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ORIGINAL INVESTIGATION

Ancestry-specific polygenic scores and SNP heritability of 25(OH)D in African- and European-ancestry populations

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Abstract

Vitamin D inadequacy, assessed by 25-hydroxyvitamin D [25(OH)D], affects around 50% of adults in the United States and is associated with numerous adverse health outcomes. Blood 25(OH)D concentrations are influenced by genetic factors that may determine how much vitamin D intake is required to reach optimal 25(OH)D. Despite large genome-wide association studies (GWASs), only a small portion of the genetic factors contributing to differences in 25(OH)D has been discovered. Therefore, knowledge of a fuller set of genetic factors could be useful for risk prediction of 25(OH)D inadequacy, personalized vitamin D supplementation, and prevention of downstream morbidity and mortality. Using PRSice and weights from published African- and European-ancestry GWAS summary statistics, ancestry-specific polygenic scores (PGSs) were created to capture a more complete set of genetic factors in those of European ($n=9569$) or African ancestry ($n=2761$) from three cohort studies. The PGS for African ancestry was derived using all input SNPs (a p value cutoff of 1.0) and had an R^2 of 0.3%; for European ancestry, the optimal PGS used a p value cutoff of 3.5×10^{-4} in the target/tuning dataset and had an R^2 of 1.0% in the validation cohort. Those with highest genetic risk had 25(OH)D that was 2.8–3.0 ng/mL lower than those with lowest genetic risk ($p=0.0463$–3.2×10^{-13}), requiring an additional 467–500 IU of vitamin D intake to maintain equivalent 25(OH)D. PGSs are a powerful predictive tool that could be leveraged for personalized vitamin D supplementation to prevent the negative downstream effects of 25(OH)D inadequacy.

Introduction

Vitamin D inadequacy, using the Institute of Medicine definition of a 25-hydroxyvitamin D [25(OH)D] concentration less than 20 ng/mL, affects almost 50% of adults in the United States, with higher prevalence in those with darker skin tones (Forrest and Stuhldreher 2011; Medicine 2011; Wang et al. 2010). Observational studies show associations between low vitamin D concentrations and numerous adverse health outcomes, including autoimmune diseases, migraines, hypertension, dyslipidemia, cardiovascular events, and cardiovascular mortality (Arshi et al. 2014; Holick 2006, 2007; Kheiri et al. 2018; Medicine 2011; Mirhosseini et al. 2017; Song et al. 2018; Wang et al. 2010). These studies are supported by recent Mendelian randomization studies which provide evidence for a causal relationship between low vitamin D concentrations and increased risk of obesity, ovarian cancer, hypertension, lower cognitive function during aging, multiple sclerosis, and all cause and cancer mortality (Afzal et al. 2014; Kueider et al. 2016; Kunutsor et al. 2014; Mokry et al. 2015; Ong et al. 2016; Vimaleswaran et al. 2013; Vimaleswaran et al.

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2014). Furthermore, some clinical trials have shown that vitamin D and calcium supplementation are important in the prevention of fractures and cardiovascular risk factors, while vitamin D supplementation alone may lower risk of cancers, diabetes and depression and may reduce inflammation and improve lung function in patients with cystic fibrosis (Arshi et al. 2014; Barry et al. 2017; Bertone-Johnson et al. 2011; Bischoff-Ferrari et al. 2005; Boonen et al. 2007; Jorde et al. 2008; Lappe et al. 2007; Pincikova et al. 2016; Schnatz et al. 2017; Weaver et al. 2016). Recent results from the Vitamin D and Omega-3 Trial (VITAL) showed null associations between vitamin D supplementation and cancer or cardiovascular disease. However, study design limits the interpretability of these findings; for example individuals with adequate 25(OH)D concentrations were included, and outside use of vitamin D before and during the trial were not restricted (Manson et al. 2018). Avoiding vitamin D inadequacy is important, however, as 25(OH)D concentrations over 50 ng/mL have been associated with increased morbidity and mortality (Medicine 2011; Melamed and Manson 2011). Clinical trials of vitamin D have shown that individual response to vitamin D supplementation is highly variable (Aloia et al. 2008; Binkley et al. 2015). 25(OH)D concentrations are influenced by genetic factors and genetic variants may determine how much vitamin D intake is required to reach an optimal 25(OH)D blood concentration (Engelman et al. 2008; Engelman et al. 2013; Nimitphong et al. 2013; Wjst 2017). Therefore, knowledge of the genetic determinants of 25(OH)D concentrations could be useful for prediction of risk for vitamin D inadequacy, personalized vitamin D supplementation, and subsequent prevention of vitamin D associated morbidity and mortality due to 25(OH)D deficiency.

