DAILY VITAMIN D₃ SUPPLEMENTATION

AS A TREATMENT FOR HEALTH DISPARITIES

by

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ABSTRACT

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There is discordance in the vitamin D literature between correlational studies, which show an association between higher vitamin D exposure and good health, and randomized controlled trials of vitamin D supplementation, which are inconclusive. I test the theory that this discordance is due to false assumptions about how vitamin D affects human health. I use the method of systematic review and meta-analysis—accepting only experimental studies that supplement with the animal version of vitamin D, D₃, not D₂ or vitamin D metabolites or analogues, as well as accepting only studies with daily rather than less-frequent but larger doses—to show that daily vitamin D₃ supplementation has a statistically-significant beneficial effect on blood pressure and markers of diabetes. Using nationally-representative correlational data, I also demonstrate that the health disparities in blood pressure, if not diabetes, will be eliminated only with new health policies dedicated to health education on the vast nutritional difference in vitamin D status between black and white Americans. As a part of this dissertation, I also developed an online multi-user web application to facilitate systematic reviews and meta-analyses.
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I – INTRODUCTION

Those of us in the field of health education look to Healthy People, the public health plan of the United States, to guide our efforts. Updated every ten years, Healthy People provides “science-based national objectives for improving the health of all Americans.” One of the plan’s four overarching goals is to “achieve health equity, eliminate disparities, and improve the health of all groups.” Yet nowhere among the over 1,200 goals of the current plan, Healthy People 2020, will you find the phrase vitamin D (U.S. Department of Health and Human Services, 2010).

I became interested in vitamin D, the sunshine vitamin, during the first semester of my graduate studies. That is when I read this illuminating paragraph in “The Fat Soluble Vitamins: A, D, E, and K” in my Introduction to Nutrition textbook:

The pigments of dark skin provide some protection from the sun’s damage, but they also reduce vitamin D synthesis. Dark-skinned people require longer sunlight exposure than light-skinned people: heavily pigmented skin achieves the same amount of vitamin D synthesis in three hours as fair skin in 30 minutes (Whitney & Rolfes, 2008, p. 380).

The paragraph made me wonder whether there was a causal relationship between health disparities, the elimination of which is an overarching goal of my profession, and disparities in vitamin D status.

Previous Research

During my graduate studies, my research colleagues and I have published four articles on vitamin D (Rajan, Weishaar, & Keller, 2016; Weishaar & Rajan, 2014;
Weishaar, Rajan, & Keller, 2016; Weishaar & Vergili, 2013), all of which were based on correlational, cross-sectional data from the U.S. National Health and Nutrition Examination Survey (NHANES). Every year, NHANES randomly samples about 5,000 Americans to obtain data about the health and diet of the U.S. population. In two-year cycles, beginning with 1999-2000, the results of the NHANES questionnaires, examinations, and laboratory assays are released, carefully hiding any personally-identifying information. NHANES uses a research design called a complex survey (Zipf, Chiappa, & Porter, 2013), which requires special analysis software, but which provides nationally-representative data. While a graduate student, I learned how to use a version of this software written in the statistical programming language R.

Our first article used linear regression to show that vitamin D status moderates the disparities in self-rated health between racial-ethnic groupings (Weishaar & Vergili, 2013). The second implemented a formula published by other researchers to show that the recommended dietary allowance of 600 international units (IU) per day for vitamin D was not high enough for children with darker skin colors or heavier body weights (Weishaar & Rajan, 2014). The third showed that the effect of age, which is the only variable factor in the current recommended dietary allowance for vitamin D (400 IUs a day for those less than 1 year old; 600 IUs a day for those from 1 to 70; 800 IUs a day for those over 70), are inconsequential compared to the effects of skin color and body weight (Rajan et al., 2016). The fourth presented the probability of vitamin D deficiency by body weight and skin color in the U.S. population age 6 and older at three different deficiency targets—because even the definition of vitamin D deficiency is currently contentious (Weishaar et al., 2016).
Vitamin D status has been associated with childhood rickets and adult bone disease since vitamin D’s discovery about 100 years ago. Since then, however, researchers have realized that bone disease is only the beginning of vitamin D’s story. Inside the nucleus of cells, genetic processes use DNA to make the proteins of life. These processes are controlled by nuclear receptors, which up- or down-regulate the genome’s production of specific proteins in response to signaling molecules. Different organisms have different numbers of these receptors, which respond to a variety of substances, some of which are produced inside the organism and some of which are obtained externally (in humans, through the diet). Human cells have 48 nuclear receptors, one of which responds specifically to at least three vitamin D metabolites, each regulating, for the most part, different genes (Tuohimaa et al., 2013). Vitamin D’s signaling function appears to control at least two percent of the human genome and has been associated with a wide range of human diseases and conditions (Holick, 2007).

These effects are profound enough to be seen in human evolution. Following an idea first proposed in 1934 (Murray, 1934) and resurrected in the 1960s (Blois, Blum, & Loomis, 1968; Loomis, 1967), Nina Jablonski, an anthropologist, suggests that as human populations moved away from the equator, individuals in those populations with lighter skin had vitamin D levels closer to those of the ancestral population and consequently better health. These disparities, over many generations, led to the evolution of the spectrum of human skin colors we see in human populations today (Chaplin & Jablonski, 2009; Jablonski, 2004; Jablonski & Chaplin, 2000; Yuen & Jablonski, 2010). According to Jablonski (2012), “The array of colors found in human skin is greater than that seen in any other mammalian species” (p. 45).
Jablonski’s theory is supported by NHANES data. Vitamin D concentrations average 17 ng/ml in non-Hispanic blacks, 21 ng/ml (26% higher) in Mexican-Americans, and 28 ng/ml (62% higher) in non-Hispanic whites (Weishaar et al., 2016). In terms of the benefits of dark skin, the most dangerous type of skin cancer, known as invasive melanoma, is 25 times more likely in U.S. whites than in African-Americans (U. S. Department of Health and Human Services, 2014).

Rural residents of Ghana living near the equator (6° N) have an average vitamin D concentration of 30 ng/ml, which is higher than any group in the U.S. (Durazo-Arvizu et al., 2014). Traditionally-living people in east Africa (4° S) have an average concentration of 46 ng/ml (Luxwolda, Kuipers, Kema, Dijck-Brouwer, & Muskiet, 2012). This is our best available estimate of vitamin D concentrations over the course of human evolution.

Another anthropologist, Kathleen Fuller, was the first to turn the theory of the evolution of human skin color around and look at it from a health perspective (Fuller, 2003). From that perspective, the theory implies that health disparities will be found in all populations with diverse skin colors. Where sunlight is intense, those with lighter skin will be at a disadvantage; where sunlight is less intense, those with darker skin will have poorer health. Fuller says, “Humans are biological organisms and the presence of disease indicates a maladaptation between the individual human organism and its environment” (p. SR9). Yet by almost trivial changes to the environment, using sun protection and vitamin D supplementation, it should be possible to prevent these sunlight-related diseases.

There are dozens of articles in the literature supporting these relationships, which are slowly gaining some acceptance among medical and nutritional professionals, but
have yet to be recognized or taken seriously either by those who study health disparities or by those who set public health policy in the United States. The biggest barrier to acceptance of these theories in U.S. health policy is discordance among the conclusions of systematic reviews and meta-analyses of randomized controlled trials of vitamin D supplementation. There have been hundreds of randomized controlled trials looking at various health and performance effects of vitamin D supplementation. There is also already an abundance of systematic reviews and meta-analyses combining groups of these trials. But their results do not agree.

The resulting controversies reduce the confidence that physicians, nutritionists, and public health professionals have when they educate their patients about vitamin D. To educate others about health you have to know something about the causes of health, and vitamin D supplementation is a great example of an area in which confusion and controversy currently reign.

**Conceptual Framework**

I propose that the discordant results of these reviews are due to three unappreciated sources of heterogeneity – the form of vitamin D given as a supplement; daily versus less-frequent but larger bolus dosing; and differences from study to study in the baseline vitamin D status of the participants.

Existing reviews typically assume that vitamin D₂ and vitamin D₃ are equally effective, but this view has been challenged. Vitamin D₂, also known as *ergocalciferol*, is produced by fungi, including yeast. Vitamin D₃, also known as *cholecalciferol*, is
produced by plants and animals (Japelt & Jakobsen, 2013). Vitamin D has a long evolutionary history going back to the development of cells with a nucleus.

Long before vitamin D was discovered, it was known that certain foods—particularly cod liver oil—would cure rickets, a disease known since antiquity. Vitamin D was discovered in 1922 after a process for destroying the vitamin A in cod liver oil was developed and the resulting oil continued to cure rickets in rats. About the same time, another traditional cure for rickets, fresh air and sunshine, was confirmed by curing rickets in children using exposure to ultra-violet light (UV) from quartz-mercury lamps. Soon researchers discovered that UV radiation would also give antirachitic properties to many foods. Then they discovered that a fungal steroid derived from ergot and called ergosterol was the substance that picked up antirachitic properties when exposed to UV light. By 1931, several research groups had purified and crystallized the resulting product, which they named ergocalciferol (Wolf, 2004).

But plants and animals, unlike fungi, do not produce ergosterol. Even today many experts think that plants, like fungi, produce vitamin D₂; this misconception is a result of fungal contamination of plants and high concentrations of ergosterols in fungi (Japelt & Jakobsen, 2013). It took until 1937 to discover that in animals the precursor that gains antirachitic properties when exposed to UV light is a form of cholesterol. The resulting substance was named cholecalciferol or vitamin D₃.

Another 50 years passed before reports appeared in the literature suggesting that vitamin D₂ was not as effective in humans as vitamin D₃ (Tjellesen, Hummer, Christiansen, & Rodbro, 1986). By 2006 Houghton and Vieth argued in the American Journal of Clinical Nutrition that “Vitamin D₂ should no longer be regarded as a nutrient
appropriate for supplementation or fortification of foods” (Houghton & Vieth, 2006, p. 696). However, now, over a decade later, most medical, nutritional, and public health professionals continue to assume that vitamin D2 and D3 are equivalent. For example, in the U.S., vitamin D supplements available by prescription (rather than over-the-counter) continue to be compounded with vitamin D2 rather than D3. Moreover, systematic reviews and meta-analyses of vitamin D trials typically make no distinction between the two.

The existing reviews also tend to assume that vitamin D supplements will be equally effective in either small daily doses or in larger, less-frequent bolus doses. The human liver rapidly converts the parent form of vitamin D to 25-hydroxyvitamin D (25(OH)D). Consequently, assays to determine vitamin D status are based on serum concentrations of 25(OH)D, which will rise no matter how researchers split the vitamin D dose, leading to the assumption that daily and bolus dosing are equally effective.

However, after the liver converts the bolus dose to 25(OH)D, there is little remaining parent vitamin D in the serum. The liver-made 25(OH)D primarily ends up attached to vitamin D binding protein, an albumin-like blood protein. This 25(OH)D, which can be removed from vitamin D binding protein and further metabolized by the kidney, has a major role in calcium balance. However, the primary form of vitamin D absorbed by cells throughout the body for DNA signaling is likely the parent form (Hollis & Wagner, 2013). Cells outside the calcium-balance system may not depend upon the 25(OH)D at all. If this theory is correct, daily dosing, which maximizes the daily levels of parent vitamin D, should have a larger impact on health than bolus dosing.
The third source of heterogeneity is differences in the baseline vitamin D status of trial participants. Vitamin D supplementation studies are different from drug studies in that drug studies can assume that participants have not received the drug from any source other than the intervention. This is simply not the case with vitamin D. In addition to the intervention dose, both the control and intervention groups are exposed to vitamin D from sunlight and dietary sources. There can be additional differences in 25(OH)D status related to body weight and other personal, cultural, and geographic characteristics of the study’s population. Randomization, in expectation, accounts for these differences within a single study, but differences between studies in the baseline vitamin D status of the subjects is typically an unanalyzed source of heterogeneity in vitamin D meta-analyses. A study with subjects having very low baseline vitamin D status may show a larger effect than a study using the same dose, but with subjects having a very high baseline vitamin D status. As a measure of total exposure to vitamin D, 25(OH)D status should be a better predictor of effect than dose.

Moreover, if serum availability of the parent form of vitamin D is the actual determinant of beneficial effects, serum 25(OH)D status should be understood as a biomarker for vitamin D exposure rather than a biomarker for effect. Nonetheless, as a biomarker of total exposure, 25(OH)D status should be a better indicator of effect than dose, which accounts for only a part of total exposure. Study-to-study differences in vitamin D exposure, as measured by the mean 25(OH)D status of the control group at outcome, is likely to be a third source of important heterogeneity in meta-analyses of vitamin D supplementation.
In addition to issues with heterogeneity, many of the vitamin D systematic reviews show a trend toward effectiveness, but that trend is not statistically significant because of the limited number of trials for any particular outcome. However, the health effects of vitamin D may be homogenous enough to combine trials with different health and performance outcomes in a single meta-analysis. This would address the statistical problem posed by the limited number of trials for any single outcome. Generalizing the outcome has a long history in meta-analysis; the first meta-analysis ever done mixed trials with various outcomes of psychotherapy (Smith & Glass, 1977).

The existing systematic reviews and meta-analyses, for the most part, accept trials of any form of vitamin D (D$_2$, D$_3$, their metabolites, and patent-protected analogues, with and without calcium supplementation) and trials of both daily supplementation and supplementation with less-frequent but larger bolus doses. Standard practice also restricts each meta-analysis to a single disease or condition, even though vitamin D status correlates with a wide range of beneficial effects on human health and performance. This restriction limits the number trials available for analysis. The literature’s discordant results may be largely due to these issues.

**Systematic Reviews and Meta-Analyses**

In order to test my hypothesis about the discordant results of systematic reviews and meta-analyses of vitamin D supplementation, it became apparent I would have to switch my own research emphasis from correlational data sets such as NHANES to the
A systematic review is a special type of scientific literature review. Systematic reviews, which can be done with or without meta-analysis, are designed to control researcher bias (Chalmers, Hedges, & Cooper, 2002). Instead of allowing a reviewer to select only literature that the reviewer agrees with, a systematic review requires the reviewer to explicitly state the strategy that will be used to discover studies (with the goal of including all relevant studies in the analysis). The reviewer must also explicitly state the criteria that will be used for including and excluding discovered studies from the review. Ideally, before the actual review process begins, the reviewer must detail this strategy and these criteria, along with additional information about the proposed review process, in an online registry. If any changes are made to the proposed process, they must be explained as part of the review itself.

A meta-analysis, which can be done with or without a systematic review, brings statistical precision to the process of examining a group of studies and determining what they mean (Chalmers et al., 2002). Before meta-analysis, reviewers often evaluated the literature by counting the number of studies with significant and non-significant results and declared the truth resided in the group with the larger count. But statistical significance is highly dependent on the number of subjects in a study; any study with enough subjects will be statistically significant. The statisticians who developed meta-analysis realized that what was important was not so much the statistical significance of the study’s effect but the size of the effect (Glass, 2015). Statisticians developed standardized metrics, called effect sizes, which could be computed for the results of any
study. They also developed methods for weighting effect sizes to determine the size or strength of the weighted-mean effect and the statistical likelihood that future studies would have a similar result. Meta-analysis also involves measuring whether the studies all have similar results, which is called homogeneity, or whether the results of the studies are heterogeneous, or statistically dissimilar. When the results are heterogeneous, meta-analysis provides statistical methods to examine the heterogeneity and to possibly discover what is driving the differences between the studies.

A combined systematic review and meta-analysis of randomized controlled trials is currently the best practice for determining whether an intervention has a causal effect, rather than just a correlational relationship. As I considered doing a structured review and meta-analysis of my own, I hesitated because these are large projects, usually done by an entire team of analysts, which involve searching the literature to find studies, reviewing them for eligibility, extracting their results and judging their quality, statistically combining the results, and writing a report of the results. And every step by every team member ought to be tracked and documented.

