Vitamin D status and its longitudinal association with changes in patterns of sleep among middle-aged urban adults

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ARTICLE INFO

ABSTRACT

Objective. We examined relationships of vitamin D status with over time changes in patterns of sleep in a longitudinal study of Whites and African-American urban middle-aged adults, while further testing effect modification by age group, sex and race and the potential roles of dietary and supplemental vitamin D.

Methods. Data on 1,760 middle-aged participants in the Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS study: Age range at v$_2$: 33-71y, mean±SD:53.0±8.8, % women: 58.4%, % African-American:60.3%) were used, with complete baseline 25-hydroxyvitamin D [25(OH)D] serum concentration data, initial selected covariates and mediators, and initial and/or follow-up data on five sub-scales (sleep duration, daytime dysfunction, sleep disturbance, sleep latency and sleep quality) of the Pittsburgh Sleep Quality Index. Mean±SD time between initial and follow-up visits: 4.1±1.5 years. Time-interval multiple mixed-effects linear regression models were used.

Results. Upon multiple testing adjustment, among Whites, initial 25(OH)D was associated with better sleep duration [25(OH)D × TIME γ±SE: -0.027±0.011, P=0.017] and sleep quality [25(OH)D × TIME γ±SE: -0.026±0.010, P=0.008] over time, with heterogeneity by race found for both relationships (P<0.05 for 25(OH)D × TIME × Race in the un-stratified model). These relationships remained unaltered after further adjustment for dietary and supplemental vitamin D, indicating that this association may be largely explained by sunlight exposure.

Limitations. Limitations included small sample size, selection bias, residual confounding and lack of objective sleep measures.

Conclusions Vitamin D status, possibly through mechanisms involving sunlight exposure, was linked to a potential improvement in sleep duration and quality among White urban adults.

Introduction

Optimal sleep patterns have tangible effects on health maintenance and prevention of chronic physical and psychological disorders(Ji et al., 2017). The National Sleep Foundation recommends 7-8 h sleep per day, with some variations by age group, gender and race (Dahl, 2004; Gamaldo et al., 2015; Gao et al., 2018; Hirshkowitz et al., 2015). Recently, sleep disorders including shorter sleep duration or excessive sleep have become a global epidemic(Kerkhof, 2017). Chronic poor sleep is linked to depressive and cardio-metabolic disorders, increased incidence of cardiovascular disease, cancer and higher mortality rates (Cappuccio et al., 2011; Gallicchio and Kalesan, 2009; Liu et al., 2012; Qin et al., 2014; Riemann et al., 2001; Riemann et al., 2020; Vgontzas et al., 2009). The frequency of sleep disorders among adults and the worsening of sleep quality over time, which negatively impacts health, highlight the need to uncover modifiable characteristics, which may include lifestyle and epigenetic factors, useful for disease prevention (Ji et al., 2017).

Biological pathways controlling the sleep-wake cycle include the

Abbreviations

25(OH)D	25-hydroxyvitamin D
CNS	Central Nervous System
CYP24a1	Cytochrome P450 Family 24 Subfamily A Member 1
CYP27b1	Cytochrome P450 Family 24 Subfamily B Member 1
GDNF	Glial Cell Derived Neurotrophic Factor
HANDLS	Healthy Aging in Neighborhoods of Diversity Across the Life Span
Hcy	Homocysteine
HEI-2010	Healthy Eating Index, 2010 edition
PSQI	Pittsburgh Sleep Quality Index

NGF	Neural Growth Factor
NT3	Neurotrophin-3
NT4	Neurotrophin-4
RXR	Retinoid-X receptor
SD	Standard Deviation
SE	Standard Error
THP-2	Tryptophan Hydroxylase Protein-2
V1	Visit 2
V2	Visit 2
VDRE	Vitamin D response element
VDR	Vitamin D receptor
WRAT-3	Wide Range Achievement Test, 3rd version

circadian clock, various neurons and hormonal factors originating from the hypothalamus and dark/light among environmental signals (Gao et al., 2018; Jones, 2011). Vitamin D, a steroid hormone which regulates calcium homeostasis, may also influence sleep quality. Serum 25-hyrdoxyvitamin D [25(OH)D] concentration (vitamin D status) is largely determined by sunlight skin exposure and by dietary and supplemental intakes (Buell and Dawson-Hughes, 2008). Despite having lower vitamin D status, some individuals with genetic polymorphisms in the vitamin D binding protein may be biologically adequate in active vitamin D, a pattern more prevalent among African-Americans (AAs) than among Whites.(Powe et al., 2013) The active form of vitamin D (1, 25-dihydroxyvitamin D_3) maintains and stabilizes intracellular signaling pathways by increasing vitamin D receptor (*VDR*) expression. (Guo et al., 2016) Furthermore, it was reported that *VDR* is expressed in brain regions regulating sleep-wake cycle including the hypothalamus (Eyles et al., 2014; Stumpf and O'Brien, 1987). Such evidence suggests that higher vitamin D status is likely inversely associated with risks of sleep disorders and poor sleep patterns.

Several epidemiologic studies examining the relationship between vitamin D status and sleep patterns and disorders have indicated a protective effect of higher vitamin D status against adverse sleep outcomes (Beydoun et al., 2014; Grandner et al., 2013; (Grandner et al., 2014) ; Massa et al., 2015; McCarty et al., 2012; Sato-Mito et al., 2011). However, controversial results were also found when using Pittsburgh Sleep Quality Index (PSQI) instrument and comparing vitamin D deficient to non-deficient groups in a cross-sectional study of pregnant women(Gunduz et al., 2016). A systematic review by Gao et al. indicated that most epidemiological studies examining vitamin D status in relation to sleep outcomes had a case-control or cross-sectional design (Gao et al., 2018). Thus, there is still paucity of studies testing the prospective relationship between vitamin D status and change in sleep patterns over time, possibly differentially by sex, age and race.

The current study examines the relationship between baseline vitamin D status with baseline and change in sleep patterns using a longitudinal study of White and AA urban middle-aged adults (Ages 33-71y, mean±SD:53.0±8.8), using PSQI sub-scales as outcomes and testing effect modification by age group, sex and race. The potential roles played by dietary and supplemental vitamin D are also explored.

Methods

Database

The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study is an ongoing prospective cohort investigation of the effects of race and socioeconomic status on change in health disparities, initiated in 2004. Utilizing an area probability sampling strategy, HANDLS spanned thirteen Baltimore, MD neighborhoods as primary sampling units. (Evans et al., 2010) HANDLS aimed at recruiting an ethnically and socioeconomically diverse sample of AAs

and white urban middle-aged adults, with the originally recruited closed cohort consisting of 3,720 participants. Interviews were conducted among participants identified by random sampling of addresses within each census tract. Participants were invited to join the study when meeting the following eligibility criteria: (1) ages 30–64; (2) not currently pregnant; (3) not within 6 months of active cancer treatment; (4) not diagnosed with AIDS; (5) capable of providing written informed consent, (6) able to produce valid government-issued identification and verifiable address (Evans et al., 2010).

The initial recruitment and examination consisted of two phases, Phase 1 whereby a dietary interview and various demographic and psychosocial scales were completed in participants' homes and Phase 2 whereby participants were examined on Medical Research Vehicles (MRV) parked in their neighborhoods(Evans et al., 2010). The baseline visit was completed between 2004 and 2009. Follow-up examinations followed a similar protocol with most data collected during the MRV visit. The present study uses data from HANDLS wave 3, the first follow-up in-person examination (v_1: 2009-2013), and wave 4, the second follow-up examination (v_2: 2013-2017), given the availability of PSQI sleep measures (OPAPC, 2019; Healthy Aging in Neighborhoods of Diversity Across the Life Span). At both visits, the PSQI was administered and two separate dietary interviews were performed, first as an in-person interview and second as a telephone interview. All dietary interviews collected data on supplement intakes including vitamin D assessments. In all our previous analyses, an average of two 24 hr recalls per visit were used to estimate food or nutrient intakes and diet quality indices (Beydoun et al., 2018a; Beydoun et al., 2018b; Beydoun et al., 2019). The v_1 PSQI assessment administered items for 5 of 7 sub-scales, as those sub-scales were considered to be the most important aspects of sleep at the time.

Present study data were derived from v_1 and v_2. The National Institute on Environmental Health Sciences' Institutional Review Board of the National Institutes of Health approved the study protocol.