Variation in or near 12 genes (*A2BP1*, *AMDHD1*, *ANO6/ARID2*, *CYP2R1*, *CYP24A1*, *DAB1*, *DHCR7*, *GC*, *GPR114*, *HTR2A*, *KIF4B*, and *SEC23A*) has been associated with serum 25(OH)D at genome-wide levels of significance through published genome-wide association studies (GWASs) in those of European or African ancestry (Ahn et al. 2010; Engelman et al. 2010; Hong et al. 2018; Jiang et al. 2018; Wang et al. 2010). However, only single-nucleotide polymorphisms (SNPs) in or near four of these genes have been replicated (*CYP2R1*, *CYP24A1*, *DHCR7*, and *GC*), and together account for a small portion of the variation in 25(OH)D concentrations, about 2.8% compared to the estimated 20–40% heritability (Engelman et al. 2008; Jiang et al. 2018; Wang et al. 2010). Such "missing heritability" is common in complex traits, and could, in part, be attributed to many SNPs with small effects that do not reach a stringent genome-wide significance threshold (Manolio et al. 2009). A polygenic score (PGS), by comprising the weighted sum of trait-associated alleles, may capture more trait variation than individual SNPs alone. PGSs have been shown to be more powerful than individual SNP-based testing, are used in a wide variety of statistical techniques (e.g., Mendelian randomization), and have shown clinical promise, predicting Alzheimer's disease incidence before the onset of symptoms that would result in a clinical diagnosis, and for dosing of antifibrinolytic drugs based on activated partial thromboplastin time (aPTT) risk scores (Desikan et al. 2017; Dudbridge 2013; Mormino et al. 2016; Tang et al. 2012).

Yet challenges remain with developing PGS. Analyses suggest that only including SNPs reaching genome-wide significance in a PGS fails to capture much of the heritable variation and reduces the PGS's prediction accuracy. However, deciding on a *p* value threshold for including SNPs a priori is challenging. Recently, software has been developed which addresses this challenge, using summary statistics from GWAS to calculate a number of PGSs across a wide range of *p* value thresholds for SNP inclusion and model fit statistics to determine the optimal threshold for predicting traits in a testing dataset, which is often less stringent than the genome-wide level (Euesden et al. 2015).

To date, only a handful of studies have calculated PGSs for vitamin D concentrations, generally using only SNPs in genes that reached the stringent *p* value threshold in existing vitamin D GWASs, therefore, missing much of the genetic contribution to the phenotype (Chandler et al. 2018; Engelman et al. 2013; Nissen et al. 2014; Shao et al. 2018; Zhang et al. 2013). Given that several studies have reported genetic-dependent response to vitamin D supplementation, PGSs hold predictive and preventive promise in relation to vitamin D concentrations (Didriksen et al. 2013; Mazahery and von Hurst 2015; Nimitphong et al. 2013).

The goal of the current study was to calculate ancestry-specific PGSs for 25(OH)D in individuals of European or African ancestry based on the results from a recent multi-ethnic GWAS meta-analysis (Hong et al. 2018), and to validate the PGS performance in an independent sample. Additionally, the proportion of SNP heritability captured by the PGS was quantified, using GCTA, and compared to that captured by the genome-wide significant SNPs.

Methods

GWAS summary statistics

The TRANS-ethniC Evaluation of vitamiN D GWAS consortium (TRANSCEN-D) performed the largest multi-ethnic vitamin D GWAS meta-analysis to date and included 13 cohorts (9 of African ancestry, 3 of Hispanic ancestry and the SUNLIGHT discovery cohort, a consortium of 15 European cohorts) (Hong et al. 2018). Here, ancestry-specific summary statistics from the African- and European-ancestry cohorts of TRANSCEN-D were leveraged for weighting of

each SNP included in the PGS (Hong et al. 2018). This is referred to as the base dataset.

Target/tuning dataset for calculation of PGS

Using weights from the base dataset, PGSs were developed in an ancestry-specific manner for subsets of European- and African-ancestry samples from the Atherosclerosis in Communities (ARIC) study, which contains European- and African- ancestry participants (Investigators 1989). These ARIC subsets are referred to as the target/tuning datasets. ARIC data were obtained through dbGaP Study Accession: phs000090.v4.p1. ARIC data were selected as the target/tuning dataset as they included both sexes and had dense genotyping, essential for development of a comprehensive and generalizable PGS. ARIC is a prospective epidemiologic study conducted across four United States sites: Wake Forest Baptist Medical Center, Winston-Salem, NC; University of Mississippi Medical Center, Jackson, MS; University of Minnesota, Minneapolis, MN; Johns Hopkins University, Baltimore, MD. ARIC includes 15,792 participants aged 45–64 years at baseline, of which 9086 have data required for this analysis (genomic data, 25(OH)D, age, sex, body mass index (BMI), location and month of blood draw) which were ascertained at ARIC visit 2 (1990–1992). Of these 9086 participants, 7178 are of European ancestry. A random sample of 1000 participants were chosen from the 7178 eligible European-ancestry participants for tuning the optimal PGS model, the remaining samples were used to validate the PGS. From the 1908 eligible participants of African ancestry from ARIC, only data from 57 participants had not been included in the TRANSCEN-D meta-analysis; these were used as the base dataset. Therefore, to ensure independence between the base and target/tuning datasets, only these 57 African-ancestry participants were selected into the target/tuning dataset. Of note, ARIC European samples were not included in TRANSCEN-D, therefore, all 9086 participants were independent of TRANSCEN-D and eligible for the present study.