With the encouragement of my advisors, I decided to create the software for doing a structured review and meta-analysis. The statistically-intense meta-analysis software I would need had already been written by others and was easily available in open-source R packages. What was missing was a good system for doing the systematic review. In terms of my time, the bulk of this dissertation involved combining open-source software packages with software I wrote myself, followed by getting it all running in the cloud so that anyone with a web browser and the link, app.open-meta.org, could access the application. This part of the project will have continuing value for me and for others.
Software like this is never finished, but as it became possible to do a bona fide systematic review and meta-analysis using the application, I completed two demonstration reviews on vitamin D supplementation. These reviews used criteria based on my conceptual framework, which requires daily vitamin D₃ supplementation. The first of these reviews was on the effect of vitamin D₃ on blood pressure and the second was on its effect on markers of diabetes.

**Specific Aims**

In the context of the specific aims of this dissertation, a beneficial effect refers to a weighted-mean effect size, from all available studies, favorable to better health, with a 95% confidence interval that does not include the no-effect value.

1. To develop a health education-focused, multi-user, open-source application for continuous online updating and replication of systematic reviews and meta-analyses.

2. To use this application to calculate the best current estimate of whether daily vitamin D₃ supplementation has a beneficial effect on systolic blood pressure.

3. To use this application to calculate the best current estimate of whether daily vitamin D₃ supplementation has a beneficial effect on markers of diabetes, such as fasting glucose and fasting insulin, glycosylated hemoglobin (HbA1c), homeostatic model assessment for insulin resistance.
(HOMA-IR) and β-cell function (HOMA-β), and the quantitative insulin-sensitivity check index (QUICKI).

The next three chapters discuss each of these three specific aims, in order, beginning with an exploration of the Open-Meta online application I have developed.
II – THE OPEN-META APPLICATION

Health professionals rely on systematic reviews and meta-analyses to determine appropriate and beneficial health policies. Organizations such as the Cochrane and Campbell collaborations and the Agency for Healthcare Research and Quality were at the forefront of developing the processes and methods used to create the systematic review and meta-analysis. These methods have also been adopted in other fields, such as nutrition and education.

**PRISMA: Best Practices for Systematic Reviews**

The best-practice procedure for conducting these studies has been documented in a body of work called Transparent Reporting of Systematic Reviews and Meta-Analyses, or PRISMA (PRISMA, 2015). (There are similar standards for reporting on the results of controlled trials called CONSORT (CONSORT, 2010).) The PRISMA Statement (Liberati et al., 2009) was originally published in 2009 and includes a checklist of items that should be included in the published report of a systematic review and meta-analysis, as well as an example flow diagram. A second related document, called the PRISMA Explanation and Elaboration (Moher, Liberati, Tetzlaff, & Altman, 2009), provides in-depth information on the items in the checklist.

In 2015 a similar checklist was published under the auspices of PRISMA, called PRISMA-P (Moher et al., 2015), which describes the information that should be included in the protocol for a systematic review and meta-analysis. Ideally, the protocol is written
and published online before the work begins (PROSPERO, 2012). Its goal is to reduce researcher bias by forcing the research team to commit to inclusion criteria and analytical methods before beginning the study, as well as to make sure the team collects all of the information that PRISMA requires in the final report. PRISMA-P also has an explanation and elaboration document (Shamseer et al., 2015) that provides additional information and examples of how to complete the protocol.

The PRISMA documents, procedures, and protocols define a systematic process for creating systematic reviews. What is missing is a systematic, multi-user, computer application that embodies that process. Research teams typically try to bring the process to life with check sheets and spreadsheets, but so many sheets result in a tedious and error-prone project. Reducing the tediousness typically results in more errors. Reducing the errors typically results in more tediousness.

**PRISMA and the Open-Meta Application**

The Open-Meta application was created to provide an online, structured process for a team of researchers who are creating a PRISMA-compliant systematic review and meta-analysis. It is intended to provide a team with support across the entire process from protocol development to publication. It is intended to be freely available and to encourage transparent crowd-sourced research. The Open-Meta application takes care of much of the tracking and tedious work of a systematic review while providing everything needed to meet the PRISMA protocol and reporting guidelines.

In theory, anyone can use the Open-Meta application to start a project. Anyone else can see the project’s protocol. Anyone intrigued by a project’s protocol can ask to
join the project. The project’s principal investigator has the ability to approve project membership and can grant permissions to each project member specifying what that member can contribute to the project. As the project progresses, anyone can see the current project status but only project members can complete tasks and move the project forward. Multiple people can work on a project simultaneously from any geographic location that has web access.

Methods

How to Build an Application in the Cloud

In addition to being an online store, Amazon, thorough its Amazon Web Services subsidiary, sells online computing resources. The Open-Meta application runs on an internet-linked computing resource provisioned by an Amazon service called Lightsail. When I set up the computing resource, I selected what operating system and major software components it would use. This basic set of components is called a stack.

One of the most popular stacks is called a LAMP stack; it consists of the components typically used to run a content management system, such as WordPress or Wikipedia. The LAMP stack consists entirely of open-source software. The L is for the Linux operating system, the A for the Apache web server, the M for the MySQL database, and the P for the PHP programming language.

The Open-Meta application is built on a slightly different stack that I call LEMRS. The L is for Amazon’s version of Linux, the E is for nginx (pronounced “engine-x”), which is a modern open-source web server slowly replacing the older Apache web server.
The M is still for MySQL. The R is for the R programming language. And the S is for Shiny, software that provides the ability to use the R language to display web pages that users can interact with. The Open-Meta application currently runs R, version 3.4.1 (R Core Team, 2017), shiny, version 1.2.0 (Chang, Cheng, Allaire, Xie, & McPherson, 2018) and a variety of add-on packages, including all of the packages in the tidyverse (Wickham, 2017).

The Open-Meta application is configured to have the nginx server deal with any URL request except those that link to an imaginary app folder. When nginx sees a URL that requires access to that folder, it is configured to pass the request to the Shiny Server, which is running the Open-Meta application. The Shiny Server will start a new session on the Amazon resource specifically for the device that has requested the URL (typically a person using a web browser) and pass anything in the URL after /app/ to the new session. Imagine for the moment that the requested link is: http://app.open-meta.org/app/?help.

**How a Simple Page Works**

At this point, control passes from the LEMRS stack to the Open-Meta software that I have written in R, which, for the most part, links together R packages and other open-source technology written by others. For example, the look-and-feel of the site is based on a Bootstrap 4 theme called Dashboard (Bootstrap Team, 2017).

Briefly, my software asks the user’s web browser if it has an Open-Meta sessionID cookie. If it does, the software looks up that sessionID in a MySQL table to determine whether the request has come from a known, logged in user or from the great unknown. If it is a user who is logged in, the software recalls a few details about that user,
including the permission level the user has. Then the software looks to see if the requested page, help, is a valid page. Back when the Open-Meta application started up, one of the things it did was load a table of all the valid pages from MySQL and store that table in memory. The requested page, help, is in this list, so it is valid.

Next the software looks in the same table to see what permission level is needed to view that page and compares it to the user’s permission level. Since anyone can see the help page, the software next loads a file called Help.R that has the additional code needed to display the page. The code in the file sends the page as HTML to the user’s browser. The user sees the help page. This all happens in computer time, so to the user it appears pretty much instantaneous.

On the help page there is a short message from me and a form for sending me an email. It looks like Figure 2.1.

At this point our Shiny session is still running, but it doesn’t have anything to do. If the user fills in the form, the user is actually interacting with the web browser software on the user’s own device, not with the Open-Meta software. (Technically, Shiny gives our software the ability to monitor exactly what the user is doing down to any mouse movements or keystrokes that occur inside the browser window, but that is typically way more information than we want to know.) However, if the user clicks one of the buttons or links I have circled in red in Figure 2.1, our session will get a buzz and will look to see what the user clicked on.

If the click was on Home, Register, Login, Help/Contact, or Cancel, our session will send a message to the browser telling it to request a different URL. Our current session will end and a new one will start using the new URL and repeat what it takes to
know who the user is and whether the URL is a valid page. Also keep in mind that several users can be doing this at the same time, each with a separate and distinct session.

Figure 2.1. Open-Meta help page with links circled in red.

On the other hand, now imagine that the user clicked the Send button in Figure 2.1. In this case our help page code gets the content the user has entered into the email form and checks to see if it is valid. If it is not, we send a message to the user’s browser saying so. This looks like Figure 2.2.

If, on the other hand, the user’s input is valid, the code puts it all in a specific format for email and sends it, with a signature validating that Open-Meta is sending it, to Amazon’s Simple Email Service, which will take care of delivering it. After that, the code,
as with the other links on this page, will tell the browser to go to a different URL, which
will end this session and start a new one.

Figure 2.2. Open-Meta help page after user clicks *Send* with invalid input.

One final detail. Note that in Figure 2.1 no one is logged in. If someone was
logged in, the *Register* link would have their login name and the Login link would say
Logout. There is a sample of what the page would look like in Figure 2.3.

Not only are the links at the top right slightly different because the user is logged
in, note that the form is no longer asking for the user’s email address. That is because the
program knows the email addresses of all users and we know who this user is. So there is
no need to ask for that. Also, if the logged-in user was the Open-Meta system
administrator, there would be no reason to send email to oneself, and the Help/Contact link would instead say *Admin* and lead to pages where administrative information is displayed and administrative options can be set.

![Open-Meta.org](image)

**Figure 2.3.** The Open-Meta contact page with a logged in user.

The *Help.R* file is one of the simplest in the Open-Meta application and consists of about 60 lines of code and comments. The Open-Meta page table currently lists 26 pages. There are about a dozen additional shared helper files that various pages load when needed. Most of these files have about 250 to 400 lines of code and comments; the largest has over 1,600.
Results

While anyone can view content in the Open-Meta application, in order to do anything else, the first step is to register for an account. To register, the user must provide a user name new to the system, a password, and a working email address. During the registration process, an email is sent to that email address with a numeric code that must be entered to complete the registration. This ensures that the email address is valid and that it belongs to the person who is registering. Passwords are stored in the database in an encrypted format using an R package called *bcrypt* (Ooms, 2018).

Initial Screens

Once a user has registered and logged in, the screen looks like Figure 2.4. In addition to the links related to the user’s account and help at the top right, there are now links in the middle of the page that display the projects the user has joined or started (*My Projects*), all the current active and completed projects (*Active Projects* and *Finished Projects*), and a link that allows the user to create a new project (*Start a Project*).

![Figure 2.4. Home screen for logged in users.](image-url)
If the user clicks on *Start a Project*, the screen in Figure 2.5 appears. Here the user enters a name for the project. As on the help page, there is additional text on this page in a yellow box that explains to the user what will happen. Boxes like this are used for additional information throughout the application.

![Figure 2.5. The screen for beginning a project.](image)

After the user clicks *Start a Project*, behind the scenes a new MySQL database is created for this project. But the user is taken to a screen for entering the project’s protocol. This page follows the requirements of the PRISMA-P protocol for systematic reviews and meta-analyses. There are over 30 individual sections on this page that must have text entered into them before other project features are activated. Among these are the exact criteria for inclusion for participants (P), interventions (I), comparisons (C), outcomes (O), and time spans (T), which together are known as the project PICOTs or PICOTS.
Each section of the protocol includes instructions for that section based on the PRISMA-P requirements. Often the instructions include references to the PRISMA-P documents.

In addition to the page for entering the project’s protocol, at this stage there are two other menu items for those who are not project members. One is Join and the other is Contact. Joining a project allows the user to receive emails sent by the Principal Investigator to the project team and allows the PI to give that user additional abilities within that project by changing the user’s role. Contact provides a form for sending an email to the PI. Those who are already project members see only the Contact menu item, except for the project’s Principal Investigator or Project Administrator, for whom this menu item is Members & Settings.

**Project Members and Settings**

The Members & Settings page is shown in Figure 2.6. On this page there are three submenu items, Project Members, Customize Data Collection Forms, and Activate without Protocol. That third item provides a way to play with the Open-Meta system without writing a protocol. The second provides a way to customize and enhance some of the Open-Meta forms that collect data. The first allows the PI to change user roles and to email individual project members or all the project’s members at once.

The Open-Meta system has the following user roles for each project:

Non-Member: Anyone can view most pages of any project.

Observer: Will also receive emails sent to All Members of the project. When users join a project, they begin with this role.
Reviewer: Can also review citations to decide if they pass or fail the project’s inclusion criteria.

Investigator: Can also extract data from studies and create analyses.

Researcher: Can also enter searches.

Principal Investigator, Co-Principal Investigator, and Project Administrator: Can also access the project’s Members & Settings and Publish pages. (These roles have all available permissions.)

Figure 2.6. The Members & Settings page, available to Principal Investigators.

After the protocol is complete (or the project has been activated without a protocol), the menu items become Protocol, Search, Review, Extract, Synthesize, Publish, and either Contact or Members & Settings, depending on the user’s role. At this point anyone can view the project’s protocol, but the protocol can no longer be edited. The
Protocol page does allow the PI to add amendments and to provide references for publications resulting from the study.

**Search for Studies**

The next step in a systematic review is to search in academic databases for publications that report the results of studies that meet the project criteria. Because the goal is to find *all* the relevant studies, the search terms used at this stage typically also find many studies that meet some, but not all, of the project’s criteria. In the field of health, the National Library of Medicine provides a database that is publically available, PubMed (U.S. National Library of Medicine, 1997), and Open-Meta can search for and automatically download the associated data from citations found on PubMed. However, most, if not all, other academic databases are not available directly to the public, but must be accessed through a research library. The Open-Meta app is not able to directly search and download from these other databases. Instead, the researcher must do the search in the academic database and download the references as if they would be loaded into reference management software such as EndNote. But instead (or in addition), the user uploads the file to Open-Meta.

Figure 2.7 shows a live search of the PubMed database for the search terms *(vitamin D*[Title/Abstract]) AND “systematic review”*[Publication Type]*. Above the bottom comment box you can see that the search found 149 citations, all of which have abstracts and PubMed IDs (PMIDs), and 131 of which have document object identifiers (DOIs), which help to both indentify duplicate articles and to find articles online. Searches can be saved without processing, which allows editing the search later.
For example the researcher might decide to change the search terms. Once the search is processed it can no longer be changed and the references cannot be deleted from the project.

Figure 2.7. Live search of the PubMed database.

Figure 2.8 shows what the screen looks like when uploading a citation file. About two-thirds of the way down the screen there is a grey *Browse* button that allows researchers to select files on their own computers to upload. In this case, a file a researcher named 180512 – *Cochrane Central 14 hits.txt* has been uploaded. In the *Query*
box, the researcher should next enter all the details about the origin of this file; most importantly the search terms used. This information is needed when writing up the results of the systematic review.

Figure 2.8. Uploading a citation file from Cochrane CENTRAL.

While files can be uploaded from any database, Open-Meta has special support for PubMed, Cochrane CENTRAL, and the Web of Science databases and will accept reference files in the following formats: PMID, MEDLINE (or .nhib), Cochrane CENTRAL export format, EndNote Desktop (.ciw), and .ris and .BibTex, one or the other of which is available on most, if not all, other databases.
Figure 2.9 shows the current list of searches for this project. In this example, the first search has been processed, so it can no longer be edited or deleted. The *Update* button would create a duplicate of this search in the list. The duplicate can be used to repeat the search at a later date to update the project with citations published since the initial search.

![Sample Project screenshot](image)

Figure 2.9. Open-Meta’s list of saved and completed searches.