Sleep quality measures

The PSQI measures sleep quality and disorders over a month (Buysse et al., 1989), from which there are several sub-scales assessing sub-optimal sleep duration, daytime dysfunction, sleep disturbance, sleep latency, sleep efficiency and sleep quality, in addition to a total score (Buysse et al., 1989(OPAPC, 2019; Healthy Aging in Neighborhoods of Diversity Across the Life Span). The PSQI was used in both v_1 and v_2 of HANDLS (Buysse et al., 1989). The instrument was administered during the MRV visit as part of the ACASI module (Healthy Aging in Neighborhoods of Diversity Across the Life Span)(PSQI codebook in HANDLS, wave 4). The scale has 19 self-report questions with response options reflecting sleeping habits for most days and nights(Buysse et al., 1989; Smyth, 2012). These questions are combined to form 7 component scores assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications

and daytime dysfunction. Each component was scored on a scale of 0 to 3 - where "0" represents "no difficulty" going up to "3" indicating "severe difficulty" (Buysse et al., 1989; Smyth, 2012). The seven component scores are added to yield one global PSQI score ranging from 0 to 21 points where "0" reflects no difficulty and "21" reflects difficulty in all areas of sleep. In this study only 5 of 7 components were used, given the lack of longitudinal data for the "sleep efficiency" component and absence of rationale for including "use of sleep medication" among possible outcomes. In fact, during v_2, all component scores were computed, while during v_1, only 5 components were available. Those components were sleep duration, daytime dysfunction, sleep disturbance, sleep latency and sleep quality. The PSQI was shown to have multi-dimensional psychometric properties, thus rationalizing the use of individual components in addition to the usual total score (Tomfohr et al., 2013).

Vitamin D status

All blood samples drawn were stored at −80°C. V_1 25(OH)D was measured by Quest Diagnostics (Chantilly, VA) using an immunoassay that includes competitive binding of serum 25(OH)D and tracer-labeled 25(OH)D to specific antibody followed by detection and quantitation via chemiluminescence reaction (Diasorin, formerly Incstar), an assay that is comparable to that of National Health and Nutrition Examination Surveys 2003-04 (interassay CV: 4-13%) (Centers for Disease Control and Prevention, 2006; Diagnostics, 2019; Diasorin)

Covariates

All analyses were adjusted for initial examination (i.e. v_1) age (y), sex (male=1, female=0), race (AA=1, White=0), self-reported household income either <125% or ≥125% of the 2004 Health and Human Services poverty guidelines (termed poverty status) ((US Department of Health and Human Services. 2004 HHS POVERTY GUIDELINES); Gamaldo et al., 2015). Age(v_1), grouped as ≤50y and >50y, sex and race were also considered as potential effect modifiers. Other v_1 covariates were selected with evidence of association with v_1 25(OH)D in the largest available HANDLS sample and prior evidence of an association with sleep disorders. Those included v_1 examination season (determined by quarter for the date of exam) (Beydoun et al., 2018b), an index of elevated blood homocysteine using eight markers, namely older age, lower serum folate, lower serum B-12, higher serum creatinine, higher serum uric acid, higher red cell distribution width, higher mean cell hemoglobin and higher alkaline phosphatase level (Beydoun et al., 2020; Beydoun et al., 2014), an index for systemic inflammation termed the inflammatory composite score obtained using principal components analysis of blood markers of elevated high sensitivity C-reactive protein, erythrocyte sedimentation rate and reduced serum iron and serum albumin levels (Beydoun et al., 2010; Beydoun et al., 2018a; Beydoun et al., 2019; Chiu et al., 2009); depressive symptoms measured with the total score on the 20-item Centers for Epidemiological Studies-Depression (CES-D) scale (Nguyen et al., 2004; Parker et al., 2017; Riemann et al., 2020), a measure of overall dietary quality, namely the 2010 version of the Healthy Eating Index (HEI-2010) (Beydoun et al., 2010;(Healthy Aging in Neighborhoods of Diversity Across the Life Span) National Cancer Institute, 2018), and history of dyslipidemia(Beydoun et al., 2018c). Other covariates considered but excluded after backward elimination in a model with 25(OH)D as the outcome were body mass index (weight/height-square, kg.m^{-2})(Beydoun et al., 2018c; Beydoun et al., 2013b), waist circumference (cm) (Beydoun et al., 2010), history or diagnosis or medications for type 2 diabetes and for hypertension (Beydoun et al., 2010); history of cardiovascular disease (atrial fibrillation, angina, coronary artery disease, congestive heart failure, or myocardial infarction)(Ji et al., 2017), literacy measured with the Wide Range Achievement task, 3rd edition (WRAT-3) (Gamaldo et al., 2015; Wilkinson, 1993), educational attainment (<High School

(HS), HS, >HS) (Gamaldo et al., 2015), current cigarette smoking, and current drug use (marijuana, opiates or cocaine)(Gibson et al., 2019; Valentino and Volkow, 2020).

Finally, two baseline measures of dietary and supplemental vitamin D were considered as potential mediators in the association between 25 (OH)D and v_1 patterns of sleep or change in this outcome between v_1 and v_2. Dietary vitamin D was assessed using the average of two 24 hr dietary recalls and a nutrient database, while supplemental vitamin D was the product of length of use (in years) with amount (in IU) of vitamin D among supplement users. Non-users were coded as "0". Details on dietary and supplemental assessment of vitamin D intakes are provided elsewhere (Beydoun et al., 2018b).

Statistical Analysis

All analyses were conducted using Stata release 16 (STATA, 2019). To describe key study variables, distributions were presented overall and stratified by age group, sex, and race. Means of continuous variables across binary groups were compared using *t*-tests, while chi-square tests for independence were used to compare distributions of categorical variables across stratifying variable groups. Moreover, these differences were also multivariable tested using multiple linear, logistic, and multinomial logit models, adjusting for age, sex, race, and poverty status. The main analysis consisted of 35 separate mixed-effects linear time interval regression models (Blackwell et al., 2006) for each of the five PSQI sub-scale scores measured up to two times at v_1 and/or v_2 and main predictor being 25(OH)D at v_1, for the total population and stratified by age group, sex and race. Each model included years elapsed between visits (*TIME*) and interaction terms between *TIME* and the main exposure and covariates. The model adjusted baseline sleep measures and change over time for covariates that were independently associated with the main exposure and previously linked to sleep patterns and disorders (See **Supplemental methods 1**). The two-way interaction terms with *TIME* are interpreted as the effects of exposures and covariates on the slope or annual rate of change in sleep patterns. Main effects of 25(OH)D and covariates were also included allowing to examine the net exposure effect on baseline sleep pattern, i.e. cross-sectional exposure-outcome association adjusting for baseline covariates. Repeated outcome measures ranged between 1.6 for the main analysis and 2 visits per participant for the sensitivity analysis. In the main analysis, we assumed the unavailability of outcomes to be missing at random (**Supplemental Methods 2**).(Ibrahim and Molenberghs, 2009) As a secondary analysis, the contribution of dietary and supplemental vitamin D to the total effects of 25(OH)D on initial (v_1) or annual rates of change in sleep pattern sub-scale scores was tested by introducing both v_1 covariates into mixed-effects regression models in addition to the adjustment set, and the % change in each total effect was examined particularly when p<0.05.

Results were plotted over *TIME* (y) and stratified by standardized 25 (OH)D levels (-1=mean-1 SD, 0=mean, +1=mean+1 SD). The overall eligible sample or a sub-group with statistically significant longitudinal association was modeled. Two- and three-way interaction terms between exposure, the effect modifier, and *TIME* were used to test for moderation by sex, race, and age. Covariates under the section specified were included in all models . Continuous covariates were centered at their means .