PGS validation cohort

PGS validation was done using data combined across participants from three multi-ethnic cohorts: ARIC, the Multi-ethnic Study of Atherosclerosis (MESA) and the Women's Health Initiative (WHI), analyzed in an ancestry-specific manner. As above, ARIC provided data on 6178 participants of European ancestry for the validation cohort. MESA is a prospective study of men and women aged 45–84 years who were recruited by Columbia University, New York, NY; Johns Hopkins University, Baltimore, MD; Northwestern University, Chicago, IL; University of Minnesota, Minneapolis, MN; University of California at Los Angeles, Los Angeles, CA and Wake Forest University, Winston-Salem, NC. Serum 25(OH)D was measured at MESA exam 1 (July 2000–August 2002). MESA data were obtained through dbGaP Study Accession: phs000209.v13.p3. MESA provided data on 1936 European- and 342 African-ancestry participants who maintained independence from TRANSCEN-D for the validation cohort. Women participating in WHI were recruited from 40 clinical centers in the United States. Serum 25(OH)D was measured as part of the Calcium and Vitamin D (CaD) Trial (Anderson et al. 2003). WHI data were obtained through dbGaP Study Accession: phs000200.v11.p3. Participants were included if they had the minimum set of variables: genome-wide data, serum 25(OH)D, age, sex, BMI, and month of blood draw. WHI provided data on 455 European- and 700 African-ancestry participants for the validation cohort. Thus, together, in the validation cohort, the European-ancestry sample included 8569 participants and the African-ancestry sample included 1042 participants.

MESA and WHI were used as validation sets because neither MESA nor WHI were optimal tuning datasets for developing a comprehensive PGS. MESA used 50 K genotyping, and had much sparser coverage post-imputation compared to the ARIC dataset that was selected as the tuning dataset. WHI only included women, which could limit the generalizability of the PGS.

Datasets used for heritability estimation

Heritability estimates were calculated using eligible participants ($N = 8838$) of both European ($n = 7119$) and African ($n = 1719$) ancestry from ARIC.

Participant consent was previously obtained for each study providing data; additionally, IRB approval was granted for this specific mega-analysis.

Data quality control

Data cleaning for phenotypic data included winsorizing 25(OH)D in the MESA and WHI samples to account for outliers (Kwak and Kim 2017). In the WHI sample, participants with 25(OH)D values far above the maximum level of detection (150 ng/mL), none of which had extreme vitamin D intake (including supplement use) or sun exposure, were removed from the sample; this included 68 participants of European ancestry and 119 participants of African ancestry. All 25(OH)D values were log transformed to improve the normality of the distribution in each cohort.

Genotyping methods are available in Supplemental Table 1 and described in more detail elsewhere (Anderson 2018; Cornelis et al. 2010; Manichaikul et al. 2012; Matise et al. 2011; Musunuru et al. 2010). In summary, QC removed: sex mismatches, samples and SNPs with high missingness (> 5%), SNPs with low minor allele count

(MAC < 10), and SNPs out of Hardy–Weinberg equilibrium (HWE < 0.05/number of SNPs; Bonferroni adjusted cutoff). Datasets were imputed using the Michigan Imputation Server (Das et al. 2016; Loh et al. 2016). European samples were imputed to the Haplotype Reference Consortium (HRC) and African samples were imputed to the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA) (Johnston et al. 2017; Loh et al. 2016). Post-imputation QC included: removing SNPs with a low-quality score (< 0.8) or MAF (< 0.1%). Additionally, sample and SNP level missingness as well as HWE cutoffs were rechecked. Supplemental Figs. 1 and 2 and Supplemental Table 1 give specifics on quality control for each cohort. QC was performed using PLINK v1.9 and vcfTools (Danecek et al. 2011; Purcell et al. 2007). Ancestry was determined by self-reported data and confirmed with principal components analysis (PCA) in PLINK using 1000 Genomes data as anchoring populations (The Genomes Project et al. 2012).

Measurement of 25(OH)D

Blood 25(OH)D concentration was measured by the studies using different assay types. WHI used the DiaSorin LIASON chemiluminescence, while both MESA and ARIC used liquid chromatography–mass spectrometry (LCMS), which is considered the gold standard for 25(OH)D measurement (McKibben et al. 2016; Robinson-Cohen et al. 2013). Vitamin D concentration [25(OH)D] was log transformed to improve normality of the distribution. To control for differences in vitamin D concentrations due to different assays, 25(OH)D concentrations were converted to z scores within studies for combined cohort analyses.

Measurement of vitamin D intake

Dietary data were collected via questionnaire. Each study used their own questionnaire. WHI used the Food Frequency Questionnaire supplemented with interview questions. ARIC and MESA both used their own implementation of a food intake questionnaire. From the questionnaire data, each study created a derived variable of typical vitamin D intake (measured in IU or mcg). All values were converted to IU for analysis. Additionally, WHI collected data on vitamin D supplement use at the same visit that 25(OH)D was assessed. The sum of vitamin D intake from food and supplements was calculated and used for supplemental and sensitivity analyses, otherwise dietary intake alone was used.