**Reviewing Studies**

As soon as a search has been processed, its studies are available for review. In this stage of a systematic review, researchers look at each study’s title and abstract to determine if the study meets project criteria. Figure 2.10 shows the *Review* feature in the Open-Meta application.
Initially, the review feature provides a way to find a specific citation or groups of citations by search on a phrase in the title or abstract, an author name, a year of publication, or a journal name. Reviews can also be searched by review status over the whole project or by review status for the current reviewer. In Figure 2.10, there has been a search for blood pressure in the title or abstract. Just above the results we see that four articles have been found and none of them have been reviewed yet (the entire page is not shown). To review these articles, the reviewer would click one of the green Review buttons, and the system would show a page like the one shown in Figure 2.11.

Figure 2.10. Selecting studies to review.
In Figure 2.11 the reviewer can *Fail* or *Pass* the study, as well as *Skip* forward or backward in the list of studies selected in Figure 2.10. The project PI can specify in the project’s settings whether a reason code must be checked before *Fail* is clicked. The reason codes shown in Figure 2.11 are the default codes (DNMPC means *does not meet project criteria*), but the PI can replace these with custom codes in the project’s settings.

![Sample Project](image)

Figure 2.11. Reviewing a study to decide if it meets the project’s criteria.

One other interesting feature of the page in Figure 2.11 is the list of *Full text links* on the line after the citation’s year and journal. The *PMID* link, if available, will open the PubMed page for this reference in another tab; this page often has a link to the actual
article. The **PMCID** link, if available, will go directly to the article, as will the **DOI** link, if available. The **Google Scholar** link, which is always available, will initiate a search for the article. These links are not usually needed for this stage of review, but they are very helpful when, for example, the abstract is missing.

Figure 2.11 also shows a submenu with the selections **Dashboard**, **Duplicates**, and **Citation List**. The dashboard displays three simple graphs showing the percentage of articles that were duplicates; the percentages for not-reviewed versus failed versus passed; and for the articles that have failed only, the number of times they have been reviewed. Ideally, multiple reviewers will examine each study, although in the Open-Meta process, as soon as any reviewer has given an article a pass, that article moves to the extraction stage for a more comprehensive review. The **Duplicates** button leads to an unfinished section of the Open-Meta application for identifying duplicate articles. Right now the application identifies duplicates by PMID, but if a publication is not in PubMed it won’t have a PMID, so this section needs further work.

**Extracting Data from Studies**

After any reviewer has clicked the **Pass** button, indicating that the citation meets the project’s criteria, the citation is visible in the Open-Meta application’s extraction process.

The **Extract** menu item has a sub-menu with three items, **Dashboard**, **PICOT Setup**, and **Extraction List**, as shown in Figure 2.12. Like the **Search** and **Review** menu items, the **Extract** menu item’s **Dashboard** displays summary data about the project’s progress in graphical form. For **Extract**, as seen in Figure 2.12, the graph on the left
displays the review status of all citations in the project, while the graph on the right displays the extraction status of the citations that have passed the Review process.

Figure 2.12. Dashboard for the extraction process.
The **PICOT Setup** submenu, as shown in Figure 2.13, allows project team members who have data extraction permission (investigator role and higher) to customize the project’s participant groups, interventions, comparisons, outcomes, and time spans. This section has its own sub-menu for selecting which study characteristic to customize. In the figure, *Time Spans* has been selected. The project team has already added a number of time spans in this figure, but is able to add more, if necessary, as the study progresses, or to edit or delete an existing time span.

![Figure 2.13. PICOT setup in the extraction process.](image)

The **Extraction List** submenu leads to a page, shown in Figure 2.14, that is much like the citation list shown in Figure 2.10. The major difference is that the extraction list shows only citations that seemed to at least one reviewer to have met the criteria of the
project during the *Review* process. As before, it is possible to search or filter the citations. Note that in Figure 2.14 there has been a search for citations that include the word *insulin* in the title or abstract, that there are 43 results, all of which have been reviewed for extraction. During this more in-depth Extract review process, nine of the studies failed to meet project criteria, while 34 have passed the extraction phase of the project.

![Figure 2.14. Selecting articles for extraction.](image)

Clicking one of the green *Extract* buttons in Figure 2.14 takes you to the page for extracting data from a study. This page has multiple features and is too long to show in
one figure. Figures 2-15 through 2-18 all show various features of the page for extracting data from a study.

![Open-Meta.org](image)

Figure 2.15. The top of the extraction page.

Figure 2.15 shows the top of the page. Like the review page shown in Figure 2.11, citation data, including the title, authors, and abstract are displayed, as are the Full Text Links for finding the entire article online. The extraction phase requires the complete article and these links facilitate the task of obtaining article access. When the project team member is working from a university or research library internet connection that will display articles the library has access to, such as the Wi-Fi connections at Teachers College, the Full Text Links are particularly powerful.

The first section below this one allows collection of study-level data and is shown at the top of Figure 2.16. The PRISMA requirements for systematic reviews include
judging the quality of each study using the questions shown in this section. The PI can also add additional questions to this section. To edit this section, the project team member clicks the green *Edit Study-Level Data* button.

The extraction page shown in Figure 2.16 has two additional sections. In the middle, above the green *Update Review* button, is where the team member will enter a final decision on whether this study meets the project’s criteria. Again, the project’s customized reason-for-failure codes are available. The team member can also leave comments about the decision, which will be helpful if the decision is reviewed.

The final section at the bottom of Figure 2.16 allows viewing, editing, or creating new arms for the study. The Open-Meta application defines an *arm* as a set of interventions, outcomes, and time spans that have the same control group. So only a study that separately tracks participant groups or comparisons will have more than one arm. For example, a study may separately track participants from different age ranges. Each age range would have its own control group and, therefore, its own extraction arm.
Figure 2.16. The middle of the extraction page.
Figure 2.17. Editing a study arm.

Figure 2.17 shows an arm being edited. When editing any section, the extraction screen is replaced with a screen that only allows canceling from or saving that section. Typically these forms can include custom questions the project’s PI has added using the Customize Data Collection Forms menu shown back in Figure 2.6. This allows the collection of additional data about the studies in the project.

The PI of the project we are looking at in this figure did not use customized participant groups or comparisons. Eligible participant group and Eligible comparison are the application defaults. However, using the feature shown in Figure 2.13, the PI has added the interventions, outcomes, and time spans needed to extract data. Typically these are added, as needed, during the extraction process. After adding needed PICOTs, editing
the Arm allows selecting the exact interventions and time spans used by the current citation. In Figure 2.17, the 800 IU/day intervention and the Baseline and 4 month time spans have been selected.

Figure 2.18. Bottom of the extraction page.

Below the green Edit Arm-Level Data button shown in Figure 2.18, there is a form for entering the data extracted from the study that is based on the PICOTs selected when setting up the arm in Figure 2.17. The Outcome dropdown lists all the outcomes.
that have been entered by the project team using Figure 2.13’s *PICOT Setup*. When a
different outcome is selected, the form fields will change to blanks if nothing has
previously been entered for that outcome or the form will show the previous entries, as in
Figure 2.18.

The dropdown labeled *Outcome is* has choices for *Continuous, Dichotomous, or An Effect Size*. The *Continuous* setting supports the following Data Formats: *Means & SEs, Means & SDs, Means & Overall SD, t-test t-value, and t-test p-value*. The
*Dichotomous* setting supports *Counts and Proportions*. The *An Effect Size* setting
supports *Cohen’s d, Hedge’s g, Odds Ratio, Log Odds Ratio, Relative Risk, Log Relative
Risk, Pearson’s r, Cohen’s f, and eta-squared*. If necessary, the effect size setting allows
an effect size resulting from a calculation the application does not natively support to be
entered.

If multiple interventions or multiple outcomes have been checked in Figure 2.17,
the data entry form in Figure 2.18 will expand to include them all. After results for an
outcome, intervention, and time span have been entered and the *Save Results* button
clicked, the effect size for that combination is listed in the results at the bottom of the
page, as shown in Figure 2.18. The Open-Meta application does not currently support
selecting which effect size to calculate. It always calculates, saves, and displays the
results in the *Hedge’s g* effect size.

**Running a Meta-Analysis**

The *Synthesize* menu is where we leave systematic reviewing behind for good and
enter the world of meta-analysis. At this time, the only submenu items on this page that
are complete are Analyze and Forest Plot. Figure 2.19 shows what Analyze looks like.

The project team can create any number of analyses with selected PICOTs. The blue View Analysis button leads to a page where the analysis is set up and displayed. It can be a long page if there are lots of PICOTs, as in the example shown in Figure 2.20.

![Open-Meta.org](image)

**Figure 2.19.** The Analyze submenu of the Synthesize process.

Each analysis has a name, a method, and selected PICOTs from all PICOTs that are available for this project. At this time the only meta-analysis method the application supports is the dependent effects model. In the example shown in Figures 2-20 (upper portion of page) and 2-21 (lower portion of page), virtually all of the PICOTs are selected. As you can see, for a large study there can be many of them. In this case only one outcome, which was declared ineligible in this study’s protocol, is not included in the
analysis. At the bottom of Figure 2.21 you can see the green button that leads to *Edit Analysis*.

![Figure 2.20. Description of a specific analysis (upper portion).](image)

The actual results of the meta-analysis appear below that button, as shown in Figure 2.22. The meaning of these results are explained in other chapters of this dissertation. But briefly, the dependent effects model allows multiple interventions, time spans, or outcomes to share the same control group. Other meta-analysis methods do not allow this. With those older methods, the researchers must choose one representative
intervention, one representative time span, and one representative outcome from each study. Obviously, this can lead to biased selections, unlike the dependent effects method, which does not require these selections.

Figure 2.21. Description of a specific analysis (lower portion).
Figure 2.22. Below the analysis settings are the actual result of the analysis.

There are examples of the Forest Plot result in other chapters of this dissertation. The other menu items on this page, including the Publish process, are incomplete. Publish will eventually make it easy for the project team to download tables, figures, and bibliographies related to the project.

Discussion

The Open-Meta application is the first freely-available multi-user application for completing systematic reviews and meta-analyses. There is only one other system
remotely like the Open-Meta application. And like the Open-Meta application, it is still in beta-test. It is the Cochrane Collaboration’s Rev Man Web (Cochrane Collaboration, 2018), which has been designed for Cochrane’s own reviewers.

**Innovations**

One of the innovative features of the Open-Meta application is the use of a statistical method that includes baseline data when calculating effect sizes. Figure 2.18 on page 39 shows an example of the form the application uses to collect this data. The pretest-posttest-control group design is a best practice and is commonly used in randomized controlled trials. However, very few, if any, online effect size calculators incorporate the baseline data for the control and intervention groups in the effect size calculation.

Since participants are assigned to the groups randomly, there is an expectation that the groups are equivalent. However, the expectations created by randomization apply only over large numbers of participants and over the long run. Given the relatively limited number of participants in most controlled trials, it would actually be a surprise if the groups were initially equivalent on the outcome measures. This is why baseline data are collected to begin with—to determine how different the control and intervention groups are on outcome and demographic variables at the beginning of the study.

In his paper *Estimating Effect Sizes From Pretest-Posttest-Control Group Designs*, Scott B. Morris (2008) notes there is not even agreement among statisticians on how to analyze this design when the full data set is available, much less when you only have summary statistics such as the mean, standard deviation, and number of subjects in each
group. When working with the full data set, Morris says, typical analysis options are a t-test on the group change scores, mixed effects analysis of variance with treatment as a between-groups factor and time span as a within-groups factor, analysis of covariance with baseline scores as a covariate, or a test of group differences using residualized change scores.

For a meta-analysis, only summary statistics are available in published reports of research studies. In this case, Morris says, three methods for determining an effect size have been suggested. They all use a Cohen’s d-like formula \( \frac{\text{outcomeMean} - \text{baselineMean}}{\text{standard deviation}} \) to separately calculate the baseline-to-outcome effect sizes for both the treatment and control groups, then they subtract the effect size of the control group from the effect size of the treatment group, and finally they multiply that by the result of a bias-correction formula. For the first method, the divisor in the effect size calculation is not a pooled standard deviation, but just the standard deviation of the control group at baseline for the control group effect size, and the standard deviation of the intervention group at baseline for the intervention group effect size.

The second method is similar, but the divisor is the pooled standard deviation of the treatment and control groups at baseline and the bias-correction formula is slightly different. In the third method, the divisor pools the four standard deviations of the treatment and control groups at both baseline and outcome measurement. However, because of dependency issues, Morris says, there is not an exact bias correction formula for this method.
Morris proceeds to examine the three methods in detail, using real and synthetic data, and reports that method two appears to be the most accurate. I wrote the R code to incorporate this method into the Open-Meta application.

With dependent effects analysis, it becomes possible to have multiple baseline groups (control plus one for each intervention). An improved method might pool the standard deviations for all these groups, but to my knowledge that has not been statistically explored.

**Limitations**

The primary limitation of the application is that it is a single-programmer project. To be successful, it needs a team of open-source developers. And, of course, it needs users. At the moment, without users, the application has received limited testing. Bugs can only be discovered through testing and usage. And they cannot be fixed until they are discovered. The application needs attention and interest.

Expanded awareness of the application and its professional usefulness among the public health and nutrition communities of educators, researchers, and policy professionals could result in the attention the application needs. Awareness in the meta-analysis statistical community and those they work with and teach would also be very helpful.

**Future directions**

There are several features of the Open-Meta application that are incomplete and must be finished: identification of duplicate citations, a system for public commenting, combining multiple citations about a single trial, finishing the meta-analysis features
related to PRISMA diagrams, sequential analysis, bias plots, and meta-regression, and finishing the Publish process.

There are also necessary improvements—for example, the application should provide a method to categorize and sort PICOTs numerically, alphabetically, or categorically. It should support entering effects in the original research metrics, such as the mm Hg metric used for blood pressure. The next chapter would have been somewhat clearer if that had been part of the original design.

However, the primary future task is to recruit users. Without users, the application has no reason to be. With users, it will also attract open-source programmers and larger organizations that want to support it. That is the ultimate goal of the project.

Conclusion

The Open-Meta application has the potential to provide health educators with the ability to use systematic reviews and meta-analyses to inform the best health care policies. It simplifies the review process while making that process totally transparent, allows multi-user teams to work on a project simultaneously, and can provide conclusive results. Its major weakness at this time is a lack of users, but that may change as people learn about its availability.
III – DAILY VITAMIN D₃ SUPPLEMENTATION AS A TREATMENT FOR HEALTH DISPARITIES IN BLOOD PRESSURE

It is well-known that high blood pressure is among the many health disparities between African- and European-Americans (Berg, 2018). It is less well-known that skin color is an evolutionary adaptation to sunlight. Darker skin is more protective against intense sunlight than lighter skin, but at the latitude of the U.S., darker skin is less effective at producing vitamin D from sunlight than lighter skin colors. Since sunlight is the major source of vitamin D in humans, there is also a large racial disparity in vitamin D status in the U.S. (Weishaar et al., 2016). Although U.S. racial health disparities are rightfully considered to have primarily social causes, in this chapter I will examine the biological disparity of vitamin D status as a cause of the racial disparity in blood pressure, as well as the potential of daily vitamin D₃ supplementation to eliminate this health disparity.

Blood pressure is measured in millimeters of mercury (mm Hg) and is reported as two numbers, systolic blood pressure is the higher number and represents the pressure when the heart is contracting, Diastolic blood pressure is the lower number and represents the minimum pressure while the heart fills with blood. For simplification, this report considers only the higher, systolic blood pressure.

My examination will have two steps. First I will confirm the degree of the disparities in systolic blood pressure and vitamin D status by analyzing U.S. nationally-representative data from the U.S. National Health and Nutrition Examination Survey
Second, I will report on the actual effect of daily vitamin D₃ supplementation on systolic blood pressure using a systematic review and meta-analysis that combines the results of all randomized controlled trials that have tested this intervention.

**Research Questions**

My research questions are:

1. In a nationally-representative sample of U.S. individuals age 8 and older, how large are the systolic blood pressure and vitamin D disparities between those individuals who self-identify as non-Hispanic black and non-Hispanic white in the U.S.?

