Walking on Sunshine

Can Vitamin D and UV-Exposure Explain Opioid Use?

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Abstract

Can Vitamin D deficiency contribute to opioid use? Though seemingly unrelated substances, the two interestingly mirror each other in effects and metabolism. Vitamin D deficiency can lead to weakness, pain, and depression. Both can interact with addiction receptors in the brain. For these reasons, some evolutionary thinkers argue sunlight, the primary source of Vitamin D, may have emerged as the very first addiction. In this framework, modern opioid use could mirror sun exposure, but without the benefits and regulation that Vitamin D provides. Thus, one's natural Vitamin D levels may be very important to explaining their interactions with opioids This paper parallels previous medical and epidemiological literature attempting to demonstrate how Vitamin D mediates the strength of opioids. Using 2003–2004 U.S. NHANES prescription use, health, and demographic data for individuals aged 20 to 84, this paper measures the impact of Vitamin D deficiency on the propensity of opioid use. A control function approach is used, leveraging milk consumption to relieve endogeneity concerns in previous studies. Unlike previous findings, we do not observe any significant effect from Vitamin D levels.

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Contents

I Introduction

This paper seeks to determine if Vitamin D levels have a causal effect on opioid use. Though Vitamin D and opioids are seemingly unrelated, recent medical research suggests the two serve complementary biological functions, exist in the same pathways, and possibly even share a common evolutionary root.

Despite its name, Vitamin D is more of a hormone than a vitamin and, hence, is far more important than its name might express. It is crucial for bodily processes such as bone growth, development, immune response, and protein synthesis. Absent Vitamin D, the body is far more susceptible to diseases, stunted development, weak and easily fractured bones, muscle weakness, pain, and more. Thus, there is a strong underlying incentive for the body to maintain sufficient Vitamin D levels. Through exposure to sunlight and diet, the body can renew its stores, however, people still struggle to get enough.

Researchers like Fisher (2023) propose this could explain the role of Vitamin D as the potential "father of all addictions," in kind explaining the link with opioids. The Ice Age, he notes, marks a natural starting point to examine what happens when humans are prone to Vitamin D deficiency. Without motivation to go outdoors and face the elements, the body, despite a need for Vitamin D, had no way of manifesting such need into action– that is until it developed an addiction to sunlight. Fell et al. (2014); Kemény et al. (2021) have supported this notion. Under various mice models, they have examined how the process of tanning, which has the express goal of protecting the skin while maintaining healthy Vitamin D production, inherently produces *endogenous opioids*, that is opioids produced naturally within the body as opposed to *exogenous opioids*, external opioids such as morphine and heroin. In this way, Vitamin D, which is naturally tasked with governing cravings for sunlight, meddles with exogenous opioid addictions and substance abuse. Where sunlight fills Vitamin D stores, and subdues the effectiveness of the opioids it produces, exogenous opioids do

not have any effect on Vitamin D and addiction runs untamed.

These findings, however, have unfortunately only been developed under mouse models, with limited epidemiological efforts to test existing hypotheses in humans. Furthermore, the existing epidemiological studies for humans, namely by Kemény et al. (2021), suffer from unclear and potentially dubious handling of survey data and additional endogeneity concerns. The models presented only feature a few controls in an ordinary logistic regression framework. This paper improves upon these findings by leveraging exogenous variation in milk consumption within the same model framework and using the same survey data. Specifically, this paper attempts to demonstrate a causal effect of Vitamin D levels on the propensity toward opioid use using the 2003–2004 U.S. National Health and Nutrition Examination Survey (NHANES) for those aged 20–84. First, with more explicit and intuitive handling of the data, the methodology of Kemény et al. (2021) is replicated. Furthermore, additional controls are added to this model formulation yielding weaker and even non-significant effects for Vitamin D deficiency, which demonstrates potential bias in the existing model framework. Using a control function approach to estimate a probit regression of prescription opioid use, this paper resolves these endogeneity issues. We exploit exogenous variation in milk consumption to effectively instrument for Vitamin D levels. Under this approach, Vitamin D levels show no significant effects on opioid use except at very extreme levels, and at that, in the opposite direction from what would be expected.

II Related Literature

II.A Background: How We Process Sunlight

Given the nature of the topic, an overview of the biology describing known human reactions to sunlight, and the main items involved are relevant and valuable to discuss.

Firstly important, is the common distinction between UV radiations, i.e. different types of sunlight. The sun emits a broad range of solar radiation, from long wavelengths, low energy invisible radio waves to microwaves, infrared light, and the colorful visible light familiar to all. At the latter end of the spectrum are ultraviolet (UV) rays, X-rays, and gamma rays. These are shorter, high energy, and invisible to human eyes. UV-radiation falls into two main categories: UVA and UVB. UVA rays are longer, lower energy waves (320 nm–400 nm) compared to UVB which are shorter and more potent (280 nm–320 nm) (Center for Science Education, 2017). Of all the Sun's light entering Earth's atmosphere, at most only about 3% reaches the ground level as UV light. Of this 3%, 95% is UVA radiation, the rest, UVB (U.S. Dept. of Health and Human Services).

Despite UV making up only a small portion of the light reaching Earth's crust, and UVB making up an even smaller portion, both play major roles in the body. UVA rays are primarily responsible for the tanning process. Given that UVA rays are longer, they pierce deeper into the dermis. The slight, deep tissue DNA damage these rays cause, triggers keratinocytes (the primary skin cells) to induce production of α-Melanocyte Stimulating Hormone (MSH), through instructions given by the proopiomelanocortin (POMC) gene (Cui et al., 2007). MSH carries these instructions that modulate surrounding melanocytes (cells producing melanin) to induce the production of melanin (brown/black pigment). This is done to protect the skin from the shorter and more damaging, UVB rays, the darker pigment slowing the rays (D'Orazio et al., 2006).

Again, although less prevalent and more damaging, UVB rays are still vital to the body.

Given that UVB rays are shorter and carry more energy, they are most dangerous to the skin. Their shorter waves do not travel as deep, leading to greater and more surface-level DNA damage and most skin diseases. Despite this, UVB rays are also majorly responsible for the production of Vitamin D within the body. For reference, about 30 minutes of midday Oslo sunlight, is equivalent to 10,000–20,000 IU of Vitamin D taken orally (Cicarma et al., 2009, 3497). Still, the risks of skin damage and disease, prompt many doctors and dermatologists to warn against the dangers of UVB exposure, and most sunscreens target these rays.