Calculation of available UV radiation

Available UV radiation was calculated based on the month of blood draw and location; participants were assigned continuous available UV radiation values. Available UV radiation values assigned were an average UV-index for the month prior to blood draw (the relevant exposure period). UV data come from the National Weather Service Climate Prediction Center historical database. When available, UV radiation values corresponded to the exact location and year of the participant's blood draw. When exact cities or years were not available, averages across nearby locations or years were used. See Supplemental Tables 2–4 for specific month, year and location values used. Descriptive statistics for available UV radiation values by site and month are also presented in Supplemental Tables 5–7; the UV radiation values ranged from 0.7 to 9.5 UV Index units.

Determining optimal PGS

An optimal p value cutoff and corresponding PGS were determined by calculating PGSs across a wide range of p value thresholds and testing the association between the PGS and log[25(OH)D] in the target/tuning dataset. First, summary statistics were attained from TRANSCEN-D, the base dataset (Hong et al. 2018; Wang et al. 2010), which included SNPS with MAF > 0.01 and tested them for association with log[25(OH)D] using an additive genetic model adjusting for age, sex, BMI, UV index and principal components (PCs) 1–10. PGSs were then calculated in PRSice v2, which computes the sum of reference allele counts at each SNP weighted by the effect size (β) for that SNP from the TRANSCEN-D consortium (Euesden et al. 2015). The reference allele could be the risk (lower 25(OH)D) or protective (higher 25(OH)D) allele. PGS weights came from ancestry-specific z scores from TRANSCEN-D that were converted to betas with the deterministic relationship: $\beta = z/(\text{sqrt}(2p(1-p) \times N))$, where p is the allele frequency for the reference SNP (Zhu et al. 2016). One tuning parameter in PGS development is the LD cutoff used for clumping to prevent SNPs in one correlated region from dominating the PGS. Here, PGSs were calculated in the target/tuning dataset using two different LD cutoffs, $r^2 \geq 0.5$ or ≥ 0.2, keeping the SNP with the strongest effect (largest z score and lowest p value) in the base dataset. SNPs in LD with one another were clumped, using the –clump-r2 option in PRSice v2. The LD cutoff that yielded the PGS that explains the most variance in 25(OH)D was used in downstream analyses. Given the small African-ancestry sample, a reference panel (remaining ARIC African-ancestry dataset $n = 1900$) was used to determine LD.

To determine which set of SNPs to include in the PGS, SNPs at or below a given p value threshold in the base dataset were included in the PGS and tested in a linear regression model for association with log[25(OH)D] in the target/tuning dataset. p value thresholds from 5×10^{-5}–0.5 were tested incrementing by 5×10^{-5} at each iteration (supplemental testing using a p value threshold of 1.0 was performed). All

testing was done using PRSice v2 (Euesden et al. 2015). The threshold with the PGS explaining the most variance in log[25(OH)D] was selected as the most optimal PGS. R^2, or the coefficient of determination, was calculated to measure the proportion of phenotypic variance explained by the model. Linear regression models were used to calculate the R^2 of a given PGS while controlling for participant age, sex, BMI, available UV radiation, and PCs for ancestry. Two PCs were controlled for in the African-ancestry and European-ancestry models, as determined based on the 'elbow' of cohort- and ancestry-specific scree plots. Sensitivity analysis was performed including dietary intake in the model, as dietary intake is a strong predictor of 25(OH)D concentrations. However, with the inclusion of dietary intake in the model, the optimal PGS (and p value cutoff) remained the same for the both cohorts, but reduced sample size substantially in the African-ancestry cohort. Therefore, to maintain sample size, dietary intake was not included in the model to determine the optimal p value cutoff (Supplemental Table 8).

PGS performance validation

PGS performance was validated in an ancestry-specific manner using participants in validation cohorts, which were combined cohorts of samples from ARIC, MESA, and WHI that maintained independence from TRANSCEN-D and PGS development samples. The PGS was applied to the participants in the validation dataset in accordance with the ancestry-specific p value cutoff. The relationship between PGS quantile and 25(OH)D was tested using a linear regression model controlling for age, sex, BMI, available UV radiation, and PCs for ancestry. Quantile plots were created depicting the relationship between PGS decile and 25(OH)D concentration. PGS and 25(OH)D concentration were normalized within each cohort. This was done to minimize the effects of different SNP sets used to discern the PGS (i.e., many missing SNPs in MESA) and different 25(OH)D assays used between cohorts. Sensitivity analyses were performed to ensure that the study design of the WHI CaD randomized control trial was not biasing the results.

Supplemental PGS analyses

The African-ancestry target/tuning cohort was small ($n = 57$) due to limited genome-wide data in those of African ancestry. To explore if the small sample reduced prediction for those of African ancestry, a PGS was created from all independent SNPs (p value cutoff = 1.0; r^2 cutoff = 0.5) in the full independent sample of African-ancestry participants which maintained independence from TRANSCEN-D ($n = 1099$) (Ware et al. 2017). Additionally, to test the importance of ancestrally matched base and target sets, this PGS was also created using European-ancestry GWAS summary statistics for weighting of the PGS.

Heritability estimation

Heritability estimates were calculated using GCTA v1.26 (Yang et al. 2011). Heritability was estimated several ways: (1) ancestry-specific overall SNP heritability, (2) ancestry-specific SNP heritability of the PGS (where sample size allowed) and (3) ancestry-specific SNP heritability of previous replicated GWAS findings in *CYP2R1*, *CYP24A1*, *DHCR7*, and *GC* (Ahn et al. 2010; Hong et al. 2018; Wang et al. 2010). In each case, the model was adjusted for age, sex, BMI, available UV, and dietary vitamin D intake.