2. Does daily vitamin D₃ supplementation have a statistically-significant beneficial effect on systolic blood pressure large enough to eliminate this disparity?

**Methods**

This study uses only previously published data without identifying information; consequently the Institutional Review Board of Teachers College, Columbia University ruled this study exempt from review and issued approval 17-220 on March 12, 2017.

The overall protocol for the systematic review and meta-analysis described here was accepted and published by the International Prospective Register of Systematic Reviews (PROSPERO) on April 2, 2017 (Weishaar, 2017). The Open-Meta application,
which was used to facilitate this systematic review and meta-analysis, also requires entering the proposed protocol as the first step of establishing a new project (Weishaar, 2018).

The primary adjustment made to the overall protocol for this dissertation is that the overall protocol proposes including all trials with any health or performance outcome. This chapter, however, is synthesizing results only from trials that measured blood pressure as an experimental outcome. Likewise, the next chapter will examine results only from trials that measured markers of diabetes.

Data Sources

**NHANES study: Research question 1.** NHANES collects cross-sectional data representative of the non-institutionalized U.S. population in two-year cycles using a randomized sampling design called a *complex survey* that uses both clustering and stratification. Data are collected on hundreds of variables from about 5,000 participants per year.

NHANES measures vitamin D status with a blood test for 25-hydroxyvitamin D (25(OH)D). However, there are actually two versions of vitamin D, one produced in yeast and fungi (vitamin D$_2$) and the other in plants and animals (vitamin D$_3$) (Japelt & Jakobsen, 2013). In humans, sunlight produces vitamin D$_3$ in the skin, which is readily converted to 25(OH)D$_3$ in the liver. 25(OH)D is strongly attracted to vitamin-D binding protein, an albumin-like component in the blood. Consequently, the amount of 25(OH)D$_3$ in a participant’s blood sample is a good measure of vitamin D$_3$ exposure. Both vitamin
D₂ and D₃ are also found in small amounts in some foods. Over-the-counter supplements typically contain vitamin D₃, while the vitamin D available by prescription is vitamin D₂.

Vitamin D data was not collected during the first two-year NHANES cycle and has not yet been released for the most recent cycles, so this chapter dropped those cycles. In addition, the 25(OH)D assay method used before 2007-2008 did not report 25(OH)D₂ and 25(OH)D₃ separately. The D₂ versus D₃ issue becomes visible in a blood pressure study, so I dropped the three cycles that did not split them out, leaving the four cycles of data collected from 2007 to 2014.

NHANES measured blood pressure data in all cycles from all participants age 8 and older. Consequently, in this chapter I dropped all data from participants younger than 8. The NHANES protocol specifies that blood pressure be measured and reported multiple times and averaged by the researcher using a prescribed algorithm (National Health and Nutrition Examination Survey, 1999).

NHANES used a self-report questionnaire to determine participant race and ethnicity in all cycles for all ages. Because this study concerns racial health disparities, we dropped all data from participants who did not self-identify as non-Hispanic black or non-Hispanic white. NHANES collected age and measured body weight in all cycles for all participants.

**Systematic review and meta-analysis: Research question 2.** The "experimental unit" in a meta-analysis is a report of the results from a study. In order to discover appropriate reports, I used the Cochrane Central Register of Controlled Trials (CENTRAL). Since 1998, Cochrane review groups have completed 11 systematic reviews of vitamin D supplementation on pregnancy, infection prevention in children,
management of asthma, treatment of chronic pain in adults, mortality (twice), cancer prevention, fracture prevention, cystic fibrosis, bone mineral density in children, and corticosteroid-induced osteoporosis. The most recent study on mortality includes more trials than any other vitamin D systematic review ever published.

CENTRAL contains a record for every study examined in its own reviews. In addition, CENTRAL is updated monthly with records of new randomized controlled trials retrieved from Medline and EMBASE, from specialized registers created by Cochrane's review groups, and from Cochrane's hand search results register. Because of the comprehensive nature of CENTRAL's database of randomized controlled trials, CENTRAL by itself should provide a systematic view of all relevant randomized controlled trials. This avoids the additional work of stage 1 reviews finding duplicative results in additional databases that are a mix of randomized controlled trials and other types of publications, which made this project feasible for a single author. Complete information on the contents of CENTRAL and how it is updated is available (Cochrane Library, 2000-2019).

My search strategy was to use the MeSH descriptor [Vitamin D] explode all trees. Preliminary searches found that additional vitamin D-related MeSH terms did not increase the number of records returned by CENTRAL. Adding additional vitamin-D related text terms vastly increased the number of records returned, but I did not have the resources to review that many papers, particularly since almost all would fail stage 1 review anyhow (these are trials in which vitamin D is mentioned somewhere in the full text; the MeSH descriptor identifies trials that are actually about vitamin D). CENTRAL is limited to trials in humans by design.
An initial download of bibliographic information completed on March 31, 2017, returned 2,470 study reports. All of these reports received a stage 1 review. The initial search was refreshed on January 10, 2019, which added 1,442 references. The vast majority of these new reports were studies recently added to CENTRAL that had been proposed at clinicaltrials.gov, an online registry for health-related randomized controlled trials. Clinicaltrials.gov is to the randomized controlled trial what PROSPERO is to the systematic review and meta-analysis. However, most of these proposed studies have no results yet. Because the January 2019 refresh included so many more additional articles than expected, only trials from this refresh with "blood pressure" or "hypertension" in the title or abstract were reviewed for eligibility in this chapter’s study.

My protocol also specified that any other vitamin D₃ trial not discovered by this process should be included in the study. I discovered, either by reference in an existing study or by a PubMed search on the clinicaltrials.gov id, 14 additional studies, which I added to the database. Of the 3,926 studies added to the Open-Meta application for this project, two were duplicates, leaving 3,924 studies. Of these, 1,037 were not reviewed for this study because they came from the January 2019 data refresh and did not appear in the "blood pressure" or "hypertension" searches, 2,510 failed stage one review, and 377 moved forward to the stage 2 or extraction function in the Open-Meta application.

Data Handling

**NHANES study: Research question 1.** All of the data used in this study are publically available on the NHANES website (National Center for Health Statistics, 2017). Each two-year cycle has its own set of data files. This study used datasets from
four cycles (2007-2008 through 2013-2014), which are distinguished by filenames containing the letters "E" through "H". For each cycle, this study used the files for:

Demographic Variables and Sample Weights: This file includes, among many other variables, variables required for the statistical analysis of a complex survey (strata, psu, mobile exam unit (MEC) weight), NHANES cycle, and participant age and race/ethnicity.

Body Measures: This is one of the examination data files, which, among other variables, includes body weight in kilograms.

Blood Pressure: This is another of the examination data files, which includes up to four measures of systolic blood pressure for each participant 8 years and older.

Vitamin D: This is one of the laboratory data files, which includes 25(OH)D$_2$ and 25(OH)D$_3$ for each participant over age 1 in the included cycles.

SEQN: Every file includes a “key” column of respondent sequence numbers, which are used to match rows in each file with particular participants. The end result after data handling is a single table with each eligible participant having a row in the table and each variable its own column.

After dropping cycles without 25(OH)D data split between D$_2$ and D$_3$, dropping ages without blood pressure data, dropping participants self-identifying from other ethnicities, and dropping cases with missing data on any of the critical variables, the dataset consisted of 16,319 unweighted cases (5,603 non-Hispanic black; 10,716 non-Hispanic white) in 124 complex survey clusters.

Systematic review and meta-analysis: Research question 2. The Open-Meta application facilitates Stage 1 Review by displaying the title and abstract of each report,
as well as other bibliographic information and, when available, links to the full text of the report. My criteria for inclusion were:

**Study:** The study had to be a randomized controlled trial.

**Participants:** Any RCT with human participants was allowed.

**Intervention:** The only allowable intervention was daily vitamin D₃ supplementation. Many of the studies in the database gave participants vitamin D₂; vitamin D metabolites, such as 25(OH)D; or vitamin D analogues, which are vitamin D-like molecules created to be patentable. Other studies used large bolus doses of vitamin D₃ at weekly or longer intervals. Both of these types of studies were ineligible for inclusion in this project.

**Comparison:** The comparison group could be no-intervention, placebo, or standard-of-care. The comparison groups had to be identical except for the daily dose of vitamin D₃, so, for example, both groups might also take an equal amount of calcium. No-intervention control groups were considered identical to placebo control groups receiving no supplementation. Study arms in which the control group received a smaller dose of vitamin D₃ than the intervention group (typically a standard-of-care control group) were accepted. In trials with intervention groups taking different dose sizes, the control group for all interventions was the group taking the smallest dose (including none). If a control group received vitamin D₃, the difference in dose size between the control and intervention group was be considered the intervention dose for that arm.

**Outcome:** Outcome measures were accepted only if the mean and a variance measure of the change in systolic blood pressure between baseline and measurement was reported for both groups (preferred), or if the mean and a variance measure of systolic
blood pressure for both of the groups was reported at baseline and at an eligible time afterward. In this case the variance of the change score had to be estimated, which is why change scores with a variance measure were preferred. Variance is typically reported as a standard deviation, standard error, or 95% confidence interval, any of which were acceptable.

Time Span: To be included, the study had to include at least one measure of blood pressure four or more weeks after the beginning of the intervention. Outcomes measured after treatment ended were ineligible for inclusion in the study. If outcomes were measured at multiple eligible time spans, they were all recorded.

The Open-Meta application makes any study that passes Stage 1 review available for data extraction. Baseline and eligible outcome blood pressure measurements of any type (normal, 24-hour, central) were recorded for each study. Studies could also fail at this stage for subsequent discovery of Stage 1 issues, as well as new issues, such as data reported without a measure of variance (usually medians rather than means).

**Statistical Analysis**

Statistical analysis for both studies was done with the statistical programming language R, version 3.4.1 (R Core Team, 2017). For the NHANES study the primary additional package was *survey*, version 2.2 (Lumley, 2004) and for the meta-analysis the primary additional package was *robumeta*, version 2.0 (Fisher, Tipton, & Zhipeng, 2017).

**NHANES study: Research question 1.** Each participant in a complex survey receives a statistical weight that essentially portrays how many people in the population that participant’s data represents. These weights adjust for non-response and for unequal
probabilities of selection (some groups are oversampled). I calculated population means using the `survey` package’s `svymean` function and regressions using its `svyglm` function. For the regressions, the explanatory variables were centered so that the intercept would represent the expected systolic blood pressure of a 40-year old non-Hispanic white, 180 pounds, with a 25(OH)D$_3$ level of 20 ng/ml.

**Systematic review and meta-analysis: Research question 2.** Randomization of participants to RCT groups creates the expectation that the groups will be exactly the same except for the intervention, but with the sample sizes typically used for an RCT this is rarely actually the case. Consequently, the Open-Meta application determines the effect size of an intervention by calculating the difference between the control and treatment groups at both baseline and outcome, then calculating the distance between the differences. For example, if the treatment group is 2 units higher than the control group at baseline and 5 units higher at outcome, the Open-Meta application calculates the effect size of the treatment as 3 units.

The Open-Meta application also uses the `robumeta` package’s dependent effects method to estimate the combined result of the studies. Robumeta has been shown to provide unbiased estimates of dependent outcomes even through the correlations between the outcomes are unknown (Moeyaert et al., 2017). All of the other methods typically used for meta-analysis, fixed effect, random effects, and mixed effects, do not allow any dependency between measures in a single study. For example, if a treatment group’s outcome is measured multiple times, these older methods require that only one of those times can be included in the analysis. Likewise, if a trial uses multiple treatment doses, the analyst has to pick just one to include in the analysis.
Allowing a researcher to choose which intervention and which time span to include in the meta-analysis can easily lead to bias. Dependent effects analysis, on the other hand, robustly estimates the correlations between the variables and allows both multiple outcome measurements over time spans and multiple interventions using a single control group. Since every measurement from a study is included, there is no chance of the researcher selecting the “best” result from the set of results found by a study. Robumeta calculates a weight, similar to the weights used by the other meta-analysis methods, for each study (studies with more participants receive more weight). When there are multiple dependent measurements within a study, robumeta distributes the study’s weight equally to the different measures.

Results

NHANES Study: Research Question 1

Because the NHANES data were collected and analyzed using complex survey techniques with appropriate weights, the results are representative of the U.S. non-institutionalized population of non-Hispanic blacks and whites, age 8 and older, during the 8-year time span beginning in 2007. Individuals in other racial/ethnicity groups and children younger than 8 are included in the NHANES data, but were not used in this study.

Table 3.1 shows selected demographics of the nationally-representative data. Both the mean and median of systolic blood pressure is 2 mm Hg higher in non-Hispanic blacks than in non-Hispanic whites. 25(OH)D$_3$ is about 12 ng/ml lower in blacks than
Table 3.1

Selected demographics of non-institutionalized U.S. subpopulations of non-Hispanic-blacks and whites, age 8 and older, in the 2007-2014 time frame.

<table>
<thead>
<tr>
<th></th>
<th>Non-Hispanic Blacks</th>
<th>Non-Hispanic Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unweighted n</strong></td>
<td>5,603</td>
<td>10,716</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure in mm Hg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% of group is higher than:</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>Median:</td>
<td>118</td>
<td>116</td>
</tr>
<tr>
<td>95% of group is lower than:</td>
<td>156</td>
<td>149</td>
</tr>
<tr>
<td>Mean (SD):</td>
<td>121.0 (18.3)</td>
<td>119.0 (16.7)</td>
</tr>
<tr>
<td><strong>25(OH)D3 in ng/ml</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% of group is higher than:</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Median:</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>95% of group is lower than:</td>
<td>33</td>
<td>48</td>
</tr>
<tr>
<td>Mean (SD):</td>
<td>17.5 (8.5)</td>
<td>28.9 (10.4)</td>
</tr>
<tr>
<td>Regressions centered on:</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>25(OH)D2 in ng/ml</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% of group is higher than:</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Median:</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>95% of group is lower than:</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Mean (SD):</td>
<td>1.6 (4.8)</td>
<td>1.5 (4.5)</td>
</tr>
<tr>
<td>Regressions centered on:</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td><strong>Body weight in pounds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% of group is higher than:</td>
<td>94</td>
<td>102</td>
</tr>
<tr>
<td>Median:</td>
<td>176</td>
<td>171</td>
</tr>
<tr>
<td>95% of group is lower than:</td>
<td>284</td>
<td>263</td>
</tr>
<tr>
<td>Mean (SD):</td>
<td>182.0 (57.9)</td>
<td>175.1 (50.3)</td>
</tr>
<tr>
<td>Regressions centered on:</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% of group is higher than:</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Median:</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>95% of group is lower than:</td>
<td>72</td>
<td>79</td>
</tr>
<tr>
<td>Mean (SD):</td>
<td>38.3 (18.9)</td>
<td>44.4 (20.0)</td>
</tr>
<tr>
<td>Regressions centered on:</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

whites, while 25(OH)D₂ levels are about the same in the two groups and much, much lower than each group’s level of 25(OH)D₃. U.S. non-Hispanic blacks, as a subpopulation,
are also somewhat younger and somewhat heavier than the non-Hispanic white subpopulation.

Table 3.2 shows four different regression models predicting systolic blood pressure in mm Hg. For these regressions, data for 25(OH)D₃, 25(OH)D₂, weight, and age were centered at 20 ng/ml, .6 ng/ml, 180 pounds, and 40 years of age to put the intercept at the center of the data and to make the intercept easier to interpret. The omnibus test for each model has a highly significant \( p \) value. In each model, the intercept estimates the systolic blood pressure of a white participant with the centered value of variables included in the regression model.

