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Vitamin D and Insomnia in a Twin Sample

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor

of Philosophy

in

Clinical Psychology

by

Katherine Anne VanBuskirk

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2015

The Dissertation of Katherine Anne VanBuskirk is approved, and it is acceptable in

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University of California, San Diego

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FIELDS OF STUDY

Major Field: Clinical Psychology

    Studies in Behavioral Medicine
    Professors Julie Wetherell and Niloofar Afari

ABSTRACT OF THE DISSERTATION

Vitamin D and Insomnia in a Twin Sample

by

Katherine Anne VanBuskirk

Joint Doctoral Program in Clinical Psychology

University of California, San Diego, 2015
San Diego State University, 2015

Professor Julie Wetherell, Chair

Vitamin D is a hormone precursor that is produced either through epidermal exposure to sunlight or dietary intake. Prevalence estimates suggest that approximately 1 billion people worldwide have insufficient vitamin D levels, which may put them at higher risk of fractures and falls, cognitive impairment, certain forms of cancer, Type I and Type II diabetes, and poor cardiovascular outcomes. Insomnia is also related to a number of these outcomes, but to date, there is little to no published research documenting the relationship between vitamin D and insomnia. Data from the University of Washington Twin Registry (UWTR) were used. The final sample contains 245 twin pairs (490 singletons, 164 monozygotic twins pairs, 81 dizygotic twin pairs). Mixed level

linear regressions were used to control for non-independence of pairs. The overall individual-level model found a significant association between vitamin D and Women's Health Initiative Insomnia Rating Scale (WHIIRS) among monozygotic twins. Vitamin D was found to significantly predict self-reported insomnia ($b = .0336$, $p = .012$, *95% CI* [.0054, .0619]), even after controlling for significant covariates such as perceived stress, sleep hours, number of wakeups, age, and sex. Among dizygotic twins, there was not a significant relationship between vitamin D and insomnia ($p > .05$). The positive association between vitamin D and insomnia was significant only among monozygotic female twins. Our results do not support our original hypotheses. Our original hypotheses predicted that there would be a significant association between vitamin D and self-reported insomnia. An association in the reverse direction anticipated based on findings of the literature were found in this study. Theoretically-driven covariates were added in planned and exploratory analyses. The association between vitamin D and insomnia persisted throughout all analyses among monozygotic female twins. Within-pair analyses suggested that the observed association between vitamin D and insomnia is not causal and is accounted for by shared genetic and/or environmental influences.

Introduction

Vitamin D and Health Outcomes

Vitamin D is a hormone precursor that is produced through skin exposure to sunlight or dietary intake. The medical field first became aware of vitamin D during the 19th century when medical professionals discovered that sunlight exposure cured and reduced the incidence of rickets and other similar skeletal deformities (Holick, 2007). Starting in 1932, nearly all milk consumed in the United States became fortified with vitamin D, which was widely supported by the medical community for mass reduction in rickets, particularly among children (Samaniego-Vaesken, Alonso-Aperte, & Vaerla-Moreiras, 2012). As of 2010, the Institute of Medicine (IOM) Food and Nutrition Board increased the Recommended Dietary Allowance (RDA) of vitamin D to 600 International Units (IU) per day (IOM, 2010). This level was increased from the previous recommendation of 400 IU per day, which had been in place since the 1930's. Current research suggests that vitamin D intake greater than 600 IU per day can be widely beneficial across a variety of domains, from physical to mental health (Vieth, et al., 2007) and researchers have raised concerns about the potentially limited effect of current RDA standards for vitamin D. Not only have the benefits of vitamin D sufficiency become a hot topic in medical research, but the prevalence and consequences of vitamin D deficiency is becoming of greater interest in the health outcomes literature (Holick, 2007; Vieth, et al., 2007).

Vitamin D deficiency is commonly defined as vitamin D levels at or below 20 nanograms/milliliter (ng/mL), which can be measured through serum vitamin D levels from blood samples. Vitamin D insufficiency is commonly considered at levels of 21 to

1

29 ng/mL and sufficiency is considered to be vitamin D levels at or greater than 30 ng/mL. Prevalence estimates suggest that approximately 1 billion people worldwide have insufficient vitamin D levels (Bischoff-Ferrari, Giovannucci, Willett, Dietrich, & Dawson-Hughes, 2006; Holick, 2007; Malabanan, Veronikis, & Holick, 1998), which may put them at higher risk of fractures and falls (Dhesi, et al., 2004; Menant, et al., 2012), osteoporosis (Hanley, Cranney, Jones, Whiting, & Leslie, 2010), cognitive impairment (Menant, et al., 2012), certain forms of cancer (Garland, et al., 2006), Type I and Type II diabetes (Mohr, Garland, Gorham, & Garland, 2008; Penckofer, Kouba, Wallis, & Emanuele, 2008), and cardiovascular events (Lee, O'Keefe, Bell, Hensrud, & Holick, 2008). Higher vitamin D levels have been found to be associated with improved muscular strength (Janssen, Samson, & Verhaar, 2002; Mowe, Haug, & Bohmer, 1999), balance (Dhesi, et al., 2002), and less frequent falls among older adults (Annweiler, et al., 2010). Sufficient vitamin D levels also enhance absorption of calcium (from an absorption rate of approximately 15% to 40%), thereby providing an essential role in bone health (Heaney, Dowell, Hale, & Bendich, 2003; Holick, 2007). Low vitamin D was also associated with reduced neuromuscular control, poor balance, and poor cognitive performance in a sample of 463 community-dwelling older adults (Menant, et al., 2012).

Vitamin D deficiency has also been found to be related to chronic pain (Atherton, et al., 2009b) and supplementation resulted in pain relief or cessation in 68% of women with musculoskeletal pain (de Torrente de la Jara, Pecoud, & Favrat, 2006) and 95% of patients with chronic low back pain (Al Faraj & Al Mutairi, 2003) in two studies. An epidemiological study found that ultraviolet irradiance and latitude were inversely associated with incidence of Type I diabetes across 51 countries (Mohr, et al., 2008).

Similarly, a meta-analysis found that the incidence of Type I diabetes was significantly reduced later in life among infants who received vitamin D supplementation (Zipitis, 2008). The risk of Type II diabetes was also found to be reduced among those with high as compared to low vitamin D intake (greater than 800 IU/day) in the Nurses' Health Study of 83,779 women (Pittas, et al., 2006). These results demonstrate the broad range of associations between vitamin D levels and the incidence and prevalence of medical disorders. As many studies do not differentiate clearly between deficient and insufficient categories of vitamin D levels, those categories will be collapsed together in the summary of findings presented in Table 1.

Table 1. Health outcomes and Vitamin D

Vitamin D Levels ≤ 29 ng/mL "Deficient + Insufficient"	Vitamin D Levels > 30 ng/mL "Sufficient"
Greater risk of:	Reduced risk of:
• Rickets (Holick, 2007) • Fractures and falls (Dhesi, et al., 2004; Gerdhem, Ringsberg, Obrant, & Akesson, 2005; Menant, et al., 2012) • Cognitive impairment (Menant, et al., 2012) • Osteoporosis (Hanley, et al., 2010) • Colon, breast, prostate, ovarian cancers (Garland, et al., 2006; Holick, 2004) • Cardiovascular events (Lee, et al., 2008) • Type I diabetes (Mohr, et al., 2008) • Chronic pain (Al Faraj & Al Mutairi, 2003; de Torrente de la Jara, et al., 2006) • Melanoma (Cornwell, Comstock, Holick, & Bush, 1992; Tang, et al., 2012)	• Falls (Annweiler, et al., 2010) • Type I diabetes (Zipitis, 2008) • Type II diabetes (Pittas, et al., 2006) • Melanoma relapse (Newton-Bishop, et al., 2009; Tang, et al., 2012) • Colon, breast, prostate, and ovarian cancers (Garland, et al., 2006; Lappe, Travers-Gustafson, Davies, Recker, & Heaney, 2007)
Reduced functioning in:	Improved:
• Balance (Menant, et al., 2012) • Neuromuscular control (Menant, et al., 2012) • Muscular strength (Bischoff, et al., 1999; Bunout, et al., 2006) • Gait speed (Bunout, et al., 2006) • Physical performance & hand grip strength (Houston, et al., 2007)	• Muscular strength (Janssen, et al., 2002; Mowe, et al., 1999) • Balance (Dhesi, et al., 2002) • Calcium absorption (Heaney, Dowell, et al., 2003) • Pain relief (Al Faraj & Al Mutairi, 2003; de Torrente de la Jara, et al., 2006)

Each individual's vitamin D levels are influenced by a number of factors, such as geographical location, skin pigmentation, season of measurement, sunlight exposure, supplement usage, dietary intake, body mass index (BMI), and more. As discussed above, milk has been fortified with vitamin D since 1930. Each cup of milk delivers approximately 100 IU of vitamin D (NIH, 2011). Other milk products, such as cheese and ice cream, are not commonly fortified. As awareness of vitamin D deficiency increases,

more foods are beginning to increase vitamin D fortification, such as certain brands of yogurt and breakfast cereals (NIH, 2011). A small number of foods also naturally contain moderate-to-high levels vitamin D, such as oily fish and cod liver oil (Holick, 2004). Using the above figures, to reach the minimum recommended intake of 600 IU/day by dietary intake alone, one would have to consume two 3.5 ounce servings of wild salmon, 6 1-cup glasses of milk, or 2 teaspoons of cod liver oil each day.

In contrast, direct sun exposure to one's arms and legs graded to skin pigmentation, latitude, and season of exposure (approximately 5 minutes for a Caucasian individual, and up to 30 minutes for those with darker skin tones) without sunscreen would produce an equivalent dose of 10,000-20,000 IU per exposure (Holick, 2004). However, rising concerns regarding melanoma and premature skin aging, as well as reduced time spent outdoors during midday hours, have reduced the likelihood of sunlight fostering sufficient vitamin D levels for individuals in modern societies (Vieth, et al., 2007). In the mid-1940s, vitamin D supplementation in food was not highly regulated, leading to excessive supplementation in certain dairy products, which led to rising incidence of vitamin D intoxication among young children (British Pediatric Association, 1956; Bauer & Freyberg, 1946). This led to a ban of vitamin D supplementation in dairy products in Europe. Vitamin D intoxication is uncommon today; the recommended Tolerable Upper Intake Level (UL) for those over age 9 is 4,000 IU per day (NIH, 2011). However, 20-week supplementation of 11,000 IU/day in a sample of men living in Omaha during the winter did not lead to serum blood levels over the recommended range (Heaney, Davies, Chen, Holick, & Barger-Lux, 2003). Vitamin D intoxication through sun exposure is largely impossible due to the breakdown of excess

previtamin D by sunlight into inactive photoproducts (Holick, 2007; Holick &

Garabedian, 2006).

The process of vitamin D metabolism via sunlight exposure is detailed

comprehensively in published reviews (Christakos, Ajibade, Dhawan, Fechner, & Mady,

2010; Holick, 2007; Lehmann & Meurer, 2010). To summarize, the epidermal layer of

the skin contains 7-dehydrocholesterol, a cholesterol precursor. This precursor reacts

when exposed to solar ultraviolet B (UVB) radiation from the sun (or full spectrum UV

bulbs) and is converted into pre-vitamin D_3, which is then immediately converted into

vitamin D_3. With excessive sunlight exposure, available vitamin D_3 will be broken down

into inactive photoproducts. When ingested, vitamin D_2 and vitamin D_3 are transported

through the blood vessels of the body. These vitamins are then stored in lipid cells and

may be released for biological uses. When circulating in the body, vitamin D is bound to

a binding protein and is then converted in the liver to 25-hydroxyvitamin D, which is

biologically inactive. Subsequently, 25-hydroxyvitamin D is converted in the kidneys to

1,25-dihydoxyvitamin D, which is biologically active and distributed and processed in a

variety of ways throughout the body (Holick, 2007). Vitamin D receptors are found

throughout the body, including in the brain (Buell & Dawson-Hughes, 2008), and have

been found to control the transcription of a large number of genes and gene products

(e.g., neurotrophins and other growth factors). Nearly every organ and cell in the human

body contains vitamin D receptors, and vitamin D controls the regulation of more than

2,000 genes. In addition, vitamin D regulates cell growth, making it essential to the

effective termination of malignant tumor cells (Holick, 2012). These genes have been

found to have possible links to schizophrenia, autism, multiple sclerosis and stress-related

processes in the brain and are currently under further investigation (Harms, Burne, Eyles, & McGrath, 2011; McCann & Ames, 2008). The link between vitamin D and bone health is firmly established in the literature and the medical field continues to explore and find new potential links between better physical health and higher vitamin D levels (Holick, 2004).

