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Original Research

Associations of 25-hydroxyvitamin D with markers of inflammation, insulin resistance and obesity in black and white community-dwelling adults

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ABSTRACT

Aims: Vitamin D is a fat-soluble vitamin classically known for its role in calcium absorption and bone health. Growing evidence indicates that vitamin D deficiency may be associated with inflammation, insulin resistance, and obesity. However, prior studies examining the association of vitamin D with metabolic risk factors had relatively low representation of individuals of black race, limiting their ability to characterize associations of vitamin D and parameters of metabolic health in black vs. white individuals.
Methods: We examined associations of 25-hydroxyvitamin D (25(OH)D) concentrations with markers of inflammation (interleukin [IL]-6, IL-10, high sensitivity C-reactive protein [hsCRP]), insulin sensitivity (adiponectin, resistin, HOMA-IR), and obesity (body mass index [BMI], waist circumference) in 1042 participants from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a large national cohort of black and white adults 45 years or older.
Results: In unadjusted analyses, lower 25(OH)D concentrations were associated with higher IL-6 and hsCRP concentrations; lower adiponectin concentrations; higher HOMA-IR; and higher BMI and waist circumference ($P < 0.05$ for all). After adjustment for sociodemographic, clinical, lifestyle, and laboratory variables, lower 25(OH) D concentrations remained associated with lower adiponectin concentrations, higher IL–6 concentrations, higher HOMA-IR, and higher BMI and waist circumference ($P < 0.05$ for all). The magnitude of these associations did not differ by race ($P_{interaction} > 0.1$).
Conclusions: Lower 25(OH)D concentrations are associated with disturbances in metabolic health in both blacks and whites. Whether correcting vitamin D deficiency could offer a beneficial therapy for disease prevention requires further study.

Introduction

Vitamin D is a fat-soluble vitamin and hormone essential for calcium absorption and bone health. Vitamin D status is most commonly determined by serum concentrations of 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Epidemiologic data have established that a large portion of the population has vitamin D deficiency, generally defined as 25(OH)D concentrations <20 ng/ml. Though vitamin D is classically known for its function in skeletal health, studies have shown that low 25(OH)D concentrations are associated with obesity, insulin resistance, and inflammation [1–6], suggesting that vitamin D has pleiotropic actions which impact numerous physiologic systems involved in metabolic health.

Prior studies that examined the associations of 25(OH)D with markers of metabolic health have been limited by relatively low representation from black individuals. This is important in that both vitamin D deficiency and established metabolic risk factors such as visceral adiposity, hypertension and inflammation are more common in black individuals than in white individuals. Further, prior studies have shown racial differences in the association of 25(OH)D with markers of insulin resistance [7,8], suggesting that the association of 25(OH)D with other metabolic risk factors may differ by race. Few studies have examined associations of 25(OH)D with markers of insulin resistance, obesity and inflammation in a large sample of black and white adults. Accordingly, we examined the association of 25(OH)D with markers of inflammation, insulin resistance, and obesity in

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participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a prospective cohort of community-dwelling black and white adults living throughout the United States (US).

Methods

Study participants

The REGARDS study is a population-based investigation of stroke incidence in black and white US adults ≥45 years of age. Details of the study design have been reviewed elsewhere [9]. Briefly, participants were recruited from the 48 contiguous US states and the District of Columbia. The study was designed to provide approximately equal representation of men and women, and oversampled black individuals and persons living in the "stroke belt/buckle" of the US (Georgia, Alabama, North Carolina, South Carolina, Tennessee, Arkansas, Mississippi, and Louisiana). Trained interviewers conducted computer-assisted telephone interviews to obtain information including participants' socio-demographics, cardiovascular risk factors, tobacco usage, physical activity, and use of medications. Following this interview, an in-home study visit was conducted that included an electrocardiograph (ECG) recording, 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 subset of participants with measured plasma 25(OH)D concentrations (n = 1042) who were randomly selected from the REGARDS Study population using a stratified sampling procedure to ensure sufficient representation of participants from high risk categories (e.g., black individuals and older participants), as previously described [10]. Briefly, all participants with at least one follow-up contact (n = 29,653) were categorized into 20 strata based on age (45–54, 55–64, 65–74, 75–84, ≥85 years), race (black or white), and sex (male or female). In each stratum, participants were randomly selected to fulfill the desired distribution: 50% black, 50% white, 50% female, 50% male, 20% age 45–54, 20% age 55–64, 25% age 65–74, 25% age 75–84, and 10% age ≥85. Each individual 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 and all participants provided written informed consent.

