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Associations of Blood Pressure, Sunlight, and Vitamin D in Community-Dwelling Adults: The Reasons for Geographic and Racial Differences in Stroke (Regards) Study

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Abstract

Background—Vitamin D deficiency/insufficiency is associated with hypertension. Blood pressure and circulating vitamin D concentrations vary with the seasons and distance from the equator suggesting blood pressure varies inversely with the sunshine available (insolation) for cutaneous vitamin D photosynthesis.

Methods—To determine if the association between insolation and blood pressure is partly explained by vitamin D we evaluated 1104 participants in the Reasons for Racial and Geographic Differences in Stroke (REGARDS) study whose blood pressure and plasma 25-hydroxyvitamin D (25(OH)D) concentrations were measured.

Results—We found a significant inverse association between systolic blood pressure (SBP) and 25(OH)D concentration and an inverse association between insolation and blood pressure in unadjusted analyses. After adjusting for other confounding variables, the association of solar insolation and blood pressure was augmented,-0.3.5±SE 0.01 mmHg/1SD higher solar insolation, p=0.01. We found the greatest of effects of insolation on SBP were observed in whites (-5.2±SE O.92 mmHg/1SD higher solar insolation, p=0.005) and in women (-3.8±SE 1.7 mmHg, p=0.024). We found that adjusting for 25(OH)D had no effect on the association of solar insolation with SBP.

Conclusions—We conclude that although 25(OH)D concentration is inversely associated with SBP, 25(OH)D it did not explain the association of greater sunlight exposure with lower blood pressure.

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Condensed Abstract—To determine if the inverse association between solar insolation and blood pressure is partly explained by vitamin D we evaluated 1104 participants in the Reasons for Racial and Geographic Differences in Stroke (REGARDS) study whose blood pressure and plasma 25-hydroxyvitamin D (25(OH)D) concentrations were measured. We found that 25(OH)D concentration varied inversely with SBP and SBP varied inversely with solar insolation but we found that adjusting for 25(OH)D had no effect on the association of solar insolation with SBP. We conclude that 25(OH)D did not explain the association of greater sunlight exposure with lower blood pressure.

Keywords

Blood pressure; vitamin D; sunshine; solar insolation; season; hypertension

Background

Numerous animal and human studies demonstrate that blood pressure varies inversely with ambient sunshine (insolation) and also with circulating vitamin D (25-hydroxyvitamin D [25(OH)D]) [1-7]. Consequently, it has been suggested that cutaneous vitamin D photosynthesis, stimulated by ultraviolet B (UVB) radiation, may have an important role in blood pressure regulation. Evidence for this comes from observed seasonal variation in SBP (lower in Summer; higher in Winter) [1,2]; lower at higher altitudes [8]. and lower closer to the equator [9,10] and higher in persons with increased skin pigmentation who have less cutaneous vitamin D synthesis in response to UVB light [11,12]. In this regard, Diffey [13] has shown that between latitudes 20-60° N available sunlight (UVB) needed for cutaneous vitamin D synthesis decreases progressively. Associations between latitude and 25(OH)D concentration have also been observed in the Southern hemisphere [14]. Systolic blood pressure increases 2.5 mmHg for each 10° of latitude north of the equator [10] possibly accounting for the incremental rise in blood pressure noted in individuals living at progressively increasing distances from the equator [15,16]. Moreover, in a small study, subjects exposed to whole body UVB radiation not only had a fall in blood pressure but also a simultaneous rise in 25(OH)D [3]. Together these findings suggest vitamin D deficiency/insufficiency may contribute to racial, seasonal, and geographic differences in blood pressure and thus may play a role directly or indirectly in pathogenesis and maintenance of hypertension and cardiovascular disease [17,18].

However, changes in vitamin D status may not be the only explanation for the effect of insolation on blood pressure. It has recently been suggested that vitamin D may not be the important factor in seasonal variability of blood pressure and cardiovascular risk [19]. For instance, Opländer et al [20] and Liu et al [21] have shown a possible role for UVA radiation in lowering blood pressure. Other data suggest the inverse association of blood pressure with insolation may be related to ambient outdoor temperature [22,23]. possibly as a result of polymorphisms in genes controlling adaptation to ambient (cold) temperature [24,25].