Sleep

Sleep is an aspect of health behavior that has far-reaching effects, affecting daily functioning, physical wellness, and mental health. Sleep patterns are highly influenced by cultural and biopsychosocial environmental influences; in westernized societies sleep has been declining due to increasing work hours and shift-work lifestyles (Akerstedt & Nilsson, 2003). Reports of daytime fatigue and sleepiness have also been noted to have increased in recent years among westernized populations (Bliwise, 1996). Disrupted sleep is often co-morbid with physical illness and psychopathology, as well as conditions such as cardiovascular disease (Wolk, Gami, Garcia-Touchard, & Somers, 2005), cognitive impairment (Foley, et al., 1999; Thomas, et al., 2000), and major depressive disorder (Tsuno, Besset, & Ritchie, 2005). In the literature, sleep may be assessed both objectively (e.g., using accelerometers, polysomnography) and subjectively (i.e., using self-report). Sleep may be assessed in terms of total sleep time, circadian rhythms, and insomnia. Insomnia has been investigated as both a cluster of symptoms and as a full syndrome (Morin, LeBlanc, Daley, Gregoire, & Merette, 2006). Insomnia symptoms (e.g., difficulty initiating or maintaining sleep) have been estimated in approximately one-third of the adult population (Klink, Quan, Kalterborn, & Lebowitz, 1992; Ohayon, 2001). Once daytime consequences of the symptoms are assessed, prevalence rates decrease to

approximately 10% (Leger, Guilleminault, Dreyfrus, Delahaye, & Paillard, 2000). Both insomnia symptoms and insomnia syndrome diagnosis have been found to be modestly, but steadily, increasing over the prior two decades in a population-based sample of 20,503 individuals living in England (Calem, et al., 2012).

According to the DSM-IV-Text Revision (American Psychiatric Association, 2000), primary insomnia is defined as difficulty initiating or maintaining sleep, or self-reported nonrestorative sleep, for at minimum 1 month. Difficulty initiating sleep is defined as taking 30 minutes or more to fall asleep more than 3 nights of the week. Difficulty maintaining sleep is assessed by multiple awakenings, difficulty falling back to sleep after an awakening, or waking too early in the morning on 3 or more nights of the week. The criterion of nonrestorative sleep is met when individuals report waking feeling moderately to severely nonrefreshed more than 3 mornings per week. In addition, to classify as a clinically-significant syndrome, the insomnia symptoms must produce clinically significant interference in one's social or occupational functioning or well-being. When using the criteria of the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV), prevalence rates have been found to be at 6% (Ohayon, 1997) and 9.5% (Morin, et al., 2006) in the general population.

In a comparison between 240 individuals with self-reported severe insomnia and 391 good sleepers, those with insomnia reported increased medical problems, increased doctor office visits, doubled rates of hospitalization, and increased use of medication (Leger, Guilleminault, Bader, Levy, & Paillard, 2002). Poorer self-reported medical and mental health were also found among individuals with severe and mild insomnia as compared to those with self-reported good sleep (Leger, Scheuermaier, Philip, Paillard, &

Guilleminault, 2001). Findings associating insomnia with increased medical problems and physician-office visits were also found in a sample of 1,926 primary care patients (Simon & VonKorff, 1997) and in a sample of 1100 managed-care patients (Hatoum, Kong, Kania, Wong, & Mendelson, 1998), even after controlling for demographics and comorbid conditions. In a survey of 10,094 managed care health plan subscribers, insomnia was related to significantly poorer scores on mental and physical health domains of the Short-Form 12 Health Survey (Roth, et al., 2011; Ware, Kosinski, & Keller, 1994). In a cross-sectional sample of 2001 individuals in a population-based study, insomnia syndrome, as diagnosed using the DSM-IV criteria, was associated with increased odds of self-reported poor physical health (OR = 5.3) and poor mental health (OR = 1.2) (Morin, et al., 2006). Self-reported insomnia was found to be associated with increased reports of heart disease, cancer, high blood pressure, diabetes, and chronic pain in a population-based study of 772 men and women living in the United States (Taylor, et al., 2007). Similar results were found in a cross-sectional sample of 47,700 individuals living in Norway. Insomnia was found to co-occur with asthma, cancer, hypertension, chronic pain conditions (e.g., arthritis, migraine, osteoporosis), and pain disorders with uncertain etiology (e.g., fibromyalgia, musculoskeletal pain disorder), even after controlling for demographics and other medical conditions (Sivertsen, Krokstad, Overland, & Mykletun, 2009).

In a systematic review and meta-analysis of prospective, population-based studies investigating the relationship between self-reported sleep and all-cause mortality, short-duration sleep was associated with increased risk of death (Cappuccio, D'Elia, Strazzullo, & Miller, 2010). Although there was significant heterogeneity among the studies, no

identifiable variables (e.g., gender, age, socioeconomic status, geographic location, definition of short sleep, length of follow-up) mediated or moderated this effect. Similar results have been found for self-reported sleep duration and disturbance and risk of developing Type II diabetes. In a systematic review and meta-analysis, short sleep duration (less than 5-6 hours/night) was associated with a 28% increased risk of developing Type II diabetes. Risk of Type II diabetes was even greater among those who had insomnia symptoms of difficulty initiating sleep (57% increased risk) and difficulty maintaining sleep (84% increased risk). Mechanisms underlying the association between sleep deprivation and Type II diabetes are theorized to include glucose intolerance, insulin resistance, and reduced insulin response to glucose (Spiegel, Tasali, Leproult, & Van Cauter, 2009).

Cardiovascular health is also highly affected by sleep. Insomnia has been found to be associated with incident coronary artery disease in a 12-year follow-up study of 1870 subjects, even after controlling for known risk factors (Ancoli-Israel, 2006; Mallon, Broman, & Hetta, 2002). A systematic review and meta-analysis of 15 prospective studies found that self-reported sleep duration was associated with 48% increased risk of developing or dying from coronary heart disease. In addition, short sleep duration was associated with a 15% increased risk of suffering a stroke during follow-up period (range: 7 – 25 years). Nearly all studies controlled for potential confounders such as age, substance use, physical activity, and health status (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011). A second meta-analysis of 13 prospective studies published one year later replicated these results and found a 45% increased risk of cardiovascular events among those who reported experiencing symptoms of insomnia (Sofi, et al., 2012). These

results have been corroborated in a study using actigraph sleep measurement methodology and computerized tomography scans to assess for coronary artery calcifications (King, et al., 2008), as well as in a study examining self-reported sleep and carotid intima-media thickness in the general population (Wolff, et al., 2008).

Finally, cancer incidence has also been found to be associated with sleep disturbance and insomnia (Blask, 2009). In an epidemiological study of female Finnish twins, sleep of 9 hours was associated with a 72% reduction in breast cancer incidence as compared to sleep of 7-8 hours (Verkasalo, et al., 2005). However, a large-scale epidemiological study (Pinheiro, Schernhammer, Tworoger, & Michels, 2006) and case-control study (McElroy, et al., 2006) found no significant association between sleep duration and breast cancer risk, suggesting that this relationship requires further investigation. Short sleep duration was associated with increased incidence of colorectal (Jiao, et al., 2013; Thompson, et al., 2011) and thyroid (Luo, Sands, Wactawski-Wedne, Song, & Margolis, 2012) cancers.

Insomnia and short sleep duration have also been found to be associated with increased rates of psychopathology. In an epidemiological study of 47,700 individuals in Norway, insomnia was found to have the strongest relationship with conditions that had a psychological component such as depression, anxiety, and pain conditions of indeterminate cause (e.g., fibromyalgia, headache) (Sivertsen, et al., 2009). In a recent meta-analysis of 21 studies assessing the relationship between insomnia and depression, those with insomnia were found to have 2.10 increased risk of developing depression (Baglioni, et al., 2011). In addition, a population-based, longitudinal study of 1,741 individuals that used polysomnography to assess insomnia symptoms found that self-

reported depressive symptoms are one of the strongest predictors of insomnia persistence over more than 7 years (OR = 9.67). Anxiety disorders, particularly panic disorder and generalized anxiety disorder, have also been found to be strongly comorbid with insomnia (Marcks & Weisberg, 2009). Given that insomnia is a formal symptom of both anxiety and depression, the co-occurrence between these disorders is to be expected. However, this relationship may be bi-directional, as depressive symptoms have been found to be reliable risk factors for insomnia (Staner, 2010). Evidence does not consistently suggest that there is a clear causal relationship between insomnia and depression, rather that underlying factors may predispose one to one or both of these conditions (Staner, 2010).

Taken together, these studies indicate that insomnia and short sleep duration are significantly associated with a wide range of physical and mental health conditions (Kyle, Morgan, & Espie, 2010). Insomnia and short sleep duration may likely increase risk of incidence of disease and mortality through a variety of biological disruptions resultant from chronic sleep deprivation (Blask, 2009; Sigurdson & Ayas, 2007). As discussed above, different pathophysiological mechanisms may be underlying the relationship between modifiable health and behavioral factors, such as vitamin D level and sleep duration and quality, and health outcomes. Of note, however, is the dearth of literature currently investigating whether or not these two variables, sleep and vitamin D deficiency, are associated with each other.

Vitamin D and Sleep Overlap

One potential mechanism that has not yet been thoroughly explored that may help to account for the associations between both insomnia and vitamin D and various health

outcomes is the link between vitamin D and sleep. Vitamin D and insomnia may be linked via inflammation, a non-specific immune system response to injury, disease, or homeostatic imbalance (Simpson & Dinges, 2007). Acute inflammation is often of short-term duration and localized; however, chronic inflammation is associated with systemic elevations of inflammatory markers, such as C-reactive protein, cytokines, and catecholamines (Libby, Ridker, & Maseri, 2002). Vitamin D acts as an immunosuppressant and serves to suppress proinflammatory cytokines in the brain and body (van Etten & Mathieu, 2005). Vitamin D deficiency was found to be associated with increased inflammatory markers in 171 healthy individuals presenting to a primary care clinic, and C-reactive protein levels were found to decrease following vitamin D supplementation in a subset of this sample at 5-year follow-up (Timms, et al., 2002). Vitamin D is also associated with regulating blood pressure, leading to less stress and inflammation in the vascular systems within the body and brain (Pfeifer, Begerow, Minne, Nachtigall, & Hansen, 2001).

The relationship between sleep and inflammation is thought to be bi-directional, in that elevations in stress hormones lead to reduced levels of sleep and insomnia (Chiu, et al., 2009; Krueger, Obal, Fang, Kubota, & Taishi, 2001), and insomnia increases levels of stress markers, such as interleukin-1, tumor necrosis factor, and interleukin-6 (Motivala, 2011; Simpson & Dinges, 2007). C-reactive protein, which is unaffected by circadian rhythms (Meier-Ewert, et al., 2001), has been shown to increase in response to sleep deprivation among healthy volunteers (Meier-Ewert, et al., 2004), to levels associated with mild cardiovascular disease (Meier-Ewert, et al., 2004; Ridker, 2001). Total time awake was found to be positively correlated with urinary free cortisol, and

catecholamines were positively associated with markers of insomnia, such as wake time after sleep onset (Vgontzas, et al., 1998). Individuals with insomnia have been found to have elevated nighttime interleukin-6 levels, proportional to duration of sleep (Burgos, et al., 2006; Simpson & Dinges, 2007).

Vitamin D may also be linked to poor sleep outcomes through regulation of dopamine. Vitamin D influences the regulation of the gene expression of tyrosine hydroxylase, an enzyme involved in the production of norepinephrine and dopamine (Ganji, Milone, Cody, McCarty, & Wang, 2010). In addition, vitamin D protects against the activity of dopaminergic neurotoxins, thereby regulating dopamine levels in the brain (Cass, Smith, & Peters, 2006; Eyles, et al., 2009; Smith, Fletcher-Turner, Yurek, & Cass, 2006). Sleep disorders have been found to be associated with dysfunctional dopaminergic functioning (Finan & Smith, 2013). Restless leg syndrome (RLS), commonly associated with insomnia, has been associated with reduced D2 receptors in the putamen (Connor, et al., 2009) and dysfunction in the nigrostriatal DA areas (Allen, 2004). RLS was found to be positively affected by low-dose dopamine agonists (Finan & Smith, 2013). Insomnia is theorized to be associated with chronic hyperarousal (Bonnet & Arand, 2010) and those with insomnia are 10 times more likely to have depression than are good sleepers (Benca & Peterson, 2008; Taylor, Lichstein, Durrence, Reidel, & Bush, 2005). Psychological stress has been found to activate dopamine production (Abercrombie, Keefe, Difrischia, & Zigmond, 1998; Horvitz, 2002); however, chronic stress may be associated with reduced ability to stimulate dopamine production in response to natural rewards (Finan & Smith, 2013; Spanagel & Weiss, 1999), thereby increasing vulnerability to major depressive disorder. A study using single photo emission computerized tomography

(SPECT) found that the basal ganglia, a major production site of dopamine in the brain, was the site of strongest perfusion irregularities when comparing between those with insomnia and healthy controls (Smith, et al., 2002). Those with insomnia had significant hypoarousal of the basal ganglia during the measured portion of NREM sleep; the authors conclude that these results may not fully contradict the hyperarousal model of insomnia, but rather provide further evidence for dopamine dysfunction in the etiology and maintenance of insomnia (Smith, et al., 2002). It is possible that sleep-related arousal contributed to by dysfunctional dopamine regulation results in chronic activation of the sympathetic stress response and HPA axis, which are mediated by cortisol and catecholamines (Finan & Smith, 2013; Vgontzas, et al., 1998). Through these mechanisms, vitamin D deficiency may contribute to dopamine dysregulation, thereby increasing vulnerability to hyper-arousal and insomnia, thereby increasing inflammation and subsequent deleterious health outcomes (see Figure 1).