To account for selection bias, a two-stage Heckman selection process was applied to the main mixed-effects regression models. In stage 1, the binary selection variable was regressed on sex, race, baseline age and poverty status using a probit model. We then calculated an inverse mills ratio using the conditional predicted probability of selection. In the second stage, this ratio variable was entered into the main causal models as a covariate.(Beydoun et al., 2013a)

Type I errors for main effects and interaction terms were set at 0.05 and 0.10, respectively,(Selvin, 2004) before multiple testing. A family-wise Bonferroni approach was used for the adjustment considering test

multiplicity. The assumption was that each sub-scale score is a distinctive substantive hypothesis.(Hochberg and Tamhane, 1987) Thus the adjusted significance levels for main effects were $p < 0.010$ (0.05/5), 0.10/5=0.020 for two-way interaction terms, 0.05 for three-way interaction terms as previous published research.(Beydoun et al., 2016)

Results

In the present study, participants of all ages were included if they completed all PSQI sub-scales that were common to v_1 and v_2, had a sub-scale score at either visit, a complete 25(OH)D assessment at v_1 and non-missing selected covariates. Common PSQI sub-scales between v_1 and v_2 included sleep duration, daytime dysfunction, sleep disturbance, sleep latency and sleep quality. Sleep efficiency was only available at v_2 and was not considered among outcomes or for participant exclusions. Of N=3,720 participants recruited into the cohort (2004-2009, Age range: 30-66y, mean ± SD: 48.3±9.4y, % women:54.7%, % AA:59.1%, % below poverty: 41.3%), up to N=2,468 had visit 1 data (Age range: 33-73y, mean±SD: 53.0±9.0y, % women: 57.7, % African American: 61.7%, % below poverty: 40.5%). V_2 data (i.e. follow-up) were available on up to N=2,171 participants (Age range: 36-77y, mean±SD: 56.6±9.1y, % women: 58.6%, % African American: 61.1%, % below poverty: 40.6%). Of 2,468 participants with complete socio-demographic data at v_1, including age, 1,548 had complete data on all 5 sub-scales of the PSQI instrument. Similarly, of 2,171 having completed v_2 on socio-demographics including age, 1,907 had data on all 5 sub-scales of PSQI at v_2. Of those, 1,200 had complete PSQI sub-scale data at both v_1 and v_2; while 2,255 had complete data on those sub-scales at either v_1 or v_2.

Furthermore, of 2,468 baseline participants (v_1), 2,264 had complete data on v_1 25(OH)D; while 2,140 had complete dietary vitamin D data based on the average of two 24 hr recalls, and 2,154 had complete

vitamin D supplementation data. V_1 covariate data including those finally selected for analyses, dietary and supplemental vitamin D reduced the initial v_1 sample from 2,468 to 1,959. The final selected sample with data on PSQI sub-scales at visits 1 or 2, 25(OH)D at v_1 and all selected covariates at v_1 was n=1,760 (k=1.6 observations/participant). For this final sample, mean±SD follow-up time was 4.1±1.5 years. Another sample used for sensitivity analysis with data on PSQI sub-scales at both visits 1 and 2, 25(OH)D at v_1 and all selected covariates at v_1 had n=1,067 (k=2 observations/participant). **Figure 1** shows the participant flowchart starting from the initial cohort through the final selected samples, using sequential exclusions from v_1 exposure to longitudinal outcome to covariates. Compared to those excluded from visit 2 (n=708 of 2,468), the final analytic sample (n=1,760) had a lower proportion of participants living below poverty based on multiple logistic regression model that included age, sex, race and poverty status as predictors for sample selection; while the sensitivity analysis sample (i.e. n=1,065) was younger, had a lower likelihood of including AAs or individuals living below poverty, compared to those excluded (n=1,403). This sample selectivity was accounted for in all models, using a 2-stage Heckman selection procedure (see statistical analysis section).

Study sample characteristics are presented in **Table 1**, by age group, sex, and race. The 25(OH)D serum concentrations at v_1 were greater among Whites than AAs, among women compared to men and among older compared to younger age groups. In contrast, dietary vitamin D consumption was higher among men than women, and higher among Whites vs. AAs in parallel with 25(OH)D. Sleep patterns varied by all three socio-demographic factors, suggesting poorer sleep among older vs. younger individuals in sleep disturbance (v_1 and v_2) and latency (v_1); poorer sleep among women compared with men in daytime dysfunction (v_1), sleep disturbance (v_1 and v_2) and sleep quality (v_1 and v_2), with the reverse for sleep latency (v_1). AAs had poorer sleep than Whites in the
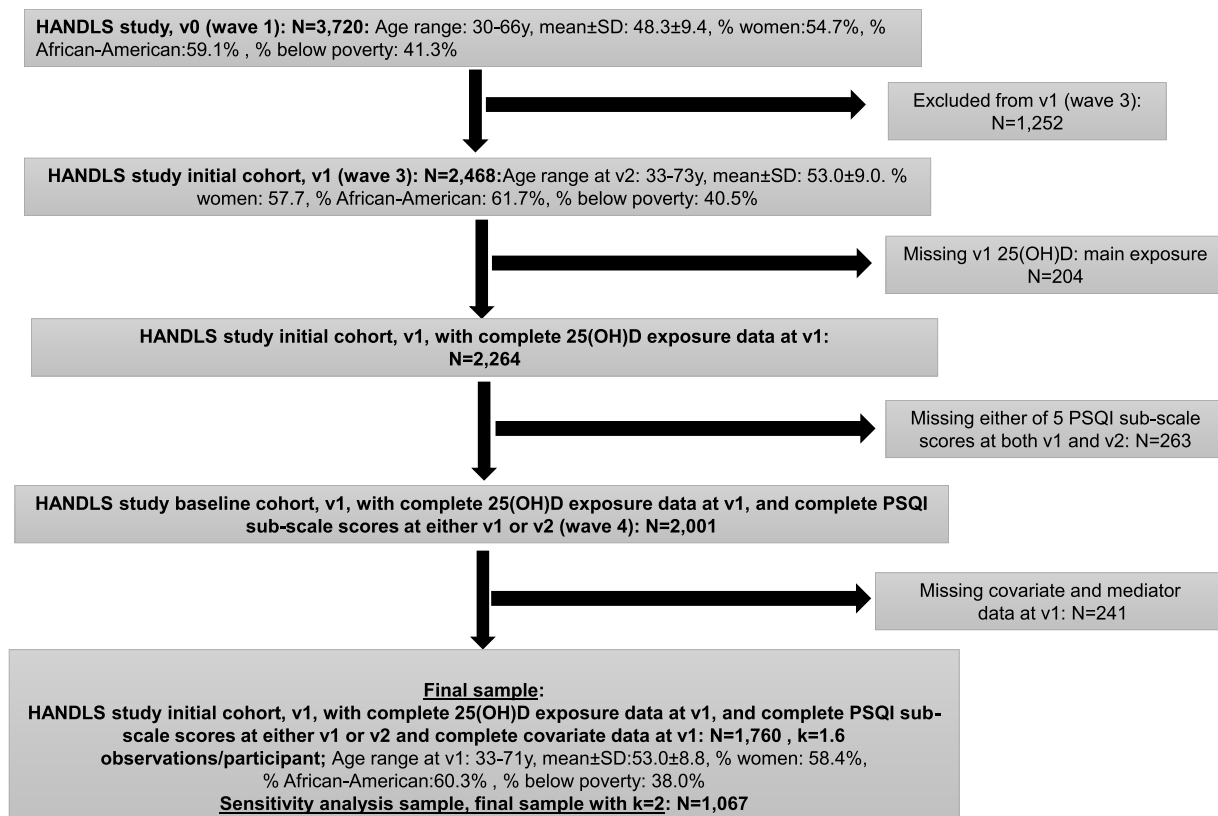

Figure 1. Participant Flowchart: HANDLS 2009-2017

Abbreviations: 25(OH)D=25-hydroxyvitamin D; PSQI=Pittsburgh Sleep Quality Index; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; v0=visit 0; v1=visit 1; v2=visit 2.

Table 1
Study sample characteristics by age group, sex, and race: HANDLS 2009-2017[a]

