Blom, thank you for your assistance refining my strategies for data analysis, as well as talking through troubleshooting during the analysis process.

Finally, to my parents, Jim Tallman and Portia Strunk, and to my sister, Tahli Tallman, thank you all for being there for me when I need you, and for supporting me throughout my educational journey. I know that I can expect to count on you all when I need you most.

Table of Contents

1. Introduction

1.1 Characteristics of Vitamin D

Vitamin D is a fat-soluble steroid hormone found in foods including fatty fish and dairy as well as some fortified foods in the US predominantly in the form of vitamin D2 (ergocalciferol). However, the predominant source of vitamin D in humans comes from endogenous conversion of 7-dehydrocholesterol into vitamin D3 (cholecalciferol) via ultraviolet radiation from exposure to the sun. This undergoes hydroxylation in the liver to form 25-hydroxyvitamin D (calcidiol or 25OHD), and then in renal tissue to form 1,25-dihydroxyvitamin D (calcitriol or 1,25OHD), which is the hormonally active form (Brannon et al., 2008). 1,25- dihydroxyvitamin D regulates calcium homeostasis and bone density and interacts with serum parathyroid hormone to modulate bone resorption (Suda et al., 2003). Vitamin D deficiency is a significant global health issue that can result in disease of the bone such as rickets or osteomalacia and osteoporosis. It is also increasingly being found to be associated with acute and chronic illnesses such as dental caries, cardiovascular disease, some cancers, preeclampsia, type 2 diabetes, and neurological disorders including dementia (Greenblatt et al., 2019; Holick, 2017; Lee et al., 2008).

1.2. Defining Sufficiency vs. Insufficiency

Severe vitamin D deficiency (<10 ng/ml serum 25OHD) and its clinical sequelae are more commonly seen in the developing world, but less clinically significant insufficiency of vitamin D (<16-20 ng/ml serum 25OHD) is relatively common in the US and other western societies (Hanley & Davison, 2005; Mitchell et al., 2012). Values for

deficiency and insufficiency appear to be somewhat varied but one review identified modulation of parathyroid hormone activity when serum 25OHD was 32 ng/ml, and suggested that this may be a better marker of sufficient serum 25OHD (Hollis, 2005). However, the author also notes that current recommendations for supplementation are insufficient to maintain serum 25OHD above this threshold (Hollis, 2005). Population health consequences of the relatively poor ability for supplementation to correct these values are compounded by a rather large prevalence rate of vitamin D insufficiencies estimated to be as high as 30 – 64 percent in the general population (Lee et al., 2008; Mitchell et al., 2012; Parva et al., 2018). Deficiency rates can be even higher in certain populations including the elderly and individuals with higher concentrations of melanin in their skin.

1.3. Physiologic Considerations

Due to the sunlight dependent nature of vitamin D synthesis in vivo, location on the planet and several other factors are directly linked to an individual's ability to maintain sufficient levels of vitamin D for optimal functioning. Due to the curvature of the earth, the amount of UV radiation varies in relation to distance from the equator. Seasonal weather patterns, in addition to latitude, may influence general patterns of activity in populations which may determine typical exposure to sunlight in a region (Webb, 2006). Aging also impacts sunlight dependent calcitriol production. In 1985, it was discovered that 7-dehydrocholesterol concentrations in skin decreased in an age-dependent manner in surgically acquired skin samples (Maclaughlin & Holick, 1985). This age-dependent reduction in a precursor to vitamin D suggests that many factors may contribute to diminished vitamin D status. A reduction in bioavailability of the

reagent for the sunlight dependent conversion of vitamin D3 in conjunction with decreased outdoor activity seen in aging populations, may create a feedback loop decreasing bone density and muscular function, closely related to calcium homeostasis, further reducing sunlight exposure due to further reduction in activity. This in turn creates a situation where increased supplementation is required to mitigate the risks of other related consequences of reduced levels of vitamin D.

While the case for vitamin D's impact on bone density and calcium is obvious, mechanisms of the reported associations with neuropsychiatric illnesses are less clear. One review reports that the cytochrome p450 enzyme required for the second hydroxylation required to activate vitamin D is found in brain tissue, and vitamin D has been found to be active in developing and adult rat brain, as well as human brain, suggesting that vitamin D is active in neurosteroid hormone signaling (McGrath et al., 2001). While vitamin D may play a role in gene expression impacting neurodevelopment and therefore diseases of neurodevelopment, it is also being found to be associated with disorders such as depression, multiple sclerosis, Parkinson's disease, and dementia which are less dependent on developmental processes (Balion et al., 2012; Bigman, 2020; Eyles et al., 2013; Greenblatt et al., 2019).