Another major source of Vitamin D is dietary intake. Compared to other organisms, humans are required to refill their Vitamin D levels somewhat more frequently, making this method of obtaining Vitamin D less primary. Some animals, often characterized by fattier livers, can more slowly deplete their stores of Vitamin D, given Vitamin D is fat-soluble and stores better in such an environment. Thus, for instance, cod, living in deep, dark waters, and with fatty livers, more efficient metabolic processes, and fewer energy expenditures, are rich in, and much more slowly deplete, Vitamin D (Fisher, 2023).

II.B Precursors: Tanning Addiction

The idea that sunlight, or more specifically, UV-radiation could be characterized by or linked to addictive properties is not a new one, at least broadly speaking. The Ancient Greeks, in fact, coined the term heliophile to embody an adjacent concept, the word translating to lover of sunlight. In terms of the scientific literature, the idea that UV-radiation and addiction were linked had been questioned as early as the 2000s with relevant precursors dating as far back as a 1983 study, which observed that the exposure to UVA rays in one white male, led to significantly greater β-endorphin and β-lipotropin levels[1].

[1] A precursor to MSH and β-endorphin.

Later studies pursued the subject, from another angle. These papers observed a curious facet of frequent tamers. Tanners had often been thought to exhibit behaviors seen as obsessive. This led some, such as Warthan et al. (2005) to ponder whether the obsession could border on addiction. Interviewing 145 beach-goers, their study revealed a statistically significant proportion of participants that met the conditions for diagnosing substance use disorder under the definitions of modified versions of the CAGE (Cut down, Annoyed, Guilty, Eye-opener) and the DSM-IV (American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) questionnaires, 26% and 53% respectively (Warthan et al., 2005). This opened the door into a new way of thinking about the prevalence and seeming obsession of frequent tanning which was previously only considered to be a body image disorder.

A concurrent study, published by Feldman et al. (2004), found that tanners, furthermore, could not only distinguish between UV and placebo tanning beds but also overwhelmingly proffered them after being conditioned to both. The study exposed 14 individuals to both UV and non-UV beds on Mondays and Wednesdays and allowed individuals to opt into additional tanning on Fridays. About 86% chose to partake in Friday tanning, and of those, 95% chose UV beds, both of which, significant results. The results, looking at tanning beds specifically, are relevant, as tanning beds operate by emitting UVA radiation.

These results sparked later clinical investigation. Hoping to find more concrete addiction-like symptoms from tanning bed use, Kaur et al. (2006) examined preferences for UV vs. non-UV tanning beds and the effect of Naltrexone on tanners. The study consisted of a small sample of 8 frequent and 8 non-frequent New York tanners (tanning 8-15 times a month compared to only at most once a month), and trials were designed as double-blind and placebo-controlled. Naltrexone, an opioid antagonist, would block the opioid receptors in the brain, which, if the UVA exposure from tanning were addictive through opioid pathways, would immediately send

the body into withdrawal. Not only did frequent tanners distinguish and prefer the UV beds as in previous studies, but they also responded strongly to the Naltrexone, with increasingly acute reactions in response to higher doses. Symptoms, which fall in line with the responses expected from an opioid, included shaking, nausea, and vomiting. The study eventually had to be stopped due to two of the four frequent tanners dropping out of the study with aggressive physiological withdrawal symptoms (pronounced jitters, shaking, and vomiting). This seemingly confirmed an opioid mechanism in explaining the addictive nature of tanning. Future research would pick up the topic again, under the broader implications of opioid mechanisms explaining addiction to UV-exposure, and not just tanning beds.

II.C Recent Work: Establishing a UV-Vitamin D Feedback Loop

More recent work in the space, establishes UV-exposure as addictive as it induces the production of β-endorphins through the tanning process. These endorphins bind to opioid receptors in the brain and manifest the traditional analgesic and behavioral symptoms of opioids (Fell et al., 2014). The strength of these opioids and other exogenous opioids is then mediated by the Vitamin D levels in the body, creating a feedback loop whereby the body encourages greater Vitamin D intake through an increased opioid response (which includes the opioid response to UV-exposure), and which does not amplify the opioid response when Vitamin D levels are high (Kemény et al., 2021). Kemény et al.'s (2021) findings track with NHANES data, where Vitamin D levels are positively associated with the odds of opioid use, as well as in predicting postoperative opioid use and outcomes (Carroll et al., 2012).

Fell et al. (2014) looked to investigate the implications of the findings by Levins et al. (1983); Cui et al. (2007) and others (Precursors: Tanning Addiction II.B), which discovered

MSH transitionally cleaved[2] into, eventually, β-endorphins. Hypothesizing that the UV-induced β-endorphins, interacted in the brain similarly to how traditional opioids do, the researchers set up randomized mouse model trials, exposing a set of mice to 50 mJ/cm^2 of UVB radiation for a 6-week period, the equivalent of 20–30 minutes of ambient midday Florida sunlight. The researchers expected to observe opioid-like effects on UV-exposed mice. Mice in the control groups were exposed to mock-UV-radiation. In a similar spirit to Kaur et al. (2006), The mice were also then injected with an opioid antagonist, Narcan, with the expectation of opioid withdrawal-like symptoms. Their results mirrored expectations. UV-exposed mice displayed significantly elevated β-endorphin levels compared to the control and knockout[3] mice, as well as analgesia (pain relief) through testing pain thresholds. Such was tested by applying increasing tensile strength in stretching the paws of the mice and by measuring the duration of paw placement on a hot plate before reactions were observed. Mice also, after 2-weeks, began to have Straub tail, a common sign of opioid dependence characterized by contraction and elevation of the tail. Furthermore, following Narcan injection, UV-exposed mice showed opioid withdrawal-like symptoms– shakes, paw tremors, teeth chatter, and rearing. The researchers also re-affirmed results, by performing a conditioned place aversion assay, essentially, a test of the place preference of the mice. After mice were familiarized with two identical spaces, injection of Narcan in one space resulted in statistically significantly longer time spent in the placebo injection environment for UV-exposed mice compared to before. This compares to no observable preference in the mock-UV-exposed mice. In all cases, opioid and opioid withdrawal behaviors were reversed with the rescue of UV-exposure.