	All	Age≤50y	Age>50y	Men	Women	Whites	African-American	P$_{age}$	P$_{sex}$	P$_{race}$
	N=1,760 Mean ±SE, %	N=646 Mean ±SE, %	N=1,114 Mean ±SE, %	N=733 Mean ±SE, %	N=1,027 Mean ±SE, %	N=698 Mean ±SE, %	N=1,062 Mean ±SE, %			
V$_1$ Exposure and mediators										
25(OH)D, ng/mL	21.8±0.3	19.6±0.4	23.1±0.4	20.6±0.4	22.7±0.4	25.4±0.4	19.4±0.3	<0.001[b]	<0.001[c]	<0.001[d]
Dietary vitamin D, μg/d	4.0±0.10	4.2±0.2	3.9±0.1	4.8±0.2	3.4±0.1	4.3±0.2	3.8±0.1	0.086	<0.001[c]	0.014[d]
Supplemental vitamin D, IU × years	2451±935	3033±2506	2115±274	1260±277	3302±1591	4430±2339	1152±201	0.64	0.28	0.087
V1 Sleep pattern PSQI sub-scale scores (Range: 0-3)										
Sleep duration	1.59±0.03	1.60±0.04	1.57±0.03	1.57±0.04	1.60±0.03	1.51±0.04	1.65±0.03	0.61	0.60	0.009[d]
Daytime Dysfunction	0.81±0.02	0.80±0.04	0.82±0.03	0.73±0.03	0.86±0.03	0.99±0.04	0.67±0.03	0.73	0.004[c]	<0.001[d]
Sleep disturbance	1.27±0.02	1.22±0.03	1.31±0.02	1.14±0.03	1.37±0.02	1.33±0.03	1.23±0.02	0.012[b]	<0.001[c]	0.004[d]
Sleep Latency	1.55±0.03	1.45±0.05	1.61±0.04	1.63±0.04	1.44±0.04	1.51±0.04	1.58±0.04	0.007[b]	0.001[c]	0.23
Sleep Quality	1.23±0.03	1.25±0.04	1.22±0.03	1.14±0.03	1.30±0.03	1.33±0.04	1.16±0.03	0.51	<0.001[c]	<0.001[d]
V2 Sleep pattern PSQI sub-scale scores (Range: 0-3)										
Sleep duration	1.30±0.03	1.33±0.05	1.28±0.04	1.36±0.05	1.26±0.04	1.16±0.05	1.40±0.04	0.44	0.11	0.0001[d]
Daytime Dysfunction	0.71±0.03	0.67±0.04	0.72±0.03	0.72±0.04	0.69±0.03	0.78±0.04	0.65±0.03	0.32	0.55	0.013[d]
Sleep disturbance	1.32±0.02	1.27±0.03	1.35±0.02	1.20±0.03	1.41±0.03	1.38±0.03	1.28±0.02	0.016[b]	<0.001[c]	0.003[d]
Sleep Latency	1.28±0.03	1.27±0.05	1.28±0.04	1.21±0.05	1.32±0.04	1.24±0.05	1.30±0.04	0.90	0.10	0.41
Sleep Quality	1.24±0.04	1.27±0.04	1.23±0.03	1.14±0.04	1.31±0.03	1.32±0.04	1.19±0.03	0.45	<0.001[c]	0.009[d]
V1 Covariates										
Age, years	53.0±0.2	43.5±0.2	58.5±0.2	53.0±0.3	53.0±0.3	53.2±0.3	52.8±0.3	<0.001	1.00	0.29
Sex, % male	41.7	41.0	42.0	_	_	42.0	41.4	0.69	_	0.82
Race, % AA	60.3	61.5	59.7	60.0	60.6	_	_	0.47	0.82	_
Poverty status, % below	38.0	38.1	38.0	34.7	40.4	32.1	41.9	0.96	0.014[c]	<0.001[d]
Season, %								0.33	0.15	<0.001
Winter	28.5	29.7	27.7	29.7	27.6	37.5	22.6			
Spring	27.6	29.1	26.7	29.5	26.2	33.5	23.6			
Summer	15.5	14.1	16.3	14.2	16.4	16.2	15.0			[d]
Fall	28.5	27.1	29.4	26.6	29.9	12.8	38.9			[d]
HEI-2010	46.4±0.29	44.8±0.5	47.4±0.4	45.4±0.4	47.1±0.4	46.6±0.5	46.3±0.3	<0.001[b]	0.004[c]	0.65
Elevated Hcy index II (Range: 0-8)	3.80±0.03	3.05±0.05	4.24±0.04	4.19±0.05	3.53±0.04	3.93±0.05	3.72±0.04	<0.001[b]	<0.001[c]	0.002[d]
Inflammatory composite score, z-score	0.02±0.03	0.10±0.05	-0.03±0.05	0.42±0.04	-0.27±0.04	0.32±0.04	-0.18±0.04	0.028[b]	<0.001[c]	<0.001[d]
CES-D total score	15.7±0.28	16.1±0.5	15.4±0.3	14.4±0.4	16.6±0.4	16.5±0.5	15.2±0.3	0.22	<0.001[c]	0.023[d]
Dyslipidemia, %	36.3	20.9	45.2	39.0	37.3	42.4	32.3	<0.001[b]	0.31	<0.001[d]

Abbreviations: 25(OH)D=25-hydroxyvitamin D; CES-D=Center for Epidemiological Studies-Depression; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; Hcy=Homocysteine; HEI-2010=Healthy Eating Index, 2010 edition; PSQI=Pittsburgh Sleep Quality Index; SE=Standard Error; v$_1$=visit 1; v$_2$=visit 2.

[a] Sample was selected with complete v$_1$ or v$_2$ sleep pattern outcomes, complete v$_1$ 25(OH)D exposure and complete v$_1$ covariates and mediators. Covariates were selected through backward elimination of a multiple linear regression with v1 25(OH)D as the outcome (See supplemental method 1 for details and description). Note that for means of v$_1$ sleep pattern PSQI sub-scale scores, N=1,377 (sleep disturbance); N=1,380 (Daytime Dysfunction); N=1,388 (Sleep latency and quality); N=1,391 (Sleep Duration). For v$_2$ sleep pattern PSQI sub-scale scores, N=1,462 for sleep duration, daytime dysfunction and sleep latency and N=1,464 for sleep disturbance and sleep quality. PSQI sub-scale scores reflected worse outcome with higher score.

[b] P<0.05, after further adjustment for sex, race, and poverty status in a multiple linear regression model for continuous variables and logistic or multinomial logistic regression models for categorical variables.

sub-scales of duration (v_1 and v_2), while having on average better sleep in terms of daytime dysfunction (v_1 and v_2), sleep disturbance (v_1 and v_2), and sleep quality (v_1 and v_2). All health-related factors that were deemed associated with 25(OH)D indicated poorer health status among Whites compared with AAs, including elevated Hcy, inflammation, depressive symptoms and dyslipidemia. Mean HEI-2010 was significantly higher among women vs. men and among older vs. younger individuals, suggesting better diet quality, while depressive symptoms (CES-D score) were more elevated among women vs. men. Men and the older group were more likely to have elevated Hcy and inflammation, compared to women and the younger group, respectively. Dyslipidemia was more prevalent with increasing age. Most of these associations were independent of other socio-demographic factors.

Table 2 shows findings from multiple mixed-effects regression models adjusted for a reduced set of covariates associated with vitamin D status including socio-demographic, behavioral and health-related factors, and season. Upon correction for multiple testing, only a few associations were observed, suggesting that among Whites, v_1 25(OH)D was associated with better sleep duration [25(OH)D × TIME γ±SE: -0.027±0.011, P=0.017] and sleep quality [25(OH)D × TIME γ±SE: -0.026±0.010, P=0.008] over time, with heterogeneity by race found for both relationships (P<0.05 for 25(OH)D × TIME × Race in the unstratified model). These relationships remained unaltered after further adjustment for the key mediators dietary and supplemental vitamin D, indicating that most of the association was explained through a non-dietary and supplemental pathway, possibly sunlight exposure. Nevertheless, among the younger group, 25(OH)D was significantly associated with better sleep quality over time in the model that was further adjusted for dietary and supplemental vitamin D (P<0.02). In contrast, the cross-sectional association between 25(OH)D and sleep quality among the older group was appreciably attenuated upon inclusion of those two factors. In both models, this association did not survive multiple testing. Predictive margins of sleep duration and quality over time are illustrated by levels of 25(OH)D in **Figure 2A**, using Model 1 mixed-effects regression parameters among Whites (mean and SD of v1 25(OH)D were ~22 and 11ng/mL, respectively). In the sensitivity analysis with k=2 observations/participant, the main findings were not altered. Specifically, for Model 1 among Whites, sleep duration estimate for 25(OH)D × TIME was -0.029±0.012, P=0.018. For Model 1 among Whites, sleep quality estimate for 25(OH)D × TME was -0.029±0.011, P=0.006. These results were largely unaltered in Model 2 (P<0.020). Thus, whether we included all available data-points or selecting those with 2 observations/participants, our results indicated that 25(OH)D was associated with better sleep duration and quality over time among Whites, independently of dietary or supplemental vitamin D intakes.

Discussion

The present study examined the relationship between vitamin D status and change in PSQI-assessed patterns of sleep in a longitudinal study of Whites and AAs urban middle-aged adults, while further testing effect modification by age group, sex and race. The potential roles of dietary and supplemental vitamin D were also explored. The study found that baseline 25(OH)D serum concentrations were associated with better sleep duration and quality over time among Whites only, with a significant effect modification by race. These relationships remained unaltered after further adjustment for dietary and supplemental vitamin D, indicating that the association was mostly explained through a non-dietary and supplemental pathway, possibly sunshine exposure.