Data collection

Plasma 25(OH)D was measured in baseline samples using a commercially-available ELISA (Immunodetection Systems, Fountain Hills, AZ). The assay range was 5–150 ng/ml. Intra-assay coefficients of variation (CVs) were 8.82–12.49%. Interleukin (IL) 6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN), with an inter-assay CV range of 6.8–7.3%. IL-10 was measured using the Milliplex MAP Human Cardiovascular Disease (CVD) Panel 3 (Millipore Corporation; Billerica, MA) run as a single-plex assay with an inter-assay CV range of 8.3–12.1%. High sensitivity C-reactive protein (hsCRP) was measured by particle enhanced immunonephelometry using the BNII nephelometer (N High Sensitivity CRP; Dade Behring, Deerfield, IL) with inter-assay CVs of 2.1–5.7% [11]. Serum glucose and insulin were measured using the Ortho Vitros 950 IRC Clinical Analyzer (Johnson & Johnson Clinical Diagnostics, Raritan, NJ) and Roche Elecsys 2010 System (Roche Diagnostics, Indianapolis, IN), respectively. Insulin resistance was assessed using the homeostasis model assessment [HOMA-IR = insulin [mg/dL] × glucose [mg/dL]/405] [12]. Fasting insulin was only obtained in participants without a history of diabetes, so calculations of HOMA-IR were only available for those without diabetes (n = 810). Resistin and adiponectin were measured using Human Serum Adipokine Panel A LINCOplex Kit (Linco Research, Inc.; St. Charles, MO). Inter-assay CVs ranges from 8.0–13.2% and 6.1–10.4%, respectively.

Age, race, sex, annual family income, educational attainment, and tobacco use history were determined by self-report. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared measured during the in-home visit. Waist circumference (in centimeters) was measured during the in-home visit using a tape measure positioned midway between the lowest rib and the iliac crest with the participant standing. Systolic and diastolic blood pressure BP were defined as the average of two measurements taken by a trained technician using a standard protocol, after the participant was seated for 5 minutes. 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. History of coronary heart disease (CHD) was defined as having any of the following: evidence of myocardial infarction on the baseline ECG, self-report of a prior history of a cardiac procedure (coronary artery bypass surgery or percutaneous angioplasty), or self-reported history of myocardial infarction. History of stroke was ascertained by self-report. Diabetes was defined as self-reported use of insulin or oral hypoglycemic agents, fasting blood glucose concentration of 126 mg/dL or higher, or a non-fasting blood glucose concentration of 200 mg/dL or higher. Dyslipidemia was defined as a serum total cholesterol concentration ≥240 mg/dL, low-density lipoprotein concentration ≥160 mg/dL or high-density lipoprotein concentration <40 mg/dL, or a self-reported prior diagnosis of high cholesterol or current use of cholesterol-lowering medications. Phosphorus and calcium concentrations were measured using standard assays. Serum intact parathyroid hormone concentrations (PTH) were measured using a commercially available ELISA (Roche Elecsys 2010, Roche Diagnostics, Indianapolis, IN) with intra- and inter-assay CVs range from 2 to 4% and 3 to 6%, respectively.