The present study aims to build on previous findings of the association between reduced serum 25OHD and dementia by observing patterns in a more real-world setting using retrospective electronic medical record data from patients seen in the University of Cincinnati Academic Health Center (Etgen et al., 2012; Jayedi et al., 2018). Specifically, we aim to use a longitudinal, epidemiologic approach to analyzing real-world, electronic medical record data to examine change in serum 25OHD between

individuals who do not develop dementia and those who do, as well as how age and other specific demographic characteristics are related to this effect in the study population. We hypothesize that there will be a significant inverse association between age and serum 25OHD and that this association will differ between individuals with and without a documented physician's diagnosis of dementia.

2. Methods

2.1 Study Design

The present study was a retrospective longitudinal cohort study. Data were queried from the University of Cincinnati Academic Health Center electronic medical record system. As this study utilized a limited dataset that did not contain personal identifiers, the University of Cincinnati Institutional Review Board granted a non-human subjects research exemption to traditional informed consent procedures.

2.2. Defining the Sample and Variables

Observations were included if the visit occurred between January 1, 2012 and August 31, 2019 for patients over the age of 65 that had at least one value for the following test as coded in the electronic medical record system: VIT D 25 HYDROXY, 25 HYDROXY, VITAMIN D-2, 25 HYDROXY, VITAMIN D-3, 25 HYDROXY, VITAMIN D, VIT D 25 HYDROXY. Data were excluded if any patient was diagnosed with dementia prior to January 1, 2012 to include terms in their encounter diagnosis, discharge diagnosis, problem list, and medical history. Patients were also excluded for diagnosis of brain injury, post-concussive disorder, psychosis, or substance abuse disorders.

The initial data query included 21,264 patients contributing data to 294,394 observations. From this, extreme observations of vitamin D values larger than 200 ng/ml were excluded. This eliminated one subject, leaving us with an overall sample size of 21,263. Observations were included in the overall model if they contributed a value for each of the variables of interest (serum 25OHD, age, gender, race, and day of the year). The largest limiting factor for inclusion in the model was the absence of vitamin D values at a visit which eliminated 244,126 observations. Serum 25OHD tests were not completed at every visit for these patients so the final model included 50,268 observations for these 21,263 people. Demographic variables including age at each visit, gender/sex, and race were included as covariates in the model due to the expectation that they may influence serum 25OHD values or risk for dementia. An additional covariate was included to control for fluctuations in serum 25OHD due to the time of year that the visit took place. This was necessary because Cincinnati is located at around 39° north latitude. There is effectively an off-season for UV radiation during the winter months at these latitudes (Webb, 2006). To operationalize this variable, observations were binarized to distinguish between the season when UV radiation is present between March 1 and October 1 and the effective UV off-season during the winter months. Finally, patients were assigned to a group based on whether they ever received a diagnosis of dementia from their physician. We considered the diagnosis of dementia to be final and did not include observations in the analysis after the first date the diagnosis of dementia was present in a patient's series of observations.

2.3. Statistical Analysis

The statistical analysis was carried out in SAS version 9.4. A mixed methods approach was used to conduct multiple linear regression analysis given the longitudinal nature of the dataset. Serum 25OHD level was used as the outcome variable. Predictors included a variable to denote dementia group as ever being diagnosed with dementia or not (primary predictor) and covariates including age, gender, race, UV status, and an interaction term between dementia group and age. The interaction term between age and dementia group was included based on an a priori hypothesis that the relationship between age and serum 25OHD may be changing at different rates in the dementia group compared to those who never received a diagnosis of dementia.

3. Results

General characteristics of the sample are presented in table 1. Both the dementia and non-dementia groups were comprised of more females than males, though the percentage of males in the dementia group is higher than in those who did not eventually get diagnosed with dementia. Prevalence of dementia in this population was around 9 percent. Representation of race by dementia group did not significantly differ between groups. Mean age in the dementia group was significantly older than the non-demented group.