After confirming in greater detail, the results of previous tanning studies (Precursors: Tan-

[2]When a molecule splits into other simpler molecules.

[3]A condition induced by altering a gene responsible for the treatment condition– in this case, each in removing a part of the POM-C gene and p53 gene, which are thought to be responsible for the downstream production of β-endorphins.

ning Addiction II.B), many of the authors sought to further explain their results (Kemény et al., 2021; Fisher, 2023). Recognizing the effect of Vitamin D in predicting postoperative opioid use (Kim et al., 2020; Carroll et al., 2012), they questioned if Vitamin D mediated this addiction mechanism, with intuitive evolutionary explanations as to why– a reward system developed to encourage the intake of a vital bodily nutrient. Examining Vitamin D levels against reported opioid use in NHANES 2003-2004 data, they found those with deficient levels (<12 ng/ml) had a 62% increase in odds of being opioid users, and those with insufficient levels (12–20 ng/ml) had 27% greater odds (compared to normal levels, of greater than 20 ng/ml). These results, all significant, stem from a logit regression controlling for age, sex, history of fractures, season of blood draw, and presence of chronic pain. The authors claim these as the major potential confounds, which supports their causal inference. Similar results appear in Opioid Use Disorder data from Mass General Hospital (2014-2016), applying the same controls.

The authors further supported these findings with a similar battery of mouse model testing as in their previous (2014) study. They measured location preferences, analogies/pain-thresholds, and dependence (all under the treatment of morphine injections). The researchers also observed location preferences under the condition of UV-exposure to validate the role of Vitamin D in mediating UV addiction. They found that Vitamin D deficient and knockout mice showed greater preference to an environment with morphine[4], indicating that deficiency amplifies the reward of exogenous opioids. Both Vitamin D deficient and knockout mice also displayed higher levels of pain tolerance in hot-plate tests. This effect diminished faster over repeated doses, with wild-type[5], control mice showing diminished effects after the fourth dose, and knockout mice after only the first dose. Such reflects a markedly increased tolerance to opioids, exacerbated by Vitamin D de-

[4]Mice were induced into Vitamin D deficiency by being fed a Vitamin D devoid diet.

[5]Mice with the typical genetic phenotype.

ficiency. After injection with Narcan, deficient and knockout mice were observed to have quicker and stronger withdrawal responses, similar to the responses described in the (2016) study. In all cases, rescue of Vitamin D levels restored behaviors and measures to the levels of the wild-type or normal diet mice groups. Finally, testing location preferences, with a UV and mock-UV environment, knockout mice exhibited more UV location preference compared to no preference in the wild-type mice, which was also restored under rescue. Such demonstrates that the body, with low Vitamin D levels likely increases the reward of sunlight, but does not do so at normal levels. This contradicts the reaction found with morphine, which occurs because UV, unlike exogenous opioids, stimulates Vitamin D levels. Thus, the authors point out the likely existence of a feedback loop between UV exposure, Vitamin D levels, and the sensitivity to opioids.

II.D Replicability & Potential Confounds

One major thread of concern of the two more recent and pivotal works is over the reliability of their inferences. Firstly, the substantial content of both papers revolves around mice models, which, although lending great control and specificity in what they permit researchers to test, raise questions of external validity. Humans are much larger and more complex organisms than mice, which opens the door to many different outcomes and explanations. As Lin (2008) describes, in reference specifically to the use of knockout mice for human inference:

> Modification of a given gene does not always result in the anticipated phenotype. In some instances, phenotypes of targeted mouse mutants were not those predicted from the presumed function of the given genes, while other null mutants revealed no apparent defects. Furthermore, the phenotypic outcome can be influenced by many environmental and genetic factors. Therefore, interpretation of the significance of the findings from studies using genetically modified mouse models is not always as straightfor-

> ward as one would expect, especially when the desire is to extrapolate the findings to humans (1)

Essentially, he states that, as it pertains to mouse models, "...it is important to keep in mind that an animal engineered to express a human gene and its protein is still an animal." (1)

Secondly, the analysis provided in humans in the work by Kemény et al. (2021), using NHANES (2003-2004) data, is limited in its small selection of controls and in method. Though the controls included do account for important confounders, and the authors claim these are the only main confounders that need to be addressed (Fisher, 2023), it would seem easy to imagine there could still exist unobservables that could distort the extent of the relationship proposed. Forrest and Stuhldreher (2011) had previously found "Vitamin D deficiency was significantly more common among those who had no college education, were obese, with a poor health status, hypertension, low high-density lipoprotein cholesterol level, or not consuming milk daily (all $p \leq 0.001$)." (1) These major correlates could represent numerous relevant yet missing controls. For instance, a simple and plausible alternative explanation for the findings Kemény et al. (2021) presents is that education levels, which are correlated with Vitamin D levels, are correlated further with opioid use. The omission of education then amplifies the reported, isolated effect of Vitamin D, misattributing the effect of education levels to Vitamin D levels, which may not have such a strong effect, in fact. Stories toward the converse are also quite plausible.

Furthermore, the applicability of the epidemiological work done by Kemény et al. (2021) is in doubt given ambiguous handling of the NHANES data. Only a very general description of what constitutes, for instance, an opioid user or an individual with fracture history is given. For instance, the NHANES collects information on only hip, wrist, and spine injuries in the 2003–2004 cycle, and it must be assumed which of these is considered. Additionally, and more chiefly worrisome, the frequencies of observations and of characteristics reported are impossible. For one, the authors note

that the NHANES provides an overall sampling of $18,324$ men and women between ages 20 and 85, while the 2003–2004 NHANES only sampled $10,122$ individuals. At best, this could be due to using a broader year range of data, despite the stated 2003–2004 range. At worst, a merging error may exist, where the reported frequencies by characteristics are attainable by allowing individuals with multiple prescriptions to be represented by multiple observations (which would overcount opioid users and the sample) and in merging unmatched individuals across the various NHANES modules (such as those who took the miscellaneous pain questionnaire but not the Vitamin D tests). In fact, proceeding with these errors in an effort to replicate results produces the exact frequencies reported by Kemény et al. (2021).

This paper seeks to resolve these issues. Firstly, the analysis taken will observe humans, using the same NHANES dataset used by Kemény et al. (2021). Furthermore, this study will improve upon the already existing analysis by Kemény et al. (2021), through the more explicit and intuitive handling of data and by applying econometric techniques specifically motivated to support causal inference.