Research examining the direct relationship between vitamin D and sleep is in its beginnings. Looking primarily at the prevalence of vitamin D deficiency among those with sleep difficulties, vitamin D deficiency was found in 54% of treatment-seeking patients in a sleep medicine clinic. This level was found to be significantly higher than is typically found among clinically normal subjects (average 29.5%) (McCarty, et al., 2013). The relationship between vitamin D and excessive daytime sleepiness was assessed in a sample of 81 sleep clinic patients with chronic nonspecific pain. Among those who were not vitamin D deficient (serum vitamin D levels greater than 20 ng/mL), there was a significant inverse relationship between vitamin D and excessive daytime sleepiness, such that those with the lowest levels of vitamin D reported highest levels of

daytime sleepiness. Among those who were vitamin D deficient, this relationship was only found among those who were African American and not Caucasians (McCarty, Reddy, Keigley, Kim, & Marino, 2012).

Vitamin D
Deficiency

↓

+ Insomnia

↓

+ Dopamine
Dysregulation

+ Inflammation

↓

+ Disease Incidence
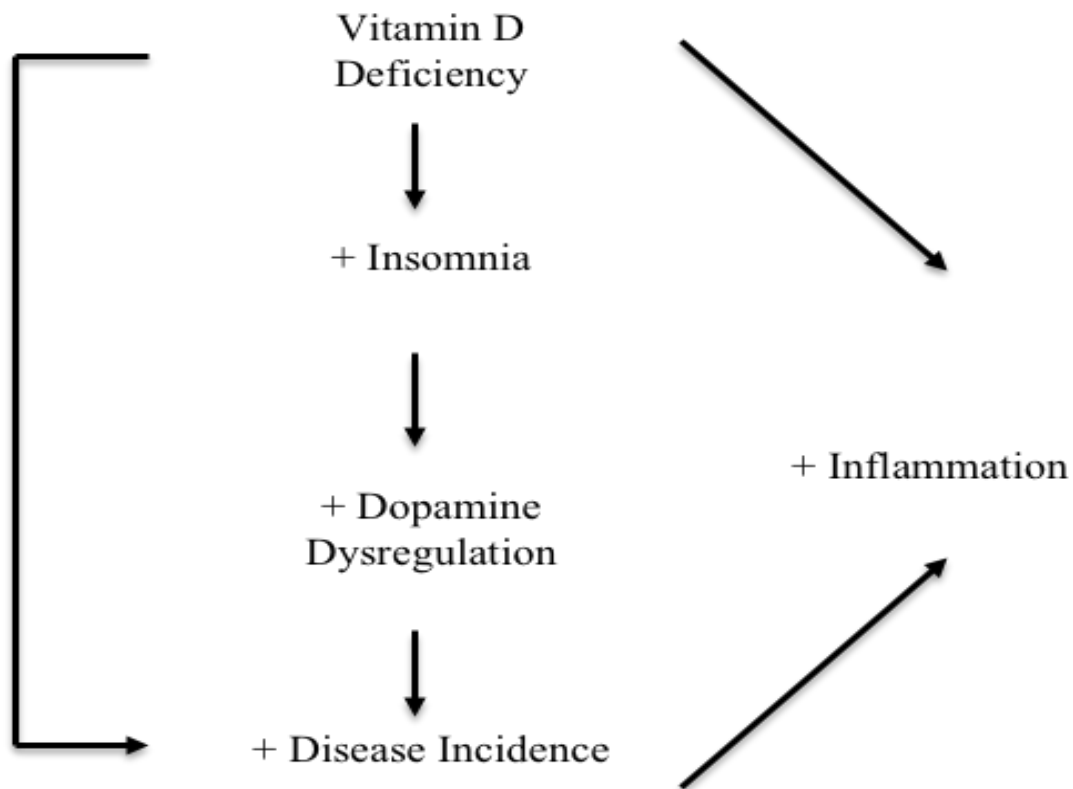
Figure 1. Vitamin D, insomnia, and inflammation

In a case study of an individual with restless legs syndrome (RLS) secondary to vitamin D deficiency that was a side effect of an anticonvulsant, carbamazepine, vitamin D supplementation resolved RLS symptoms within 6 weeks (Prakash, Bhanvadia, & Shah, 2010). In addition, in the cerebrospinal fluid (CSF) of 5 patients with early-onset RLS, there were significantly greater levels of vitamin D binding protein as compared to

non-affected controls (Patton, et al., 2013). In a study examining the link between

obstructive sleep apnea (OSA) and vitamin D in 190 non-diabetic individuals, those with

the most severe levels of OSA had significantly lower vitamin D levels as compared to

age and BMI-matched controls. These researchers also found lower vitamin D levels with

greater severity of insulin resistance among age and BMI-matched controls. Low-grade

systemic inflammation is proposed as one mechanism underlying both OSA and insulin

resistance and diabetes, adding support to the inflammation hypothesis linking vitamin D

and sleep impairment. As such, researchers suggest that these findings point to a role for

vitamin D supplementation to improve health outcomes among those with OSA and

insulin resistance (Bozkurt, et al., 2012). Patients with fibromyalgia and vitamin D

deficiency were found to have increased sleep disturbance, restless legs syndrome, mood

disturbance, and cognitive complaints as compared to those with fibromyalgia but

sufficient vitamin D levels (Olama, Senna, Elarman, & Elhawary, 2013). Finally, in a

sample of 54 Swedish adolescents with depression, vitamin D supplementation for 3

months was associated with improved mood symptoms and reduced sleep difficulties

(Hogberg, et al., 2012).

In an uncontrolled trial of vitamin D supplementation among a sample of 28

veterans with chronic pain and vitamin D insufficiency or deficiency, vitamin D

supplementation was found to significantly improve pain, sleep latency, sleep duration,

and reports of general health, even after controlling for multiple confounders (Huang,

Shah, Long, Crankshaw, & Tangpricha, 2013). In addition, an uncontrolled trial of

vitamin D supplementation in 1500 treatment-seeking patients with a variety of sleep

disorders evidenced remediation of sleep difficulties in most patients over a 2-year

period. Patients were supplemented such that vitamin D levels were maintained in a range

of 60-80 ng/mL, far greater than the typical deficiency cut-off of 20 ng/mL (Gominak &

Stumpf, 2012). The methods and analyses from this trial are not yet published; therefore,

results are speculative. However, these findings and hypotheses suggest that the intention

of this proposal is extremely timely and may have a strong impact on the literature.

Overall, this area of research is in its very beginnings; however, hypotheses

investigating the validity, implications, and mechanisms of the potential association

between vitamin D and sleep disturbance are in development (Anderson & Tufik, 2012;

Gominak & Stumpf, 2012). A literature search of PsycInfo and Medline on July 17, 2013

produced only 59 articles with mention of vitamin D and sleep at the abstract level, and

produced 0 articles for vitamin D and insomnia. Given the lack of research investigating

the relationship between vitamin D and insomnia, the literature would benefit not only

from more well-controlled cross-sectional studies of this relationship, but also research

that is able to better understand causal links. Twin research improves our ability beyond

what is typically available within standard cross-sectional studies of singletons, as will be

discussed below.

Twin Research

Twins provide unique advantages in the study of causal influences on outcomes.

Within health-outcomes research, investigators seek to identify predictor variables that

clearly exert a causal influence on measured outcomes. In this way, we seek to

understand which variables contribute to and prevent the development and maintenance

of diseased states. However, due to ethical constraints, investigators are unable to

randomly assign individuals to levels of certain important predictor variables (e.g., force

one group of individuals to become cigarette smokers and a comparison group to avoid smoking), thereby often impeding the ability to precisely identify causal mechanisms. In the absence of the ability to randomize individuals to health-impacting variables, investigators are able to conduct observational research that seeks to first determine which variables appear to be associated with each other. Twin studies provide a unique advantage to observational research, in that it allows us to better estimate causality between variables while remaining within the ethical constraints mentioned above (McGue, Osler, & Christensen, 2010).

For example, researchers have found a significant and consistent association between general intelligence and education level and healthy lifestyle habits (Deary, Walley, Batty, & Starr, 2006; Gottfredson, 2004; Johnson, Turkheimer, Gottesman, & Bouchard, 2010). A twin study was undertaken to assess the relationship between intelligence, education, and substance use to determine if substance use may be one of the mechanisms by which long-term health and intelligence/education may be related. Twin designs allow for quasi-experimental control because if monozygotic twins are discrepant in intelligence and/or educational attainment, any associated differences in substance use behaviors cannot be related to genetic confounds or shared family environment due to the fact that these variables are inherently controlled for in comparisons within monozygotic twin pairs. These researchers found that when examining this association within twin pairs, higher IQ and education level were associated with greater substance use at age 24, thereby contradicting the cross-sectional healthy lifestyle findings. Therefore, the association observed at an epidemiological level of intelligence and/or education correlating with lower substance use may be resultant from genetic and familial

influences on an environment that supports healthy choices, rather than direct influence of intelligence/education on substance use (Johnson, Hicks, McGue, & Iacono, 2009; Johnson, et al., 2010). This is an example of the improved ability to better isolate mechanisms underlying associated variables provided by twin methodologies.

Assuming twins were raised together, monozygotic and dizygotic twins share common environmental influences upon behavior and later outcomes, particularly health-related outcomes. In addition, monozygotic twins share approximately 100% of their genes and dizygotic twins typically share approximately 50% of their genes. By examining relationships within and between MZ and DZ pairs, we are able estimate heritability of disorders or traits, as well as assess the impact of genetic and familial factors on health and behavioral outcomes. Twin designs control for both genetic and shared familial factors, without the necessity to precisely specify all potential mechanisms involved, thereby allowing for the investigation of unshared environmental influences on outcomes. In this capacity, twin designs can function as quasi-experimental tests of environmental influences on outcomes in the absence of randomized experimental designs (Johnson, et al., 2010). When assessing the causal nature of an association between predictor and outcome variables, observing the strength of the relationship between monozygotic and dizygotic twins is descriptive (see Figure 2).
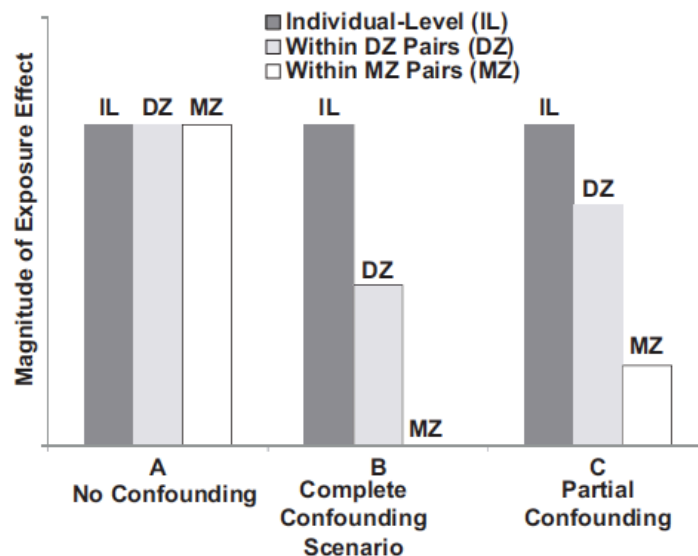
The individual-level association tests for the association between predictor and outcome variables across all twins. If the effect remains consistent across all individuals, DZ, and MZ twin pairs (A), then no genetic or familial confounding is suggested, thereby suggesting a potentially causal link between the predictor and outcome variables. If the association is found to be nonsignificant within MZ pairs (B), there is no support for a causal association as complete confounding is suggested. If the relationship is significant, but attenuated, among MZ twin pairs, partial genetic confounding is suggested, thereby providing some evidence for causal influence between predictor and outcome variables. Figure 2 from McGue et al. (2010).

Figure 2. Discordant twin design effects

As the relationship between vitamin D and insomnia is currently unaddressed in the literature, twin design provides a unique advantage to first assess the cross-sectional relationship among these variables, as well as examine whether this relationship remains significant after adjustment for familial environment and genetic influence. If the relationship remains significant within monozygotic and dizygotic twin pairs, supportive

evidence is established for a causal influence of vitamin D on insomnia and sleep outcomes.

Twin Research in Vitamin D

Vitamin D has been investigated in a number of twin studies. A heritability study using 510 male twins from the Vietnam Era Twin Registry found that the heritability of vitamin D was affected by season of measurement such that 70% of variation in vitamin D levels was explained by genetic factors during the winter. However, during the summer, 53% of the variation in vitamin D levels was explained by shared environmental factors, and 47% of variation was explained by unique factors (Karohl, et al., 2010). Interestingly, these results contrast with those of an earlier study of 204 same-sex twins from the Swedish Twin Registry. In this study, genetic factors accounted for 48% of variance during the summer, with shared environment accounting for 25% and unique factors accounting for 26% of the variance. During the winter, shared environmental factors accounted for the majority of the variance (73%) and unique factors accounted for 27% of the variance. Genetic influences did not account for variance in vitamin D levels in the winter (Snellman, et al., 2009).