SNP heritability estimates were calculated using all genotyped and imputed SNPs for both the European- and African-ancestry populations from ARIC; this was 8,315,761 and 9,335,785 SNPS, respectively. Partitioned heritability estimates were discerned paralleling methodology described by the SUNLIGHT consortium (Jiang et al. 2018). To estimate heritability captured by the PGS, heritability was calculated twice; once using the clumped set of SNPs used to determine the PGS (228,867 SNPs for European ancestry and 850,697 for African ancestry) and a second time using the clumped set of SNPs with SNPs included in the PGS removed (228,526 SNPs for European ancestry and 818,428 for African ancestry). The difference in heritability estimates between these two models was the heritability explained by the PGS. Heritability could not be directly calculated from the SNPs in the PGS because one of the assumptions made by the GCTA modeling is an average null effect of the SNPs on the outcome. Of note, the African-ancestry sample was too small for this analysis to be valid, so heritability attributed to the PGS was only calculated in those of European ancestry. In discerning the heritability captured by previous replicated GWAS studies, heritability was calculated using a reduced set of SNPs: the full genotyped and imputed set with top GWAS findings (and SNPs in the surrounding LD block) removed (Jiang et al. 2018; Johnson et al. 2008). The difference between this estimate and the overall heritability estimates was the heritability attributed to previous replicated GWAS findings. Additionally, a second heritability estimate was calculated that included novel findings. This included SNPs from *AMDHD1* and *SEC23A* in those of European ancestry and SNPs from *KIF4B*, *HTR2A* and *ANO6/ARID2* in those of African ancestry (Hong et al. 2018; Jiang et al. 2018). Table 1 summarizes the SNPs and LD blocks removed in each scenario. LD block size was determined using the Plots mode of the SNAP tool by the Broad (Johnson et al. 2008). All models were fit separately for European- and African-ancestry samples.

Table 1 Previous GWAS SNPs

SNP ID	Chromosome	Position[e]	Gene	EU LD block size (kb)	AFA LD block size (kb)
rs2282679	4	72608383	*GC*	1200	2
rs79666294[a]	5	155047146	*KIF4B*	NA[c]	200
rs10741657	11	14893332	*CYP2R1*	480	300
rs12785878	11	71456403	*NADSYN1/DHCR7*	120	84
rs719700	12	45635426	*ANO6/ARID2*	NA[c]	2
rs10745742	12	95964751	*AMDHD1*	50	NA[d]
rs1410656	13	46968386	*HTR2A*	NA[c]	28
rs8018720	14	39086981	*SEC23A*	180	NA[d]
rs6013897[b]	20	54125940	*CYP24A1*	10	4

SNP single-nucleotide polymorphism, *EU* European ancestry, *AFA* African ancestry, *LD* linkage disequilibrium

[a]Not in ARIC African-ancestry imputed data; using the RAGGR tool by USC, SNP rs17570361 was found to be a good proxy (r^2 0.94)

[b]Not in ARIC African-ancestry imputed data; no proxy for rs6013897, so SNPs within 2 kb of its position (52742479) were removed

[c]Novel African-ancestry SNP

[d]Novel European-ancestry SNP

[e]Build 37

Results

Determining the optimal PGS

Table 2 shows sample characteristics for each analysis. Table 3 shows statistics for the best performing PGS for each ancestry in the target/tuning and validation datasets while controlling for age, sex, BMI, available UV radiation, and PCs for ancestry. In both ancestries, the PGS using the LD cutoff of 0.5 was more strongly associated with and explained more of the variance in log[25(OH)D] than did the PGS using the LD cutoff of 0.2 (Supplemental Table 9). Therefore, this was the LD cutoff utilized going forward. In the European-ancestry analyses, the optimal PGS explained 1.4% of the variance in log[25(OH)D] ($p = 9.3 \times 10^{-5}$) in the target/tuning dataset and 1.0% of the variance ($p = 1.1 \times 10^{-23}$) in the validation cohort. In the African-ancestry analyses, the PGS explained 2.9% of the variance in log[25(OH)D] ($p = 0.11$) in the target/tuning dataset and 0.2% of the variance ($p = 0.15$) in the validation cohort. Of note, the optimally performing PGS in the African-ancestry target/tuning dataset contained many more SNPs than that from the European-ancestry dataset, mostly due to the less stringent p value cutoff, but also because a larger number of SNPs remained post-clumping (850,697 vs 228,867) due to smaller LD blocks in the African-ancestry sample and more input SNPs from the TRANSCEN-D summary statistics (8.4 million in the African-ancestry vs 1.2 million in the European-ancestry sample). Figure 1 depicts the results visually, where a taller bar corresponds to a larger percent of the phenotypic variance explained by the PGS.