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 [13]. Albumin and creatinine were measured in a random spot urine specimen by nephelometry (BN ProSpec Nephelometer, Dade Behring, Marburg, Germany) and Modular-P chemistry analyzer (Roche/Hitachi, Indianapolis, IN), respectively. Spot urine albumin-to-creatinine ratio (UACR) was calculated in mg/g. Prevalent CKD was defined as an eGFR <60 ml/min/1.73 m^2 or a UACR ≥30 mg/g.

Statistical analyses

Standard descriptive statistics were used to examine demographic, clinical and laboratory characteristics of the participants in the overall sample across clinically-relevant categories of 25(OH)D (<20 ng/ml, 20–29 ng/ml, ≥30 ng/ml). To account for the stratified sampling design of the subcohort, all analyses were weighted by the inverse probability of the random cohort sampling fraction. Linear regression models were used to examine the association of 25(OH)D as the primary independent variable with markers of inflammation (IL-6, IL-10, hsCRP), insulin resistance (resistin, adiponectin, HOMA-IR) and BMI and waist circumference as the dependent variables of interest. The initial models were adjusted for age, sex, race, and region of residence. The second model was adjusted for parameters in Model 1 plus indices of socioeconomic status (annual household income, educational achievement), history of diabetes

Table 1
Baseline characteristics according to 25-hydroxyvitamin D (25(OH)D) concentrations in the cohort random sample (analyses weighted to the full cohort). Results presented as means (95% confidence interval) or frequencies

	25(OH)D <20 ng/ml	25(OH)D 20–29 ng/ml	25(OH)D ≥30 ng/ml
Weighted N	8737	10,580	8709
Age, years (95% CI)	64.5 (63.6,65.4)	65.3 (64.5,66.2)	65.1 (64.1,66.1)†
Male (%)	36	46	51†
Black (%)	75	32	18†
Region of residence[a]			
Non-stroke belt (%)	47	49	45†
Stroke belt (%)	53	51	55
Systolic blood pressure, mm Hg (95% CI)	130.2 (128.0,132.4)	126.8 (125.1,128.6)	124.7 † (122.7,126.7)
Diastolic blood pressure, mm Hg (95% CI)	78.2 (77.0,79.3)	76.1 (75.2,77.2)	74.6 (73.3,75.9) †
Less than high school education (%)	18	11	6†
Annual income <$20,000/year (%)	24	11	12†
Physical activity (%)			
None	44	32	25†
1 to 3 times per week	31	42	33
4 or more times per week	24	25	41
Co-morbidities			
Current smoking (%)	19	11	12†
Diabetes (%)	33	20	10†
Coronary heart disease (%)	13	16	20†
Atrial fibrillation (%)	8	9	9
Dyslipidemia (%)	63	56	60
eGFR, ml/min/1.73 m^2 (95%CI)	88.8 (86.2,91.4)	85.7 (83.7,87.7)	83.2 (81.0,85.5)†
eGFR <60 ml/min/1.73 m^2 (%)	10	7	8†
Albumin to creatinine ratio, mg/g (95% CI)	49.4 (28.7,70.2)	27.9 (15.6,40.3)	22.5 (13.8,31.3)†
Urinary ACR >30 mg/g (%)	18	11	10†
Parathyroid hormone, pg/ml (95% CI)	59.0 (53.9,64.2)	42.7 (40.9,44.6)	37.5 (35.4,39.5)†
Calcium, mg/dL (95% CI)	9.2 (9.1,9.3)	9.1 (8.9,9.2)	9.2 (9.1,9.3)
Phosphorus, mg/dL (95% CI)	3.5 (3.4,3.5)	3.5 (3.4,3.5)	3.5 (3.4,3.6)

eGFR, estimated glomerular filtration rate; ACR, albumin to creatinine ratio.
[a] Stroke belt includes persons living in US stroke belt (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas) or buckle (coastal plain regions of Georgia, North Carolina and South Carolina) states.
† P-value < 0.05.