The genetic heritability of vitamin D was also assessed in a sample of 226 male and female same-sex, adolescent twins living in rural areas of China, using models that controlled for age, gender, physical activity, student status, and season. The variance in vitamin D unaccounted for by these covariates was strongly influenced by genetic factors (68.9%) and unique factors (31.1%). Shared environmental factors were not found to influence this model (Arguelles, et al., 2009). The results from these three studies are clearly mixed and a clear estimate of heritability from vitamin D may not be possible

given the current state of the literature. However, Johnson et al. argue that heritability estimates may be merely capturing environmental influences and subject characteristics specific to samples from which inferences are drawn. The effect of causal genetic influences is heavily contingent on those factors presented by causal environmental influences (Johnson, 2007; Johnson, et al., 2010). Highly heritable traits are strongly subject to environmental influences; therefore, genetic heritability estimates provide limited long-term value to determining the ultimate cause of an outcome. However, twin research remains extremely valuable to outcomes research as twin designs provide improved abilities to understand the potential causal effects of variables on behavioral and health-related outcomes (Johnson, et al., 2010).

A handful of co-twin studies have investigated the relationship between vitamin D and various outcomes. In a co-twin study of 368 middle-aged male twins, the relationship between vitamin D and myocardial blood flow measured by positron emission tomography was assessed. In twin pairs discordant for vitamin D sufficiency, coronary flow reserve (the ratio between myocardial blood flow at rest and after stress) was significantly lower among vitamin D insufficient twins than sufficient co-twins. This association may help to explain increased cardiovascular risk found among those with vitamin D insufficiency (Karohl, et al., 2013). In a co-twin study examining the behavioral and nutritional risk factors for macular degeneration, twins with more advanced stage of macular degeneration tended to be heavier smokers, and co-twins with less advanced macular degeneration tended to have higher dietary vitamin D and betaine (found in fish, grains, and spinach) intake as measured by a food frequency questionnaire. In addition, differences in vitamin D intake between discordant co-twins were found to be

larger when degeneration difference was also greater (Seddon, Reynolds, Shah, & Rosner, 2011).

Co-twin studies have also found that genetic effects have little influence on neonate vitamin D levels and instead maternal vitamin D levels are the predominant influence (Novakovic, et al., 2012). In contrast, genetic influences were found to contribute significantly to the variance in vitamin D levels among those with multiple sclerosis (Orton, et al., 2008). Randomized controlled trials using monozygotic twins have provided evidence for the effectiveness of calcium and vitamin D supplementation on bone density in peripubertal women (Greene & Naughton, 2011) and the ineffectiveness of sole vitamin D supplementation on bone density in young postmenopausal women (Hunter, et al., 2000). These studies demonstrate that the influence of vitamin D is beginning to be studied within twin samples and a wide range of health outcomes. In addition, these studies provide immense value to better understanding if vitamin D is simply a correlate or potential causal effect behind the number of different associations found between vitamin D and health outcomes.

Physical Activity as a Covariate

Given the myriad associations found among vitamin D, insomnia, and potential health outcomes, research investigating these relationships would be remiss without addressing potential covariates and confounds. One primary covariate of interest in this relationship is physical activity, which has also been found to be associated with vitamin D (Brock, Cant, Clemson, Mason, & Fraser, 2007; Brock, et al., 2010; Ha, Cho, Lee, & Kang, 2013; Lym & Joh, 2009; Waschbisch, et al., 2012). The relationship between physical activity and vitamin D levels is difficult to interpret at present due to differences

in measurement across studies, lack of control groups, and lack of measurement of important confounding variables such as sunscreen usage, degree of skin coverage when outdoors, and hours of sun exposure. Increased physical activity was found to be associated with increased vitamin D levels even after controlling for hours of sun exposure in a sample of 295 men (Scragg, Holdaway, Jackson, & Lim, 1992). In addition, in a study of 1255 individuals over age 65, vitamin D was found to be significantly related to total physical activity, indoor physical activity, and outdoor physical activity, but the majority of these relationships became nonsignificant after adjustment for confounders. Women who had the greatest amount of physical activity indoors (greater than 150 minutes/day) were found to have significantly higher vitamin D as compared to those who had the lowest indoor physical activity (less than 41 minutes/day). These results were found also for outdoor activity, such that women in the highest quartile of outdoor activity (greater than 55 minutes/day) had significantly higher vitamin D levels than did those in the lowest quartile (less than 9 minutes/day). All relationships were nonsignificant in men. These results lean in favor of an effect of high levels of physical activity on vitamin D; however, the minutes of exercise captured by the quartiles were not consistent between indoor and outdoor exercise (van den Heuvel, van Schoor, de Jongh, Visser, & Lips, 2013). In another study, overall physical activity was not found to significantly predict vitamin D levels. However, when physical activity was further specified into vigorous versus non-vigorous exercise, 57 Vietnamese-born elderly individuals who did not vigorously exercise had a significantly increased risk of vitamin D deficiency as compared to those who did endorse vigorously exercising, even after controlling for sun exposure. However, these results were not consistent across the other

subset of the study, 101 Australian-British elderly born individuals (Brock, et al., 2007).

Once measurement of overall sun exposure is incorporated into analyses, the relationship

between physical activity and vitamin D becomes even more mixed and inconsistent.

Other studies do not support a direct link between physical activity and vitamin D

metabolism. A study of 300 Saudi Arabian children and adolescents found no significant

relationship between physical activity as measured by accelerometers and vitamin D

levels when the model contained multiple confounders, including daily sun exposure (Al-

Ghamdi, Lanham-New, & Kahn, 2012). One study of 390 New Zealand residents found

that physical activity was associated with increased vitamin D levels, but that this effect

was best accounted for by place of activity (outdoor as compared to indoor), and level of

activity did not account for significant variation among levels. As such, the authors

concluded that the finding linking physical activity to vitamin D was likely confounded

by sun exposure (Scragg, et al., 1995) . In addition, the only two studies in the literature

that directly measured levels of vitamin D before and after bouts of physical exercise did

not find a positive association (Looker, 2007). In an uncontrolled investigation of

metabolic changes in response to rest and training periods over 7 weeks among 9 male

marathon runners, levels of vitamin D were unchanged throughout various phases of

physical activity (Klausen, Breum, Sorensen, Schifter, & Sonne, 1993). In addition,

vitamin D levels were observed to decrease, rather than increase, after strenuous exercise

in a sample of 21 active, elderly individuals (Maimoun, et al., 2005).

Taken together, the literature has not yet clarified whether a direct relationship

exists between physical activity and vitamin D levels (Al-Othman, et al., 2012; Looker,

2007). While a recent meta-analysis found that physical activity was included as a

confounder in 14 of 36 studies investigating the relationship between vitamin D and mental health (VanBuskirk, Afari, Gallo, & Wetherell, In Preparation), physical activity may serve as a variable that merits further investigation. If a significant relationship in fact does exist, the directional properties of this relationship are not yet clear. It is possible that vitamin D and physical activity are linked by a bi-directional relationship in that physical activity may influence vitamin D metabolism and higher vitamin D levels may lead to reduced levels of fatigue, thereby increasing rates of physical activity.

Physical activity has also been found to be associated with insomnia and sleep quality. A meta-analysis found that acute and chronic exercise increased slow wave sleep and total sleep time, but was not associated with sleep onset latency or amount of REM sleep. Sleep quality was found to be significantly associated with amount of exercise and timing of exercise (Kubitz, Landers, Petruzzello, & Han, 1996). Similar results were found for a second meta-analysis of 38 studies; moderate effect sizes were found between acute exercise and slow wave sleep, REM sleep, REM latency, and total sleep time (Youngstedt, O'Connor, & Dishman, 1997). A 3-year, population-based study of 14,001 elderly Japanese individuals found habitual physical activity to be associated with reduced incidence of insomnia, particularly related to sleep maintenance (Inoue, et al., 2013). Lower physical activity was also found to be associated with increased insomnia among 1678 patients on dialysis (Anand, et al., 2013). In addition, exercise training, particularly aerobic exercise, was found to be an effective treatment for chronic insomnia in a systematic review of the literature (Passos, Poyares, Santana, Tufik, & Mello, 2012) and a moderately effective treatment for sleep disturbance in elderly populations specifically in a Cochrane Library systematic review (Montgomery & Dennis, 2002). As

such, the relationship between physical activity and sleep has moderate evidence within the literature; however, the understanding of physical activity and vitamin D remains preliminary. Further understanding of the impact of vitamin D on insomnia, with the ability to account for physical activity levels in this relationship will improve current understanding of the impact of vitamin D on sleep health.

Confounding Variables

There are a number of variables that influence levels of vitamin D. Vitamin D is negatively correlated with BMI, in theory due to the fact that vitamin D is stored in fat cells and may be stored rather than freely accessible for bodily functions in those with higher amounts of body fat (Lagunova, Porojnicu, Lindberg, Hexeberg, & Moan, 2009; Vimaleswaran, et al., 2013; Wortsman, Matsuoka, Chen, Lu, & Holick, 2000). In addition, weight loss has been associated with increasing vitamin D levels (Rock, et al., 2012). Smoking status has also been found to be confounded with vitamin D, such that smoking reduces available vitamin D levels (Brot, Jorgensen, & Sorensen, 1999). Ethnicity affects vitamin D levels due to higher levels of melanin present in darker skin pigmentation, leading to reduced vitamin D synthesis (Matsuoka, Wortsman, Haddad, Kolm, & Hollis, 1991). Women have also been found to have higher rates of vitamin D than do men (L. K. Johnson, et al., 2012). Physician-diagnosed medical comorbidities may also influence vitamin D levels and sleep through overall medical health, as well as propensity to be prescribed vitamin D supplementation (Chatfield, Brand, Ebeling, & Russell, 2007). Self-reported pain symptoms have also been found to be associated with insomnia (Nicassio, et al., 2012) and vitamin D levels (Atherton, et al., 2009a). Finally, the relationship between mental health and insomnia has been well-established (Riemann,

2007; Taylor, et al., 2005), and as such, variables of psychological distress will be used to control for this contribution to the variance in insomnia. These consistently demonstrated confounding variables are necessary to account for in the investigation of any relationship between vitamin D and insomnia so as to best isolate a potentially causal role of vitamin D.

Summary and Limitations of Literature

As discussed above, the literature adding to the understanding of vitamin D is growing exponentially and has found a large number of links between vitamin D levels and various mental and physical health outcomes. There are several areas of growth that will widely benefit the literature. First, there are only a handful of studies using twin designs to better understand the potential causal role of vitamin D. Second, the relationship between vitamin D and sleep disturbance is not yet understood and we have found no published studies examining the relationship between vitamin D and insomnia. Therefore, the literature will benefit from the following proposal not only in understanding more about the relationship between vitamin D and sleep disturbance, but it will be one of the first investigations of vitamin D and insomnia. In addition, the following proposal will have the ability to examine this relationship both at the general level, but also will be able to examine for effects of potential causality through a co-twin design.

Specific Aims

Specific aims are 1) to examine the association of vitamin D levels and insomnia; 2) to assess the confounding effects of physical activity level on the association between vitamin D and insomnia; 3) to assess if season of measurement moderates this

relationship; and 4) if the relationship between vitamin D and insomnia is significant, to explore whether genetic and familial factors contribute to the link between vitamin D and insomnia. Hypotheses are: 1) Vitamin D is significantly associated with sleep outcomes, above and beyond any association accounted for by covariates in the model (e.g., depression); 2) controlling for physical activity in the regression model will reduce the association thereby suggesting that physical activity is a confounding variable in the link of vitamin D and insomnia; 3) that this relationship will be moderated by season of measurement such that the relationship will be stronger in the spring-summer as compared to fall-winter months; and 4) that these associations will remain significant after controlling for genetic and shared environmental confounds.

Overall, our first goal in these proposed analyses is to accurately assess the effect of individual vitamin D level on individual insomnia score, free of confounding by family-level influences. Our second overarching goal is to evaluate whether twin pair-averaged vitamin D level has an independent impact on individual insomnia, beyond that contributed by individual vitamin D level. It is not directly obvious as to why the vitamin D status of one's co-twin has a direct effect on an individual's insomnia; however, twin pair-averaged vitamin D may serve as a proxy for relevant family-level characteristics, including both genetic and environmental factors

Method

Participants

Twins aged 18 and older are identified to the University of Washington Twin Registry (UWTR) through the Washington State Department of Licensure. Those twins who respond to mailed invitation to study participation fill out a survey of sociodemographics, physical and psychological health status, and self-reported zygosity using standardized questions found to classify zygosity correctly approximately 95% of the time (Eisen, Neuman, Goldberg, Rice, & True, 1989; Torgersen, 1979). Those who consent and return the mailed survey provide identification for their co-twin, whom is subsequently contacted by the UWTR and invited to participate, as well. Twin pairs are scheduled for in-person assessments of height, weight, and blood sampling and are invited to participate in new studies as they are initiated. Data are under the direction of each study's Principal Investigator for a 3-year period, after which data become a permanent part of the Registry database and are accessible for use by others. Serum vitamin D data are available on 284 twin pairs (167 monozygotic twin pairs, 117 dizygotic twin pairs), and of these, 281 pairs provided insomnia data. Thirty-six twin pairs were opposite-sex dizygotic twins and were listwise deleted from the dataset due to inability to control for this degree of variance in these analyses. The final sample contains 245 twin pairs (490 singletons; 164 monozygotic twins pairs, 81 dizygotic twin pairs). The sample has 342 female participants (69.8%), with an overall mean age of 27.05 years ($SD = 10.03$). The sample is 3.7% Hispanic, 86.3% White, 3.3% Black, 6.1% Asian/Pacific Islander, 0.6% Native American, and 3.7% "Other". All twins in this sample were reared together until at least 15 years of age.