To determine if 25(OH)D may explain the association of insolation and blood pressure, we examined the association between insolation and blood pressure in 1104 free-living

participants in the Reasons for Racial and Geographic Differences in Stroke (REGARDS) study whose blood pressure and plasma 25(OH)D concentrations had been measured.

Methods

Study Participants

The REGARDS study is a population-based investigation of stroke incidence in black and white United States (US) adults ≥45 years of age. Details of the study design have been reviewed elsewhere [26]. Briefly, participants were recruited from the 48 contiguous United States and the District of Columbia. Participants lived between latitudes 25.82°N-47.79°N and longitudes 69.78°W-122.86°W. The study was designed to provide approximately equal representation of men and women, and oversampled blacks and persons living in the “stroke belt/buckle” of the US, both groups who have excess stroke mortality. The stroke belt states include Mississippi, Louisiana, Arkansas, Alabama, Georgia, South Carolina, North Carolina and Tennessee. The buckle of the stroke belt consists of the coastal plain of North Carolina, South Carolina, and Georgia. Trained interviewers conducted computer-assisted telephone interviews to obtain information including participants' socio-demographics, cardiovascular risk factors, cigarette smoking, physical activity, and use of medications. Following this call, an in-home study visit was conducted that included an electrocardiograph (ECG) recording, blood pressure measurement, an inventory of medications and collection of blood and urine samples.

Overall, 30,239 black and white adults were enrolled between January 2003 and October 2007 (42% black, 55% women). For this study, we used a cohort random sample of REGARDS participants with measures of mineral metabolism (n=1,104) selected using a stratified random sampling procedure to ensure sufficient participants from high-risk categories were represented (e.g., black individuals and older participants). Participants were randomly selected and stratified into 20 groups by sex, race and age (45-54, 55-64, 65-74, 75-84, >=85 years). The distribution across the strata is as follows: 50% black, 50% white; 50% female, 50% male; 20% aged 45-54, 20% aged 55-64, 25% aged 65-74, 25% aged 75-84 and 10% aged 85 or older. Each individual in the subcohort was assigned a weight that was calculated as the inverse of their sampling fraction, with the sample weight representing the number of individuals in the full REGARDS cohort represented by that one person in the subcohort. All analyses were performed using this weight which effectively makes the results reflect the original sample (as indicated by the weighted N). The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers. All participants provided written informed consent.

Data Collection

Phlebotomy was performed at the participant's home by trained personnel using standard procedures. Participants were instructed to fast for 10-12 hours and samples were shipped overnight on ice to the REGARDS central laboratory as previously described [27]. The exposure of interest was 25(OH)D concentrations measured in baseline plasma samples using a commercially-available ELISA (Immunodiagnostic Systems, Fountain Hills, AZ).

The assay range was 5-150 ng/ml. Intra-assay CVs were 8.82-12.49%. Serum intact parathyroid hormone concentrations (PTH) were measured using a commercially available ELISA (Roche Elecsys 2010, Roche Diagnostics, Indianapolis, IN). Fibroblast growth factor 23 (FGF23) was measured using a second-generation C-terminal ELISA (Immutopics, Santa Clara, CA) with inter-assay CVs of 2.3-9.0%.

Age, race, and sex were determined by self-report. Following a standardized protocol, weight, height, and waist circumference were measured during the initial subject examination at the in-home visit. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Physical activity was assessed through a single question: “How many times per week do you engage in intense physical activity, enough to work up a sweat,” with response options of: none, 1-3 times/week or >4 times/week. Serum creatinine was calibrated to an international isotope dilution mass spectroscopic (IDMS)-traceable standard, measured by colorimetric reflectance spectrophotometry. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation [28].

Determination of Blood Pressure—During the in-home examination, BP was measured two times by a trained technician following a standardized protocol and regularly tested aneroid sphygmomanometer (American Diagnostic, Hauppauge, NY). Participants were asked to sit for 3 minutes with both feet on the floor before the BP measurement. Where possible, blood pressures were taken in the left arm and a large size cuff was used if the arm circumference was >13 inches. Both the cuff bladder width and pulse obliteration level were recorded. The cuff was inflated to 20 mm Hg above the pulse obliteration level and slowly deflated (~2 mm Hg/s). This process was repeated to obtain the second blood pressure on the same arm. A 30 second rest occurred between BP measurements. BP quality control was monitored by central examination of digit preference and retraining of technicians took place as necessary. The two BP measurements were averaged for the current analyses.