III Data

III.A NHANES: Overview of the Dataset & Data Collection Processes

The fundamental data of interest will come from the U.S. National Health and Nutrition Examination Survey (NHANES). This dataset collects information on Vitamin D levels over a range of years, which will be the primary independent variable of interest. The NHANES also collects information on numerous other demographic, economic, and medical characteristics which will be considered for inclusion in analyses as controls.

The NHANES itself is a publicly accessible collection of cross-sectional datasets offered through the Centers for Disease Control and Prevention (CDC). The survey is "designed to assess the health and nutritional status of adults and children in the United States" and is unique in combining interviews and physical examinations. The survey examines a nationally representative sample of about 10,000 persons each year. These persons represent the total non-institutionalized civilian population residing in counties of the 50 states and the District of Columbia, 15 counties of which are visited each year.

The NHANES uses a stratified four-stage probability sampling design. The first stage involves randomly selecting primary sampling units (PSU) from, almost all counties of the U.S. which had been identified in the 2000 U.S. Census, with some adjacent counties combined due to size restrictions. Of these PSUs, the probability of selection was determined relative to population size, with some exceptions made based on highly concentrated areas of particular demographics of interest such as African, Mexican, and Asian Americans. The second stage of sampling involved segmenting PSU, yielding on average 24 segments per PSU to be surveyed. The third and fourth stages of sampling involved randomly selecting decision units (often households) to actually approach and then, within such, selecting individuals to survey. The methods and procedures

employed in the survey were approved by the Institutional Review Board (IRB), and documented consent was obtained from participants.

III.B NHANES: Construction of Relevant Variables

Vitamin D levels were assayed[6] either using an equilibrium radioimmunoassay procedure (1988–2006) or a liquid chromatography-tandem mass spectrometry procedure. (2007 onwards)[7][8] by a central laboratory with quality assurance and monitoring.

Regarding measured serum Vitamin D levels, individuals are categorized into four exhaustive conditions for the purpose of analysis– deficient, insufficient, normal, and high. These correspond to the following ranges respectively and are according to the Institute of Medicine (US) Only

Table 1: Vitamin D Status and Corresponding Levels

Vitamin D Status	Vitamin D Level (nmol/L)
Deficient	less than 30
Insufficient	30–50
Normal	50–125
High	greater than 125

Source: Institute of Medicine (US)

those participants who participated in the Vitamin D tests administered by the NHANES will be analyzed and those with missing Vitamin D measurements will be dropped.

The Opioid use variable will be constructed as a dummy based on methods similar to those taken by Kemény et al. (2021). This involves parsing through the prescription drugs module of the

[6] An analytic procedure for assessing or measuring the presence, amount, or functional activity of a particular molecule.

[7] Essentially, very fancy ways to accurately measure the concentration of Vitamin D in a person's blood.

[8] These radioimmunoassayed results were actually transformed by the CDC to more closely match results of more recent survey cycles which use liquid chromatography-tandem mass spectrometry. This was done because it was determined LC-MS gave more accurate results of Vitamin D levels.

NHANES which recorded participant information on prescription drugs taken in the past month. The relevant items will be the type of drug coded into the data (opioid analgesics are of interest). These correspond to prescription drugs coded as analgesic narcotics or narcotic combos. Respondents with unknown and uncategorizable medications and no other opioid usage were considered to be non-opioid users. Multiple instances of opioid use by the same respondent or multiple non-instances were both recorded as one observation. That is, an individual is assigned a value for being or not being an opioid user based on all of their medications reported. Additionally, extra-legal drug use will be examined through data reported in the drug use questionnaire. The substances heroin and morphine will represent opioid drug use in this context, as these also constitute analgesic opioids.

As for the controls to be considered:c chronic pain is generated as a dummy variable for those reporting pain lasting for over a year. The sole respondent who did not know how long they experienced lasting pain was dropped.

History of fracture was determined by those who reported having fractured a wrist, hip, or their spine in the past. Those who did not know, refused to answer, or were missing were excluded.

May–October blood drive is generated as a dummy variable based on which months the participant was tested for the medical examination and Vitamin D tests administered by NHANES.

Race is constructed as a categorical variable for Non-Hispanic Whites, Hispanics, Non-Hispanic Blacks, and others[9].

Age is considered based on the age at medical examination. This is because the age reported at examination will be more relevant than the age reported in the demographics questionnaire as it will not have the possibility of being an imputed age. Since the data is top-coded at 85 years old, only those up to age 84 will be considered. Those under 20 will not be considered as such

[9]Includes Asians, Native Americans, Multiracial-Non-Hispanics, etc.

a young population represents a host of issues considering development and social habits. Those with missing age values are dropped.

Specific to this paper, milk consumption is also of interest as an instrument for Vitamin D levels. NHANES tracks participant dietary information, including features of individual milk consumption for a broad range of ages. The data collected, which this study will use, in particular, is survey participants' milk drinking habits over the past 30 days, where participants respond to having either "never," "rarely," (less than once a week) "sometimes," (more than once a week but less than once a day) and "often" (once a day or more). Those who responded varied, who refused, who didn't know, or who were missing were excluded from the dataset. The remaining responses were then constructed into a four-level factor variable for milk consumption.

III.C Descriptive Statistics

Table 2: Observable Counts

Class	Count
Opioid User	259
Deficient	239
Insufficient	577
High	24
Chronic Pain	392
Male	996
History of Fracture	301
May – October Season of Blood Draw	1,231
Hispanic	447
Non-Hispanic Black	367
Other	86
Non-College Graduate	1,812
<50% Household Income	1,345
Total Sample	2,266

Source: NHANES 2003–2004

Following construction, the above were observed in the sample for each given attribute. Observables that would be expected to be balanced, are, such as gender and season of blood draw. Opioid users, notably, account for about 11% of those sampled. Vitamin D levels follow expectations, with the bulk of the sample having normal levels, and decreasing counts toward deficient and high levels. High levels are a very small minority of all levels observed.

As continuous variables, the weighted average BMI measurement for the survey sample was about 28.8 kg/m^2 with a survey-weighted standard deviation of 0.18. For Vitamin D level, the weighted average was about 63.52 nmol/L with a weighted standard deviation of 1.62.