Table 2. Demographic and clinical characteristics of twins divided by zygosity

Variable	Monozygotic Twins	Dizygotic Twins
Age, *mean (SD)*	27.68 (10.28)	25.78 (9.40)
Females (*%*)	72.6	64.2
White (*%*)	85.4	88.3
Hispanic (*%*)	3.7	3.7
Body Mass Index, *mean* (*SD*)	24.67 (4.31)	25.47 (5.84)
Perceived Stress Scale	11.16 (6.68)	11.70 (6.48)
Vitamin D, *mean* (*SD*) (*ng/mL*)	29.12	12.49
Vitamin D Deficient (<20 ng/mL) (*%*)	21.3	27.2
WHIIRS, *mean* (*SD*)	11.04 (4.17)	11.26 (4.48)

Measures

Vitamin D

Each twin participant completed a blood draw on the same day as completing self-report assessments during the period of data collection from years 2004 through 2010. For each twin pair, plasma cryovials were transported from the UWTR to the University of Washington Department of Laboratory Medicine for the vitamin D assays in late 2012. Samples were measured using high-performance liquid chromatography coupled with tandem mass spectrometry to assess level of serum 25-hydroxyvitamin D (25(OH)D) (Wootton, 2005). Vitamin D was also assessed using a food frequency questionnaire (FFQ), a self-report questionnaire that assesses for frequency of consumption and portion size of approximately 125 items over defined periods of time (e.g., last month, last 3 months). The FFQ was developed by the Nutrition Assessment

Shared Resource (NASR) of Fred Hutchinson Cancer Research Center (FHCRC) (NASR, n.d.). The FFQ may be used to identify amount of vitamin D consumed.

Insomnia

Insomnia symptoms were measured using the 5-item Women's Health Initiative Insomnia Rating Scale (Levine, et al., 2003). This scale assesses symptoms of insomnia and sleep disturbance over the prior 4 weeks with questions such as, "did you have trouble falling asleep?" and "did you have trouble getting back to sleep after waking too early?". The items are endorsed according to a 5-point scale with responses ranging from "no, not in the last 4 weeks" to "yes, 5 or more times a week". Test-retest reliability has been found to be .96 for same-day administration and .66 for administration after 1 year or more. Internal consistency was found to be good ($\alpha = .79$) (Levine, et al., 2003). Participants also self-reported total average sleep time in the prior 4 weeks.

Physical Activity

The International Physical Activity Questionnaire (IPAQ) Long Form is a 27-item self-report questionnaire that assesses leisure, domestic, work-related, and transport-related physical activity (Craig, et al., 2003). The questionnaire was developed for use cross-nationally and has been translated into at least 8 different languages (Gauthier, Lariviere, & Young, 2009). Test-retest reliability averaged at 0.80 from a 12-country reliability study, with the highest reliability found in a sample from the United States (0.96). Criterion validity of the self-report questionnaire as compared to accelerometers found fair to moderate agreement, which is consistent with other self-report questionnaires for physical activity (Craig, et al., 2003).

Psychological Distress

Self-reported perceived stress was measured using the Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983). The PSS is a 10-item scale assessing the degree to which participants report stressful experiences within the past 30 days. Items consist of questions such as, "in the last 30 days, how often have you felt that you were unable to control the important things in your life?" which are endorsed on a 5-point scale from "never" to "very often". Higher PSS scores have been found to be correlated with self-reported depression and anxiety symptoms and number of stressful life events (Cohen, et al., 1983). The Kessler Psychological Distress Scale (K10) is a 10-item questionnaire assessing anxiety and depressive symptoms over the prior 4 week period (Kessler, et al., 2002). Items consist of questions such as, "during the last 30 days, about how often did you feel nervous?" and "during the last 30 days, about how often did you feel depressed?" to which respondents endorse scores on a 5-point scale ranging from "none of the time" to "all of the time". Scores on the K10 have been found to correlate positively with scores on the mental health component score of the SF-12, number of consultations sought for mental health treatment in the prior year, and probability of meeting criteria for a psychiatric diagnosis in the prior 12 months (Andrews & Slade, 2001). The K10 has been found to have high internal consistency ($\alpha = 0.84$) and reliably predicted presence of an affective disorder as detected using the Mini International Neuropsychiatric Interview (MINI) (Hides, et al., 2007; Lecrubier, et al., 1997).

Substance Use

Smoking status was assessed using self-reported questions such as, "do you now smoke cigarettes every day, some days, or not at all?" and "have you stopped smoking

for 1 day or longer because you were trying to quit smoking?" Alcohol use was also

assessed using similar self-report questions such as, "during the last 30 days, how many

days did you have at least 1 drink of any alcoholic beverage?" and "considering all types

of alcoholic beverages, how many times during the last 30 days did you have 5 or more

drinks on one occasion?"

Sunlight Exposure

A proxy variable was created to best capture estimated sunlight exposure, or

Direct Normal Irradiance, a measure of the solar irradiation striking the earth's surface

(National Renewable Energy Laboratory, n.d.). This variable was calculated using a

national map application created by the National Renewable Energy Laboratory (NREL)

through the U.S. Department of Energy. This application uses data from 1998 through

2009 of average Direct Normal Irradiance in sun-hours per day for each month of the

year (NREL, 2012). By using a self-reported address, estimated sunlight hours per day

may be calculated.

Accelerometer Data

Participants from the UWTR Chronic Widespread Pain ancilliary study wore

Actiwatch accelerometers (Respironics, 2009) for 7 days of their research participation.

These data are available on approximately 31% of the entire twin dataset. Actiwatch data

may be processed through proprietary software to produce various indices of physical

activity and sleep. This device has been found to produce valid and reliable data for

physical activity (Gironda, Lloyd, Clark, & Walker, 2007) and sleep (Benson, et al.,

2004).

Zygosity

Zygosity for this sample was obtained using DNA testing obtained through Oragene saliva sampling. This is a non-invasive sampling method that allows for the extraction of DNA from saliva. Oragene saliva samples are processed in the laboratory at the Twin Registry. Comparing 16 sites within the humane genome determines zygosity. One site is a sex identification marker and the other 15 sites are called short tandem repeats (STRs). STRs are short DNA sequences that are repeated, forming a chain. The number of repeats varies between individuals, and the 15 sites compared provide enough sample for individual identification. Among dizygotic twin pairs, 25-75% of repeats will match and among monozygotic twins pairs, 100% of the repeats will match. Polymerase chain reaction (PCR) is used to amplify the 16 target sites, the DNA is sequenced, and the lengths of the STRs are compared to determine zygosity.

The University of Washington Twin Registry

The University of Washington Twin Registry is funded by the National Institutes of Health (NIH) and various other mechanisms, including the American Recovery and Reinvestment Act. In Washington state, driver's license numbers are generated according to an individual's last name, first initial, and date of birth. As such, twins are at risk of being assigned duplicate numbers. Therefore, the state of Washington requires all driver's license applicants to report whether or not they are a twin so as to avoid assigning duplicate license numbers. Starting in 1998, the University of Washington retained permission to create a twin registry using identified twins through the Washington Department of Licensing. Each week, the Registry receives contact information and demographics of newly-identified twins in Washington state. These

twins are then contacted by mail with an invitation to participate and an introductory survey of socioeconomic status, health and lifestyle questions, and zygosity. Informed consent is obtained from all research participants. The University of Washington Human Subjects Review Committee, the UCSD, and SDSU Institutional Review Boards have approved this study.

The data for this proposal were collected through the Twin Registry Supplemental Module from participants recruited for 4 different ancillary studies of the UWTR. The Supplemental Module study consists of an in-person physical examination where a nurse measures height, weight, waist circumference, blood pressure, temperature, heart rate, breathing speed, and blood oxygen levels. Blood, saliva, urine, and cheek cell samples are taken and participants complete self-report questionnaires on demographics, physical and mental health functioning, health-related behaviors. The majority of the participants (61.3%) were recruited to participate in a study of immune functioning. Participants were healthy volunteers and potential participants were excluded if they had a previous diagnosis of diabetes, cancer, autoimmune disease, or terminal illness, had symptoms of flu, common cold, or illness for 2 weeks prior to blood draw, or had taken antibiotics within 30 days of study participation. Approximately 30% of participants were recruited to participate in a study of posttraumatic stress disorder (PTSD) and chronic widespread pain (CWP) symptoms. In addition to previously mentioned criteria, twin pairs were required to be female, willing to restrict alcohol and caffeine consumption 2 weeks prior to study and during the course of the study, and drug-free per a urine toxicology at the outset of the study. Approximately 4% of participants were recruited as part of an inflammation and obesity study wherein twin pairs were required to be discordant for

obesity status (BMI > 30). An additional 4% of participants were recruited as part of a herpes simplex virus (HSV) study. Twin pairs were required to be concordant for HSV Type 1 and were excluded from this study if they had received immunosuppressant treatment in the 30 days prior to study enrollment. Regardless of the unique tasks of each ancillary study, participants were required to complete the Twin Registry Module physical exam, tasks, and questionnaires. Statistical analyses will be conducted to determine any significant differences between these four sub-samples prior to full analyses.

Missing Data

Data were assessed for missing data patterns. All participants had serum vitamin D values. For all other variables, percent of missing data was approximately 2%. In an example using a sample of 398 clinical patients with a history of pulmonary embolism, several forms of imputation were compared. In this example, results from data built using single unconditional imputation, single conditional imputation, and multiple imputation were not found to be significantly different (van der Heijden, Donders, Stignen, & Moons, 2006). Current statistical methods for imputation do not typically account for the clustered nature of correlated data. Advanced statistical methods have been newly developed; however, the efficacy of these methods diminish significantly with decreasing cluster sizes (van Buuren, 2011). Given that in this twin sample, clusters consist of two observations, the expectation-maximization (EM) function was used to generate imputed values. EM is an iterative algorithm for finding maximum likelihood estimates of parameters in statistical models (Dempster, Laird, & Rubin, 1977). Data were imputed using the EM algorithm embedded within SPSS 20.0.

Statistical Analyses

Descriptive statistics using means and standard deviations for continuous variables and frequencies for categorical variables were calculated. Skewness and kurtosis were examined. The IPAQ summary scores and Kessler K10 were transformed to better approximate normality using the log transformation. The SF8 Mental Component Summary Score was transformed using a squared transformation while the SF8 Physical Component Summary Score was transformed using a cubed transformation. The serum vitamin D value demonstrated slight kurtosis. A square root transformation demonstrated skewness and kurtosis values within normal limits; however, using this transformed version of the variable would impede clear interpretation of the data. As such, analyses were completed with the untransformed variable. All other variables had skew and kurtosis values within normal limits. Skewness and kurtosis values are displayed in Table 3. Transformed skewness and kurtosis values are displayed in Table 4. Descriptive statistics for primary variables are displayed in Table 5.

Table 3. Skewness and kurtosis of primary variables

Variable	Skewness	Kurtosis
Serum Vitamin D	.82	1.15
PSS	.54	-.07
Kessler K10	1.63	2.81
IPAQ Vigorous METs	3.86	18.25
IPAQ Moderate METs	3.93	21.69
IPAQ Total PA METs	3.54	16.02
IPAQ weekly sitting	.68	.09
SF-8 PCS	-1.791	5.917
SF-8 MCS	-1.35	2.13
WHIIRS	.78	.25

Table 4. Skewness and kurtosis of transformed variables

Variable	Transformation	Skew	Kurtosis
Serum vitamin D	Square Root	.09	.33
IPAQ Moderate METs	Log	-1.65	3.83
IPAQ Vigorous METs	Log	-.59	-1.31
IPAQ Total PA	Log	-1.06	4.43
Kessler K10	Log	.98	.69
SF-8 MCS	Squared	-.88	.44
SF-8 PCS	Cubed	-.83	1.74

Correlation matrices were generated to allow for the examination of correlations between predictors (e.g., vitamin D, physical activity) and potential confound variables

(e.g., BMI, self-reported pain symptoms). Values are presented in Tables 5-10. The correlation between vitamin D and insomnia was also assessed. Potential confound variables found to interact with predictor variables consistently in the literature were retained and controlled for in subsequent analyses. Vitamin D levels, insomnia symptoms, and physical activity were measured as continuous variables. A subsample analysis was conducted to assess the association between self-reported physical activity as measured by the IPAQ and objective physical activity as measured by accelerometers. In addition, a subsample analysis was conducted with the similar goal of assessing the relationship between self-reported insomnia (WHIIRS) and objective sleep measurement.