(except for models examining HOMA-IR), CHD, stroke, and lifestyle habits (cigarette smoking, physical activity) and season of blood draw. The third model further adjusted for laboratory parameters (eGFR, UACR, calcium, phosphorus, and intact PTH). Because IL-6, IL-10, resistin, adiponectin, hsCRP and UACR were not normally distributed, we log-transformed these variables for all analyses. We examined effect modification by race status by testing the significance ($P < 0.1$) of multiplicative interaction terms in the models. When significant interaction was detected, we analyzed stratified models. A two-tailed P value <0.05 was considered statistically significant for all analyses other than the tests for interaction, in which a P value < 0.1 was considered statistically significant. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics of study participants according to categories of 25(OH)D concentrations are depicted in Table 1. Lower 25(OH)D concentrations were associated with female sex, black race, higher systolic and diastolic blood pressure, lower educational achievement and income, a greater prevalence of current smoking, diabetes, and dyslipidemia, and higher eGFR and intact PTH concentrations.

Table 2 presents markers of inflammation, insulin resistance and obesity by 25(OH)D categories. Lower 25(OH)D concentrations were associated with higher BMI, waist circumference, IL-6, and hsCRP concentrations and higher HOMA-IR, and lower concentrations of adiponectin. There were no statistically significant associations of 25(OH)D with IL-10 or resistin. Race did not modify the associations of 25(OH)D with any of these markers ($P_{interaction} > 0.1$ for all, Supplementary Table S1).

Table 3 depicts multivariable adjusted associations of 25(OH)D with markers of inflammation, insulin resistance and obesity. Plasma 25(OH)D concentrations were inversely associated with log-transformed IL-6 concentrations after adjustment for sociodemographic variables, geographic region of residence, and clinical, lifestyle, and laboratory factors (0.14 log-unit lower IL-6 per 10 ng/ml higher 25(OH)D, $P < 0.001$). In contrast, the inverse association of 25(OH)D with hsCRP in the unadjusted analysis presented in Table 2 was attenuated and no longer statistically significant after adjustment for age, sex, race and geographic region of residence (Model 1, Table 3).

With respect to markers of insulin resistance, plasma 25(OH)D concentrations were directly associated with adiponectin concentrations (0.09 log-unit higher adiponectin per 10 ng/ml higher 25(OH)D, $P < 0.001$) and inversely associated with HOMA-IR (0.13 log-unit lower HOMA-IR per 10 ng/ml higher in 25(OH)D, $P < 0.001$) in models adjusted for sociodemographic, clinical, and laboratory variables. There was no association of 25(OH)D with resistin in any multivariable-adjusted model. Race did not modify the associations of 25(OH)D with any of the markers of inflammation or insulin resistance ($P_{interaction} > 0.1$ for all).

Higher 25(OH)D concentrations were associated with lower BMI (–0.72 kg per 10 ng/ml higher 25(OH)D, $P = 0.002$) and waist circumference (–2.3 cm per 10 ng/ml higher 25(OH)D, $P < 0.001$) in fully adjusted models. Race did not modify the associations of 25(OH)D with either of the measures of obesity ($P_{interaction} > 0.1$ for both).

Discussion

In this study, we found that lower 25(OH)D concentrations were associated with higher IL-6 and HOMA-IR, lower adiponectin, and

Table 2
Clinical and laboratory parameters by category of 25-hydroxyvitamin D. Values given as mean (95% confidence interval) or median [interquartile range]