Determination of Atmospheric Data—The current residence from the original recruitment file plus updated information from the participant at the time of scheduling the in-home exam was used to establish each participant's address, which was then geocoded using SAS/GIS batch geocoding. Information obtained from SAS/GIS with 80% accuracy or greater was utilized in these analyses. The results from the SAS/GIS procedure were validated against a commercially available program http://www.geocode.com using the Haversine formula [29]. A mean difference of only 0.23 kilometers and a maximum difference of 0.95 kilometers were found between the two algorithms.

We used data from the National Aeronautics and Space Administration (NASA) – National Oceanic and Atmospheric Administration (NOAA) NLDAS-2 dataset to determine ambient sunlight radiation and temperature. Solar radiation in Watts/meter^2 (W/m^2) measures instantaneous solar radiation reaching the earth's surface. The NLDAS-2 dataset is based on model reanalysis data and remotely sensed and ground observations, and consists of a grid surface with ~14 km resolution over North America [30]. NLDAS-2 solar radiation that was assessed for 24 hours at one-hour intervals and its daily integration was used to calculate a

daily total, referred to herein as daily “insolation.” The units of “insolation” are kilojoules/meter^2/day (Kj/m^2/d). For this study, we linked REGARDS participants' residential location with daily insolation and temperature values to calculate the solar insolation for each participant during the 8-week period prior to and including the REGARDS in-home study visit [19,31].

Statistical Analyses

Descriptive statistics were obtained for the population, utilizing appropriate weighting based on the sample scheme described above and are expressed as either mean (95% CI) or frequency (percent). Weighted linear regression was used to first establish that a relationship exists between 25(OH)D and systolic blood pressure (SBP) and separately, 25(OH)D and sunlight exposure. Once these relationships were established, we used weighted linear regression models to examine the association of solar insolation with SBP in sequential models. The first model was unadjusted. The second model then adjusted for mean temperature (linear and quadratic), season, demographics (age, race, sex, region); lifestyle factors (physical activity, screen time); medical factors (current use of anti-hypertension medications, BMI); and laboratory measures (calcium, phosphorus, PTH and FGF 23). Next, 25(OH)D was added to the model that included solar insolation and SBP, to determine the impact of the addition of this variable on the relationship between sunlight exposure and SBP. Linear regression diagnostics were assessed to ensure that assumptions of the model were met. All tests were two-tailed and a p value <0.05 was considered statistically significant for all analyses. All analyses were repeated, with DBP as the primary outcome. Further, analyses stratified by race and sex were performed based on pre-specified hypotheses that associations between sunlight and BP may differ by race and sex.

Results

Table 1 presents the characteristics of the sample, weighted for the stratified sampling. The results from examining the relationship between insolation and 25(OH)D are provided in Table 2. In the unadjusted model, each 1 standard deviation higher insolation (5275 Kj/m^2/d) associated with 1.8±0.38 ng/ml higher 25(OH)D ($p<0.001$). This association remained significant in the fully adjusted model. Next, we examined the relationship between 25(OH)D and SBP, and found that each 1ng/ml higher 25(OH)D was associated with 0.21±0.06 mmHg lower BP ($p<0.001$).

Table 3 presents the parameter estimate for the weighted linear regression models examining the relationship between solar insolation and SBP. In models that did not include 25(OH)D concentrations, each 1 SD higher solar insolation was associated with 1.4 mmHg (SE=0.54) lower SBP ($p=0.012$) in the unadjusted model (Model 1). After adjustment for season, mean 8-week temperature and demographic, clinical and laboratory variables (Model 2), the magnitude and statistical significance of this association increased (each 1 SD higher solar insolation was associated with 3.5±1.4 mmHg lower SBP, $p=0.010$). Season was the covariate that was responsible for most of the change in the regression coefficient in the fully adjusted model. Adjusting for 25(OH)D did not meaningfully change the association of solar insolation with SBP in either the unadjusted or fully adjusted model. To determine if there