Results of the repeated measures multiple linear regression model showed a significant association between eventual diagnosis of dementia and vitamin D values over time ($t= -2.93$, $F= 8.56$, $p=0.0034$). The age association with serum 25OHD over time was not significant ($t= 0.61$, $p= 0.54$); however, the interaction term between

age and dementia status was significant (t= 3.99, F=15.94, p<0.0001). This supports our hypothesis that the relationship between age and serum 25OHD values is different based on dementia group. Mean serum 25OHD values for several select values of age are presented in figure 1. Gender (t= 13.83, F=191.21, p<0.0001), black or African American race (t= -22.14, F= 58.82, p<0.0001), and season (t= 4.89, F=23.95, p<0.0001) were significant predictors of vitamin D level in the model. Specifically, belonging to the groups for male gender, or black or African American race were associated with lower serum 25OHD levels.

4. Discussion

4.1. Model Context

This analysis shows that serum 25OHD levels differed between individuals who received a diagnosis of dementia during the period from which these records were retrieved and those who did not. Estimates of the prevalence of dementia from an epidemiologic perspective are not well established due to the diverse nature of dementia diagnosis and some limitations in study designs according to a recent analysis of Medicare claims, making it difficult to contextualize samples with the larger population (Goodman et al., 2017). A significant association was found for age, the interaction between age and dementia group, gender, race, and UV season.

4.2. Interest in Parathyroid Hormone

Estimates of the mean serum 25OHD levels show that individuals who did not develop dementia had slightly higher levels of vitamin D in the blood than their counterparts who did develop dementia. This validates findings of previous work from

our group (Greenblatt et al., 2019), as well as those of studies in the literature showing an association between lower levels of serum 25OHD and increased risk for dementia and general cognitive decline (Annweiler et al., 2009; Jayedi et al., 2018). While the magnitude of this difference is on the order of 3 ng/ml, a seemingly insignificant difference, it's important to remember that the threshold for modulation of parathyroid hormone has been estimated to be roughly 32 ng/ml. As described earlier, parathyroid hormone may represent a physiologic marker of vitamin D sufficiency in that this level is required to modulate it. While it is discussed briefly in several of the studies referenced throughout this paper, the mechanism of action and specific relationship of parathyroid hormone with cognition and dementia is less well understood. It was described in a review of twenty-seven studies that increased levels of parathyroid hormone may lead to dysregulation of calcium in neurons leading to dysfunctional signaling; however, the quality of data was in question, and this reduces the ability to make causal inferences from this body of evidence (Lourida et al., 2015). Nonetheless, there is evidence for a potential clinically significant threshold in risk for sequelae of vitamin D insufficiency, and that even a small amount of variability around this threshold for parathyroid hormone activation may lead to greater or lesser risk for developing dementia. Future research is needed to elucidate the nature of parathyroid hormone's role in cognitive decline and dementia.

4.3. Age and Vitamin D

As humans age, the concentration of precursors of vitamin D in the skin becomes lower, thereby reducing the efficiency of the sunlight dependent conversion and reducing levels of circulating vitamin D. This would lead one to assume that there

should be a significant association in the model; however, in this cohort, the relationship between vitamin D level and age was not significant. This contrasts with demonstrated relationships showing increased vitamin D deficiency as age increases (Aspray & Francis, 2008). One possible explanation for this, and a significant limitation of this study, is that electronic medical record data were queried based on the presence of vitamin D levels, but we lacked information about why these individuals were receiving testing and what brought them to the clinic. This may account for the large variance in this sample and mask the expected reduction in vitamin D levels over time. The interaction between age and dementia group was statistically significant. This points to the property of the sample that rates of change in serum vitamin D may be different in the dementia group vs the no dementia group. The significance of this interaction makes sense given that the body of evidence suggests reduced vitamin D is associated with greater risk for dementia. It is from this evidence that we can infer the individuals with dementia may be having a more rapid decline in serum 25OHD levels compared to individuals who do not later go on to develop dementia.