Positive associations of serum 25(OH) vitamin D with sleep quality and duration are consistent with past research (Beydoun et al., 2014;

Dogan-Sander et al., 2019; Ekinci et al., 2018; Massa et al., 2015). Despite lower mean serum 25(OH)D, AA scored better than Whites at v_1 and v_2 on daytime dysfunction, sleep disturbance, and sleep quality PSQI sub-scales. Their mean serum level was <20ng/ml, the level indicative of vitamin D deficiency. In contrast, Bertisch and colleagues reported vitamin D deficiency was strongly associated with shorter sleep duration in AAs (Bertisch et al., 2015). McCarty and colleagues found sleepiness to be significantly and positively correlated with vitamin D deficiency in AA but not white adults (McCarty et al., 2012).

Exposure to sunlight, seasonal variation, and latitude, are factors that contribute to the variance of serum 25 (OH) D levels(Choi et al., 2020; Darling et al., 2019; Orces et al., 2019; Valtuena et al., 2013). With adequate sunlight exposure, no significant differences between sleep duration and vitamin D status was found among participants in the Korean National health and Nutrition Examination Surveys (Choi et al., 2020). McCarty and colleagues (2012) reported no seasonal variation in serum vitamin D levels among AA. Yet they found that among individuals with vitamin D deficiency, AA had greater sleepiness scores compared to whites.

Comparing findings of this study with others may present difficulties due to different methods used to assess sleep quality and vitamin D status. The variability between analytical methods for quantification of vitamin D has been discussed elsewhere(Stokes et al., 2018). Careful standardization of measurement procedures is needed to enhance our knowledge of the relationship between vitamin D and sleep.

The auto-radiographic and histochemical studies of Stumpf and Obrien revealed that vitamin D was more than a calcium homeostatic steroid hormone.(Muscogiuri et al., 2019) Recent experimental studies have indicated that the circadian clock in the central nervous system may be regulated by vitamin D, due to the presence of *VDR* and 1 α-hydroxylase in the human brain(Muscogiuri et al., 2019). These vitamin D receptors are expressed abundantly in the anterior and posterior parts of the hypothalamus, within the substantia nigra, midbrain central gray, raphe nuclei, and the nucleus reticularis pontis oralis and caudalis, regions that appear to coordinate the sleep-wake state and the paralysis of the bulbar and somatic musculature during sleep.(Musiol et al., 1992) Vitamin D can bind to these receptors, thus regulating sleep and affecting its quality.(Muscogiuri et al., 2019) Another pathway by which vitamin D, specifically calcitriol (1-α 25-(OH)2D), can affect sleep quality, is through the regulation of tryptophan's conversion into 5-hydroxytryptophan via its action on tryptophan hydroxylases (TPH)-2. In fact, it was reported that calcitriol triggers expression of tryptophan hydroxylase-2 (TPH2), the initial and rate-limiting enzyme in the biosynthetic pathway to 5-hydroxytryptamine, in cultured rat serotonergic neuronal cells(Sabir et al., 2018). More generally, calcitriol expresses VDRE, or vitamin D response element, which associates with promoters of numerous target genes and co-activator molecules(Muscogiuri et al., 2019). Consequently, 5-hydroxytryptophan is metabolized to serotonin, thus producing the sleep hormone, melatonin.(Muscogiuri et al., 2019) A narrow range of 25(OH)vitamin D3 blood levels may be necessary to produce normal sleep and clinical trials are needed to determine the effects of vitamin D3 supplementation on sleep disorders, including insomnia, obstructive sleep apnea and rapid eye movement related apnea(Gominak and Stumpf, 2012).The detailed mechanisms are shown in **Figure 2B**.

Our study has several notable strengths. First, it is one of few longitudinal studies examining the association of a robust marker of vitamin D status with change in sleep patterns over time. Most previous research testing similar hypotheses had cross-sectional or case-control designs, according to a recent systematic review (Gao et al., 2018). Second, many of these studies focused on a global measure of sleep,

Table 2

Patterns of sleep at v1 and annual rate of change between v1 and v2 in relation to vitamin D status at v1: mixed-effects regression models, overall and stratified by race: HANDLS 2009-2017[a]

	All	Age ≤50y	Age >50y	Men	Women	Whites	African-American	P_{age} [b]	P_{sex} [b]	P_{race} [b]
	N=1,760	N=646	N=1,114	N=1,027	N=733	N=698	N=1,062			
	$\gamma \pm SE$	$\gamma \pm SE$	$\gamma \pm SE$	$\gamma \pm SE$	$\gamma \pm SE$	$\gamma \pm SE$	$\gamma \pm SE$			
MODEL 1: v1 25(OH)D, per 10 ng/mL increase + v_1 Covariates										
Sleep duration										
25(OH)D	-0.024±0.024 P=0.32	-0.007±0.046 P=0.89	-0.030±0.029 P=0.29	-0.022±0.030 P=0.46	-0.038±0.041 P=0.35	+0.047±0.037 P=0.21	**-0.082±0.032 P=0.010**	0.45	0.77	***0.059***
25(OH)D × TIME	-0.006±0.007 P=0.37	-0.010±0.014 P=0.48	-0.006±0.009 P=0.46	-0.006±0.009 P=0.54	-0.006±0.013 P=0.66	**-0.027±0.011 P=0.017**[c]	+0.009±0.010 P=0.34	0.65	0.70	**0.021** [c]
Daytime Dysfunction										
25(OH)D	+0.033±0.019 P=0.087	+0.023±0.036 P=0.52	***+0.041±0.023 P=0.075***	**+0.055 ±0.024 P=0.024**	-0.005±0.032 P=0.87	+0.047±0.031 P=0.12	+0.016±0.025 P=0.51	0.87	0.16	0.42
25(OH)D × TIME	-0.003±0.007 P=0.67	+0.008±0.013 P=0.53	-0.007±0.009 P=0.39	-0.001±0.009 P=0.39	+0.057±0.012 P=0.63	-0.011±0.012 P=0.39	+0.003±0.035 P=0.70	0.95	0.47	0.31
Sleep disturbance										
25(OH)D	+0.023±0.015 P=0.12	+0.027±0.028 P=0.33	+0.018±0.017 P=0.29	+0.024±0.018 P=0.19	+0.016±0.025 P=0.53	+0.028±0.022 P=0.57	+0.018±0.020 P=0.37	0.90	0.65	0.96
25(OH)D × TIME	***-0.008±0.004 P=0.085***	-0.011±0.008 P=0.18	-0.005±0.005 P=0.33	-0.005±0.005 P=0.36	-0.011±0.08 P=0.15	-0.008±0.007 P=0.27	-0.008±0.006 P=0.13	0.98	0.88	0.89
Sleep Latency										
25(OH)D	+0.008±0.026 P=0.75	+0.030±0.049 P=0.54	-0.006±0.030 P=0.83	+0.011±0.032 P=0.73	+0.002±0.004 P=0.96	+0.010±0.040 P=0.80	+0.002±0.034 P=0.95	0.70	0.58	0.70
25(OH)D × TIME	+0.003±0.008 P=0.69	-0.003±0.015 P=0.82	+0.004±0.009 P=0.72	+0.008±0.010 P=0.45	-0.006±0.014 P=0.68	+0.003±0.013 P=0.83	+0.004±0.011 P=0.70	0.78	0.52	0.82
Sleep Quality										
25(OH)D	-0.020±0.019 P=0.28	+0.055±0.037 P=0.14	**-0.053±0.022 P=0.015**	-0.014±0.024 P=0.56	-0.037±0.030 P=0.22	+0.034±0.029 P=0.24	**-0.066±0.025 P=0.010**	**0.041**	0.52	***0.064***
25(OH)D × TIME	-0.008±0.001 P=0.23	**-0.027±0.012 P=0.022**	+0.002±0.007 P=0.81	-0.001±0.001 P=0.26	-0.004±0.010 P=0.70	**-0.026±0.010**[c] **P=0.008**	+0.008±0.008 P=0.35	**0.018** [c]	0.62	**0.044** [c]
MODEL 2: v_1 25(OH)D, per 10 ng/mL increase + v_1 Covariates + v_1 dietary and supplemental vitamin D										
Sleep duration										
25(OH)D	-0.026±0.024 P=0.28	-0.011±0.047 P=0.81	-0.015±0.030 P=0.61	-0.026±0.030 P=0.39	-0.029±0.041 P=0.49	0.039±0.037 P=0.29	**-0.083±0.033 P=0.013**	0.43	0.79	***0.065***
25(OH)D × TIME	-0.006±0.007 P=0.35	-0.011±0.014 P=0.45	-0.011±0.009 P=0.24	-0.006±0.009 P=0.53	-0.006±0.012 P=0.63	**-0.027±0.011 P=0.018** [c]	+0.007±0.010 P=0.47	0.62	0.69	**0.019**[c]
Daytime Dysfunction										
25(OH)D	+0.032±0.019 P=0.098	+0.022±0.036 P=0.55	***+0.041±0.024 P=0.085***	**+0.053 ±0.024 P=0.029**	-0.004±0.032 P=0.89	+0.047±0.03 P=0.13	+0.015±0.026 P=0.55	0.85	0.14	0.43
25(OH)D × TIME	-0.004±0.007 P=0.58	+0.007±0.013 P=0.61	-0.007±0.009 P=0.45	-0.009±0.009 P=0.31	+0.005±0.012 P=0.66	-0.012±0.012 P=0.31	+0.006±0.009 P=0.54	0.89	0.41	0.28