was an interaction between solar insolation, 25(OH)D and season we examined a three-way interaction term for these covariates and found that it was not statistically significant (p-value >0.99). We also analyzed for all possible two-way interactions and found that none were significant: solar insolation/25(OH)D (p=0.14), solar insolation/season (p=0.73), 25(OH)D/season (p=0.61). Neither temperature nor temperature-squared was significant in the multivariable model whether or not insolation was included. There was no statistically significant association between solar insolation and DBP in any of the models whether adjusted or unadjusted for plasma 25(OH)D.

We also examined the parameter estimates and p-values for the relationship between insolation and SBP in unadjusted and adjusted models both with and without further adjustments for plasma 25(OH)D for blacks and whites, respectively and also in men and women. For the race-stratified results, we found no statistically significant associations between insolation and SBP in either the unadjusted or adjusted models with or without adjustment for 25(OH)D, in black participants. However, in white participants, there was an inverse association between sunlight exposure and SBP in both the unadjusted model (each 1 SD higher solar insolation was associated with 1.3±0.92 mmHg lower SBP, p=0.038) and after adjustment for season, temperature, demographic, clinical and laboratory variables (each 1 SD higher solar insolation associated with 5.2±0.92 mmHg lower SBP, p=0.005). Season was the covariate responsible for most of the increase in the magnitude and statistical strength of the association in whites. Further adjustment for 25(OH)D did not have a meaningful effect on these associations in whites.

For the sex-stratified results, we found a small but statistically significant inverse association between sunshine exposure and SBP in men (each 1 SD higher solar insolation associated with 1.8 ± 0.77 mmHg lower SBP, p=0.017) in the unadjusted model that was attenuated and no longer statistically significant in the fully adjusted model, with or without further adjustment for 25(OH)D (each 1 SD higher solar insolation associated with a 2.3±2.2 mmHg lower SBP, p=0.30). In women there was no significant association between insolation and SBP in the unadjusted model. However, the magnitude of this association was augmented and became statistically significant in the fully adjusted model each 1 SD higher solar insolation associated with a -3.8±1.7 mmHg, p=0.024), and was unaffected by further adjustment for plasma 25(OH)D.

Discussion

The present study demonstrates that insolation is inversely associated with SBP independently of potential confounders. Furthermore, in pre-defined sub-analyses, solar insolation was inversely associated with SBP in whites but not blacks and in women but not men. Contrary to our central hypothesis, we found no evidence that 25(OH)D explained the association of greater sunlight exposure with lower blood pressure.

The absence of any significant effect of 25(OH)D concentration on the inverse association between insolation and SBP was surprising. While we found a significant inverse association between SBP and 25(OH)D concentration and a significant association between sunlight exposure and 25(OH)D concentration (Table 3), adjusting for 25(OH)D had no meaningful

impact on the association of solar insolation with SBP in any model. These findings suggest that sunshine-related changes in vitamin D photosynthesis may not be the mechanism by which insolation lowers blood pressure. Other studies also suggest the effect of vitamin D on systolic blood pressure is small. A study of a smaller subject population (n=58) receiving 24 exposures of whole body UVB radiation over a (twelve week period [32] revealed a 19.5 ng/ml (48.9 nM/L) increase in 25OHD but a negligible change in SBP, 0.2 mmHg. In a large Mendelian randomization study, Vimaleswaran et al [33] noted a 0.21 mmHg decrease in SBP associated with a 10 percent increase in 25(OH)D concentration. The changes in the ratios of 25(OH)D to SBP in these studies seem quite small considering that UV radiation rises or falls by about 10 percent for every 10° North or South latitude associated with about a 10 percent rise or fall in 25(OH)D [13,14]. Because SBP has been observed to decrease 2.5 mmHg for each 10° North or South [10], these small effects of insolation on 25(OH)D production and subsequently on systolic blood pressure may not be clinically important.