In supplementary analyses for the African-ancestry cohort, the optimal PGS from the two-stage analysis was compared to the PGS derived using the full African-ancestry sample that was independent from TRANSCEN-D ($n = 1099$; p value cutoff = 1.0; r^2 cutoff = 0.5), using the same underlying comparison that was used to determine the optimal PGS in the two-stage design. The PGS using the full African-ancestry sample that was independent from TRANSCEN-D ($n = 1099$; p value cutoff = 1.0; r^2 cutoff = 0.5) explained more variance (0.31% vs 0.2%) and had a stronger association ($p = 0.0545$ vs 0.15) than the optimal PGS determined from PRSice using the small tuning cohort ($n = 57$) and larger validation cohort ($n = 1042$), therefore, this PGS was chosen as most optimal and used moving forward. In additional analyses to test the importance of ancestrally matched base and target sets, the PGS (p value cutoff = 1.0; r^2 cutoff = 0.5) developed from European-ancestry TRANSCEN-D summary statistics only explained 0.14% of the variance ($p = 0.1897$; worse performance than the PGS developed from African-ancestry TRANSCEN-D summary statistics that explained 0.31% of the variance in 25(OH)D [$p = 0.0545$]). Results are shown in Table 3 and Supplemental Table 10.

After the optimal, ancestry-specific PGS was discerned, the relationship between the PGS and 25(OH)D was investigated using ancestry-specific combined cohorts of samples from ARIC, MESA and WHI, which maintained independence from the TRANSCEN-D (and tuning, for

Table 2 Sample characteristics

Sample	Metric	European-ancestry set	African-ancestry set
PGS development sample (from ARIC)	Sample size	1000	57
	% Female	53.2	49.1
	Mean age (SD) (years)	57.1(5.7)	55.6 (6.2)
	Mean BMI (SD) (kg/m^2)	27.3 (4.8)	28.6 (5.7)
	Mean available UV radiation (SD) (units)	5.0 (2.5)	7.1 (2.4)
	Mean vitamin D intake (SD) (IU)	219.2 (135.2)	221.2 (137.3)
	Mean 25(OH)D (SD) (ng/mL)	25.7 (8.7)	20.9 (7.8)
PGS validation sample (from ARIC, MESA and WHI)[a]	Sample size	8569	1042
	% Female	56.1	84[b]
	Mean age (SD) (years)	58.9 (7.7)	62.0 (8.5)
	Mean BMI (SD) (kg/m^2)	27.5 (5.0)	30.8 (6.3)
	Mean available UV radiation (SD) (units)	4.9 (2.5)	5.4 (2.5)
	Mean vitamin D intake (SD) (IU)	172.3 (157.0)	99.7 (126.1)
	Mean 25(OH)D (SD) (ng/mL)	26.5 (9.7)	19.2 (13.6)
Heritability estimation sample (from ARIC)	Sample size	7119	1719
	% Female	53.6	63.5
	Mean age (SD) (years)	57.1 (5.7)	56.4 (5.8)
	Mean BMI (SD) (kg/m^2)	27.3 (4.8)	30.2 (6.2)
	Mean available UV radiation (SD) (units)	5.0 (2.5)	6.9 (2.3)
	Mean vitamin D intake (SD) (IU)	222.8 (144.4)	215.7 (150.3)
	Mean 25(OH)D (SD) (ng/mL)	25.9 (8.8)	19.1 (7.1)

PGS polygenic score, *SD* standard deviation, *BMI* body mass index, *UV* ultraviolet

[a]MANOVA global test (performed in SAS (version 9.4) revealed differences in one or more variables by cohort, therefore, cohort was adjusted for in all models that included multiple cohorts

[b]Notably, greater % female than other sets, because this set includes independent samples in MESA ($n=342$) and WHI ($n=700$)

Table 3 Performance of optimal PGS in each ancestry

Ancestry	p value cutoff	# SNPs	Cohort	PGS R^2 (model R^2)	p value[a]
European	0.00035	341	Tuning ($n=1000$)	0.014 (0.14)	9.3×10^{-5}
			Validation ($n=8569$)	0.0098 (0.17)	1.1×10^{-23}
African	0.01265	32,269	Tuning ($n=57$)	0.029 (0.49)	0.11
			Validation ($n=1042$)	0.002 (0.03)	0.15
African	1.0	NA[b]	Full independent ($n=1099$)	0.003 (0.04)	0.05

SNPs single-nucleotide polymorphism, *PGS* polygenic score

[a] p value for association between PGS and log[25(OH)D]

[b]This PGS was created via mega-analysis of three cohorts; # SNPs varies by cohort

those of European ancestry) samples. Characteristics of these samples are summarized in Table 2. Figures 2 and 3 show ancestry-specific plots for 25(OH)D by decile of the PGS. In general, those with greater genetic risk (lower PGS and quantile) have lower 25(OH)D concentrations. For a clinically based interpretation, in the European validation cohort (Fig. 2, $n=8569$), those with the lowest PGS have vitamin D concentrations 3.0 ng/mL lower than those with the highest PGS ($p=3.2\times10^{-13}$). Figure 3 shows the trend for those of African ancestry ($n=1099$; combined tuning and validation samples from Table 2); those with the lowest PGS have vitamin D concentrations 2.8 ng/mL lower than those with the highest PGS ($p=0.0463$). Results from the PGS determined using the separate tuning and validation cohorts are included in Supplemental Fig. 3.