4.4. Race Considerations

Race is also a significant predictor of vitamin D level in the model. Humans are believed to have originated from Africa and as such developed a darker complexion to protect against damage from solar radiation. As populations migrated away from the equator, gene expression of skin pigmentation changed in response to reduction in solar radiation in higher latitudes resulting in lighter complexions. While this adaptation occurred over many thousands of years, advancements in global travel and trade have led to voluntary migration of individuals to new places the world over; however, there

were also forced migrations of large populations of Africans to more poleward latitudes in the form of slave trading leading to the establishment of diasporas. These migrations occur at such rates that adaptation of skin pigmentation was not possible and resulted in a differential ratio of skin pigmentation to UV radiation present in the environment for these individuals. This likely results in a reduced efficiency to conduct the sunlight dependent conversion of 7-dehydrocholesterol into vitamin D3. As a result, darker skinned individuals living in northern latitudes have been shown to have lower levels of vitamin D (Ames et al., 2021). Contrary to this finding, yet another study discovered skin pigmentation did not play a role in vitamin D levels, and instead reported a strong association with baseline cholesterol levels and vitamin D suggesting that the relationship between skin pigmentation and vitamin D levels is more nuanced and warrants further exploration in future studies (Bogh et al., 2010).

4.5. Gender and Vitamin D

Gender specific differences in vitamin D values were also statistically significant. Mean serum 25OHD levels for females in the sample were higher than that of their male counterparts. This is consistent with the results of a large meta-analysis of global serum 25OHD levels (Hagenau et al., 2009). It has been postulated that the gender differences in serum 25OHD levels may be dependent on the difference in adiposity between men and women at similar BMI values (Gallagher et al., 2000; Mitchell et al., 2012). This difference in baseline fat stores between men and women may contribute to differential vitamin D measurements in serum due to the fat-soluble nature of vitamin D, suggesting women may have better vitamin D storage capacity and release it into the blood to maintain slightly higher values though further research is needed to explore this

relationship. This may pose one mechanism for observed difference in serum 25OHD levels. In this study, a higher percentage of males were present in the dementia group than females when compared to the no dementia group, but gender effects are less well understood. One such study seeking to examine gender differences in prevalence of dementia noted no differences for undifferentiated dementia and Alzheimer's dementia but did note a higher prevalence vascular dementia in women, citing higher general mortality rates for men as a potential explanation for this difference (Copeland et al., 1999). Gender differences in vitamin D levels appear to have a plausible physiologic underpinning, but due to uncertainty with respect to gender associations in dementia prevalence, further research to determine whether these serum 25OHD observations translate to tangible differences in risk for dementia.

4.6. Limitations

This study is not without limitations due in part to issues inherent in the type of retrospective electronic medical record data query carried out to gather data. One such limitation is the difficulty in carrying out longitudinal data analysis because of temporal misalignment of variables in the dataset. When querying data from an electronic medical record, there is no way to guarantee that each patient will have values present for every variable of interest at each given timepoint. As a result, proper assignment of variable values at each timepoint becomes difficult. As more studies of large scale electronic medical record data become possible to due to increasing usage across health systems and improvements in technology, special care will need to be taken to implement policies conducive to proper data collection. Specific health system-wide policies could be tailored to address the type of data collected at clinic visits and how it

is entered into the electronic medical record system such that ease of query and analysis is taken into consideration.

4.7. Sample and Methods Context

In comparison to the gold standard randomized clinical trial, studies of limited datasets from electronic medical records have limitations based on how data is queried, and you cannot account for how data were collected or entered for a given patient at a given clinic. Our retrospective electronic medical record review lacked some specific information regarding the type of clinic visited, why the patient sought treatment, and the reason for ordering labs; all pieces of information that may be controlled for and collected in a prospective study. These data could help with interpreting the wide range in serum 25OHD by patient. We received information regarding whether individuals were receiving vitamin D supplementation in the form of prescription orders. While formulation was entered, total daily dose was not. In addition, this may change over time due to active titration or occurrence of side effects, and there is no way to record compliance, side effects or adverse events that may impact outcome variables. Follow-up data tailored to our aims was not possible, so we had to rely on less stringent data cleaning techniques to avoid dramatic reduction in sample sizes. Possible solutions to missing data in this context are imputation methods to estimate values for individuals. In cases of variables with limited numbers of missing data, this may be a reasonable way to address this issue and provide better temporal resolution, though in the case of data that may be more sparsely present, imputation can introduce unwanted artifacts by virtue of including large numbers of values inferred from trends in the dataset. Yet another limitation due to the nature of the study design is that it is retrospective, and

availability of data is intimately related to individual patient healthcare utilization patterns. The implications of this are less clear. One possible problem associated with this is that the people whose data are included may just be more conscious about their health, which could represent attempting to be more diligent about their health, or it could mean the sample is generally in poorer health and explain why they are seeking laboratory vitamin D testing and multiple follow-ups with their doctor. Further research, particularly in the field of biostatistics to develop adequate techniques for dealing with large scale electronic medical record datasets such as these will prove instrumental in advancing the capacity for monitoring and inference in more real-world settings than the gold standard randomized clinical trial.