There may be alternative explanations for why vitamin D not affect the association of solar insolation and SBP. In this regard, Opländer et al [20] found that total body irradiation with UVA radiation ($20J/cm^2$), not felt to affect vitamin D photosynthesis, acutely induced a significant increase in flow-mediated vasodilation and a transient fall in mean arterial pressure associated with an increased release of nitric oxide from cutaneous photo-labile NO derivatives . Similarly, Liu et al [21] found that forearm exposure to UVA radiation produced a transient fall in blood pressure and increased blood flow related to increased circulating NO. However, an effect on vascular tone role for UVB radiation cannot be excluded because exposing the forearm to UVB wavelengths also could increase the cutaneous microcirculation nitric oxide synthase (NOS) activity [34]. Unfortunately none of these authors measured serum concentrations of 25(OH)D which would have been important because significant-increases in 25(OH)D production have been reported with exposure to UVA radiation in at least one study [32,35]. And, in other studies, vitamin D deficiency has been demonstrated to alter the function of the vascular endothelium [36-39]. Conversely, Scragg et al [32] found neither exposure to UVA or UVB radiation significantly lowered blood pressure, although both increased 25(OH)D concentrations.

Despite these conflicting results, they still may help explain the race differences we noted for blood pressure and insolation. White skin allows substantially more UVA and UVB radiation to penetrate than black skin resulting from barriers to UV radiation caused by greater melanin content and the thicker stratum corneum in blacks [40,41]. This may then contribute to the greater cutaneous vascular reactivity seen variably in whites as compared to blacks thereby affecting blood pressure [42].

Another explanation may be that the seasonal association of blood pressure with insolation as well as racial and geographic differences in blood pressure are related inversely to ambient outdoor temperature. Argilés et al [23] noted blood pressure correlated inversely with monthly maximal temperatures and Kent et al [22] showed an inverse association of blood pressure and temperature that was statistically significant though quite small. Other studies also support this view [43,44]. Another by Hancock et al [25] suggests that adaptation to cold climate may have placed selective pressure on candidate genes for common metabolic disorders. And, Young et al [24] have presented evidence suggesting the

susceptibility of Africans of the diaspora to develop hypertension may be related to the genetic consequences of adaptation to colder environments. Unlike the foregoing, the present study shows that in a multivariable model, temperature did not influence the parameter estimate (β) of the association of insolation and SBP.

Our study shows that season was an important negative confounder of the association of solar insolation with systolic blood pressure—when adjusting for season, the magnitude and statistical significance of this association was enhanced. This could not be explained either by concentration of 25(OH)D or temperature, thus season was not a surrogate for either variable. The reasons for the effect of season are uncertain but may relate to the fact that season strongly correlates with solar insolation and also has a strong impact on blood pressure. The mechanism(s) whereby season affect(s) blood pressure is(are) uncertain but may also relate to effects of insolation on seasonal cortisol and melatonin production [45, 46]. Further, solar insolation can vary markedly across each season, especially across different regions of the United States. As such, controlling for these effects may have allowed for the independent association of solar insolation with SBP to become more apparent.

Our findings should be interpreted cautiously; first because it is a cross-sectional analysis. Furthermore, other than regional insolation data we have no direct information about participant sunlight exposure, such as time spent out of doors, rather we measured solar insolation. Moreover, we have no information regarding participant skin type, how much and what type of clothing was worn during the period of interest, nor do we know the air quality or the amount of cutaneous vitamin D-stimulating UV radiation reaching the skin surface. All these factors are important in determining sunlight availability [47-49]. Also, because our participants were free-living, the study data were gathered in participants who were allowed to continue whatever medications they were on, including antihypertensive medications and/or vitamin supplements. As a consequence, although we failed to establish that 25(OH)D concentrations accounted for the association of insolation with SBP, we cannot exclude any indirect contribution of vitamin D through its observed associations with the function and dysfunction of other organ systems [17-18].

In conclusion, although we found that plasma 25(OH)D concentration varies directly with insolation and that insolation has a strong inverse association with SBP, we did not find an effect of 25(OH)D on the association of insolation with blood pressure in either the unadjusted or adjusted models. We found that the greatest of effects of insolation on SBP were observed in whites and in women. The association of insolation, and blood pressure remains complex and incompletely understood and requires further investigation.