IV Methodology

IV.A Replication

First, in replicating the results of Kemény et al. (2021) a multivariate analysis using logistic regression modeling will be employed. The dependent variable will be an indicator for opioid consumption, and the independent variables will include the variable of interest– serum Vitamin D levels– and controls such as age, gender, ethnic groups, a history of fracture indicator, an indicator for chronic pain (lasting over a year), and season of blood drawn (1 November to 30 April or 1 May to 31 October). Just as Kemény et al. (2021) Vitamin D levels will be expressed as a factor variable, with the notable addition of a "High" levels category. As an equation, the model can be represented as

$$\ln\left(\frac{P(\text{Opioid User}=1|\vec{X})}{1-P(\text{Opioid User}=1|\vec{X})}\right)=\beta_1\text{VitD}_i+\beta\cdot\vec{X}, \tag{1}$$

where $\vec{X}$ represents a vector of controls. The β_k's taken as a whole denote the estimated parameterization of the model under maximum likelihood estimation. Results will be interpreted based on these coefficients as adjusted odds ratios, i.e.

$$\text{OR}(X_k)=\frac{P(\text{Opioid User }=1|\vec{X})}{P(\text{Opioid User }=0|\vec{X})}=e^{\beta_k\cdot X_k}=e^{\beta_k}$$

and will demonstrate the ceteris paribus marginal effect on the odds of opioid use relative to the base (omitted) class. Considering serum Vitamin D levels, ratios will be relative to those with normal levels. For instance, a model showing an unadjusted odds ratio of 1.62 for those with deficient levels, can be taken to mean that those with deficient Vitamin D levels have a 62% increased odds to use opioids compared to those with normal levels. Statistical significance of results, p-values are obtained using χ^2 tests.

IV.B Analysis of Endogeneity

In order to investigate the potential endogeneity inherent to this simple model, the effect of including common and strong correlates of both opioid incidence and serum Vitamin D levels will be examined. Such would violate the model assumptions of statistical independence.

Thus, if included in the original model, these variables reflect marked changes in the economic and statistical significance of the effects already postulated, these variables would suggest the endogeneity of serum Vitamin D levels. The inclusion of these variables would then serve to begin improving the model, though likely not completely resolving the issue of committed variables.

IV.C Potential Instruments

Considering the potential endogeneity that Vitamin D levels present, an instrumental-like approach could prove valuable. Individuals may augment their Vitamin D levels, whether consciously or unconsciously, as a product of their education, income, and with or through their lifestyle habits, and preferences. Many of these factors logically relate to one's expected propensity toward opioid use, and, even more troubling, these are quite hard to observe. Thus, a characteristic of individuals that is isolated from these confounders, yet still relevant to Vitamin D levels is desirable. As such, a consistent and more reliable estimate is available. Fortunately, given the natural processes underlying the biosynthesis of Vitamin D in humans, two domains shelter plausible instruments, these being the two main sources of bodily Vitamin D production– UVB radiation and diet.

UVB radiation would be a natural and intuitive choice for an instrument. On the surface, it passes both the fundamental assumptions for any IV approach. UVB is certainly a strong predictor of Vitamin D levels, but, more crucially, radiation is also reasonably exogenous. Common corre-

lates with Vitamin D levels, and dangerous omissions of our original models, such as income, BMI, and education (Forrest and Stuhldreher, 2011) are hardly linked with UVB exposure. Though one may assume the effect of temperature could be misrepresented as Vitamin D levels through UV in such an environment, temperature actually is not much associated with UV level, where UV exposure is more a function of sun angle (which is why sunburns can occur in the winter and why UV levels typically peak after midday, around 2 to 3 PM). (Australian Government Bureau of Meteorology, 2020). Brightness, likewise, is not a strong correlate, where UV levels can remain high with partial overcast, which even magnifies levels in some cases as UV rays become more concentrated through broken clouds.

Unfortunately for this study, though UV levels are easily accessible through satellite measurements such as the ERA5, unrestricted access to any individual geographic identifiers is virtually nonexistent due to HIPAA constraints and globally accepted regulations. Thus, without gaining restricted access through the NHANES or another similarly composed health dataset, or by aggregating to the national observation level with multiple regional datasets, say, for adjacent European nations, linking individuals to surface UV levels is impossible.

IV.D Instrumenting Using Milk Consumption

Another path to a plausible instrument for Vitamin D levels, and the one that this paper will take, lies along dietary features. This is because diet comprises a still significant, albeit less prominent, source of Vitamin D in the body. More specifically, this paper will use milk consumption, notable for its already rich Vitamin D contents and also high-fat content, as its source of exogenous variation.

Given these qualities, milk consumption is a strong predictor of Vitamin D levels, which Forrest and Stuhldreher (2011) recognizes. Similar to UV radiation, milk consumption is also

reasonably exogenous, at least for the purposes of this study. For one, milk is a common dietary staple across socioeconomic demographics. Milk consumption as a whole is well balanced along income levels (McGuire, 2012). Furthermore, the takeup of whole and reduced fat milks is similarly balanced and roughly equal. Milk, also, is a well-stocked good across the country, being it a widely considered food staple. Despite milk sales diminishing with the growing popularity of milk alternatives such as oat milk, soy milk, etc, the 2003–2004 cycle period which this study focuses on predates this emerging trend. The increased prevalence and risk of lactose intolerance with age is also not much of a factor, given that age is an easily observable attribute, and one included in this analysis.

The specific approach this paper will take to estimate the marginal effect of Vitamin D levels on propensity toward opioid use is, despite the dominant wording used, actually a control function approach and not instrumental variables. Though technically different, these are intuitively procedurally and, in terms of output, equivalent, less a few small differences. The control function approach is necessary for this scenario, as it is one of the few instrumental variable-like frameworks that exist for classification models. A traditional 2SLS IV approach would certainly be possible, although, for the purposes of this study, it is severely limited by the constraints on functional form for linear probability models. The results yielded under control function, are like 2SLS, consistent estimators of their population parameters under the same assumptions of the instrument's linear correlation with the endogenous variable, strict endogeneity, and normality of errors.