4.8. Conclusions

In a large cohort of patients from the University of Cincinnati Academic Health Center care network, we identified a significant association between dementia diagnosis status and serum 25OHD levels. In conjunction with this association, an age by diagnosis interaction term, race, gender, and seasonal UV fluctuation were also significant. Due to the large number of subjects included in this analysis, statistical power is such that even small differences will achieve statistical significance. Consequently, we have discussed the validity of these associations with respect to extant literature and have determined that further research, particularly in the form of large, randomized clinical trials can help to better understand the magnitude and downstream implications of these findings as it pertains to risk for dementia. In addition to understanding the health implications for risk of dementia, biostatistical advancements in handling large electronic medical record datasets will improve the

ability to use the vast amount of data being collected at health systems every day to improve the lives of patients globally.

5. Implications for Public Health

The implications of this analysis for public health are many. Firstly, we determined that there is a relationship between serum vitamin D levels and risk for dementia. Programs targeting at-risk groups should consider talking with their intended audiences about vitamin D and the myriad health implications of insufficiency, as well as recommend supplementation to limit the impact of vitamin D insufficiency on patients and healthcare systems. Age was not significant in our model and estimates of vitamin D level by age did not match the expected downward trend in D levels with age that is present in much of the extant literature. Due to the relationship of dementia with low vitamin D levels, individuals who may be experiencing bone density disorders such as rickets, osteomalacia, or osteoporosis may be at increased risk for dementia and could benefit from more close monitoring and dementia screening to attempt to observe dementia onset earlier. This could lead to a compounding effect as multiple health conditions may concentrate in these people due to the complex relationship between vitamin D, calcium, and parathyroid hormone and disorders of imbalances in these compounds.

Race and gender have increasingly come to the forefront of public health discussions as the existence of health disparities has become clearer and is of significant interest to public health policy worldwide. While we found a significant effect of race on serum 25OHD levels, the nature of the relationship as it is presented in the

literature remains unclear. A study assessing dementia risk while controlling for education, cognitive test scores, and other potential confounders found that black patients were at greater risk for dementia than their white counterparts (Shadlen et al., 2006). Because findings related to vitamin D levels are not well understood, and there is already a baseline increased risk for dementia, public health programming and research to determine plans of action to reduce burden of disease for individuals with dark skin are needed. Taking gender and race into consideration in these programs will help to better tailor resources in communities at greatest need and improve health literacy and access to care for people who may be more vulnerable to poor health outcomes. With specific respect to race, it is relevant for global health because any individuals with mismatched complexion to the UV radiation levels of the environment they live in may experience sub optimal sunlight dependent vitamin D production.

Methods for public health monitoring and research should also be flexible in response to challenges associated with the type of large scale electronic medical record data analysis as carried out in this study. Partnering with biostatisticians to better determine ways to leverage the vast quantities of data being collected in electronic medical records systems daily around the world will put the field of public health in a position to increase the understanding of health without having to rely solely on large, expensive clinical trials as the gold standard for research. It is also important to focus on developing and changing electronic medical record systems in a way that is conducive to using the data after it has been collected to better serve populations globally. The changes needed will revolve around setting policies and standards for how individuals treating and interacting with patients access and enter data into their charts at the

individual patient level. Improving workflows at this level will allow for greater use of the end stage aggregate data to improve population health alongside treating patients as their needs become apparent.

6. Attainment of MPH Competencies

6.1. Core Competencies

Conducting this large, retrospective cohort study provided an opportunity to demonstrate the attainment of the following MPH competencies. I was able to analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software, as appropriate, using SAS 9.4 and excel to accomplish these goals. I was also able to Assess population needs, assets and capacities that affect communities' health through examining the prevalence of vitamin D insufficiency and dementia in Cincinnati and the public health implications associated with these issues. The thesis paper format was useful in communicating audience-appropriate public health content, both in writing and through oral presentation, to be completed at the end of the semester.