The first model simply confirms that, as a subpopulation, non-Hispanic blacks have higher blood pressures than non-Hispanic whites by about 2 mm Hg. This is the same result we saw in Table 3.1 on page 60 in terms of group means and medians. The second model adds 25(OH)D₃ status. This regression indicates that a difference of 10 ng/ml in 25(OH)D₃ is associated with a 0.8 mm Hg drop in blood pressure. Note that in this model the coefficient for non-Hispanic black is not statistically significant, which can lead to the interpretation that, from a correlational perspective, 25(OH)D₃ status completely moderates, or explains, U.S. racial disparities in systolic blood pressure. Model 3 is like model 2, but using 25(OH)D₂ instead of D₃. In this model, an increase in 25(OH)D₂ is associated with higher, rather than lower, systolic blood pressure. Finally, model 4 includes age and weight as well as 25(OH)D₃ and shows that a 10-ng/ml change in 25(OH)D₃ is associated with a larger drop in blood pressure than a 10-pound change in body weight. However, a 10-year change in age is associated with a blood pressure change 6 to 8 times larger than either 10 ng/ml of 25(OH)D₃ or 10 pounds of body weight.
Table 3.2

Predictors of systolic blood pressure in mm Hg in U.S. non-Hispanic blacks and whites age 8 and older in the 2007-2014 time frame.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic Black</td>
<td>2.01 ± 0.6***</td>
<td>1.09 ± 0.6</td>
<td>1.99 ± 0.6***</td>
<td>3.41 ± 0.5***</td>
</tr>
<tr>
<td>10 ng/ml 25(OH)D_3</td>
<td></td>
<td>-0.8 ± 0.2***</td>
<td></td>
<td>-0.6 ± 0.1***</td>
</tr>
<tr>
<td>10 ng/ml 25(OH)D_2</td>
<td></td>
<td></td>
<td>2.6 ± 0.4***</td>
<td></td>
</tr>
<tr>
<td>10 years age</td>
<td></td>
<td></td>
<td></td>
<td>3.9 ± 0.1***</td>
</tr>
<tr>
<td>10 pounds weight</td>
<td></td>
<td></td>
<td></td>
<td>0.47 ± 0.03***</td>
</tr>
<tr>
<td>Intercept^1</td>
<td>119 ± 0.3***</td>
<td>120 ± 0.4***</td>
<td>120 ± 0.4***</td>
<td>118 ± 0.3***</td>
</tr>
<tr>
<td>Omnibus test^2</td>
<td>F(1,63)=12.6***</td>
<td>F(2,62)=19.3***</td>
<td>F(2,62)=38.2***</td>
<td>F(4,60)=1406***</td>
</tr>
<tr>
<td>R^2</td>
<td>.002</td>
<td>.004</td>
<td>.007</td>
<td>.264</td>
</tr>
</tbody>
</table>

1. The intercept can be interpreted as the average blood pressure in mm Hg for white 40-year olds, weighing 180 pounds, with a 25(OH)D_3 level of 20 ng/ml.
2. The omnibus test used for a complex survey regression is the Wald Test. Table shows unstandardized regression coefficients ± their standard error. *** p < .001

Systematic Review and Meta-Analysis: Research Question 2

Table 3.3 presents the results of my systematic review and meta-analysis. I extracted systolic blood pressure data from 30 studies reporting 49 outcomes (some studies included multiple vitamin D_3 doses, others measured blood pressure multiple times or multiple ways, others did combinations of these). Rho is “the assumed average
intercorrelation across the observed effect sizes” (Tanner-Smith & Tipton, 2014). Rho was initialized at .8 and a sensitivity analysis (bottom of Table 3.3) determines whether the results are robust to other values of Rho. In this case, the effect size, its standard error, and the estimate of $\tau^2$ are robust to Rho values from 0 to 1. In this analysis, $I^2$, which is the ratio of heterogeneity to total variance and which varies from 0 to 1, is relatively low. Likewise $\tau^2$, which is an estimate of between-study variance and which is in the same metric as the effect size ($\tau$ un-squared is the standard deviation of the effect size estimate), is also low. These low values indicate that the relationship between daily vitamin D$_3$ supplementation and blood pressure is not wildly affected by the kinds of differences there are in these 30 studies in terms of participant characteristics, vitamin D$_3$ dose, time span of supplementation, and so on.

Table 3.3

Results of meta-analysis of the effect of daily vitamin D$_3$ supplementation on systolic blood pressure

<table>
<thead>
<tr>
<th>Dependent Effects Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Robust variance estimation for correlated effects with small sample corrections)</td>
</tr>
<tr>
<td>Number of studies = 30</td>
</tr>
<tr>
<td>Number of outcomes = 49 (min = 1, mean = 1.63, median = 1, max = 6)</td>
</tr>
<tr>
<td>Rho = 0.8</td>
</tr>
<tr>
<td>$I^2$ = 32.5</td>
</tr>
<tr>
<td>$\tau^2$ = 0.0198</td>
</tr>
<tr>
<td>Est</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Effect size</td>
</tr>
</tbody>
</table>

---

Signif. codes: < .01 *** < .05 ** < .10 *

---

Sensitivity Analysis

<table>
<thead>
<tr>
<th>Rho</th>
<th>0</th>
<th>0.2</th>
<th>0.4</th>
<th>0.6</th>
<th>0.8</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect Size</td>
<td>0.0971</td>
<td>0.0971</td>
<td>0.0971</td>
<td>0.0971</td>
<td>0.0971</td>
<td>0.0971</td>
</tr>
<tr>
<td>Std. Error</td>
<td>0.0447</td>
<td>0.0447</td>
<td>0.0447</td>
<td>0.0447</td>
<td>0.0447</td>
<td>0.0447</td>
</tr>
<tr>
<td>$\tau^2$</td>
<td>0.0196</td>
<td>0.0196</td>
<td>0.0197</td>
<td>0.0198</td>
<td>0.0198</td>
<td>0.0199</td>
</tr>
</tbody>
</table>
Finally, Table 3.3 shows that when the studies are combined, there is a statistically significant positive effect of 0.097, with a 95% confidence interval of [0.005, 0.189], and a \( p \)-value of .04. The effect size is in units called Hedge’s \( g \) and represents the effect size in standard deviations of systolic blood pressure. The standard deviation for blood pressure over the entire population is not shown in Table 3.1 on page 60, but a similar calculation shows that it is 16.87 mm Hg. That gives us an estimate of the effect size of daily vitamin D\( _3 \) supplementation on systolic blood pressure of 0.098 * 16.87 = 1.65 mm Hg—a little less than the 2.0 mm Hg racial health disparity in the U.S. for blood pressure.

Table 3.4 lists all of the studies included in this meta-analysis with relevant facts about each study.

Table 3.4

<table>
<thead>
<tr>
<th>Study</th>
<th>Industry funding</th>
<th>Randomization</th>
<th>Blinding of staff</th>
<th>Blinding of subjects</th>
<th>Attrition and exclusions</th>
<th>Outcome</th>
<th>Dose</th>
<th>Time Span</th>
<th>Control n</th>
<th>Intervention n</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Pan, Wang, Li, Kao, &amp; Yeh, 1993)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>H</td>
<td></td>
<td>Systolic BP</td>
<td>200</td>
<td>3</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>(Pfeifer, Begerow, Minne, Nachtigall, &amp; Hansen, 2001)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td></td>
<td>Systolic BP</td>
<td>800</td>
<td>2</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>(Zittermann et al., 2009)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td></td>
<td>Systolic BP</td>
<td>3332</td>
<td>12</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>(Maki et al., 2011)</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td></td>
<td>Systolic BP</td>
<td>1200</td>
<td>2</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>(Nikooyeh et al., 2011)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td></td>
<td>Systolic BP</td>
<td>1000</td>
<td>3</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Study</td>
<td>Industry funding</td>
<td>Randomization</td>
<td>Blinding of staff</td>
<td>Blinding of subjects</td>
<td>Attrition and exclusions</td>
<td>Outcome</td>
<td>Dose</td>
<td>Time Span</td>
<td>Control n</td>
<td>Intervention n</td>
</tr>
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<tr>
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<td>H</td>
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<td>3</td>
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<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Central Systolic BP</td>
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<td>4</td>
<td>37</td>
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<td>(Larsen, Mose, Bech, Hansen, &amp; Pedersen, 2012)</td>
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<td>L</td>
<td>L</td>
<td>24-hour Systolic BP</td>
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<td>5</td>
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<tr>
<td>(Muldowney et al., 2012)</td>
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<td>L</td>
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<td>L</td>
<td>L</td>
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<td>Systolic BP</td>
<td>400</td>
<td>12</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>(Asemi, Samimi, Tabassi, Shakeri, &amp; Esmailzadeh, 2013)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<td>Systolic BP</td>
<td>400</td>
<td>2</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>(Breslavsky et al., 2013)</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>H</td>
<td>Systolic BP</td>
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<td>12</td>
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<td>19</td>
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<td>(Chai, Cooney, Franke, &amp; Bostick, 2013)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Systolic BP Both +Ca</td>
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<td>6</td>
<td>22</td>
<td>23</td>
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<td>(Forman et al., 2013)</td>
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<td>3</td>
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<td>L</td>
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<td>Systolic BP</td>
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<td>L</td>
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<td>Blinding of staff</td>
<td>Blinding of subjects</td>
<td>Attrition and exclusions</td>
<td>Outcome</td>
<td>Dose</td>
<td>Time Span</td>
<td>Control n</td>
<td>Intervention n</td>
</tr>
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<tr>
<td>(Molina et al., 2014)</td>
<td>L</td>
<td>H</td>
<td>H</td>
<td>H</td>
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<td>Systolic BP</td>
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<tr>
<td>(Mose et al., 2014)</td>
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<td>H</td>
<td>H</td>
<td>L</td>
<td>24-hour Systolic BP</td>
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<td>Systolic BP</td>
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<td>3</td>
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<td>(Arora et al., 2015)</td>
<td>L</td>
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<td>L</td>
<td>L</td>
<td>24-hour Systolic BP</td>
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<td>L</td>
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<td>L</td>
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<td>Systolic BP</td>
<td>2100</td>
<td>6</td>
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<td>(Pilz et al., 2015)</td>
<td>L</td>
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<td>L</td>
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<td>24-hour Systolic BP</td>
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<td>Central Systolic BP</td>
<td>3000</td>
<td>4</td>
<td>18</td>
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<td></td>
<td></td>
<td></td>
<td>Systolic BP</td>
<td>3000</td>
<td>4</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>(Yin et al., 2016)</td>
<td>L</td>
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<td>U</td>
<td>U</td>
<td>L</td>
<td>Systolic BP</td>
<td>700</td>
<td>12</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>(Zerofsky, Jacoby, Pedersen, &amp; Stephensen, 2016)</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Systolic BP</td>
<td>1600</td>
<td>3</td>
<td>26</td>
<td>25</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systolic BP</td>
<td>1600</td>
<td>6</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>(Mousa et al., 2017)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Systolic BP</td>
<td>4000</td>
<td>4</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>(Tomson et al., 2017)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Systolic BP</td>
<td>2000</td>
<td>6</td>
<td>101</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Systolic BP</td>
<td>2000</td>
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<td>Systolic BP</td>
<td>4000</td>
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<td>Systolic BP</td>
<td>4000</td>
<td>12</td>
<td>101</td>
<td>102</td>
</tr>
</tbody>
</table>

Notes: Risk of Bias ratings are L = Low, H = High, U = Unclear. Dose is in International Units (IU) per day. Time Span is the amount of time between supplementation start and outcome measurement in months. The last two columns show the number of participants in the control and intervention groups.
Figure 3.1 is a forest plot of the results of the studies included in the meta-analysis.

The conclusion of almost every study (the ones where the confidence interval line crosses zero) was that vitamin D₃ does not lower blood pressure, yet combined, the same studies show that there is, in fact, a true beneficial effect.
Figure 3.1. Forest Plot of trials included in systolic blood pressure study.
Discussion

The results of this chapter’s study suggest that in the U.S., those who self-identify as non-Hispanic black have higher systolic blood pressure than those who self-identify as non-Hispanic white. Overall, this racial difference is small, about 2 mm Hg. Our NHANES-based correlational results suggest it would require a change in 25(OH)D status of about 25 ng/ml (2 mm Hg / -0.8 mm Hg per 10 ng/ml change in 25(OH)D) to close the systolic blood pressure gap between blacks and whites, however, the actual black-white 25(OH)D gap is about 11 ng/ml. Yet, at the same time, this study’s correlational results also indicate that in a statistical sense, the black-white difference in 25(OH)D status completely moderates, or explains, the gap in blood pressure.

Results from this chapter’s systematic review and meta-analysis show that daily vitamin D₃ supplementation has a statistically significant beneficial effect on blood pressure. In the mix of studies included in our analysis, this effect was about 1.65 mm Hg. These results support the theory that biological differences in skin color lead to biological differences in vitamin D₃ status, which in turn lead to biological differences in systolic blood pressure. In other words, this health disparity is at least in part due to differences in vitamin D₃ status that can be eliminated with vitamin D₃ supplementation.

Why This Study Contradicts Prior Research

There have been at least six prior systematic reviews on the effect of vitamin D on blood pressure, none of which found an effect.

Witham and colleagues (Witham, Nadir, & Struthers, 2009) combined 11 studies, nine of which were ineligible for the current study (six did not use vitamin D₃, two did
not supplement daily, one did not provide a variance estimate). Two of studies from this analysis are included here (Pan et al., 1993; Pfeifer et al., 2001). Witham and colleagues concluded, “We found weak evidence to support a small effect of vitamin D on blood pressure in studies of hypertensive patients.”

Pittas and colleagues (Pittas et al., 2010) combined 10 studies, eight of which were ineligible for the current study (five did not supplement daily, two had invalid comparisons (the intervention group was given additional supplements besides vitamin D) and one did not provide a variance estimate). Two of the studies from this analysis are included here (Pfeifer et al., 2001; Zittermann et al., 2009). Pittas and colleagues concluded, “An association between vitamin D status and cardiometabolic outcomes is uncertain. Trials showed no clinically significant effect of vitamin D supplementation at doses given.”

Dolinsky and colleagues (Dolinsky, Armstrong, Mangarelli, & Kemper, 2013) systematically reviewed 35 studies related to vitamin D and cardiometabolic risk in children. Only one of these studies was an RCT. That study (Dong et al., 2010) did not provide either a mean or variance estimate for blood pressure but merely reports in the text that there were no statistically significant differences. Dolinsky and colleagues conclude, “Insufficient evidence was available to conclude that vitamin D supplementation yields cardiometabolic benefit.”

Manousopoulou and colleagues (Manousopoulou, Al-Daghri, Garbis, & Chrousos, 2015) combined 15 studies, 11 of which were ineligible for the current study (eight did not supplement daily and three did not include blood pressure measures). Four of the studies are included here (Maki et al., 2011; Salehpour et al., 2012; Wamberg et al., 2013;
Zittermann et al., 2009). Manousopoulou and colleagues conclude, “This systematic review highlights a paucity of interventional studies examining the effects of vitamin D status improvement on cardiovascular risk factors among otherwise healthy adults with obesity.”

Beveridge and colleagues (Beveridge et al., 2015) combined 46 studies, 32 of which were ineligible for the current study (20 did not supplement daily, ten did not use vitamin D₃, two did not provide a variance estimate). Fourteen of the studies are included here (Breslavsky et al., 2013; Chai et al., 2013; Forman et al., 2013; Gepner et al., 2012; Larsen et al., 2012; Muldowney et al., 2012 (2 studies); Pfeifer et al., 2001; Salehpour et al., 2012; Shab-Bidar et al., 2011; Toxqui et al., 2013; Wamberg et al., 2013; Wood et al., 2012; Zittermann et al., 2009). Beveridge and colleagues conclude “Meta-analysis of the change in blood pressure between baseline and the final follow-up for each trial revealed no clinically or statistically significant effect.”