Mixed effects linear regression models, which account for the non-independence of twins within a pair, have been used widely within the literature to examine within-pair and between-pair relationships of exposure on outcome (Begg & Parides, 2003; Carlin, Gurrin, Sterne, Morley, & Dwyer, 2005; McGue, et al., 2010). These data were considered to be multilevel, or clustered, with each individual twin considered to be level-1 and the twin pair considered to be level-2. In these analyses, we sought to understand the within-pair and between-pair effects. Given that half-pair data may still contribute to the between-pair effects estimation, these analyses also are advantageous in their ability to appropriately handle missing data (Begg & Parides, 2003). These analyses were informed by published standards of McGue, Osler, & Christensen (2010) and Carlin et al. (2005). To understand the mathematical logic of these analyses, let y_{ij} be the observed outcome (i.e., WHIIRS score) for the jth twin (j = 1 or 2) in the ith twin pair (i = 1, 2…, N) and let x_{ij} be the exposure value (i.e., vitamin D score in ng/mL) for this same

individual. Using this notation individual-level regression equation of insomnia on vitamin D is given by the models:

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \varepsilon_{ij.} \tag{1}$$

$$WHIIRS'_{ij} = \beta_0 + \beta_1 VitD_{ij} + \varepsilon_{ij}. \tag{1}$$

In this model, β_0 is the random intercept term and β_1 is the effect of exposure on outcome at the individual level. Random error is accounted for by the term, ε_{ij}. WHIIRS and vitamin D were entered into the model as fixed factors, with the intercept and twin pair entered as random factors. The analyses were adjusted for confounders and demographic variables, which were also entered into the model as fixed factors.

Next, provided that examination of correlation matrices support physical activity as a covariate in the model, IPAQ (as a continuous variable) was entered as a fixed effect:

$$WHIIRS'_{ij} = \beta_0 + \beta_1 VitD_{ij} + \beta_2 IPAQ_{ij} + \varepsilon_{ij.} \tag{2}$$

Season, as a categorical fixed effect 2-level dummy-coded variable (spring-summer vs fall-winter), was investigated as a moderator of the relationship between vitamin D and insomnia, to assess if the vitamin D-insomnia relationship is attenuated depending on the time of year of measurement:

$$WHIIRS'_{ij} = \beta_0 + \beta_1 VitD_{ij} + \beta_2 IPAQ_{ij} + \beta_3 Season1_{ij} + \beta_4\ Season2_{ij} + \beta_5 VitD*Season1_{ij}$$

$$+ \beta_6 VitD*Season2_{ij} + \varepsilon_{ij} \tag{3}$$

Nonsignificant predictors were dropped from the model to avoid over-specification.

Next, the models were further specified by modeling within-pair and between-pair effects separately for MZ and DZ twins using zygosity-stratified within-pair models. The regression model can thus be stated as:

$$y_{ij} = \beta_0 + \beta_W (x_{ij} - \overline{x}_{i.}) + \beta_B \overline{x}_{i.} + \varepsilon_{ij.}$$

$$WHIIRS'_{ij} = \beta_0 + \beta_W (VitD_{ij} - \overline{VitD_{i.}}) + \beta_B \overline{VitD_{i.}} + \varepsilon_{ij} \tag{4}$$

In this model, $\overline{x}_{i.}$ or $\overline{VitD_{i.}}$, is the cluster-level mean for the exposure value (vitamin D)

for each twin pair. Therefore, $(x_{ij} - \overline{x}_{i.})$ is the cluster-specific deviation from the cluster-

level mean and this term is considered "cluster-specific" centered (Begg & Parides,

2003). β_W, therefore, estimates the effect of vitamin D on insomnia within discordant-twin

pairs, and β_B provides an estimate of the effect of vitamin D on insomnia at the cluster, or

twin-pair, level. WHIIRS and vitamin D were entered into the model as fixed factors,

with the intercept and twin pair entered as random factors. Those predictors and

interactions found to be significant in previous analyses were also be entered into the

model as fixed factors. All analyses were adjusted for confounders and demographic

variables.

     If a significant effect of vitamin D and physical activity on insomnia remained in

MZ twins, a potential causal link is suggested. If this effect is also found in the analyses

using only DZ twins, stronger support for a causal relationship between these two

predictor variables and insomnia would have been obtained. All models were adjusted to

control for demographic and confounding variables (e.g., gender, race, BMI, smoking

status) to assess the extent to which any significant relationships persist after controlling

for known confounds. All analyses were completed using SPSS version 20.0.

Significance was established at $p < 0.05$.

<center>**Results**</center>

Aim 1. Examine The Association of Vitamin D Levels and Insomnia

Correlation matrices are presented in Table 5-6. Results from mixed level

regressions are presented in Table 7. Correlation matrices were generated to determine

significant confounding variables ($p < .05$) to be controlled for in subsequent analyses.

Vitamin D and WHIIRS each demonstrated concurrent and discriminant validity in these

analyses. These results suggested that our WHIIRS scale and vitamin D values were

performing as was anticipated given the expectations garnered from the literature. No

significant differences were found between UWTR study samples on main outcomes or

demographic variables (*p's* > .05). The PSS and K10 scales had a high correlation with

each other. To avoid redundancy in the models, K10 was dropped from subsequent

analyses. PSS was chosen for subsequent analyses due to its untransformed nature

(thereby lending greater clarity to interpretation) and its more common use within the

literature.

WHIIRS and vitamin D levels had a significant positive association ($r = .112$, $p =$

.013), suggesting that higher levels of insomnia were associated with higher vitamin D

levels. Mixed level linear regressions were used to control for non-independence of pairs

to further assess this relationship. These analyses were stratified across zygosity. The

overall individual-level model found a significant association between vitamin D and

WHIIRS among monozygotic twins. Vitamin D was found to significantly predict self-

reported insomnia ($b = .0336$, $p = .012$, *95% CI* [.0054, .0619]), even after controlling for

significant covariates such as perceived stress, sleep hours, number of wakeups, age, and

sex. Nonsignificant covariates were dropped from the model (e.g., drinks per month,

<center>44</center>

smoking, BMI, race, ethnicity). Among dizygotic twins, there was not a significant relationship between vitamin D and insomnia after controlling for the above significant covariates ($b = .0114$, $p = .654$, *95% CI* [-.039, .0619]). The following analyses were conducted exclusively on monozygotic twins as the relationship was not significant among dizygotic twins.

Aim 2. Assess the Confounding Effect of Physical Activity Level on the Association Between Vitamin D and Insomnia

Prior to conducting further analyses, correlation matrices were generated to assess the association between primary variables and IPAQ indices. Vitamin D was positively associated with log-transformed total weekly vigorous METs ($r = .241$, $p < .001$), log-transformed total weekly physical activity METs ($r = .094$, $p = .038$), and total weekly sitting minutes ($r = -.149$, $p = .001$). WHIIRS scores were not found to be significantly associated with any IPAQ summary scores ($p's > .05$). When added to the above model in separate analyses, IPAQ log-transformed total weekly vigorous METs ($b = -.153$, $p = .314$, *95% CI* [-.452, .145]), IPAQ log-transformed total weekly physical activity METs ($b = -.454$, $p = .269$, *95% CI* [-1.07, .182]), and IPAQ total weekly sitting minutes ($b = -.0001$, $p = .408$, *95% CI* [-1.261, .352]) were each non-significant predictors.

Aim 3. Assess Whether Season Moderates the Association Between Vitamin D and Insomnia

Date of blood draw and completion of self-reported questionnaires were determined to be identical across study participants. Next, season was dichotomized between Fall/Winter and Spring/Summer according to the solstice dividing these seasons. This dichotomous variable was entered into the above mixed models that retained

significant covariates. Season of assessment was not found to be a significant predictor in the model among monozygotic twins ($b = .051$, $p = .873$, *95% CI* [-.576, .678]). Average annual direct normal irradiance was not found to be significantly correlated with WHIIRS or vitamin D levels (*p's* > .05).

Aim 4. Explore Whether Genetic and Familial Factors Contribute to Any Significant Association Determined in Previous Analyses

Within-pair mixed models were used to determine if genetic and/or familial environmental factors contributed to the above relationship between vitamin D and insomnia. For each individual twin, a difference score was computed by obtaining the difference between the individual twin's vitamin D score and the average score for the twin pair. The difference score and pair average score were entered into the models to determine within-pair effects. These results were stratified across zygosity. Among monozygotic twins, the vitamin D difference score was not significant ($b = -.0005$, $p = .986$, *95% CI* [-.0645, .0634]), suggesting that there is a genetic and/or shared environmental contribution to the relationship between vitamin D and insomnia. These results do not support a causal relationship between vitamin D and insomnia.

Graph 1. WHIIRS scores across Vitamin D quartiles
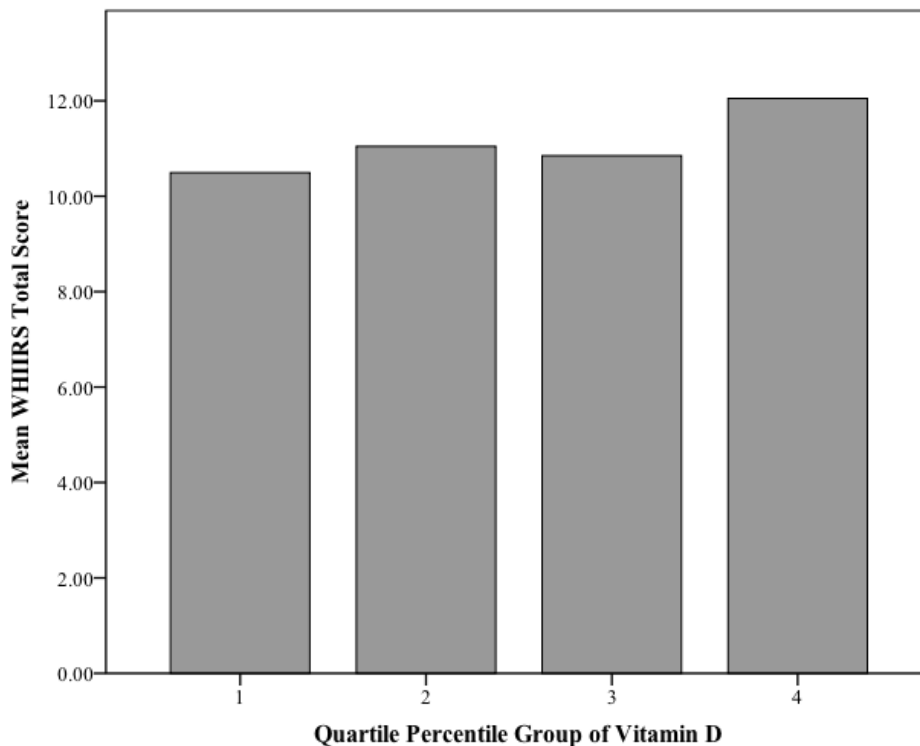
Subsample Analyses Using Accelerometer Data

Physical Activity

In an unpublished study conducted on a subsample dataset prior to this dissertation proposal (n = 82 pairs), IPAQ summary scores were validated against objective accelerometer data. The accelerometer outcome variable was calculated as a total score for the 7 days that the participant wore the device. Mixed model regression analyses accounting for non-independence of twin pairs found that higher scores on the accelerometer were associated with higher scores in Total ($b = 38.89$, $p = .002$, *95% CI* [15.22, 62.56]), Moderate ($b = 79.56$, $p = .003$, *95% CI* [26.88, 132.23]), and Walking ($b = 73.13$, $p = .005$, *95% CI* [22.43, 123.83]) weekly METs IPAQ sub-scales. A significant

negative association was also found for the Sitting IPAQ sub-scale (b = -122.67, p = .003, *95% CI* [-202.84, -42.49]). There was a nonsignificant association between vigorous METs per week (b = 34.09, p = .224, *95% CI* [-21.12, 89.32]) and 7-day total activity on the actigraph (Godfrey, 2014).

Sleep

The WHIIRS was also validated against objective measures of sleep using the accelerometer data subsample in monozygotic twins. Bivariate correlations were computed to assess the relationship between self-reported insomnia score and objective actigraph data scores of sleep variables. WHIIRS was positively and significantly associated with the summed 7-day total physical activity accelerometer score (r = .251, p = .003) and total sleep time (r = .241, p .015). Therefore, higher scores of self-reported insomnia were associated with greater physical activity and greater sleep time as measured by actigraphs. Actigraph total sleep time was significantly associated with self-reported sleep hours (r = .216, p = .014) in the expected direction. Mixed model regression analyses accounting for non-independence of twin pairs found that higher scores on the WHIIRS were predicted by total duration of rest bout (i.e., total time in bed whether sleeping or not) (b = 12.82, p = .031, *95% CI* [1.18, 24.46]. These results suggest that higher self-reported insomnia are associated with greater time spent in a resting state (although not specifically sleeping). WHIIRS was not found to be significantly predicted by percent sleep time as measured by accelerometers (b = -.07, p = .38, *95% CI* [-.23, .09]). WHIIRS was also not found to be significantly predicted by sum total of wake bouts as measured by actigraph (b = .27, p = .79, *95% CI* [-1.67, 2.21]). Finally, WHIIRS was not found to be significantly predicted by total sleep time as measured by actigraph

(b = 10.70, p = .06, *95% CI* [-.26, 21.66]). One item from the WHIIRS measure assesses directly for sleep-related distress. This sleep distress item was not significantly associated with any of the objective actigraph measures of sleep (*p's* > .05).