In essence, the control function approach seeks of using the exogenous instrument to predict the endogenous component of the relevant explainer and thus control for this endogeneity by its predictions inclusion in the model. Breaking this down, where milk consumption is the instrument

and Vitamin D, the endogenous covariate,

$$\text{VitD} = \beta_1 \text{Milk Consumption}_i + \beta \cdot \vec{X} + \varepsilon_i \tag{2}$$

$$\text{Opioid User} = \beta_1 \text{VitD}_i + \beta \cdot \vec{X} + \upsilon_i. \tag{3}$$

Here, υ_i can be decomposed into both an endogenous and exogenous component, to reshape Equation 3 into

$$\frac{\text{Opioid User}}{\sqrt{1-\rho^2}} = \frac{\beta_1 \text{VitD}_i + \beta \cdot \vec{X} + \left(\rho \frac{\varepsilon_i}{\sigma} + \nu\right)}{\sqrt{1-\rho^2}} \tag{4}$$

(after rescaling to have a constant variance of 1) where

$$\upsilon_i \sim N\left(\rho \frac{\varepsilon_i}{\sigma}, \sqrt{1-\rho^2}\right).$$

Then, ε_i can be predicted from Equation 2 and substituted into Equation 4. From this, after choosing the desired link function, where we will use the inverse normal CDF to attain a probit regression, and using MLE[10], causal β_k can be estimated[11] (Rios-Avila, 2013).

It is important to note that in order to proceed under the control function approach, Vitamin D enters the model as a single continuous variable rather than as a 3-level factor variable as before. This is crucial in order to avoid the "forbidden regression" (Angrist and Pischke, 2009, p. 142). The choice of controls that enter the model is also carefully considered so as not to reintroduce endogeneity into the model. Thus, the control set used includes chronic pain, age, gender, fracture history, and BMI, given that these are plausibly relevant and omitted variables from a simple model.

[10] See Heckman and Robb (1985) and Sohil et al. (2022) for more detailed information on control functions/MLE.

[11] Note that it is possible to use a logistic link, and it would be preferable to do so to keep continuity with the literature. Doing so, however, requires knowledge of the joint distribution for error terms, which is complicated to pin down. Most other IV-like logit methods also require this.

These enter as they had in the replication model. Controls excluded should not drive any bias due to their exclusion since the control function approach we take already ensures the consistency of our estimate of Vitamin D levels.

Further, the interpretations of the estimated model coefficients are now notably harder to intuit and relate to the adjusted ORs from the original work of Kemény et al. (2021). In order to draw clear interpretations and aid in these comparisons with the literature, average marginal effects will be considered at various serum Vitamin D levels, allowing comparisons between ranges. The same AME measures will also be computed for the replication models, allowing for comparison.

V Results

V.A Replication

The first column of Table 3 shows the results of the logistic regression model from Equation 1 and which most closely mirrors Kemény et al.'s (2021) model for prescription opioid users on Vitamin D levels. The model, taken causally, implies that Vitamin D deficiency and insufficiency correspond, respectively, to a 72.0% and 51.4% increase in the odds of being a prescription opioid user as compared to those with normal levels. This falls in-line with the hypothesis that lower Vitamin D levels would exacerbate the effects of opioid use and thus the odds for opioid use. The results also are in-line numerically with the findings of Kemény et al. (2021). Though slightly different, the direction of the impact of Vitamin D levels is in the correct direction. The effects of controls are mostly in the correct directions, except for the effect of being male. High Vitamin D levels, a new inclusion, also show significantly increased odds toward opioid use, 346%. This is a curious result that was not previously considered in the literature. Such may result from the negative effects of high Vitamin D levels, which could somehow interact with the mechanism controlling the Vitamin D–opioid exacerbation relationship.

V.B Potentially Ommitted Variables

This prior model, as explained earlier, is a somewhat naive approach to validating the proposed relationship between Vitamin D levels and opioid use.

Although it does control for some characteristics, it potentially suffers from looming validity concerns that hamper any confidence in the causal inferences proposed. Omitted variables are one glaring concern. Given the conclusions of Forrest and Stuhldreher (2011), education, BMI, and potential income are all correlates of Vitamin D deficiency, which may also very plausibly

Table 3: Replication & Expanded Control Set Models

	(1)	(2)	(3)	(4)
Defficient	1.73*	1.61*	1.45	1.40
	(2.54)	(2.27)	(1.85)	(1.65)
Insufficient	1.52*	1.48*	1.45*	1.41*
	(2.43)	(2.29)	(2.34)	(2.24)
High	3.25*	3.97**	3.96**	4.01**
	(2.38)	(3.03)	(3.13)	(3.15)
Chronic Pain	4.01***	3.71***	3.57***	3.55***
	(9.15)	(9.07)	(8.44)	(8.51)
Age at Examination	0.99*	0.99**	0.98**	0.98**
	(-2.80)	(-3.01)	(-3.33)	(-3.35)
Male	1.30	1.33	1.38	1.38
	(1.24)	(1.37)	(1.71)	(1.71)
History of Fracture	1.22	1.21	1.22	1.23
	(0.96)	(0.90)	(0.95)	(1.00)
May – October	1.03	1.02	1.00	0.99
Season of Blood Draw	(0.13)	(0.06)	(-0.01)	(-0.04)
Hispanic	0.97	0.88	0.83	0.83
	(-0.13)	(-0.48)	(-0.61)	(-0.63)
Non-Hispanic Black	0.85	0.82	0.76	0.75
	(-0.89)	(-1.00)	(-1.34)	(-1.41)
Other	1.02	1.06	1.03	1.04
	(0.06)	(0.15)	(0.07)	(0.09)
Non-College Graduate		2.17**	1.75*	1.73*
		(3.20)	(2.91)	(2.85)
<50% Household Income			1.95*	1.94*
			(2.48)	(2.48)
Body Mass Index				1.01
				(0.77)
Observations	2261	2261	2261	2261

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Source: NHANES 2003–2004

be linked with opioid use. Including these variables in modeling the effect of Vitamin D levels, dramatically weakens the results of the original model (Table 3, columns 2–4). In the last model (4) with the largest control set, odds ratios for deficiency and insufficiency drop by as much as 33 and 10 percentage points respectively. Furthermore, the inclusion of an expanded control set paints deficiency as statistically insignificant, and insufficiency is now more weakly significant compared with before (though still passable). High Vitamin D levels, interestingly, are impervious to the new inclusions. In fact, it seems high levels absorb some of the effects originally seen. Most all other controls retain their effects. The new additions show quite meaningfully, boasting large ORs (except BMI).