Hussin and colleagues (Hussin et al., 2017) combined 16 studies, 13 of which were ineligible for the current study (eleven did not supplement daily (and three of those did not use D₃,) and two did not report variance). Three of the Hussin and colleagues studies are included here (Breslavsky et al., 2013; Gepner et al., 2015; Larsen et al., 2012). Hussin and colleagues concluded, “Vitamin D supplementation did not improve endothelial function.”

This summary of previous studies suggests that to find an effect of vitamin D supplementation on blood pressure, the supplementation has to be daily and has to be vitamin D₃.
This Study’s Theoretical Model of Vitamin D Action

The reason eligibility for my study was limited to trials testing daily vitamin D₃ is related to my conception of the role of vitamin D in humans. Vitamin D is a signaling molecule. Its role in whole-body, or endocrine, signaling was discovered first and is all many researchers know about vitamin D. In this role, the kidney separates 25(OH)D from vitamin D binding protein and, as necessary, converts it into 1,25(OH)2D. The kidney puts both the new 1,25(OH)2D and the remaining 25(OH)D back in the bloodstream, where they again rapidly attach to vitamin D binding protein. A few kinds of cells have the ability to absorb vitamin D binding protein and to remove the attached vitamin D compounds. The level of 1,25(OH)2D in the bloodstream acts to control human calcium balance. Bones provide not only structural support but also act as a calcium warehouse, the key to which is vitamin D binding protein-bound 1,25(OH)2D.

However, vitamin D is also involved in cell-to-cell, or paracrine, signaling as well as inside-cell, or autocrine, signaling. Deep in their genetic machinery, cells have nuclear receptors, which up- and down-regulate specific genes. One of these responds specifically to vitamin D and its metabolites. Most models of vitamin D action assume that only 1,25(OH)2D can activate this vitamin D receptor, however, it has been shown that the precursor 25(OH)D, as well as the breakdown product 24R,25(OH)2D also activate the vitamin D receptor and, for the most part, up- and down-regulate different genes (Tuohimaa et al., 2013).

In my conception of the role of vitamin D in humans, however, it is the basic sunlight-diet, or parent, form of vitamin D that is absorbed by most cells (Hollis & Wagner, 2013). In my conceptual model, this form also activates the vitamin D receptor.
But because the liver rapidly converts this parent form into 25(OH)D, supplementing with large bolus doses of vitamin D provides plenty of the parent form for only a day or two. Soon the bolus dose is all converted to 25(OH)D and bound to vitamin D binding protein, while the quantity of parent vitamin D rapidly drops back to the unsupplemented level. Researchers can see the reflection of their bolus dose in a blood test for 25(OH)D, but they are not actually giving the participant the equivalent of a daily dose of the parental vitamin D. Bolus doses greatly exaggerate parental vitamin D exposure. That is why I did not include studies that use them in my analysis.

Given this model of vitamin D’s action, it also becomes apparent that supplementing with the vitamin D metabolites 25(OH)D or 1,25(OH)2D, or with vitamin D analogues, will not have a beneficial effect on vitamin D’s autocrine or paracrine actions. The reason is that those forms attach to vitamin D binding protein and cannot get inside most cells. The parent form of vitamin D, on the other hand, is not as strongly attracted to vitamin D binding protein as the vitamin D metabolites and is free to be absorbed by cells that do not have the cell-surface structures that absorb vitamin D binding protein.

Likewise, I did not include studies that used vitamin D$_2$ as an intervention because I have no reason to expect that a molecule from fungus and yeast will work as well in animals as the animal’s own molecule, vitamin D$_3$.

**Limitations**

The glaring weakness of this study is that it was completed by a single researcher. Systematic reviews are typically undertaken by a team so that team members can check
each other’s work. In this case, all of the studies from the original search received only a single review and worse, the studies found by the update to the original search received a review only if the terms “blood pressure” or “hypertension” were in the title or abstract. Likewise, a single researcher did all the data extraction. On the other hand, I found more than twice as many studies that measured the effect of daily vitamin D₃ supplementation on blood pressure as the next-larger previous meta-analysis.

**Strengths**

The strengths of this study are that it uses dependent effects analysis to allow the inclusion of multiple outcomes, intervention groups, and time spans from the same study, which traditional meta-analysis does not allow. It also combines nationally-representative correlational data for strong external validity with a dependent effects meta-analysis of randomized controlled trials for strong internal validity. Typically researchers have to find a balance between external and internal validity and do not get to have both.

The correlational NHANES data speak to my first research question—average racial systolic blood pressure disparities in the U.S. are about 2 mm Hg. Average 25(OH)D₃ disparities are about 12 ng/ml. The systematic review and meta-analysis data address my second research question—daily vitamin D₃ supplementation does have a beneficial effect on systolic blood pressure that, although small, with proper dosing may be large enough to eliminate this health disparity.
Conclusion

This study supports the hypothesis that skin-color dependent disparities in vitamin D status in the U.S. population are a biological determinant of racial health disparities in blood pressure. In a nationally-representative sample of U.S. non-Hispanic blacks and non-Hispanic whites age 8 and older during 2007-2014, the average systolic blood pressure of black participants was about 2 mm Hg higher than white participants. In a systematic review and meta-analysis of the effect of daily vitamin D₃ supplementation on blood pressure, I show that such supplementation has a statistically significant systolic blood pressure-lowering effect that could eliminate much or all of this disparity.

For simplification, the results for diastolic blood pressure were not included in this report. Although daily vitamin D₃ supplementation also has a statistically significant effect on diastolic blood pressure, the effect size is quite small and unlikely to be clinically significant.

Let me emphasize that there is nothing surprising about these findings to those who assume that skin color is an evolutionary adaptation to sunlight intensity. From a health perspective, that evolutionary adaptation implies that we should expect to find health disparities in any population with a variety of skin colors. While U.S. racial health disparities are rightfully considered to have social causes, the U.S. public health system will never eliminate racial health disparities if it continues to ignore the skin-color-determined disparity in vitamin D status, which can easily and successfully be eliminated with daily vitamin D₃ supplementation.
IV – DAILY VITAMIN D₃ SUPPLEMENTATION AS A TREATMENT FOR HEALTH DISPARITIES IN DIABETES

Much about this chapter is similar to the previous chapter. What will be different is that rather than disparities in systolic blood pressure, this chapter will examine disparities in the biological markers of diabetes. Unlike before, this chapter will first present the systematic review and meta-analysis examining the effect of daily vitamin D₃ supplementation on the markers of diabetes. This meta-analysis demonstrates the inclusion of multiple dependent outcomes rather than just one. Next I will discuss some of the same markers for diabetes in the U.S. population using data from NHANES. This time, however, many of the relationships are non-linear. To capture the maximum amount of information from the data, instead of using linear regression, I will use non-linear, spline-based regression, which is best understood with figures rather than tables.

Research Questions

My research questions are:

3. Does daily vitamin D₃ supplementation have a statistically-significant beneficial effect on the biological markers of diabetes in the U.S. population?

4. If so, do the vitamin D disparities between those who self-identify as non-Hispanic black and non-Hispanic white in the U.S. seem to account for the health disparities we find in diabetes?
Methods

The Institutional Review Board of Teachers College, Columbia University ruled this study exempt from review and issued approval 17-220 on March 12, 2017.

As detailed in the previous chapter, the overall protocol for the systematic review and meta-analysis described here was accepted and published by PROSPERO—the International Prospective Register of Systematic Reviews—on April 2, 2017 (Weishaar, 2017) and in the Open-Meta application (Weishaar, 2018). The primary adjustment made to the overall protocol for this chapter’s study is that it is synthesizing results only from trials that measured a marker of diabetes as an experimental outcome, rather than any reported outcome as specified in the protocol.

Data Sources

The data sources for this chapter’s systematic review were exactly the same as those described in the last chapter on pages 51 to 54.

Systematic review and meta-analysis: Research question 3. As mentioned previously, the initial search was refreshed on January 10, 2019, which added 1,442 references. Because the January 2019 refresh included so many more additional articles than expected, for this study, only trials with diabetes, glucose, or insulin in the title or abstract were reviewed for eligibility. As before, 377 studies moved forward to the stage 2 or extraction function in the Open-Meta application.

NHANES study: Research question 4. In the study presented in the previous chapter, I used NHANES data collected during the four two-year cycles from 2007 to
2014. This was because only those cycles had vitamin D data that split apart vitamin D$_2$ and vitamin D$_3$.

In this chapter’s study, on the other hand, our primary interest is markers of diabetes. One of those markers, hemoglobin A1c (HbA1c) reports the percentage of a certain type of blood molecule that has a sugar attached to it. It is a marker for the average blood glucose level over the last two to three months—that is, it is a marker for glucose exposure, just as 25(OH)D is a marker for vitamin D exposure. It is also used as a diagnostic marker for diabetes. Levels below 5.6% are considered normal, 5.7% to 6.4% are considered prediabetes, and 6.5% and above indicate diabetes (Pippitt, Li, & Gurgle, 2016). HbA1c has been assayed from participant blood draws in all cycles of NHANES. NHANES only draws blood for HbA1c from participants age 12 and older, consequently I dropped all data from participants younger than 12.

Two other important markers of diabetes, glucose and insulin, which are also measured in blood, require that the participant’s blood be drawn after a period of fasting. For a fasting blood test, NHANES draws the participant’s blood in the morning and the participants are instructed not to eat anything the day of the test until after the blood draw. Because of this requirement, NHANES measures fasting plasma glucose and fasting plasma insulin in only one-half of its participants (those who are examined in the morning rather than in the afternoon). However, these markers have been measured in all cycles.

Because the fasting blood draws drastically reduces the sample size, for this chapter’s study, in addition to the four two-year cycles used in the previous chapter’s study, this chapter includes the three prior cycles from 2001 to 2006, for a total of seven
cycles from 2001 to 2014. Now we cannot distinguish between vitamin D$_2$ and vitamin D$_3$, but as we saw in the last chapter, the level of vitamin D$_2$ in most participants is quite small compared to the level of vitamin D$_3$. On the other hand, including these cycles almost doubles our sample size.

The studies included in the systematic review often included three other markers of diabetes that are not in the NHANES dataset. Homeostatic model assessment is a method used to estimate insulin resistance (HOMA-IR) and β-cell function (HOMA-β). Insulin resistance means that the body’s cells absorb less glucose for a given level of insulin than normal. β-cells, which are in the pancreas, are the body’s insulin-producing cells. In Type I diabetes, the β-cells have ceased to function. In Type II diabetes, the rest of the body’s cells require increasing amounts of insulin to absorb the same amount of glucose. Another marker for insulin resistance is called the Quantitative Insulin Sensitivity Index (QUICKI). Although none of these markers are reported in NHANES, they can all be calculated from fasting glucose and fasting insulin. I added all three to the NHANES dataset using the following formulas. With $I$ as fasting insulin in µU/mL and $G$ as fasting glucose in mmol/L:

$$\text{HOMA-IR} = \frac{(I \times G)}{22.5} \quad \text{(Wallace, Levy, & Matthews, 2004)}$$

$$\text{HOMA-β} = \frac{(20 \times I)}{(G - 3.5)} \quad \text{(Wallace et al., 2004)}$$

And, with $I$ as fasting insulin in µU/mL and $G$ as fasting glucose in mg/dL:

$$\text{QUICKI} = \frac{1}{\log(I) + \log(G)} \quad \text{(Katz et al., 2000)}$$

Again, because this chapter’s study concerns racial health disparities, I dropped all data from participants who did not self-identify as non-Hispanic black or non-
Hispanic white. NHANES collected age and measured body weight in all cycles for all participants.

**Data Handling**

**Systematic review and meta-analysis: Research question 3.** Data handling for the systematic review was identical to the data handling in the previous study, as described on pages 54 to 57, with the exception that the review and extraction search terms were *diabetes*, *glucose*, and *insulin* rather than *blood pressure* and *hypertension*.

**NHANES study: Research question 4.** This chapter’s study used datasets from seven cycles (2001-2002 through 2013-2014), which are distinguished by filenames containing the letters "B" through "H". In addition to the files used in the previous chapter’s study, described on pages 54 and 55, this study included:

- **Glycohemoglobin:** This is a Laboratory data file, which includes a measure of HbA1c for each participant 12 years and older.

- **Plasma Fasting Glucose & Insulin:** This is also a Laboratory data file, which, in addition to measures of glucose and insulin, has a special weight for complex survey analysis that expands the half-sample of fasting participants to nationally-representative data.

- **Vitamin D:** For the first three cycles, a value for 25(OH)D in blood is provided in nmol/L that does not distinguish between vitamin D₂ and vitamin D₃. For the four remaining cycles, separate values for D₂ and D₃, again in nmol/L, are provided. Over the fourteen-year span, NHANES has used different types of assays for 25(OH)D and has adjusted the values in earlier cycles to match the current assay. For the first three cycles I
converted the value in nmol/L to ng/ml, the metric typically used by U.S. medical laboratories, by dividing by 2.4959. For the last four cycles, I converted the D\textsubscript{2} and D\textsubscript{3} to ng/ml separately and then added them together. For D\textsubscript{2} the conversion was a division by 2.4233 and for D\textsubscript{3} it was a division by 2.4959.

For analyses that did not include fasting plasma or fasting glucose, I included all participants without missing data and used the complex survey weights appropriate for that sample (MEC weights). For analyses that did include fasting plasma or fasting glucose, only half the sample was available and I used the complex survey fasting weights.

After dropping cycles without 25(OH)D data, dropping ages without needed blood test data, dropping participants self-identifying from other ethnicities, and dropping cases with missing data on any of the critical variables, the full dataset consisted of 28,890 unweighted cases (9,860 non-Hispanic black in 209 complex survey clusters; 19,030 non-Hispanic white in 213 complex survey clusters). The fasting dataset consisted of 13,790 unweighted cases (4,623 non-Hispanic black in 199 complex survey clusters; 9,167 non-Hispanic white in 212 complex survey clusters).

**Statistical Analysis**

Statistical analysis for both research questions in this chapter was done with the statistical programming language R and a variety of add-on packages, as described on page 57.

**Systematic review and meta-analysis: Research question 3.** The analysis was as described on pages 58 and 59. In addition, for outcomes where lower scores are better,
including fasting glucose, fasting insulin, HbA1c, HOMA-IR, and HOMA-β, the sign of the effect size was flipped so that better scores on an outcome always resulted in positive effect sizes.

**NHANES study: Research question 4.** In addition to the packages used in the last chapter’s study, the NHANES analysis in this chapter uses the splines package (R Core Team, 2017) with linear regression to explore non-linear relationships between variables. A “spline” is a curve that can be described mathematically. To use this package, I wrapped the predictor variables in the splines function and declared the number of splines, or “knots” to use. The splines function creates duplicates of the predictor variables for each of the knots. The regression output, which is basically otherwise uninterpretable, is then used to predict the dependent variable over the range of a predictor variable (in this study, each analysis was limited to a single predictor variable). The predicted result, with a 95% confidence interval, can then be graphed. If the graph lines are too wiggly, the model has been “overfit” and the statistician reduces the number of knots and runs it all again. If the lines seem too straight, the number of knots can be increased. The final graphs are based to certain degree on the judgment of the statistician as to when a model has the right visual fit.

**Results**

**Systematic Review and Meta-Analysis: Research Question 3**

Table 4.1 presents the results of my systematic review and meta-analysis in a revised format from the last chapter. Here the first line shows the results for the meta-
analysis that included all outcomes. On the following lines, we see the results for the individual outcomes, one at a time, from separate analyses.