Parameter	Overall	Category 1 (<20 ng/ml)	Category 2 (20–30 ng/ml)	Category 3 (>30 ng/ml)	*P*
25(OH)D ng/ml	25.3 (24.1,26.5)	14.7 (14.4,15.1)	24.7 (24.4,25.1)	38.0 (36.9,39.0)	<0.001
Obesity measures					
Body mass index (kg/m^2)	29.2 (28.8,29.6)	31.1 (30.2,31.9)	28.9 (28.4,29.6)	27.4 (26.7,28.1)	<0.001
Waist circumference (cm)	95.7 (94.7,96.7)	99.9 (97.9,101.9)	95.0 (93.4,96.6)	91.8 (90.1,93.5)	<0.001
Inflammatory markers					
Interleukin-6 (pg/ml)	2.7 [1.8,4.2]	3.4 [3.0,3.7]	2.7 [2.5,2.9]	2.1 [1.9,2.3]	<0.001
Interleukin-10 (pg/ml)	9.0 [6.0,13.2]	9.0 [8.1,9.9]	8.9 [8.0,9.8]	9.1 [8.3,9.8]	0.17
hsCRP (mg/L)	2.1 [0.9,4.9]	2.8 [2.3,3.3]	2.0 [1.7,2.3]	1.7 [1.3,2.0]	<0.001
Insulin resistance markers					
HOMA-IR	2.2 [1.3,3.5]	2.7 [2.3,3.0]	2.3 [2.1,2.5]	1.8 [1.5,2.1]	<0.001
Resistin (pg/ml)	24.1 [18.3,30.8]	24.7 [23.1,26.4]	23.4 [21.9,24.9]	24.6 [23.6,25.9]	0.33
Adiponectin (ng/ml)	10.8 [6.0,18.8]	9.3 [8.3,10.3]	11.8 [10.4,13.1]	12.7 [10.4,15.1]	<0.001

Abbreviations: hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homeostatic model assessment of insulin resistance.

Table 3
Associations between 25-hydroxyvitamin D and markers of inflammation (interleukin-6, high-sensitivity C-reactive protein, and interleukin-10), insulin resistance (resistin, adiponectin, homeostasis model assessment-insulin resistance), and obesity measures (body mass index, waist circumference)

	Inflammatory markers			Insulin resistance markers			Obesity measures	
	IL-6	hsCRP	IL-10	Resistin	Adiponectin	HOMA-IR	BMI	Waist circumference
Model 1								
β	−0.14	−0.06	−0.02	−0.02	0.09	−0.13	−1.1	−3.2
P-value	<0.001	0.18	0.63	0.31	0.003	<0.001	<0.001	<0.001
Model 2								
β	−0.11	−0.02	−0.02	−0.02	0.10	−0.12	−0.87	−2.6
P-value	<0.001	0.67	0.47	0.33	0.004	<0.001	<0.001	<0.001
Model 3								
β	−0.11	−0.01	−0.03	−0.01	0.13	−0.13	−0.72	−2.3
P-value	<0.001	0.93	0.53	0.44	<0.001	<0.001	0.002	<0.001

Abbreviations: IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein; IL-10, interleukin-10; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index.
β-coefficients for IL-6, hsCRP, IL-10, resistin, and adiponectin are presented as log-unit change in each parameter per 10 ng/ml change in 25(OH)D.
Model 1 is adjusted for age, sex, race, region of residence.
Model 2 is adjusted for variables in Model 1 plus indices of socioeconomic status, history of diabetes (except for HOMA-IR models), coronary heart disease, stroke, lifestyle habits (tobacco usage, physical activity) and season of blood draw.
Model 3 is adjusted for variables in Model 2 plus eGFR, log albumin-to-creatinine ratio, phosphorus, calcium and intact parathyroid hormone.

higher waist circumference and BMI independently of other risk factors in community dwelling adults. Furthermore, the magnitude and strength of these associations did not differ significantly by race. These data support the findings of prior studies that vitamin D is independently associated with markers of metabolic health and unlike prior studies, suggest that these relationships do not differ by race.