V.C IV Probit Model

Following through with the IV probit model described in IV.D and a slightly more restrictive control set, yields interesting and contradicting results to Kemény et al. (2021). The results are similar to what the expanded control set Model (4) from Table 3 seems to indicate, which is no evidence of a discernable effect or even a positive effect on opioid use propensity for higher vitamin D levels in some instances. This can stem from a multitude of reasons, ranging from subtleties missing in their interpretations to weaknesses in their identification strategy.

Table 4 outlines the estimated parameterization of the model. A Wald test of exogeneity rejects the assumption that Vitamin D is exogenous at the 5% level (albeit with p-value of 0.0496), and thus it is likely correctly specified using this control function approach. Average marginal effects under this model were computed at various Vitamin D levels and plotted in Figure 1 along with associated 95% confidence intervals. Marginal effects seem quite small and positive at all levels, with only slight differences across the range. The marginal effect generally increases with levels, though, at almost all levels, effects are not statistically different from the null. This is

Table 4: IV Probit Model

	Opioid User	Vitamin D (nmol/L)
Vitamin D (nmol/L)	0.01	
	(0.88)	
Chronic Pain	0.73***	-1.22
	(7.30)	(-0.78)
Age at Examination	-0.01*	-0.07
	(-2.35)	(-1.54)
Male	0.11	0.47
	(1.17)	(0.44)
History of Fracture	0.11	1.69
	(1.01)	(1.30)
Body Mass Index (kg/m^2)	0.02	-0.95***
	(1.76)	(-9.41)
Milk Consumption (Past 30 days)		4.27***
		(11.90)
ρ_1	-0.28	
	(-0.99)	
$\ln \sigma_2$	3.14***	
	(68.58)	
Corr($\varepsilon_{\text{Vitamin D}}$, $\varepsilon_{\text{Opioid User}}$)	-0.27	
sd($\varepsilon_{\text{Vitamin D}}$)	23.19	
Wald Test of Exogeneity: $\chi^2 = 38.6$, p-value: $= 0.0496$		
Observations	2261	

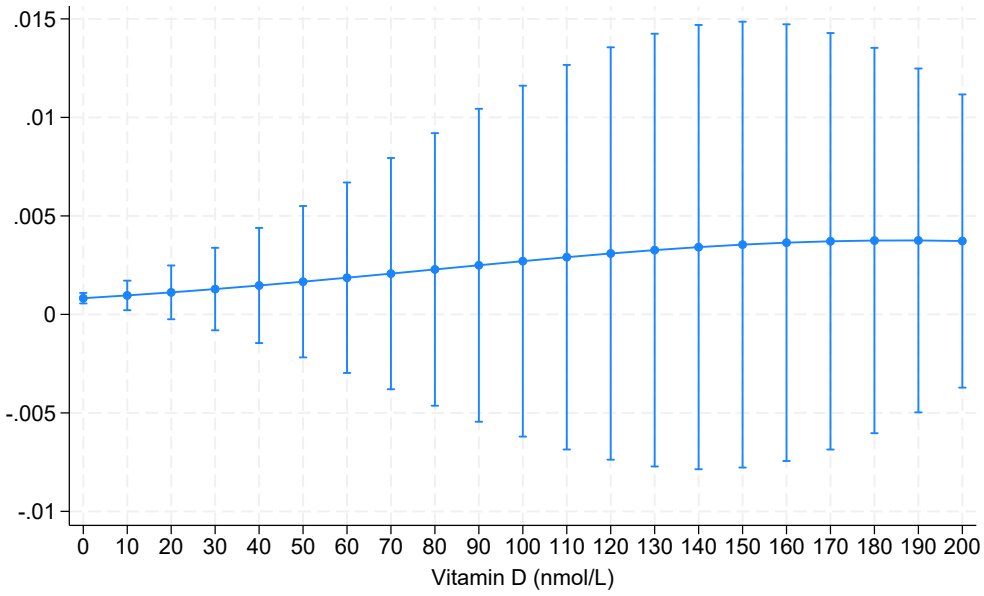
t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Source: NHANES 2003–2004

contrary to expectation, where effects were expected to be negative (have a positive associated impact on opioid use propensity for lower Vitamin D levels) and to have an increasing magnitude toward lower levels of Vitamin D. Technically, at very low levels of Vitamin D between 0 and about 30 nmol/L, marginal effects are statistically significant enough to purport a non-zero impact, however, even these effects are still minimal at around 0.1 to 0.15 percentage points decrease for each unit decrease in level. For movements between 0 and 30 nmol/L this amounts to still only an approximate 6 percentage point change. Furthermore, this purported effect is in the opposite direction to what was hypothesized, suggesting a lower swing leads to a decreased propensity toward opioid use. Even for these values, significance is shoddy.

Figure 1: (IVprobit) AME at Various Vitamin D Levels
w/ 95% Confidence Interval



Source: NHANES 2003–2004

Table 5: Logistic vs GLM Binomial w/ log link

	RRRs	Adjusted ORs
Defficient	1.26	1.40
	(1.44)	(1.65)
Insufficient	1.24	1.41*
	(1.66)	(2.24)
High	2.77**	4.01**
	(2.98)	(3.15)
Chronic Pain	2.67***	3.55***
	(8.27)	(8.51)
Age at Examination	0.99**	0.98**
	(-3.04)	(-3.35)
Male	1.28	1.38
	(1.69)	(1.71)
History of fracture	1.22	1.23
	(1.22)	(1.00)
May – October	0.99	0.99
Season of Blood Draw	(-0.07)	(-0.04)
Hispanic	0.88	0.83
	(-0.51)	(-0.63)
Non-Hispanic Black	0.79	0.75
	(-1.41)	(-1.41)
Other	1.06	1.04
	(0.19)	(0.09)
Non-College Graduate	1.56*	1.73*
	(2.55)	(2.85)
<50% Household Income =1	1.74*	1.94*
	(2.55)	(2.48)
Body Mass Index	1.01	1.01
	(1.11)	(0.77)
Observations	2261	2261