6.2. Epidemiology Concentration Competencies

Assessing demographic characteristics and their relationship to serum 25OHD levels as a risk factor for dementia adequately meets the competency to utilize epidemiologic data and methods for outbreak investigation, infectious disease and chronic disease surveillance, determination of risk factors, disease prevention trials, and the evaluation of screening tests. Effective use of epidemiologic terminology and conducting basic epidemiologic analyses using multiple linear, logistic, Cox, and

Poisson regression were attained using multiple linear regression in determining the relationships between serum 25OHD and the predictors of interest. Understanding the limitations in this analysis as well as the relevance of its results to the field demonstrate the ability to understand epidemiologic inference in the context of causal networks and the ability to consider bias, confounding, and effect modification. Critical review the scientific literature, integration of the findings across studies, and making appropriate public health recommendations were integral to the production of this final thesis product. This project also showcases the design and conduct epidemiological studies to address public health priorities and advance current knowledge.

References:

Ames, B. N., Grant, W. B., & Willett, W. C. (2021). Does the high prevalence of vitamin d deficiency in african americans contribute to health disparities? In *Nutrients* (Vol. 13, Issue 2, pp. 1–25). MDPI AG. https://doi.org/10.3390/nu13020499

Annweiler, C., Schott, M. A., Allali, G., Bridenbaugh, S., Kressig, R., Allain, P., Herrmann, F., & Beauchet, M. O. (2009). *Association of vitamin D deficiency with cognitive impairment in older women Cross-sectional study at www*. www.neurology.org.

Aspray, T. J., & Francis, R. M. (2008). Vitamin D deficiency - Can old age learn from childhood? In *Age and Ageing* (Vol. 37, Issue 1, pp. 6–7). https://doi.org/10.1093/ageing/afm183

Balion, C., Griffith, L. E., Strifler, L., Henderson, M., Patterson, C., Heckman, G., Llewellyn, D. J., & Raina, P. (2012). *Vitamin D, cognition, and dementia A systematic review and meta-analysis*. www.neurology.org

Bigman, G. (2020). Vitamin D metabolites, D3 and D2, and their independent associations with depression symptoms among adults in the United States. *Nutritional Neuroscience*, 1–9. https://doi.org/10.1080/1028415X.2020.1794422

Bogh, M. K. B., Schmedes, A. v., Philipsen, P. A., Thieden, E., & Wulf, H. C. (2010). Vitamin D production after UVB exposure depends on baseline vitamin D and total cholesterol but not on skin pigmentation. *Journal of Investigative Dermatology*, *130*(2), 546–553. https://doi.org/10.1038/jid.2009.323

Brannon, P. M., Yetley, E. A., Bailey, R. L., & Picciano, M. F. (2008). *Overview of the conference "Vitamin D and Health in the 21st Century: an Update" 1-4*. https://academic.oup.com/ajcn/article/88/2/483S/4650424

Copeland, J., McCracken, C., Dewey, M., Wilson, K., Doran, M., Gilmore, C., Scott, A., & Larkin, B. (1999). Undifferentiated dementia, Alzheimer's disease and vascular dementia: age-and gender-related incidence in Liverpool The MRC-ALPHA Study. In *BRITISH JOURNAL OF PSYCHIATRY* (Vol. 1, Issue 0).

Etgen, T., Sander, D., Bickel, H., Sander, K., & Förstl, H. (2012). Vitamin D deficiency, cognitive impairment and dementia: A systematic review and meta-analysis. In *Dementia and Geriatric Cognitive Disorders* (Vol. 33, Issue 5, pp. 297–305). https://doi.org/10.1159/000339702

Eyles, D. W., Burne, T. H. J., & McGrath, J. J. (2013). Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. In *Frontiers in Neuroendocrinology* (Vol. 34, Issue 1, pp. 47–64). https://doi.org/10.1016/j.yfrne.2012.07.001

Gallagher, D., Heymsfield, S., Heo Moonson, Jebb, S., Murgatroyd, P., & Sakamoto, Y. (2000). *Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index*. https://academic.oup.com/ajcn/article/72/3/694/4729363

Goodman, R. A., Lochner, K. A., Thambisetty, M., Wingo, T. S., Posner, S. F., & Ling, S. M. (2017). Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011–2013. *Alzheimer's and Dementia*, *13*(1), 28–37. https://doi.org/10.1016/j.jalz.2016.04.002