Exploratory Analyses

The above results present a complicated picture of the relationship between vitamin D and insomnia. In addition, the objective and subjective measurements of sleep quality and duration did not consistently correlate with each other. Exploratory analyses were conducted to further examine these relationships.

Information regarding medical comorbidities, doctor visits, medication use, and supplementation were explored. Correlation matrices were generated to assess which variables may significantly correlate with outcome variables. Self-reported pain (SF8 Bodily Pain subscale) was a significant predictor in the model (b = -.001, p < .001, *95% CI* [-.001, -.0004]). The significant positive association between vitamin D and WHIIRS remained after adding this predictor to the model. Total number of medical conditions was not a significant predictor (b = .566, p = .414, *95% CI* [-.795, 1.929]). Number of self-reported doctor visits was also found to be nonsignificant in this model (b = .101, p = .643, *95% CI* [-.326, .528]). A dichotomous variable of whether or not participants had been hospitalized in the prior year was also entered into the model and was nonsignificant (b = .0585, p = .834, *95% CI* [-.489, .606]). Self-report assessment of participants' general health (SF-8 General Health subscale) was not a significant predictor in the model (b = .003, p = .905, *95% CI* [-.055, .063]). Current use of vitamin A, C, or B supplementation was entered as a dichotomous variable and was found to be nonsignificant (b = .298, p = .524, *95% CI* [-.62, 1.22]).

Data were also available from all participants on use of common medications such as beta-blockers, steroids, and oral contraceptives. Data on most medications were used rarely (e.g., by 10 or fewer participants). Therefore, the impact of these medications was not explored due to limited power. One-hundred and four participants reported taking oral contraceptive medications at the time of assessment. This variable was entered into the above model and was found to be significant (b = 1.069, p = .048, *95% CI* [.007, 2.13]). Upon addition of this variable to the model, the association between vitamin D and insomnia became non-significant (b = .034, p = .06, *95% CI* [-.001, .070). These analyses were replicated on a selected dataset of only monozygotic female twins. Upon replicating the above analyses to this subset of the full dataset, the oral contraceptive variable no longer a significant predictor in the model (p > .05). These exploratory analyses found that the positive association between vitamin D and WHIIRS was accounted for by a significant positive correlation only among monozygotic female participants (r = .19, p = .006). When this same correlation was pursued among dizygotic twins or male monozygotic twins, the correlation was not significant (p > .05).

Table 5. Correlation matrix of primary variables in monozygotic twins

	VitD[a]	WHIIRS[b]	PSS[c]	K10[d]	SF8 MCS[e]	SF8 PCS[f]	SF8 BP[g]	IPAQ VIG METs[h]	IPAQ MOD METs[i]	IPAQ Total PA[j]
VitD[a]	1	.17**	-.06	-.07	.06	-.04	-.12*	.22**	.01	.08
WHIIRS[b]	.17**	1	.25**	.28**	-.29**	-.16**	-.27**	-.03	.01	-.05
PSS[c]	-.06	.25**	1	.73**	-.72**	-.10	-.17**	-.01	.13*	.07
K10[d]	-.07	.28**	.73**	1	-.71**	-.12*	-.21**	-.01	.10	.03
SF8 MCS[e]	.06	-.29**	-.72**	-.71**	1	-.05	.18**	.07	-.03	.07
SF8 PCS[f]	-.04	-.16**	-.10	-.12*	-.05	1	.63**	.03	.01	-.07
SF8 BP[g]	-.12*	-.26**	-.17**	-.21**	.18**	.63**	1	-.001	-.07	-.02
IPAQ VIG[h]	.22**	-.03	-.001	-.01	.07	.03	-.001	1	.31**	.59**
IPAQ MOD[i]	.006	.01	.13*	.01	-.03	.01	-.07	.31**	1	.67**
IPAQ Total PA[j]	.08	-.05	.07	.03	.07	-.07	-.02	.59**	.67**	1

[a]Serum Vitamin D; [a]Serum Vitamin D; [b]Women's Health Initiative Insomnia Rating Scale; [c]Perceived Stress Scale; [d]Kessler K10 Scale – log transformed; [e]Short-Form-8 Mental Component Scale – squared; [f]Short Form-8 Physical Component Scale – cubed; [g]Short Form-8 Bodily Pain Scale – squared; [h]IPAQ Vigorous METs/week – log transformed; [i]IPAQ Moderate METs/week – log transformed; [j]IPAQ Total Physical Activity/week – log transformed; *p < .05, **p < .01

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Table 6. Correlation matrix of primary variables in dizygotic twins

	VitD[a]	WHIIRS[b]	PSS[c]	K10[d]	SF8 MCS[e]	SF8 PCS[f]	SF8 BP[g]	IPAQ VIG METs[h]	IPAQ MOD METs[i]	IPAQ Total PA[j]
VitD[a]	1	-.002	-.18*	-.03	.11	.16*	.04	.30**	.11	.13
WHIIRS[b]	-.002	1	.25**	.34**	-.28**	-.11	-.24**	-.12	-.05	-.08
PSS[c]	-.18*	.25**	1	-.66**	-.70**	-.20*	-.32**	-.17*	-.13	-.11
K10[d]	-.03	.34**	-.66**	1	-.74**	-.13	-.37**	-.10	-.12	-.08
SF8 MCS[e]	.11	-.28**	-.70**	-.74**	1	-.02	.33**	.11	.11	.08
SF8 PCS[f]	.16*	-.11	-.20*	-.13	-.02	1	.59**	.10	-.05	.11
SF8 BP[g]	.04	-.24**	-.32**	-.37**	.33**	.59**	1	.07	-.04	.02
IPAQ VIG[h]	.30**	-.12	-.17*	-.10	.11	.10	.07	1	.29**	.56**
IPAQ MOD[i]	.11	-.05	-.13	-.12	.11	-.05	-.04	.29**	1	.71**
IPAQ Total PA[j]	.13	-.08	-.11	-.08	.08	.11	.02	.56**	.71**	1

[a]Serum Vitamin D; [a]Serum Vitamin D; [b]Women's Health Initiative Insomnia Rating Scale; [c]Perceived Stress Scale; [d]Kessler K10 Scale – log transformed; [e]Short-Form-8 Mental Component Scale – squared; [f]Short Form-8 Physical Component Scale – cubed; [g]Short Form-8 Bodily Pain Scale – squared; [h]IPAQ Vigorous METs/week – log transformed; [i]IPAQ Moderate METs/week – log transformed; [j]IPAQ Total Physical Activity/week – log transformed; *p < .05, ** p < .01

Table 7. Correlation matrix of primary variables in monozygotic female twins

	VitD[a]	WHIIRS[b]	PSS[c]	K10[d]	SF8 MCS[e]	SF8 PCS[f]	SF8 BP[g]	IPAQ VIG METs[h]	IPAQ MOD METs[i]	IPAQ Total PA[j]
VitD[a]	1	.19**	-.14*	-.19**	.16*	.003	-.08	.18**	.07	.11
WHIIRS[b]	.19**	1	.21**	.25**	-.21**	-.15*	-.21**	.07	.13	.11
PSS[c]	-.14*	.21**	1	.73**	-.73**	-.14*	-.18**	.01	.17*	.16*
K10[d]	-.19**	.25**	.73**	1	-.67**	-.281**	-.26**	.05	.16*	.16*
SF8 MCS[e]	.16*	-.21**	-.73**	-.67**	1	.07	.28**	.06	-.10	-.01
SF8 PCS[f]	.003	-.15*	-.14*	-.281**	.07	1	.55**	.001	-.05	-.11
SF8 BP[g]	-.08	-.21**	-.18**	-.26**	.28**	.55**	1	-.03	-.13	-.07
IPAQ VIG[h]	.18**	.07	.01	.05	.06	.001	-.03	1	.22**	.52**
IPAQ MOD[i]	.07	.13	.17*	.16*	-.10	-.05	-.13	.22**	1	.70**
IPAQ Total PA[j]	.11	.11	.16*	.16*	-.01	-.11	-.07	.52**	.70**	1

[a]Serum Vitamin D; [a]Serum Vitamin D; [b]Women's Health Initiative Insomnia Rating Scale; [c]Perceived Stress Scale; [d]Kessler K10 Scale – log transformed; [e]Short-Form-8 Mental Component Scale – squared; [f]Short Form-8 Physical Component Scale – cubed; [g]Short Form-8 Bodily Pain Scale – squared; [h]IPAQ Vigorous METs/week – log transformed; [i]IPAQ Moderate METs/week – log transformed; [j]IPAQ Total Physical Activity/week – log transformed; *p < .05, ** p < .01

Table 8. Correlation matrix of additional primary variables of in monozygotic twins

	VitD[a]	WHIIRS[b]	Age (years)	BMI[c]	DNI[d]	Drinks Per Month	Sleep Hours	Number Wake Ups	Doctor Visits
VitD[a]	1	.17**	.02	-.21*	.05	-.03	-.11	.05	.17**
WHIIRS[b]	.17**	1	.26**	.08	.05	-.06	-.16**	.59**	.15**
Age (years)	.02	.26**	1	.16**	.02	.08	-.14*	.23**	.06
BMI[c]	-.21**	.08	.16**	1	-.21**	.07	.04	.13*	.12*
DNI[d]	.05	.05	.02	-.21**	1	-.02	-.08	.11*	-.01
Drinks Per Month	-.03	-.06	.08	.07	-.02	1	.04	-.02	-.04
Sleep Hours[e]	-.11	-.16**	-.14*	.04	-.08	.04	1	-.04	-.11
Number Wake Ups[f]	.05	.59**	.23**	.13*	.11*	-.02	-.04	1	.08
Doctor Visits[g]	.17**	.15**	.06	.12*	-.01	-.04	-.11*	.08	1

[a]Serum Vitamin D; [b]Women's Health Initiative Insomnia Rating Scale; [c]Body Mass Index; [d]Direct Normal Irradiance; *p < .05, ** p < .01

Table 9. Correlation matrix of additional primary variables in dizygotic twins

	VitD[a]	WHIIRS[b]	Age (years)	BMI[c]	DNI[d]	Drinks Per Month	Sleep Hours[e]	Number Wake Ups[f]	Doctor Visits[g]
VitD[a]	1	-.002	.03	-.32*	-.12	-.05	.04	.03	.12
WHIIRS[b]	-.002	1	-.03	.08	-.04	.09	-.12	.54**	.14
Age (years)	.03	-.03	1	.23**	-.06	-.01	-.23**	.04	-.01
BMI[c]	-.32**	.08	.23**	1	-.06	-.01	-.03	.04	.09
DNI[d]	-.12	-.04	-.06	-.06	1	-.14	.08	-.03	-.15
Drinks Per Month	-.05	.09	-.01	-.01	-.14	1	-.09	.01	-.11
Sleep Hours[e]	.04	-.12	-.23**	-.03	.08	-.09	1	-.08	-.01
Number Wake Ups[f]	.03	.54**	.04	.04	-.03	.01	-.08	1	.21**
Doctor Visits[g]	.11	.14	-.01	.09	-.15	-.11	-.01	.21**	1

[a]Serum Vitamin D; [b]Women's Health Initiative Insomnia Rating Scale; [c]Body Mass Index; [d]Direct Normal Irradiance; *p < .05, ** p < .01

Table 10. Correlation matrix of additional primary variables in monozygotic female twins

	VitD[a]	WHIIRS[b]	Age (years)	BMI[c]	DNI[d]	Drinks Per Month	Sleep Hours[e]	Number Wake Ups[f]	Doctor Visits[g]
VitD[a]	1	.19**	.15*	-.23**	.01	.05	-.09	.07	.11
WHIIRS[b]	.19**	1	.21**	.06	.03	.02	-.11	.60**	.12
Age (years)	.15*	.21**	1	.10	-.01	.11	-.04	.16*	.09
BMI[c]	-.24**	.06	.09	1	-.16*	.09	.08	.07	.17*
DNI[d]	.01	.03	-.01	.16*	1	.08	-.05	.10	-.001
Drinks Per Month	.05	.02	.11	.09	.08	1	.04	-.05	.08
Sleep Hours[e]	-.09	-.11	-.04	.08	-.05	.04	1	.03	-.11
Number Wake Ups[f]	.07	.60**	.16*	.07	.10	-.05	.03	1	.06
Doctor Visits[g]	.11	.12	.09	.17*	-.001	.08	-.11	.06	1

[a]Serum Vitamin D; [b]Women's Health Initiative Insomnia Rating Scale; [c]Body Mass Index; [d]Direct Normal Irradiance; *p < .05, **p < .01

Table 11. The association of vitamin D and WHIIRS in monozygotic and dizygotic twins

	Monozygotic Twins		Dizygotic Twins	
Vitamin D	b	95% CI	b	95% CI
Adjusted[a]	.04[b]	[.005, .06][b]	.0114	[-.04, .07]
Within-Pair Analyses	-.0005	[-.06, .06]		

[a]Analyses adjusted for Perceived Stress Scale score, self-reported sleep hours, self-reported number of wake-ups, age, sex; [b]$p = .012$