Table 2 (*continued*)

	All	Age ≤50y	Age >50y	Men	Women	Whites	African-American	P_{age} [b]	P_{sex} [b]	P_{race} [b]
	N=1,760	N=646	N=1,114	N=1,027	N=733	N=698	N=1,062			
	γ±SE	γ±SE	γ±SE	γ±SE	γ±SE	γ±SE	γ±SE			
MODEL 1: v1 25(OH)D, per 10 ng/mL increase + v_1 Covariates										
Sleep disturbance										
25(OH)D	+0.022±0.015 P=0.14	+0.026±0.028 P=0.35	+0.021±0.018 P=0.23	+0.022±0.018 P=0.23	+0.020±0.026 P=0.44	+0.028±0.022 P=0.22	+0.017±0.022 P=0.41	0.29	0.14	0.31
25(OH)D × TIME	**-0.008±0.004 P=0.085**	-0.011±0.008 P=0.18	-0.007±0.005 P=0.22	-0.005±0.005 P=0.35	-0.011±0.008 P=0.14	-0.008±0.007 P=0.26	**-0.010±0.006 P=0.088**	0.23	0.12	0.33
Sleep Latency										
25(OH)D	+0.006±0.026 P=0.83	+0.027±0.049 P=0.59	+0.003±0.031 P=0.92	+0.008±0.032 P=0.80	+0.008±0.043 P=0.85	+0.011±0.040 P=0.79	+0.004±0.035 P=0.90	0.71	0.58	0.68
25(OH)D × TIME	+0.003±0.008 P=0.72	-0.003±0.001 P=0.87	-0.000±0.001 P=0.96	+0.008±0.010 P=0.45	-0.006±0.014 P=0.65	+0.002±0.014 P=0.88	-0.000±0.011 P=0.98	0.85	0.48	0.84
Sleep Quality										
25(OH)D	-0.021±0.019 P=0.27	+0.055±0.037 P=0.14	**-0.038±0.022 P=0.091**	-0.016±0.024 P=0.51	-0.027±0.030 P=0.38	+0.032±0.029 P=0.27	**-0.055±0.026 P=0.037**	0.038[c]	0.49	0.55
25(OH)D × TIME	-0.008±0.006 P=0.19	**-0.029±0.012[c] P=0.016**	-0.003±0.007 P=0.71	-0.010±0.008 P=0.23	-0.006±0.010 P=0.59	**-0.027±0.010[c] P=0.006**	+0.004±0.008 P=0.61	0.014[c]	0.56	0.017[c]

Abbreviations: 25(OH)D=25-hydroxyvitamin D; CES-D=Center for Epidemiological Studies-Depression; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; Hcy=Homocysteine; HEI-2010=Healthy Eating Index, 2010 edition; PSQI=Pittsburgh Sleep Quality Index; SE=Standard Error; v_1=visit 1; v_2=visit 2.

[a] Sample was selected with complete v_1 or v_2 sleep pattern outcomes, complete v_1 25(OH)D exposure and complete v_1 covariates and mediators. Covariates were selected through backward elimination of a multiple linear regression with v1 25(OH)D as the outcome (See supplemental method 1 for details and description). Mixed-effects linear regression models included v_1 covariates among fixed effects predicting the intercept and the slope in model 1. Model 2 additionally included two mediators: dietary vitamin D and supplemental vitamin D (See supplemental method 2 for details). In models 1 and 2, v_1 covariates included age, sex, race, poverty status, season, HEI-2010, Elevated Hcy index II, inflammatory composite score, CES-D total score, dyslipidemia. Continuous exposures, covariates and mediators are centered at their respective means. PSQI sub-scale scores reflected worse outcome with higher score. Continuous age was entered among covariates, even in models stratified by age group.

[b] Based on a separate unstratified model with 2-way and 3-way interaction terms added between age group, sex, or race group and v_1 25(OH)D and with 25(OH)D × TIME. Main effects of TIME, stratifying variable (i.e. age group, sex, or race) and v_1 25(OH)D are also included in this model, among others.

[c] Statistically significant after adjustment for multiple testing; P<0.010 for main effects, P<0.020 for 2-way interaction terms, P<0.05 for 3-way interaction terms.
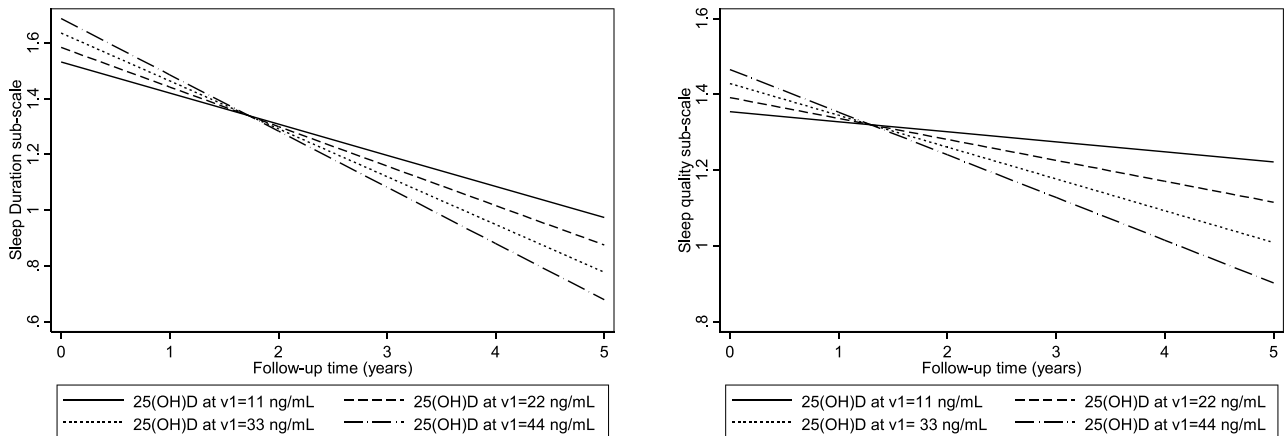
Figure 2A. Predictive margins for (A.1.) sleep duration and (A.2.) sleep quality PSQI sub-scales across v_1 25(OH)D levels among Whites: HANDLS 2009-2017
Abbreviations: 25(OH)D=25-hydroxyvitamin D; PSQI=Pittsburgh Sleep Quality Index; HANDLS=Healthy Aging in Neighborhoods of Diversity Across the Life Span; v1=visit 1; v2=visit 2.
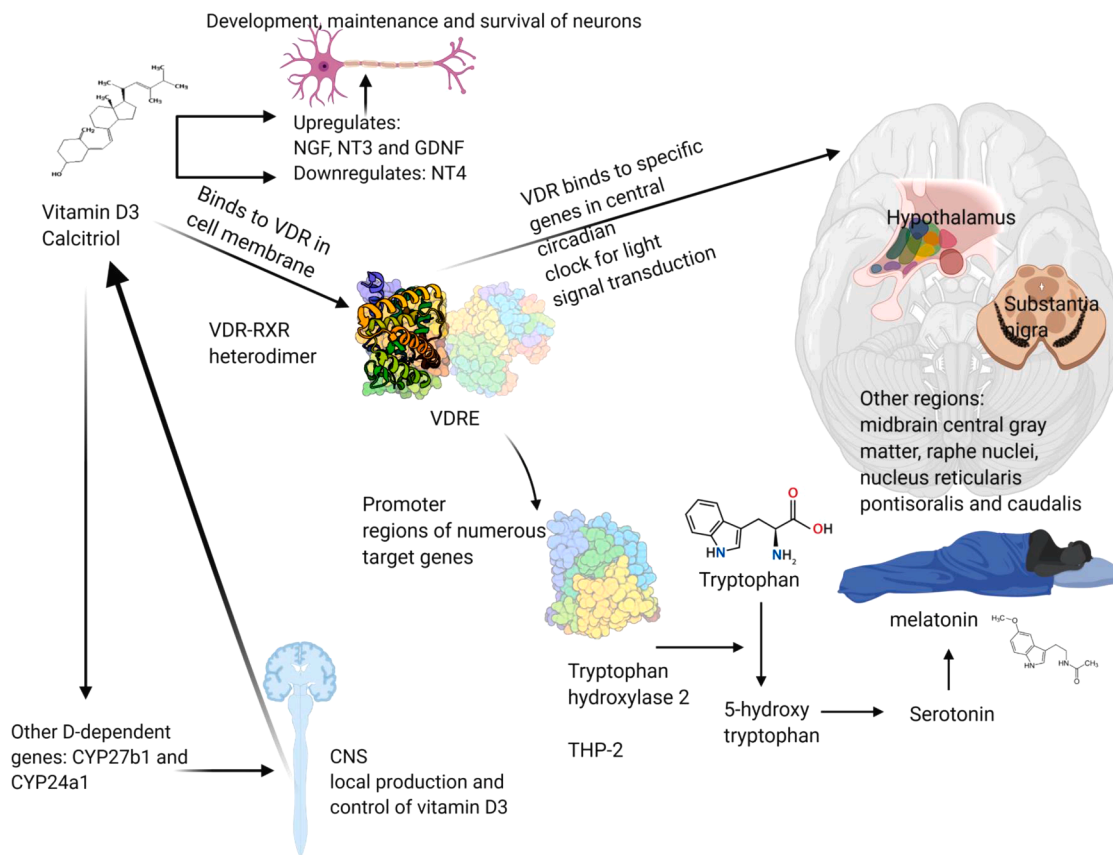*Note*: PSQI sub-scale scores reflected worse outcome with higher score.