Sensitivity analyses showed there was no significant difference in 25(OH)D concentration between participants on the treatment arm compared to the placebo arm in the participants from WHI. Additionally, there was no significant difference in PGS-25(OH)D trend in WHI compared to the other cohorts.

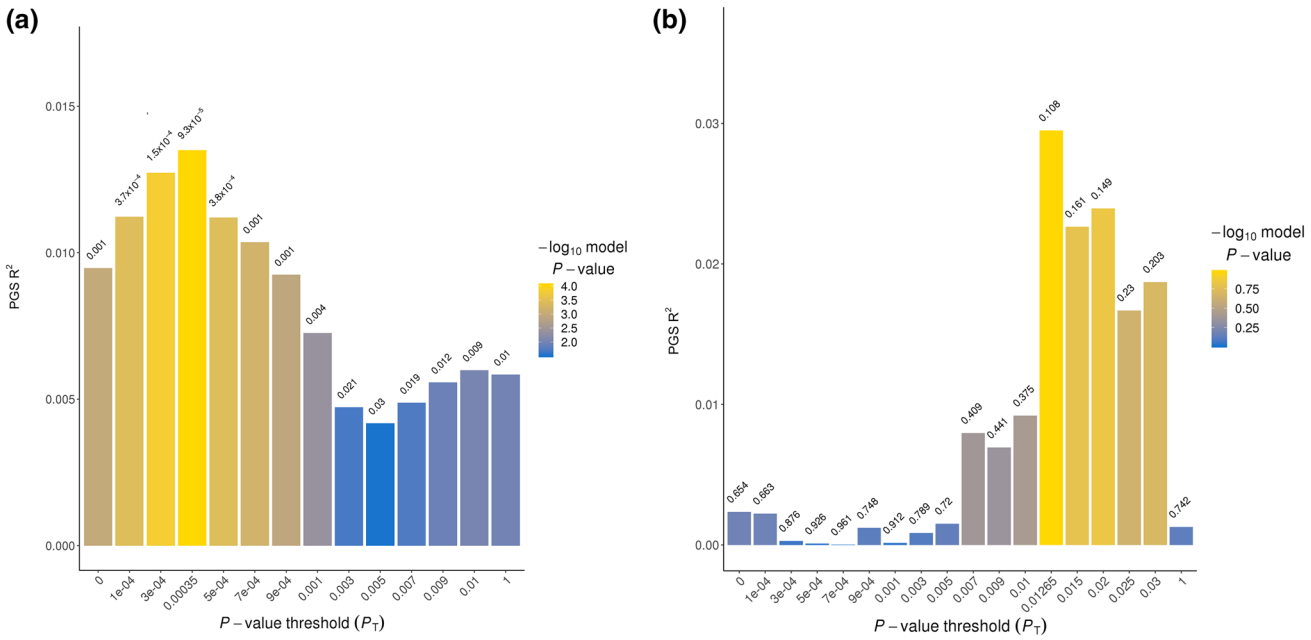

Fig. 1 The polygenic score (PGS) performance in those of European or African ancestry. The *x*-axis displays selected *p* value thresholds for single-nucleotide polymorphisms (SNPs) included in the PGS. The *y*-axis displays the proportion of phenotypic variance captured by the PGS. Yellow bars correspond to a strong association (more significant *p* value) between the PGS and log(25(OH)D than do blue bars. In **a**, the most optimally performing PGS has the tallest bar (*p* value threshold = 0.00035) and captures 1.4% of the variance in log[25(OH)D]. In **b**, the most optimally performing PGS has the tallest bar (*p* value threshold = 0.01265) and captures 2.9% of the variance in log[25(OH)D]

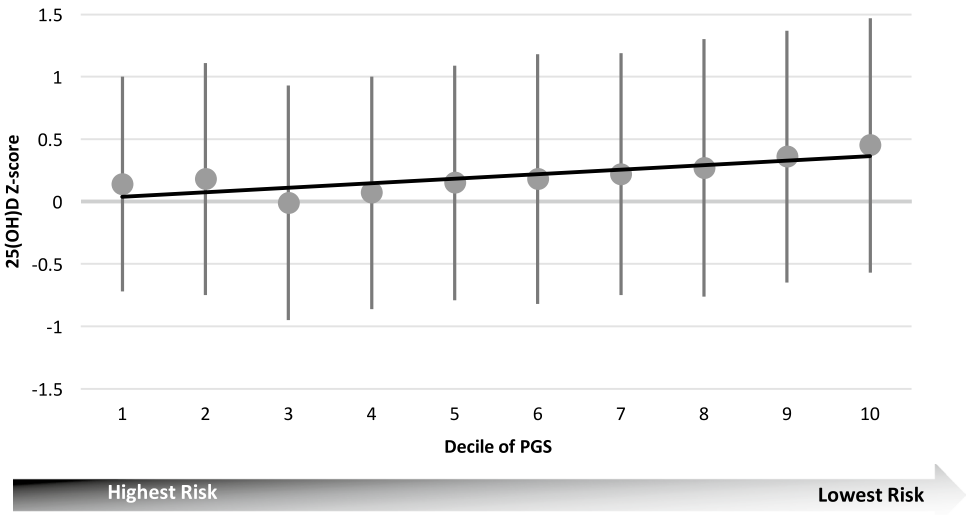

Fig. 2 Visual representation of the association between polygenic score (PGS) decile and normalized vitamin D concentrations in the validation cohort those of European ancestry (*n* = 8569). The *x*-axis is the PGS decile, where lower decile means more risk of low vitamin D concentrations. The *y*-axis is vitamin D concentrations (normalized for comparison between cohorts). The trend is that when the PGS decreases (i.e., higher genetic risk), 25(OH)D concentrations decrease. Moving from the lowest risk to the highest risk decile decreases vitamin D concentrations by 3.0 ng/mL