I extracted outcomes on eight markers of diabetes from 31 studies reporting 97 outcomes (most studies included multiple markers of diabetes, one study also included multiple vitamin D₃ doses, and one study had a single marker and single dose but measured the outcome at multiple time points). The diabetes-related outcomes were HbA₁c, fasting glucose, fasting insulin, HOMA-IR, HOMA-β, QUICKI, and, from a study that ran for 24 months, the number of participants beginning diabetes treatment and the number developing diabetes (since there is only one study for those two outcomes a separate meta-analysis is not possible and Table 4.1 reports on just six individual outcomes).

Figure 4.1 is a forest plot of the results of the studies included in the meta-analysis. The conclusion of almost every study (the ones where the confidence interval line crosses zero) was that daily vitamin D₃ supplementation does not have an impact on markers of diabetes, yet combined, the same studies show that there is, in fact, a true, small, beneficial effect.

Table 4.2 lists all of the studies included in this meta-analysis with relevant facts about each study.
Table 4.1
Results of meta-analyses of the effect of daily vitamin D₃ supplementation on markers of diabetes.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Studies</th>
<th>Outcomes</th>
<th>Est</th>
<th>SE</th>
<th>p</th>
<th>95% CI</th>
<th>Sig</th>
<th>I-sq</th>
<th>Tau.sq</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Outcomes</td>
<td>31</td>
<td>97</td>
<td>0.220</td>
<td>0.082</td>
<td>0.012</td>
<td>.052, .387</td>
<td>**</td>
<td>73.6</td>
<td>0.107</td>
<td>OK</td>
</tr>
<tr>
<td>HbA1c</td>
<td>13</td>
<td>17</td>
<td>0.141</td>
<td>0.110</td>
<td>0.228</td>
<td>-.103, .386</td>
<td>54.7</td>
<td>0.076</td>
<td>OK</td>
<td></td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>24</td>
<td>28</td>
<td>0.129</td>
<td>0.103</td>
<td>0.225</td>
<td>-.085, .343</td>
<td>75.3</td>
<td>0.155</td>
<td>OK</td>
<td></td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>18</td>
<td>20</td>
<td>0.332</td>
<td>0.134</td>
<td>0.024</td>
<td>.050, .615</td>
<td>**</td>
<td>75.8</td>
<td>0.223</td>
<td>OK</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>14</td>
<td>16</td>
<td>0.402</td>
<td>0.166</td>
<td>0.031</td>
<td>.042, .762</td>
<td>**</td>
<td>80.8</td>
<td>0.284</td>
<td>OK</td>
</tr>
<tr>
<td>HOMA-β</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUICKI</td>
<td>9</td>
<td>11</td>
<td>0.570</td>
<td>0.222</td>
<td>0.034</td>
<td>.056, 1.08</td>
<td>**</td>
<td>84.6</td>
<td>0.435</td>
<td>OK</td>
</tr>
</tbody>
</table>

Not enough studies for a Dependent Effects analysis.
Studies

Asemi-2013
0400 IU/day-HOMA-B-2 months
0400 IU/day-HOMA-IR-2 months
0400 IU/day-Insulin-2 months
0400 IU/day-QUICKI Score-2 months

Avenell-2009
0800 IU/day-Began Diabetes treatment-24 months
0800 IU/day-Developed Diabetes-24 months

Belenchia-2013
4000 IU/day-Fasting Plasma Glucose-6 months
4000 IU/day-HOMA-IR-6 months
4000 IU/day-Insulin-6 months
4000 IU/day-QUICKI Score-6 months

Breslavsky-2013
1000 IU/day-Fasting Plasma Glucose-12 months
1000 IU/day-HBA1c-12 months
1000 IU/day-HOMA-B-12 months
1000 IU/day-HOMA-IR-12 months
1000 IU/day-Insulin-12 months

Calcium and Vitamin D for Diabetes Mellitus Trial
2000 IU/day-Fasting Plasma Glucose-4 months
2000 IU/day-Fasting Plasma Glucose-4 months
2000 IU/day-HBA1c-4 months
2000 IU/day-HBA1c-4 months

Calcium-Dogh-Diabetes Project (NCT01229851)
1000 IU/day-Fasting Plasma Glucose-3 months
1000 IU/day-HBA1c-3 months
1000 IU/day-HOMA-IR-3 months
1000 IU/day-Insulin-3 months
1000 IU/day-QUICKI Score-3 months

Carrillo-2013
4000 IU/day-HOMA-IR-3 months
4000 IU/day-Insulin-3 months

Foroozanfard-2017
1000 IU/day-Fasting Plasma Glucose-3 months
1000 IU/day-HOMA-IR-3 months
1000 IU/day-Insulin-3 months
1000 IU/day-QUICKI Score-3 months
4000 IU/day-Fasting Plasma Glucose-3 months
4000 IU/day-HOMA-IR-3 months
4000 IU/day-Insulin-3 months
4000 IU/day-QUICKI Score-3 months

Gabbay-2012
2000 IU/day-HBA1c-12 months
2000 IU/day-HBA1c-18 months
2000 IU/day-HBA1c-6 months

Gepner-2012
2500 IU/day-Fasting Plasma Glucose-4 months

Harris-2012
4000 IU/day-Fasting Plasma Glucose-3 months
4000 IU/day-HBA1c-3 months
4000 IU/day-HOMA-IR-3 months
4000 IU/day-Insulin-3 months

Jamilian-2017
1000 IU/day-HOMA-IR-3 months
4000 IU/day-HOMA-IR-3 months

Javed-2015
1600 IU day 2000-400 in controls-Fasting Plasma Glucose-3 months
1600 IU day 2000-400 in controls-HOMA-IR-3 months
1600 IU day 2000-400 in controls-insulin-3 months
1600 IU day 2000-400 in controls-QUICKI Score-3 months
Figure 4.1. Forest Plot of trials included in markers of diabetes study.
Table 4.2

Studies on the effect of daily vitamin D₃ supplementation on markers of diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Industry funding</th>
<th>Randomization</th>
<th>Blinding of staff</th>
<th>Blinding of subjects</th>
<th>Attrition and exclusions</th>
<th>Outcome</th>
<th>Dose</th>
<th>Time Span</th>
<th>Control n</th>
<th>Intervention n</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Avenell, Cook, MacLennan, &amp; McPherson, 2009)</td>
<td>L L L L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Began Treatment</td>
<td>Developed Diabetes</td>
<td>800</td>
<td>24</td>
<td>1028</td>
<td>1083</td>
</tr>
<tr>
<td>(Zittermann et al., 2009)</td>
<td>L L L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Fasting Plasma Glucose</td>
<td>HbA1c</td>
<td>3332</td>
<td>12</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>(Nikooyeh et al., 2011)</td>
<td>L L L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Fasting Plasma Glucose</td>
<td>HbA1c</td>
<td>1000</td>
<td>3</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>(O'Sullivan et al., 2011)</td>
<td>L L L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Fasting Plasma Glucose</td>
<td>HOMA-IR</td>
<td>600</td>
<td>1</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>(Shab-Bidar et al., 2011)</td>
<td>L L H</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>Fasting Plasma Glucose</td>
<td>HbA1c</td>
<td>1000</td>
<td>3</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Insulin, QUICKI Score, FP Glucose Stored Serum, HbA1c Stored Serum, Insulin Stored Serum, QUICKI Stored Serum.
<table>
<thead>
<tr>
<th>Study</th>
<th>Industry funding</th>
<th>Randomization</th>
<th>Blinding of staff</th>
<th>Blinding of subjects</th>
<th>Attrition and exclusions</th>
<th>Outcome</th>
<th>Dose</th>
<th>Time Span</th>
<th>Control n</th>
<th>Intervention n</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gabbay, Sato, Finazzo, Duarte, &amp; Dib, 2012)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HbA1c, HbA1c, HbA1c</td>
<td>2000</td>
<td>6</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>(Gepner et al., 2012)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose</td>
<td>2500</td>
<td>4</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>(Harris, Pittas, &amp; Palermo, 2012)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HbA1c, HbA1c, HbA1c</td>
<td>4000</td>
<td>3</td>
<td>46</td>
<td>43</td>
</tr>
<tr>
<td>(Soric, Renner, &amp; Smith, 2012)</td>
<td>L L H L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HbA1c</td>
<td>2000</td>
<td>3</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>(Asemi et al., 2013)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HOMA-B, HOMA-IR, Insulin, QUICKI Score</td>
<td>400</td>
<td>2</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>(Belenchia, Tosh, Hillman, &amp; Peterson, 2013)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose, HOMA-IR, Insulin, QUICKI Score</td>
<td>4000</td>
<td>6</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>(Breslavsky et al., 2013)</td>
<td>U L L L H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HbA1c, HOMA-B, HOMA-IR, Insulin</td>
<td>1000</td>
<td>12</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>(Carrillo et al., 2013)</td>
<td>U L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HOMA-IR, Insulin</td>
<td>4000</td>
<td>3</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>(Putman et al., 2013)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose, Insulin</td>
<td>800</td>
<td>3</td>
<td>25</td>
<td>29</td>
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<tr>
<td>(Salehpour et al., 2012)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HbA1c, HOMA-IR, Insulin</td>
<td>1000</td>
<td>3</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Study</td>
<td>Industry funding</td>
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<td>Blinding of staff</td>
<td>Blinding of subjects</td>
<td>Attrition and exclusions</td>
<td>Outcome</td>
<td>Dose</td>
<td>Time Span</td>
<td>Control n</td>
<td>Intervention n</td>
</tr>
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<td>----------------</td>
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<tr>
<td>(Toxqui et al., 2013)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose</td>
<td>200</td>
<td>2</td>
<td>54</td>
<td>55</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose</td>
<td>200</td>
<td>4</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>(Wamberg et al., 2013)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose</td>
<td>7000</td>
<td>6</td>
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<td>22</td>
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<tr>
<td>(Kampmann et al., 2014)</td>
<td>L L L L L</td>
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<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose</td>
<td>5600</td>
<td>3</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>HbA1c</td>
<td>5600</td>
<td>3</td>
<td>8</td>
<td>7</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insulin</td>
<td>5600</td>
<td>3</td>
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<td>7</td>
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<tr>
<td>(Raja-Khan et al., 2014)</td>
<td>U L L L L</td>
<td></td>
<td></td>
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<td>Fasting Plasma Glucose</td>
<td>12000</td>
<td>3</td>
<td>15</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>HOMA-IR</td>
<td>12000</td>
<td>3</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insulin</td>
<td>12000</td>
<td>3</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>QUICKI Score</td>
<td>12000</td>
<td>3</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>(Ryu et al., 2014)</td>
<td>U L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose</td>
<td>1000</td>
<td>6</td>
<td>65</td>
<td>64</td>
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<tr>
<td>(Yap et al., 2014)</td>
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<td></td>
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<td>Fasting Plasma Glucose</td>
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<td>80</td>
<td>78</td>
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<tr>
<td>(Javed et al., 2015)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose</td>
<td>1600</td>
<td>3</td>
<td>23</td>
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<td></td>
<td>HOMA-IR</td>
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<td></td>
<td>Insulin</td>
<td>1600</td>
<td>3</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>QUICKI Score</td>
<td>1600</td>
<td>3</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>(Grübler et al., 2016)</td>
<td>L L L L L</td>
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<td></td>
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<td>Fasting Plasma Glucose</td>
<td>2800</td>
<td>2</td>
<td>92.5</td>
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<td></td>
<td></td>
<td></td>
<td>HbA1c</td>
<td>2800</td>
<td>2</td>
<td>92.5</td>
<td>92.5</td>
</tr>
<tr>
<td>(Li &amp; Xing, 2016)</td>
<td>L L L L L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting Plasma Glucose</td>
<td>1000</td>
<td>4</td>
<td>49</td>
<td>48</td>
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<tr>
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Notes: Risk of Bias ratings are L = Low, H = High, U = Unclear. Dose is in International Units (IU) per day. Time Span is the amount of time between supplementation start and outcome measurement in months. The last two columns show the number of participants in the control and intervention groups.

**NHANES Study: Research Question 4**

Because the NHANES data were collected and analyzed using complex survey techniques with appropriate weights, the results are representative of the U.S. non-institutionalized population of non-Hispanic blacks and whites, age 12 and older, during the 14-year time span from 2001 to 2014. Individuals in other racial/ethnicity groups and children younger than 12 are included in the NHANES data, but were not used in this study.

Figures 4.2, 4.3, and 4.4 are based on the full (not fasting) dataset and show the mean effect of age, weight, and vitamin D exposure on HbA1c, the diagnostic marker for
diabetes. Individuals with HbA1c levels over 6.5% are considered to have diabetes while levels between 5.7% and 6.5% result in a diagnosis of pre-diabetes.

Figure 4.2. Impact of age on mean HbA1c percentage.

In these figures, the darker line presents data for non-Hispanic blacks and the lighter line for non-Hispanic whites. The lines show both the actual mean and the 95% confidence interval for the mean. Where the 95% confidence interval is wider there are fewer participants with those characteristics in the NHANES data. Where the lines overlap there is no statistically significant difference between the groups. Figure 4.2
confirms that at all ages there is a health disparity in HbA1c levels and that blacks are likely to become pre-diabetic 16 years before whites.

Figure 4.3. Impact of weight on mean HbA1c percentage.

Figure 4.3 shows the impact of weight on HbA1c status. Again we see a health disparity. Blacks, on average, are likely to become pre-diabetic at about 180 pounds, while whites, on average, do not become pre-diabetic until they are 55 pounds heavier.
Figure 4.4 shows that for non-Hispanic whites, HbA1c percentages decline as vitamin D status increases. For non-Hispanic blacks, on the other hand, HbA1c percentages increase with higher vitamin D levels. The very wide confidence interval for blacks at higher vitamin D levels reflects the fact that there are very few non-Hispanic blacks in the U.S. population with 25(OH)D levels over 30 ng/ml.
Figures 4.5 though 4.8 are based on the fasting subsample of NHANES. The results are still nationally-representative because the fasting complex survey weights were used in these analyses. The figures show mean fasting glucose (upper lines) and fasting insulin (lower lines) by HbA1c in Figure 4-5, by age in Figure 4-6, by weight in Figure 4-7 and by vitamin D exposure in Figure 4-8.
Figure 4.6. Relationship of mean fasting glucose and fasting insulin scores with age.
Figure 4.7. Relationship of mean fasting glucose and fasting insulin scores with weight.
Figure 4.8. Relationship of mean fasting glucose and fasting insulin scores with vitamin D exposure.
Discussion

**Systematic Review and Meta-Analysis: Research Question 3**

Although it is more typical for a systematic review and meta-analysis to examine a very specific outcome with a variety of interventions, it is not unusual to combine a variety of related outcomes for one specific intervention as I have done here. In fact, the very first systematic review and meta-analysis combined multiple outcomes (Smith & Glass, 1977).

The first row of Table 4.1 shows that the combined outcomes have a small but statistically-significant effect size of 0.220, \( p = .012 \), with a 95% confidence interval of [0.052, 0.387]. The effect size is in units called *Hedge’s g* and represents the effect size in standard deviations of the comingled scores for the diabetes markers. The signs of the effect sizes on markers for which lower scores indicate better health were reversed so that beneficial effects are always positive. A Hedge’s g effect of 0.220 is considered small, but it is more than double the size of the effect we saw for systolic blood pressure in the previous chapter’s study. In the analyses for individual outcomes, the two outcomes related to glucose, HbA1c and fasting glucose, are not statistically significant. However, the three related to insulin, fasting insulin and the markers for insulin sensitivity, HOMA-IR and QUICKI, are all statistically significant.

On the other hand, note that in all cases the measures of study homogeneity, \( I^2 \) and \( \text{Tau}^2 \), are quite large (\( I^2 \) values over 50 are considered high and \( \text{Tau}^2 \), which is in the same metric as the effect size, in these analyses is typically more than half as large as the effect size). The values we saw for \( I^2 \) and \( \text{Tau}^2 \) in the last chapter’s analysis of blood
pressure were much smaller. These large values mean the results of the individual studies are heterogeneous (inconsistent or all over the place). Moreover, the heterogeneity does not go away when we look at the outcomes one-by-one.