t statistics in parentheses

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Source: NHANES 2003–2004

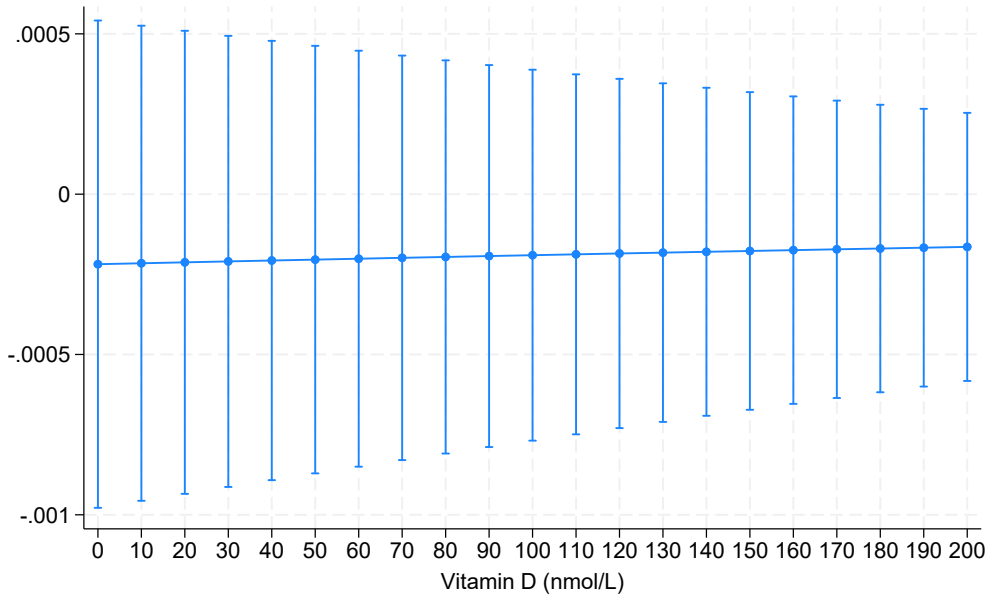
These results, which fail to validate earlier results, may differ so drastically for a number of reasons. One simple and interesting possible explanation is that these results are actually, in fact, not too dissimilar from the results stated in the original model proposed in the literature. That is, it may be possible that the original model results were accurate, but the conclusions drawn were not due to a mistake in the model's interpretation.

Model output from the logistic estimations was taken as adjusted odds ratios. Adjusted odds ratios, though semantically, conceptually, and mathematically very similar to relative risk ratios (a ratio of probabilities), are not the same as relative risk. For instance, Model (4) from (Table 3) shows that individuals with deficient Vitamin D levels have an associated 40% increased adjusted odds of being opioid users. This may sound like a 40% increase in the probability or likelihood of being an opioid user, but it is not; it reflects a change in the odds. For an example of the difference between probability and odds, the probability of a coin flip resulting in eads is 1:2, but the odds are 1:1. Where probabilities reflect the ratio of a possible event to all possible events occurring, odds represent the ratio of probabilities of an event occurring to that event not occurring. This means an odds ratio then reflects a ratio of ratios of ratios. This is very hard to intuit, despite what it may semantically sound like, say, when hearing that the odds of opioid use increase 62%. In fact, re-estimating the replication model using a binomial distribution with a log link function instead of a logit link, which produces outputs that are actually relative risk ratios, shows that the associated adjusted relative risk increase is only about 26%[12]. In this model, all low-level statuses are non-significant too.

Additionally, it is important to note that both odds ratios and relative risk ratios are just that, relative. The measures reflect changes in odds and propensity from the base case, those with normal

[12]This particular GLM is not as preferred as a probit or logit as it does not quite match the expected distribution of opioid use, which is a binary response, although it is likely accurate enough to demonstrate the point.

Figure 2: (Logit) AME at Various Vitamin D Levels
w/ 95% Confidence Interval



Source: NHANES 2003–2004

levels. Occurance of opioid use in the overall dataset, however, is already quite low, with opioid users making up only about 11% of the sample (Table 2), where the decomposition of Vitamin D levels would show even lower. Thus, say if the likelihood of opioid use changed from say 1% in individuals with normal levels to 2% in those with deficient levels, a whopping increase of 100% would be reported. As such, even minute changes in odds and propensity will seem large in terms of relative changes. Examining the original models using average marginal effects instead of odds ratios (Table 5), draws a somewhat more similar picture to the IV probit model. Here, marginal effects at all levels are, as expected, negative. Unfortunately, the magnitude of these effects is still, and significantly more so, very minuscule. Again, effects are hardly distinguishable from the null.

As previously hypothesized, endogeneity was a valid danger to the original model specification, but through this view, it appears now that regardless, it was not impactful in showing any

statistically meaningful results beyond what conclusions could be drawn from an expanded control set formulation of the original model. Overall, it appears that high levels may actually be significant contributors to the propensity to use opioids; however, even estimates for these effects are quite varied. The mechanism explaining why high levels, if their effects are taken as significant, is uncertain and would require further investigation and support from medical research.

VI Discussion & Conclusion

The opioid epidemic represents a substantial burden to economies and to the lives of millions of people and families. Overall, estimates of the economic costs of opioid misuse as a total loss of productivity, life, etc. within the U.S. range anywhere between as low as $18B a year and as high as $500B a year Fuhrmann-Berger (2018); Maclean et al. (2020). On average, 128 Americans will lose their lives to opioid overdose every single day. Death as a cause of opioid overdose has only increased year over year since 1999. CDC (1990–2023)

Although previous epidemiological and medical literature had been hopeful to the emergence of Vitamin D supplementation as an easy, accessible, cheap, and effective combatant to rising opioid use, this paper was not able to determine any meaningful effect from Vitamin D on propensity of opioid use through the exogenous variation in milk consumption. The lessons of this analysis, however, are still valuable, such as in reaffirming the importance of careful and transparent data cleaning processes, mindful model specification, and careful model interpretations. Furthermore, despite the results not supporting Vitamin D usage to halt opioid use, it is unlikely any increased Vitamin D intake or promotion posed a significant health, financial, or economic risk. More likely than not, Vitamin D awareness is a net positive on these factors.

Still, future research on this matter would benefit, such as in replicating the analysis using different instruments. A good launching point would be to leverage weather variation in UVB radiation as an alternative instrument for UVB exposure and would require restricted access to geographic identifiers in health data. This may provide a stronger source of variation, with which to examine effects, and might lead to more telling, statistically significant results. An examination of why high Vitamin D may lead to a higher propensity of opioid use, if it shows significantly higher in future studies, would also be interesting and valuable.

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