The associations between vitamin D and insulin resistance, inflammation, and obesity have been previously reported. Consistent with the findings of the current study, prior studies found an inverse association of serum 25(OH)D concentrations with insulin resistance [1,5,6] and pro-inflammatory markers such as IL-6 and CRP [14,15]. Similarly, multiple prior studies have shown an inverse association of BMI with 25(OH)D, which is attributed to the fat-soluble nature of vitamin D and sequestration into adipose tissue [2,16]. However, these previous studies included relatively low numbers of black individuals, precluding definitive examination of race differences. This is important in that several prior studies showed racial heterogeneity in the association of vitamin D with markers of metabolic health. In the National Health and Nutrition Examination Surveys from 1988 to 1994 (NHANES III) and from 2001 to 2006, lower 25(OH)D concentrations were shown to be associated with greater prevalence of insulin resistance and diabetes in non-Hispanic white and Mexican-American participants, but not in non-Hispanic black participants [7,8]. Conversely, our results showed that the association between circulating 25(OH)D concentrations, insulin resistance, inflammation and obesity does not differ by race, as other studies have suggested [17]. Further, to our knowledge, this is the first study to examine the association of 25(OH)D with adipokines such as resistin and adiponectin and markers of inflammation beyond hsCRP such as IL-6 and IL-10 in a population-based sample with an adequate representation of black individuals. Thus the current study adds to the literature by indicating that 25(OH)D concentrations may be an important marker of metabolic health in both blacks and whites.

Although low 25(OH)D concentrations have been linked to insulin resistance, inflammation, and obesity in several observational studies including the current one, the effect of vitamin D supplementation remains uncertain. Whereas animal studies have found vitamin D supplementation during deficiency can improve insulin resistance, these findings have not been reliably reproduced in human subjects [18–21]. Similarly, trials of vitamin D supplementation have not been shown to affect inflammation in human participants [14,22]. Though vitamin D supplementation has not aided in weight loss, it has been found that obese subjects experience a decreased dose response to vitamin D supplements [2]. There are several important differences between animal and human trials. Most human trials have included relatively healthy participants who are not always vitamin D deficient. Furthermore, the dose of supplementation and goal 25(OH)D concentration varied greatly between studies. Most studies lasted approximately 3 months, often during winter months, and only a few were 6 months to a year or more in duration. In order to appreciate any role vitamin D may have in insulin resistance, inflammation, and obesity, it is possible that vitamin D supplementation

should focus on vitamin D deficient individuals with chronic disease conditions particularly amenable to vitamin D replacement, such as diabetes [23]. Interestingly, adjusting for physical activity did not affect the magnitude or strength of the associations of 25(OH)D with insulin resistance, inflammation and obesity, suggesting that the associations described herein do not merely reflect healthier lifestyle but may instead represent direct biological links between lower 25(OH)D and poor metabolic health.

This study had several strengths worth mentioning. The large, bi-racial REGARDS population allowed us to examine the association of 25(OH)D with indices of metabolic health in blacks and whites. Additionally, the participants were geographically diverse, and therefore regions with different rates of sun-exposure were all represented. However, there are also important weaknesses to consider. First, this observational and cross-sectional study cannot answer the ongoing questions of causality, directionality, or time course of the associations found. Additionally, 25(OH)D was the only vitamin D metabolite measured. Vitamin D binding protein, 24,25 $(OH)_2D$ and 1,25$(OH)_2D$ were not measured, which may have provided important insight into other factors that may impact associations of 25(OH)D with insulin sensitivity and/or differences in these associations by race [24].

In conclusion, these findings bolster the link between vitamin D deficiency and metabolic health and supports the notion that vitamin D deficiency and poor metabolic health are relevant to both black and white individuals. So far, vitamin D supplementation has not yet been shown to substantially improve metabolic health parameters such as insulin sensitivity and inflammation in human trials, despite experimental data showing direct causal links between vitamin D deficiency and poor metabolic health. However, as the prevalence of metabolic syndrome in the general population continues to rise, this area of research remains relevant, particularly in populations such as black individuals who have a higher overall prevalence of vitamin D deficiency and are at increased risk of poor metabolic health [25]. Further randomized controlled trials in clearly deficient individuals with chronic disease conditions are warranted.

Conflict of interest

The authors declare they have no conflicts of interest.

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Appendix. Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcte.2016.06.002.

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