Figure 2B. Biological mechanisms for association between vitamin D and sleep
Abbreviations: CNS=Central Nervous System; CYP24a1=Cytochrome P450 Family 24 Subfamily A Member 1; CYP27b1=Cytochrome P450 Family 24 Subfamily B Member 1; GDNF=Glial Cell Derived Neurotrophic Factor; NGF=Neural Growth Factor; NT3=Neurotrophin-3; NT4=Neurotrophin-4; RXR=Retinoid-X receptor; THP-2=Tryptophan Hydroxylase Protein-2; VDR=Vitamin D receptor; VDRE=Vitamin D response element;
Note: Figure created in Biorender, http://www.biorender.com
Source: (Muscogiuri et al., 2019)

sleep duration or sleep disorders rather than several patterns of sleep as was done in this study. Third, our findings have external validity as they may reflect similar populations in U.S. urban areas of similar size (Evans et al., 2010). Fourth, our study included a wide range of measures that could be adjusted for in our statistical models, including the key confounders of vitamin D-sleep associations such as season, markers of elevated Hcy and inflammation, several co-morbid conditions and some of the most important mediators, including dietary and supplemental

intakes of vitamin D.

In light of specific limitations, our study findings need to be interpreted with caution. First, sample size precluded analysis of effect modification by age group, sex, and race simultaneously which leads to examine each of those modifiers in isolation, while adjusting for the remaining two. Second, the potential for selection bias triggered by missing data cannot be discounted. Nevertheless, our use of two-stage Heckman selection process was able to at least adjust for differences in basic socio-demographic groups between the selected and unselected groups. Third, our analysis lacked objective measures of sleep parameters, with a potential for non-differential misclassification, likely inducing biased measures of association towards the null value. Specifically, the PSQI instrument is unable to discern between individuals with or without sleep disorders such as insomnia and sleep apnea. Nevertheless, the use of sub-scales within the PSQI instrument allows us to examine specific aspects of sleep as opposed to a global measure. Finally, despite inclusion of potentially confounding variables that were shown to be associated with the main exposure (i.e. 25(OH)D at v_1), residual confounding cannot be ruled out, including by other comorbidities, physical activity, family history of cardio-metabolic disorders, cerebrovascular disease or cancer, as well as type of work schedule (e.g. shift work).

In summary, vitamin D status, possibly through mechanisms involving sunlight exposure, was linked to potential improvement in sleep duration and quality among White urban adults. Further longitudinal studies are needed to replicate our findings in comparable populations before randomized controlled trials can be conducted.

Contributors

May A. Beydoun: Study concept, literature search and review, plan of analysis, data management, statistical analysis, write-up and revision of the manuscript.

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Disclaimer

The views expressed in this article are those of the authors and do not reflect the official policy of Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or the U.S. Government.

(a) Financial disclosure: This work was supported in full by the Intramural research Program of the NIH, National institute on Aging.

(b) Non-financial disclosure: None declared.

Conflict of Interest

All authors declare no conflict of interest.

Acknowledgements

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.12.145.

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Vitamin D status and its longitudinal association with changes in patterns of sleep among middle-aged urban adults

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Supplemental materials

Supplemental method 1: Covariate description and selection

A.1. Socio-demographic

Additional socio-demographic confounders included educational attainment (0 ≤ High School (HS); 1 = HS and 2 ≥ HS), the Wide Range Achievement Test (WRAT) letter and word reading subtotal scores to measure literacy, and marital status (1=married, 0=not married) (1).

A.2. Lifestyle

Smoking and drug use
Current use of opiates, marijuana or cocaine ("current" *vs*. "never or former") and smoking status ("current" vs. "never or former") were considered.

Adiposity measures
Measured body mass index (BMI, kg/m^2) and waist circumference were considered among potential confounders.

Healthy Eating Index 2010-
   The Healthy Eating Index (HEI-2010) total score, based on two 24-hr recalls administered at baseline, was used as a measure of overall dietary quality. See steps for calculating HEI-2010 at http://appliedresearch.cancer.gov/tools/hei/tools.html and http://handls.nih.gov/06Coll-dataDoc.html.

Depressive symptoms
  Depressive symptoms were operationalized using the CES-D at baseline and follow-up. The 20-item CES-D is a self-reported symptom rating scale assessing affective and depressed mood.(2) A score of ≥16 on the CES-D is reflective of elevated depressive symptoms (EDS), (3) and predicts clinical depression based on the Diagnostic and Statistical Manual, fourth edition (DSM-IV) criteria.(4) Four CES-D sub-domains exhibiting an invariant factor structure between The National Health and Nutrition Examination Survey I and pilot HANDLS data (5) were computed. We tested our hypotheses using total and domain-specific CES-D scores: **(1)** Somatic complaints; **(2)** Depressive affect; **(3)** Positive affect and **(4)** Interpersonal problems.(5)

A.3. Health-related

Baseline chronic conditions included self-reported history measurement, biomarker-based measurement, and medication-based measurement, of type 2 diabetes, hypertension,

dyslipidemia and cardiovascular disease. Dyslipidemia was based on self-report, while type 2 diabetes was determined using a combination of self-report, serum glucose criteria and medication. The same was conducted for hypertension. Additionally, a composite of cardiovascular disease history was added in which self-reported stroke, congestive heart failure, non-fatal myocardial infarction or atrial fibrillation combined into a yes/no variable.

A.4. Other biomarkers

All laboratory tests selected for this study were done at Quest Diagnostics, Chantilly, VA.

Inflammatory composite score (ICS)

High sensitivity C-reactive protein (CRP)

High sensitivity CRP (hs-CRP) was analyzed with an immunoturbidimeter (Siemens/Behring Nephelometer II), using 0.5-1 mL of plasma. A range of 1-10 mg/dL indicates average to high cardiovascular risk and >10 mg/dL suggests an infection or a chronic inflammation.

Serum albumin

Using 0.5-1 mL samples of plasma prepared with heparin and refrigerated for up to 30 days, albumin was measured with spectrophotometry, with an expected reference range of 3.6-5.1 g/dL[6, 7].

Erythrocyte Sedimentation Rate (ESR): Using 5 mL of refrigerated whole blood stored in lavender-top EDTA tubes, the ESR was tested within 24 hr of blood draw. This test used automated modified Westergren photochemical capillary-stopped flow kinetic analysis.[8, 9] The Mayo Clinic reports a reference of 0-22 mm/hr for men and 0-29 mm/hr for women[10] and is considered a proxy measure for serum fibrinogen.[11]

Serum iron: 0.5-1 mL of fasting serum was collected, transported at room temperature (with heparin added) and refrigerated or frozen subsequently. Serum iron was measured with spectrophotometry, [12, 13] with reference ranges for men aged ≥30y set at 50-180 µg/dL, and for women: 20-49y (40-190 µg /dL) and 50+y(45-160 µg /dL). [13]

The ICS consisted of the first principal component for hs-CRP, albumin, ESR and serum iron, as described in two previous studies[6, 14].