Graph 2. Mean vitamin D levels across oral contraceptive use
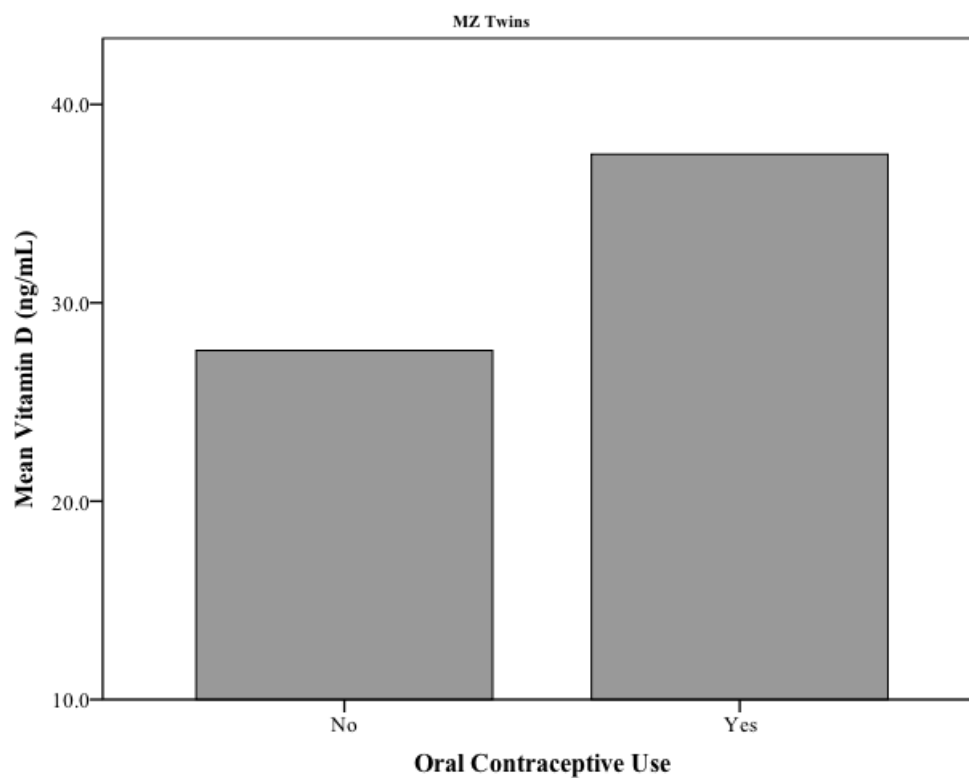
Graph 3. Mean WHIIRS scores across oral contraceptive use
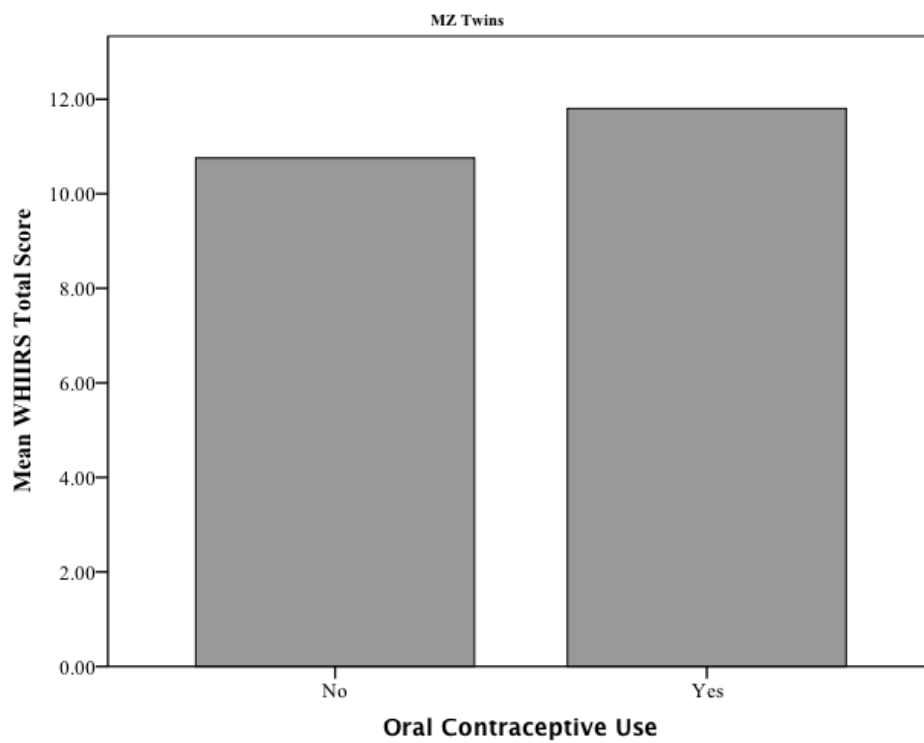
Discussion

This study examined the relationship between vitamin D levels and self-reported insomnia in a sample of 245 twin pairs enrolled in the University of Washington Twin Registry. The participants in this sample were initially recruited into four different ancillary studies of the Twin Registry; however, there were no significant differences among the sub-study samples.

Our results do not fully support our original hypotheses. Our original hypotheses predicted that there would be a significant association between vitamin D and self-reported insomnia. This hypothesis was supported by the data, but in the reverse direction anticipated based on findings of the literature as a whole. Vitamin D is overall considered to be protective for health and supplementation is widely recommended for those at deficient levels (Holick, 2012). Additionally, the literature has found consistent evidence suggesting that insomnia is detrimental to health and functioning (Ancoli-Israel, 2006; Sivertsen, et al., 2009). While we would not be able to assess direction of causality in this current study, it was hypothesized that higher levels of vitamin D would be associated with lower levels of insomnia, and vice versa. However, this hypothesis was not supported. Exploratory analyses were conducted to determine third variables that may account for the positive relationship between vitamin D and insomnia found among monozygotic female twins. One potential variable explored was oral contraceptive use.

One study found that blood serum vitamin D levels were 39% higher among oral contraceptive users as compared with non-users, even after controlling for height, weight, and vitamin D intake through food. In this same study, those who discontinued oral contraceptives saw a reduction in vitamin D levels (mean change was -25.5 +/- 17.7

nmol/L or 10.2 +/- 7.1 ng/mL), whereas those who were consistent on oral contraceptives maintained consistent vitamin D levels (Harris & Dawson-Hughes, 1998). Vitamin D was also found to be increased with estrogen therapy in post-menopausal women with osteoporosis (Gallagher, Riggs, & DeLuca, 1980). These findings have also been supported in rodent models in which vitamin D was found to be essentially involved in the production of estrogen in both male and female rodents (Kinuta, et al., 2000).

Oral contraceptives have also been found to impact sleep outcomes. Those taking oral contraceptives have been found to have increased body temperature (Baker, et al., 2004; Kattapong, Fogg, & Eastman, 1995) and increased melatonin levels (Wright & Badia, 1999). In addition, those taking oral contraceptives were found to have increased stage 2 nREM sleep and decreased slow wave sleep in a study using polysomnography (Baker, et al., 2004). Reduced slow wave sleep has been found to be associated with increased fatigue and discomfort (Lentz, Landis, Rothermel, & Shaver, 1999). While this variable did appear to account for the relationship between vitamin D and insomnia when running the analyses among monozygotic twins; once male twins were removed from the dataset oral contraceptives were no longer significant. This suggests that the significant effect we found was potentially an artifact of the dataset and not a pure finding. Among monozygotic female twins, the subset of the dataset that had a positive significant relationship between vitamin D and insomnia, the significant association persisted above and beyond any other theoretically-driven covariates added to the model.

Our second and third hypotheses, that physical activity and season of measurement would affect the above relationship were not supported. Physical activity may therefore not directly be related to vitamin D synthesis and may instead be

confounded by amount of time spent outdoors. Our lack of support for season as a moderating variable may be related to limited seasonal variation in the state of Washington as compared to other areas of the world. Replication of these findings among other populations in other areas of the world may better assess if our failure to support this hypothesis was a true null finding.

Our hypothesis that the significant relationship between vitamin D and insomnia would persist above and beyond genetic and/or familial environment contribution was not supported by these results. First, the results were found at the overall-level only among monozygotic female twins. Among dizygotic twins there was no significant overall relationship between vitamin D and self-reported insomnia. The within-pair analyses found that the association among monozygotic twins was no longer significant. Therefore, the association between vitamin D and insomnia does not appear to be causal, but may instead be contributed to by some form of genetic/familial contribution that is shared among monozygotic twins.

The literature exploring the genetic underpinnings of these and other biological mechanisms is one in its early stages that is steadily growing with time. One study established that estrogen and vitamin D may have genetic interactions such that one genotype combination will predict significantly higher bone mineral density as compared to other genotype combinations. A significant gene x gene interaction was found among this sample of women. Those who had one genotype combination (*Pvull* estrogen receptor and bb vitamin D receptor) had significantly higher average bone mineral density as compared to those with a different genotype combination (*Pvull* estrogen receptor and BB vitamin D receptor) (Willing, et al., 1998). These findings in the

literature corroborate the possibility that the association between self-reported insomnia and observed vitamin D levels in blood serum may have linkages at the genetic level.

The results of this study support previous observations in the literature of discrepancies between subjective and objective measures of health outcomes and associated distress. This discrepancy has been documented within the insomnia literature. Individuals with non-clinical sleep patterns tend to underestimate latency and overestimate total sleep time, overall underreporting sleep problems (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008) (Lockley, Skene, & Arendt, 1999). In contrast, those with clinical insomnia have been found to overreport sleep problems, underreporting total sleep time, and overreporting wake after sleep onset and wake ups (Means, Edinger, Glenn, & Fins, 2003) (Rosa & Bonnet, 2000). Therefore, the measurement of sleep is a complicated task that may be divided into total sleep time, stages of sleep, sleep perception, perceived and nonperceived sleep disruption, daytime sleepiness, and fatigue. Our study found that higher vitamin D levels were associated with higher levels of self-reported poor sleep quality and duration. These results may also be accounted for by differences in measurement. Actigraph total sleep time was significantly associated with self-reported number of sleep hours, but no other self-reported indices of sleep or psychological distress. When comparing the association between total sleep time and vitamin D, there was no significant relationship. These results suggest that vitamin D may be associated with perceived fatigue and poor sleep quality, but may not be associated with objectively measured sleep time.

Future Directions

This study brings attention to multiple opportunities for future investigation. As technology continues to advance to bring measurement to greater levels of sophistication and accessibility, researchers will have better abilities to precisely measure health outcomes. Sleep is a health outcome in which measurement is particularly broad as perceived and objective sleep indices may vary widely within the same individual. Future research should continue to measure sleep in subjective and objective manners to better differentiate and define whether objective and subjective sleep measurement can be considered similar or discrete constructs. In addition, vitamin D will likely continue to be of interest to health researchers as we attempt to understand predictors of health maintenance and improvement. Gathering precise data on vitamin D ingestion, particularly through supplementation, is extremely helpful in this line of research as it helps to differentiate between vitamin D that is synthesized through epidermal exposure to sunlight and that which is supplemented through artificial means. In addition, continuing to use twin research to our advantage greatly accelerates the rate of research. If the above finding was demonstrated in a cross-sectional, non-twin study alone, it may have been assumed that higher vitamin D levels were associated with poorer sleep. However, by utilizing the advantage of twin methodology, we were able to better determine if a causal link should be hypothesized. Our results do not suggest that vitamin D leads to worse insomnia or vice versa. Instead, our results suggest that there may be other genetic or familial environmental factors that are contributing to the overall observed association. Future research will be greatly assisted by continuing to explore

cutting edge research investigations with the unique advantages afforded by twin registries.

Strengths and Limitations

The proposed study has a number of strengths. This study will be the first to investigate the relationship between vitamin D and insomnia, and was uniquely advantaged to better assess for a potentially causal relationship than would be a standard cross-sectional study of singletons. Vitamin D was measured through blood serum levels, adding greater precision to the overall estimation of effects. This study also benefitted from the ability to assess the validity and reliability of its subjective measures through a sub-sample calibration study using objective actigraph measures of physical activity and sleep.

The study is characterized by a number of limitations, as well. Our study sample is limited in size as vitamin D and insomnia data were available on 245 twin pairs. Our study would also have had greater statistical and inferential power if data were collected over multiple time points rather than a single time point. The study sample was comprised of predominantly White women; as such, our results may be most appropriately generalized to similar populations. These results would benefit replication in more diverse, gender-balanced samples. In addition, our subjective measure of insomnia was a 5-item measure. A longer, more comprehensive measure of sleep perception and quality may have afforded better ability to assess different aspects of self-reported insomnia. The IPAQ variable, despite multiple attempts at transformation to improve normality, continued to maintain skew and kurtosis outside of common recommendations. Results using these variables should be interpreted with caution and

merit replication. This study may also have been improved upon with the use of a well-validated subjective and objective measure of insomnia and sleep quality on all participants. The WHIIRS was found to be associated with total duration of rest as measured by accelerometers; however, there was limited association between the subjective and objective forms of sleep measurement. These results may further provide evidence (as discussed above) that self-report measurement of insomnia may capture discrepant aspects of perceived sleep as compared with objectively measured sleep indices. Despite these limitations, this study may still provide unique contribution to the literature as it is the first investigation into the potential association between vitamin D and insomnia and has great strengths in a number of important covariates and the genetic control of a twin sample.

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