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Table 1

Characteristics of the study population, weighted for the stratified sampling presented as mean (95% CI) or weighted n (%)

Age	65.1 (64.9, 65.3)
Sex	
Women	15311 (55%)
Men	12461 (45%)
Self-reported race	
Black	11354 (41%)
White	16418 (59%)
Region*	
Belt	9757 (35%)
Buckle	5197 (19%)
Non-Belt	12818 (46%)
Annual Household Income	
< $20k	4366 (16%)
$20k-$34k	6460 (23%)
$35k-$75k	8560 (31%)
>=$75k	4788 (17%)
Refused	3599 (13%)
Education	
< high school	3468 (28%)
High school graduate	6368 (23%)
Some college	7758 (28%)
College graduate and above	10178 (37%)
Season of Baseline Visit	
Winter	6290 (23%)
Spring	6011 (22%)
Summer	7325 (26%)
Autumn	8147 (29%)
Exercise	
None	9306 (34%)
1-3 times per week	9950 (36%)
>3 times per week	8246 (30%)
TV Watching	
None	208 (1%)
1-6 hrs/week	3395 (15%)
1 hr/day	1237 (6%)
2 hrs/day	5478 (24%)
3 hrs/day	5222 (23%)

4+ hrs/day	6911 (31%)
Current Anti-hypertensive Meds	13935 (52%)
Body Mass Index (kg/m^2)	29.1 (28.7, 29.5)
eGFR (ml/min/1.73m^2))	85.9 (84.8, 87.0)
Serum Calcium (mg/dL)	9.2 (9.1, 9.3)
Serum Phosphate (mg/dL)	3.5 (3.45, 3.52)
Serum PTH (pg/mL)	46.3 (44.4, 48.1)
Plasma FGF 23 (RU/ml)	124 (96, 152)
Solar Insolation (8-week mean) (Kj/m^2/day)	17442 (17064, 17820)
Mean Temperature (8-week mean) (centigrade)	16.7 (16.2, 17.3)
Plasma Vitamin D (25 OHD (ng/mL)	25.8 (25.1, 26.4)
Systolic blood pressure (mmHg)	127 (126, 128)
Diastolic blood pressure (mmHg)	76.3 (75.6, 77.0)

Participants lived between Lat.25.82°N-47.79°N and 69.78°W-122.86°W Long. Buckle refers to the following states: LA, MS, AL, AK, GA, NC, SC, and TN. Belt refers to the regions along the coasts of NC, SC, and GA. Differences in the total weighted n across different rows are due to missing data.

Abbreviations: eGFR: estimated glomerular filtration rate; PTH: parathyroid hormone: FGF23: fibroblast growth factor 23

Conversion to SI units: Calcium: mg/dl × 0.25= mM/L; Phosphorus: mg/dl × 0.323= mM/L; PTH: pg/ml × 2.5= ng/L.

Table 2

Association between differences in 25(OH)D and Solar insolation (1 standard deviation change in exposure)

	Plasma 25(OH)D (ng/ml)	
	Beta (SE)	**p-value**
Model 1	1.8 (0.38)	<0.0001
Model 2	1.7 (0.81)	0.042

Values are mean. Bracketed numbers are standard error of the mean (SE).

Model 1: unadjusted

Model 2: adjusted for mean 8-week temperature (linear and quadratic), season, age, race, sex, region, physical activity, screen time, current use of anti-hypertensive drugs, body mass index, calcium, phosphate, parathyroid hormone, fibroblast growth factor 23.

Table 3

Parameter estimates for systolic blood pressure (standard error) and p-value for a 1 standard deviation change in solar insolation

	Unadjusted for 25(OH)D		Adjusted for serum 25(OH)D	
	Beta (SE)	**p-value**	**Beta (SE)**	**p-value**
Model 1	-1.4 (1.3)	0.012	-1.0 (0.55)	0.069
Model 2	-3.5 (1.4)	0.010	-3.5 (1.3)	0.010

SE= standard error of the mean.

Model 1: unadjusted

Model 2: adjusted for mean 8-week temperature (linear and quadratic), season, age, race, sex, region, physical activity, screen time, current use of anti-hypertensive drugs, body mass index, calcium, phosphate, parathyroid hormone, fibroblast growth factor 23.