Greenblatt, H. K., Adler, C., Aslam, M., Welge, J., & Krikorian, R. (2019). Vitamin D level predicts all-cause dementia. *Nutrition and Healthy Aging*, *5*(2), 141–147. https://doi.org/10.3233/NHA-190065

Hagenau, T., Vest, R., Gissel, T. N., Poulsen, C. S., Erlandsen, M., Mosekilde, L., & Vestergaard, P. (2009). Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: An ecologic meta-regression analysis. *Osteoporosis International*, *20*(1), 133–140. https://doi.org/10.1007/s00198-008-0626-y

Hanley, D. A., & Davison, S. (2005). *Vitamin D Insufficiency in North America*. https://academic.oup.com/jn/article/135/2/332/4663654

Holick, M. F. (2017). The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Reviews in Endocrine and Metabolic Disorders*, *18*(2), 153–165. https://doi.org/10.1007/S11154-017-9424-1

Hollis, B. W. (2005). *Symposium: Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency Circulating 25-Hydroxyvitamin D Levels Indicative of Vitamin D Sufficiency: Implications for Establishing a New Effective Dietary Intake Recommendation for Vitamin D 1*. https://academic.oup.com/jn/article/135/2/317/4663651

Jayedi, A., Rashidy-Pour, A., & Shab-Bidar, S. (2018). *Vitamin D status and risk of dementia and Alzheimer's disease: A meta-analysis of dose-response †*. https://doi.org/10.1080/1028415X

Lee, J. H., O'Keefe, J. H., Bell, D., Hensrud, D. D., & Holick, M. F. (2008). Vitamin D Deficiency. An Important, Common, and Easily Treatable Cardiovascular Risk Factor? In *Journal of the American College of Cardiology* (Vol. 52, Issue 24, pp. 1949–1956). https://doi.org/10.1016/j.jacc.2008.08.050

Lourida, I., Thompson-Coon, J., Dickens, C. M., Soni, M., Kuźma, E., Kos, K., & Llewellyn, D. J. (2015). Parathyroid hormone, cognitive function and dementia: A systematic review. *PLoS ONE*, *10*(5). https://doi.org/10.1371/journal.pone.0127574

Maclaughlin, J., & Holick, M. F. (1985). *Aging Decreases the Capacity of Human Skin to Produce Vitamin D3*.

McGrath, J., Feron, F., & Eyles, D. (2001). mcgrath 2001-vitamin d neurosteroid effects. *Trends in Neurosciences*.

Mitchell, D. M., Henao, M. P., Finkelstein, J. S., & Burnett-Bowie, S. A. M. (2012). Prevalence and predictors of vitamin D deficiency in healthy adults. *Endocrine Practice*, *18*(6), 914–923. https://doi.org/10.4158/EP12072.OR

Parva, N. R., Tadepalli, S., Singh, P., Qian, A., Joshi, R., Kandala, H., Nookala, V. K., & Cheriyath, P. (2018). Prevalence of Vitamin D Deficiency and Associated Risk Factors in the US Population (2011-2012). *Cureus*. https://doi.org/10.7759/cureus.2741

Shadlen, M. F., Siscovick, D., Fitzpatrick, A. L., Dulberg, C., Kuller, L. H., & Jackson, S. (2006). Education, cognitive test scores, and black-white differences in dementia risk. *Journal of the American Geriatrics Society*, *54*(6), 898–905. https://doi.org/10.1111/j.1532-5415.2006.00747.x

Suda, T., Ueno, Y., Fujii, K., & Shinki, T. (2003). Vitamin D and bone. *Journal of Cellular Biochemistry*, *88*(2), 259–266. https://doi.org/10.1002/jcb.10331

Webb, A. R. (2006). Who, what, where and when-influences on cutaneous vitamin D synthesis. In *Progress in Biophysics and Molecular Biology* (Vol. 92, Issue 1, pp. 17–25). https://doi.org/10.1016/j.pbiomolbio.2006.02.004

Appendix I

Table 1.

General Sample Characteristics

	n	Age, Mean(SD)	Female(%)	White(%)	Serum 25OHD
Total Sample	21263	71.4(7.7)	14854 (69.9)	16713(78.6)	
Dementia	1898	77.0(8.5)	1209 (63.7)	1475(77.7)	31.2(14.7)
No Dementia	19365	71.3(7.6)	13645 (70.5)	15238(78.7)	28.7(14.9)
Group Differences			$p < 0.0001$	$p = 0.58$	

Figure 1.