Index of elevated Hcy

Folate and cobalamin

Participants were asked to fast for ≥8 hours prior to the MRV visits, and serum specimens in volumes of 2 mL were collected and frozen at −80°C. Similar procedures were adopted for serum folate and cobalamin, both measured using chemiluminescence immunoassay (Siemens Centaur) by Quest Diagnostics, Chantilly, VA (15, 16), and previously validated against other automated methods with coefficient of variation (CV) < 10% (17, 18). Dietary and supplemental intakes of folate and cobalamin were shown to moderately correlate with their corresponding serum biomarkers in HANDLS and national surveys (1, 19, 20).

Serum uric acid (SUA)

 SUA measurements are useful in the diagnosis and treatment of renal and metabolic disorders, including renal failure, gout, leukemia, psoriasis, starvation or other wasting conditions, as well as in patients receiving cytotoxic drugs. Using 1 ml of fasting blood serum, uric acid was measured using a standard spectrophotometry method. The reference range for adult men is 4.0-8.0 mg/dL, whereas for women the range is 2.5-7.0 mg/dL. (http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=905) Other reference ranges were also recently suggested and depend on the menopausal status of women. Those reference ranges are based on predictive value for gout outcomes among healthy individuals and do not necessarily predict other pathologies. Thus, based on recent research evidence, a "normal" SUA value is suggested to be <6.0 mg/dL for all healthy adult individuals.

Serum creatinine

Using participant fasting blood specimens, baseline serum creatinine was measured at the National Institute on Aging, Clinical Research Branch Core Laboratory, using a modified kinetic Jaffe method (CREA method, Dade Dimension X-Pand Clinical Chemistry System, Siemens Healthcare Diagnostics Inc., Newark, DE) for a small group of participants (n=88). However, most participants (n=1,528) had baseline serum creatinine analyzed at Quest Diagnostics, Inc. by isotope dilution mass spectrometry (IDMS) (Olympus America Inc., Melville, NY) and standardized to the reference laboratory, Cleveland Clinic. While inter-assay coefficients of variation (CV) for this sample could not be calculated due to the use of only one or the other measurement of creatinine at baseline, only intra-assay CVs (mean/SD) could be estimated. These were 0.192 and 0.187 for the CREA and the IDMS methods, respectively.

MCV: Also known as erythrocyte mean corpuscular volume, MCV is measured using standard electronic cell sizing/counting/cytometry/microscopy. Similar to other hemogram measures (e.g. ESR), a microtainer 1 mL whole blood in an EDTA (lavender-top) tube was transported at room temperature to the laboratory facility.(8)

MCH: The hematologic index MCH was calculated as follows: MCH = Hb/RBC.

Red cell distribution width (RDW)

RDW was calculated by automated Coulter DXH 800 hematology analyzer as part of peripheral complete blood count (Beckman Coulter, Brea, CA), and expressed as coefficient of variation (%) of red blood cell volume distribution. The analyzer underwent regular calibration every three months and quality control procedures according to manufacturer's recommendations (8). Clinical analysis typically includes two RDW measurements, i.e. the RDW-coefficient of variation (CV, unit: %), which we adopted in this study, and the RDW-Standard Deviation (SD, unit: fL) from which RDW-CV is obtained. RDW-CV=RDW-SD×100/MCV, where MCV is the mean cell volume. The normal range for RDW-CV is 11.0 - 15.0%. Thus, the RDW-CV (%) depends on width of the distribution (normal range: 40-55 fL) curve and MCV.(21)

Alkaline phosphatase (ALP)
This liver enzyme was measured at Quest diagnostics using spectrophotometry. URL: https://testdirectory.questdiagnostics.com/test/test-detail/234/alkaline-phosphatase?cc=MASTER

The full list of the eight components of Index II for elevated Hcy(22) are: Age, serum folate, serum vitamin B-12, serum creatinine, red cell distribution width, mean cell hemoglobin, serum cotinine, serum uric acid and alkaline phosphatase. Cut-point for individual components are: Serum folate, Log_e, in *nmol/L*, < 2.83; Serum creatinine, Log_e , in *µmol/L* ≥4.481; Older age, in years, ≥49, Serum vitamin B-12, Log_e, in *pmol/L* ,<5.74; Mean cell hemoglobin, Log_e, in *pg*, ≥3.422; Red cell distribution width, Log_e, in %, ≥2.553; Serum Uric Acid, Log_e, in *µmol/L*, ≥5.826; Serum alkaline phosphatase, Log_e, in *µmol/L*, ≥4.356 U/L.

Table S1. Predictors of 25-hyrdoxyvitamin D at v1 in largest HANDLS sample: Backward elimination, multiple linear regression models

	Model 1 (N= 1,547)		Model 2 (N= 1,967)	
	β	SE	β	SE
Age (years)	0.24***	0.04	0.23***	0.03
Sex: Male vs. Female	-1.99**	0.61	-2.07***	0.52
Race: African-American vs. White	-5.84***	0.61	-5.85***	0.52
Poverty Status: Below vs. Above	-0.88	0.57	-0.73	0.50
Education Status				
HS vs. <HS	-0.20	1.10	-	-
>HS vs. <HS	0.38	1.21	-	-
WRAT-3 total score	0.05	0.04	-	-

V_1 Season				
Spring vs. Winter	0.43	0.70	0.89	0.64
Summer vs. Winter	3.95***	0.83	3.90***	0.71
Fall vs. Winter	-0.23	0.71	0.26	0.66
Current Smoking	0.29	0.58	-	-
Current drugs	0.23	0.76	-	-
HEI-2010	0.10***	0.02	0.11***	0.02
Body Mass Index	-0.08	0.76	-	-
Waist circumference	-0.02	0.04	-	-
Eight Risk Factor index for elevated Hcy	-0.87***	0.22	-0.84***	0.20
Inflammatory Composite Score	0.81**	0.24	1.02***	0.21
CES-D total score	-0.06**	0.02	-0.05**	0.02
High Cholesterol	1.66	0.60	1.31*	0.51
Hypertension	-0.58	0.62	-	-
Diabetes	-0.84	0.67	-	-
Cardiovascular Disease	-0.17	0.67	-	-

P***<0.001, p**<0.01, p*<0.05

Supplemental methods 2: Mixed-effects regression models

The main multiple mixed-effects regression models can be summarized as follows:

Multi-level models vs. **Composite models**

Eq.

1.1-1.4

$$Y_{ij} = \pi_{0i} + \pi_{1i}Time_{ij} + \varepsilon_{ij}$$

$$\pi_{0i} = \gamma_{00} + \gamma_{0a}X_{aij} + \sum_{k=1}^{l}\gamma_{0k}Z_{ik} + \zeta_{0i}$$

$$\pi_{1i} = \gamma_{10} + \gamma_{1a}X_{aij} + \sum_{m=1}^{n}\gamma_{1m}Z_{im} + \zeta_{1i}$$

$$Y_{ij} = \gamma_{00} + \gamma_{0a}X_{aij} + \sum_{k=1}^{l}\gamma_{0k}Z_{ik}$$
$$+ \gamma_{10}Time_{ij} + \gamma_{1a}X_{aij}Time_{ij}$$
$$+ \sum_{m=1}^{n}\gamma_{1m}Z_{im}Time_{ij}$$
$$+ (\zeta_{0i} + \zeta_{1i}Time_{ij} + \varepsilon_{ij})$$

Where Y_{ij} is the outcome (Each PSQI sub-scale score measured at v_1 and/or v_2) for each individual "i" and visit "j"; π_{0i} is the level-1 intercept for individual i; π_{1i} is the level-1 slope for individual i; γ_{00} is the level-2 intercept of the random intercept π_{0i}; γ_{10} is the level-2 intercept of the slope π_{1i}; Z_{ik} is a vector of fixed covariates for each individual *i* that are used to predict level-1 intercepts and slopes and included baseline age (Age_base) among other covariates. X_{ija}, represents the main predictor variable [v_1 25(OH)D]; ζ_{0i} and ζ_{1i} are level-2 disturbances; ε_{ij} is the within-person level-1 disturbance. Of primary interest are the main effects of each exposure X_a (γ_{0a}) and their interaction with *TIME* (γ_{1a}), as described in a previous methodolgical paper.(23)

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