When heterogeneity is high in meta-analysis, it is appropriate to investigate whether the heterogeneity can be explained. For example, perhaps it is related to dose size or to baseline 25(OH)D, or to the age of the participants in each study. When that kind of data is available for each study, we can use a statistical method called meta-regression to search for the sources of the heterogeneity. In this case, the Open-Meta application has not matured enough to collect these additional data points on each study. Moreover, the results of the NHANES part of this study are enlightening in this respect.

But it is clear that the answer to research question 3, does daily vitamin D$_3$ supplementation have a statistically-significant beneficial effect on the biological markers of diabetes in the U.S. population, is yes, it does.

**NHANES Study: Research Question 4**

Figures 4.2, 4.3, and 4.4 all have HbA1c on the y-axis. Figure 4.2 shows the mean HbA1c percentage for non-Hispanic blacks and whites by age. At every age there is a health disparity between the groups. The graph points out that on average, a non-Hispanic black’s HbA1c percentage will indicate pre-diabetes at age 41, while for non-Hispanic whites this happens 16 years later, at age 57.

Figure 4.3 shows the same analysis in terms of weight. On average, a non-Hispanic black’s HbA1c percentage will indicate pre-diabetes at about 180 pounds, while for a non-Hispanic white this does not happen until about 235 pounds. However, in this
graph, note how the 95% confidence intervals of the two groups overlap at low weights. This indicates there is no statistically significant difference between the groups until weight exceeds about 125 pounds.

Figure 4.4 shows the same analysis in terms of vitamin D exposure. This figure is the most remarkable of the figures in this analysis. It clearly shows that for non-Hispanic whites, a diagnosis of pre-diabetes is associated only with very low vitamin D levels and the association decreases as vitamin D exposure increases. For non-Hispanic blacks, on the other hand, increasing vitamin D exposure is associated with an increasing likelihood of a diagnosis of pre-diabetes. This is the kind of finding that suggests an explanation for the heterogeneity in our meta-analysis results. There are few non-Hispanic blacks with 25(OH)D levels over 30 ng/ml, but the 95% confidence intervals take that into account. Could there be something different about non-Hispanic blacks with 25(OH)D levels that high, something unrelated to vitamin D, that is associated with an increased risk for diabetes? Or is there something different about non-Hispanic whites with 25(OH)D levels that high, something unrelated to vitamin D, that is associated with a reduction in the risk for diabetes? To tease out answers to these questions, we would need to do a meta-analysis on the effect of daily vitamin D₃ supplementation on diabetes using only studies in which all of the participants were African Americans. But at the moment there are not enough studies like that to do a meta-analysis.

Figures 4.5 though 4.8 all have fasting glucose and fasting insulin on the y-axis. Figure 4.5 shows the mean values for glucose and insulin across the diagnostic values of HbA1c. In this figure, note that the lines for insulin completely overlap for non-Hispanic blacks and non-Hispanic whites. For glucose, on the other hand, non-Hispanic blacks
reach diagnostic levels for pre-diabetes with lower mean blood glucose than whites. But what does this mean? At one extreme, perhaps non-Hispanic blacks, on average, do a stricter pre-blood draw fast. At the other extreme, perhaps the HbA1c diagnostic criteria should vary by race, with non-Hispanic blacks entering pre-diabetes at a higher HbA1c percentage than whites. In any case, the lower mean fasting glucose scores for non-Hispanic blacks across mean HbA1c percentages is unexpected.

Figures 4.6 and 4.7, which show mean glucose and insulin values by age and weight, suggest that for both glucose and insulin the means for the two groups are very close together, although not completely overlapping. In these two figures there is little evidence for any diabetes-related health disparity at all.

Finally, in Figure 4.8, we see glucose and insulin levels over vitamin D exposure in the two groups. As in Figure 4.4, we again see that for non-Hispanic whites, higher exposure to vitamin D is associated with better glucose and insulin levels. But this relationship does not hold for non-Hispanic blacks. These relationships are difficult to interpret, but, in part, may indicate why there is so much more heterogeneity in the meta-analysis of the effect of daily vitamin D₃ supplementation on markers of diabetes than in the similar meta-analysis on blood pressure.

The only viable answer to our remaining research question, do the vitamin D disparities between those who self-identify as non-Hispanic black and non-Hispanic white in the U.S. seem to account for the health disparities we find in diabetes, is that we do not know. Our research on this question has raised more questions than answers.
Limitations and Strengths

As noted in the previous chapter, the glaring limitation of the systematic review and meta-analysis it was done by a single reviewer rather than by a team, using software which is new and which has not been thoroughly tested.

The strengths of this study are that it combines nationally-representative correlational data with a dependent effects meta-analysis of controlled trials. Dependent effects meta-analysis allows the inclusion, from a single study, of multiple intervention groups, outcomes, and time-separated outcome measurements that all depend on the study’s single control group. Yet without the insights provided by the NHANES correlational data, the study in this chapter would have reached the conclusion that daily vitamin D₃ supplementation would help eliminate health disparities in diabetes. With this additional data, we realize the situation is more complex than it appears, and we just do not know what the impact of additional vitamin D₃ exposure would be on the U.S. health disparities in diabetes.

Conclusion

The structured review and meta-analysis of controlled trials in this chapter’s study supports the hypothesis that daily vitamin D₃ supplementation has a beneficial effect on markers for diabetes. However, our examination of nationally-representative correlational data from NHANES shows very different responses to vitamin D exposure in non-Hispanic blacks and whites. While supplementation has a beneficial effect on diabetes for
non-Hispanic whites, it is not clear whether it helps non-Hispanic blacks nor whether it would help to diminish the U.S. racial health disparity in diabetes.

Future studies should begin with the correlational data to develop theories of why vitamin D exposure appears to have the opposite impact on diabetes in non-Hispanic whites and blacks. Those theories can then be tested with experimental studies, which of course, can be combined using systematic review and meta-analysis.
V – CONCLUSION

In the Introduction I listed three specific aims of this project. In this chapter I will review the results for each of these three specific aims, identify the limitations and strengths of the findings for each specific aim, and address the implications of these findings for research and practice.

Review of Specific Aims

Specific Aim 1

*To develop a health education-focused, multi-user, open-source application for continuous online updating and replication of systematic reviews and meta-analyses.*

Chapter II, The Open-Meta Application, describes the development and status of this application. Although a project like this can be continuously improved and, thus, is never complete, the application has developed to the point that it can be used to efficiently complete a *bona fide* systematic review and meta-analysis. It is health-education focused, multi-user, and open-source. Continuous online updating and replication are possible but have not yet been demonstrated with actual projects. The application’s availability will continue upon completion of this dissertation.

**Limitations.** The application has two major types of weaknesses. One type pertains to missing features. The other type pertains to missing popularity and usage.

Missing features include some related specifically to meta-analysis: PRISMA diagrams, sequential analysis, bias plots, and meta-regression. Others are related to a
more comprehensive system for identifying duplicate citations, a system for public commenting, and a better system for dealing with multiple publications reporting different outcomes from a single study. There are also issues related to cleaning up the database in the extraction phase when “negative” actions take place, such as changing a citation from pass to fail, or removing a PICOT from an arm, or removing an arm from a study. I am committed to adding these and additional features as part of a continuous improvement process for the application.

The second type of weakness relates to a lack of users and developers. Long term survival of the application will require recruiting both users and developers and encouraging them to recruit additional users and developers in a viral process. The upcoming release of the Cochrane Collaboration’s *RevMan Web* (Cochrane Collaboration, 2018) will create major competitive pressure, while also endorsing the need for this type of application.

Neither of these limitations, fortunately, is necessarily permanent. My next steps for this project are to add missing functionality to the Open-Meta application while expanding its use. I plan to work with professors and librarians to encourage students to learn about and use the application. Much of the work of a structured review relies on skills that librarians have already developed, making the Open-Meta application something that libraries may be interested in sponsoring. At the same time, existing organizations that promote the use of structured reviews and meta-analyses may be interested in promoting its use and I intend to investigate that further with some of these organizations.
**Strengths.** At the same time, the Open-Meta application has some considerable strengths. First, other than *RevMan Web*, there is nothing else like it. Unlike *RevMan Web*, the Open-Meta application is open-source and *open* in the sense that anyone can start or join a project. Cochrane also sponsors Cochrane Crowd (Cochrane Collaboration, 2016), which by name appears to be similar to the Open-Meta application, but is actually limited to crowd sourcing the identification of randomized controlled trials, just one of the aspects of the Open-Meta Reviewer role.

The Open-Meta application operationalizes the PRISMA process, from the writing and online publication of a protocol at the beginning of a project to supporting PRISMA-compliant publication. *RevMan Web* does not appear to incorporate publication of protocols nor does it allow anyone with an interest to join a project.

Another major advantage of the Open-Meta application is its reliance on and support for dependent effects analysis. The automatically-customized form that Open-Meta uses to collect data in the extraction phase (see Figure 2.18 on page 39) expands to include all interventions and time spans related to a single control group, as defined in the settings for a study arm (see Figure 2.17 on page 38). The Open-Meta application is the only resource where this type of form is available.

The exclusive availability of this type of form results from the lack of its need with the meta-analysis methods of fixed effects, random effects, and mixed effects. With these methods, dependency of several measures on a single control group is not allowed, so there is no such form. Like Open-Meta itself, dependent effects analysis does not currently have enough users. Open-Meta and dependent effects analysis should become popular together.
Implications for Practice. The Open-Meta application makes it much easier for students to learn how to complete and for teams of even graduate students to actually complete systematic reviews and meta-analyses. This helps to inform evidence-based practice in health education and other fields. Moreover, the systematic review provides a methodology for students to develop familiarity with the academic literature in selected areas of study, which is the first step to developing true expertise. An additional benefit is the ability to take full advantage of the research base that already exists, which is often underutilized.

My intention is to continue developing the Open-Meta application and to continue to use it to create systematic reviews and meta-analyses. If other researchers become interested in it, I could either set up a non-profit organization to provide the application with a home and long-term support. Another option would be to transfer it to an existing organization that could provide the support the application requires.

In either case, the application can be used by those in health, nutrition, education, and other fields to develop gold-standard data their profession can rely on. The application could also be used to train students about the details of PRISMA, structured reviews, and the statistical fine points of meta-analysis. The more students who are trained using Open-Meta, the more users it will have and the more attention it will receive.

Specific Aim 2

To use this application to calculate the best current estimate of whether daily vitamin D₃ supplementation has a beneficial effect on systolic blood pressure.
Chapter 3, Daily Vitamin D₃ Supplementation as a Treatment for Health Disparities in Blood Pressure, addresses this specific aim. The conclusion of that chapter is that daily vitamin D₃ supplementation does have a small but significant effect on blood pressure. While the effect is not large enough to use vitamin D₃ as a blood pressure drug, it does appear large enough to reduce, but not eliminate, health disparities in blood pressure.

**Limitations.** The major weakness of this study is that the systematic review and meta-analysis was completed by a single researcher. Because of a lack of resources, only one research database, Cochrane CENTRAL, was searched for articles and those were reviewed for project criteria only once. Some articles found by the January update weren’t reviewed at all if they did not have the words blood pressure or hypertension in the title or abstract. Nonetheless, no previous review found as many trials of daily vitamin D₃ supplementation with a measured blood pressure outcome as this one.

**Strengths.** The strengths of this study fall in two major areas. First, the study was theory-driven, as explained in the section, This Study’s Theoretical Model of Vitamin D Action, on pages 72-73. The research literature is full of correlational studies that show an association between vitamin D and health and randomized controlled trials that are not effective. This study explains why. First, as this study’s theoretical model suggests, studies of “vitamin D supplementation” must restrict themselves to daily supplementation only with vitamin D₃. Second, as this study’s systematic review and meta-analysis suggest, the effect, while statistically significant, is too small for trials with limited numbers of participants to detect.
The second strength of this study is that it combines strong external validity, using nationally-representative correlational data, with strong internal validity, using a meta-analysis of randomized controlled trials. In addition, the meta-analysis used dependent effects analysis, which allowed including multiple outcomes, interventions, and time spans from the same study.

**Specific Aim 3**

*To use this application to calculate the best current estimate of whether daily vitamin D₃ supplementation has a beneficial effect on markers of diabetes, such as fasting glucose and fasting insulin, glycosylated hemoglobin (HbA₁c), homeostatic model assessment for insulin resistance (HOMA-IR) and β-cell function (HOMA-β), and the quantitative insulin-sensitivity check index (QUICKI).*

Chapter 4, Daily Vitamin D₃ Supplementation as a Treatment for Health Disparities in Diabetes, addresses this specific aim. The findings of the study were that daily vitamin D₃ supplementation has a statistically significant beneficial effect on markers of diabetes overall as well as on specific markers related to insulin resistance but not specific markers related to glucose levels. However, the correlational part of this study raised questions about whether these effects occurred equally in both non-Hispanic-whites and blacks.

**Limitations.** In addition to all the weaknesses listed above for Specific Aim 2, this study has the weakness that the findings do not support the vitamin D theories that are the basis of this dissertation and that are discussed in the introductory chapter’s section, Conceptual Framework, on pages 5 to 9. Research findings that do not support a
theory require that the theory be refined or abandoned. This particular theory has enough research support that abandonment seems unnecessary, but at this time I have no theoretical explanation for the findings. A stronger, future study will.

**Strengths.** This study has all of the strengths listed above for Specific Aim 2. It also shows why the combination of correlational and experimental data in the same study is a strength. Without the NHANES correlational data, this study would have concluded that daily vitamin D$_3$ supplementation is indeed a treatment for health disparities in diabetes. With that correlational data, however, this conclusion is not possible. While at the moment the results of this study do not fit the expected pattern, there is a pattern there somewhere that we just have to find, but have not found yet.

**Conclusion**

In 2014, the Cochrane Collaboration released a major systematic review and meta-analysis titled *Vitamin D supplementation for prevention of mortality in adults* (Bjelakovic et al., 2014). The following comes from the results section of the article’s abstract:

Vitamin D decreased mortality in all 56 trials analysed together….When different forms of vitamin D were assessed in separate analyses, only vitamin D$_3$ decreased mortality….Trial sequential analysis supported our finding regarding vitamin D$_3$, with the cumulative Z-score breaking the trial sequential monitoring boundary for benefit, corresponding to 150 people treated over five years to prevent one additional death (p. 2).

Although the researchers did a separate analysis of vitamin D$_3$ supplementation, they did not do a similar analysis removing studies that used bolus dosing, which would have strengthened their results even further. And even though their own trial sequential
analysis favored vitamin D₃ supplementation for the prevention of mortality, the conclusion of the study was not that vitamin D₃ is safe and effective for improving health, but that “further placebo-controlled randomized trials seem warranted” (p. 2).

In this dissertation I have shown that there is a statistically-significant causal effect of daily vitamin D₃ supplementation that supports the existence of a causal relationship in the correlational data on vitamin D found in nationally-representative studies like NHANES by using systematic review and meta-analysis.

The vitamin D literature’s discordant results are, in part, a result of the assumption that vitamin D₂ and vitamin D₃ are equally effective, although we were warned over a decade ago that they are not (Houghton & Vieth, 2006). They are a result, in part, of the false assumption that 25(OH)D is a measure of effectiveness rather than exposure and of the false assumption that what happens with vitamin D in the human system for calcium balance is the end of the vitamin D story. The best assumption we have is that the parent form of vitamin D₃, produced by sunlight in the skin and obtained through the diet, including by supplementation, is absorbed by cells throughout the body and is used as a signaling molecule to regulate specific genes to the benefit of human health.

Health educators, nutritionists, and other public health professionals and institutions will not eliminate health disparities until they begin to make correct assumptions about the role of vitamin D in human health.
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