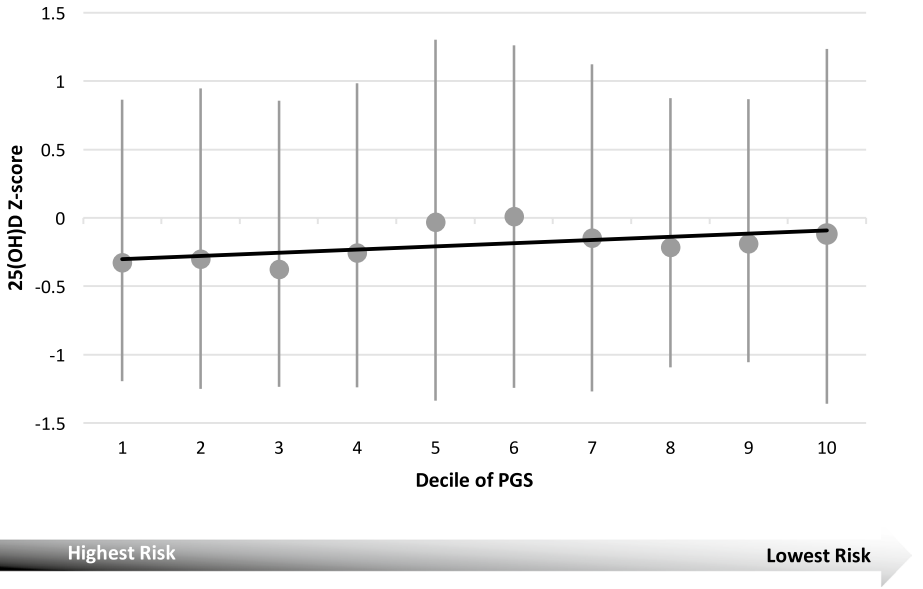

Fig. 3 Visual representation of the association between polygenic score (PGS) decile and normalized vitamin D concentrations in those of African ancestry ($n = 1099$). The *x*-axis is the PGS decile, where lower decile means more risk of low vitamin D concentration. The *y*-axis is vitamin D concentrations (normalized for comparison between cohorts). The trend is that when the PGS decreases (i.e., higher genetic risk) 25(OH)D concentrations decrease. Moving from the lowest risk to the highest risk quintile decreases vitamin D concentrations by 2.8 ng/mL ($p = 0.0463$)

[a]Results shown reflect the PGS using the full African-ancestry sample that was independent from TRANSCEN-D (n=1,099; p-value cutoff = 1.0; r^2 cutoff = 0.5)

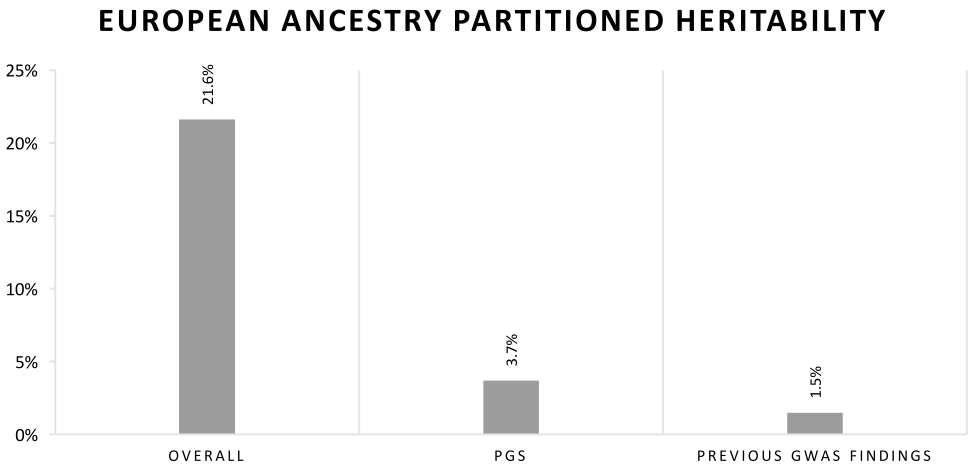

Fig. 4 Overall, single-nucleotide polymorphism (SNP) heritability, polygenic score (PGS) SNP heritability and replicated genome-wide association study (GWAS) SNP heritability in those of European ancestry. Where sample allowed for calculation, the PGS explains more heritability than previous replicated GWAS findings, albeit leaving much of the heritability unexplained

Heritability estimation

Participant characteristics are summarized in Table 2. Overall and stratified SNP heritability estimates for those of European or African ancestry are summarized in Fig. 4 and Supplemental Fig. 4, respectively. SNP heritability is 32% in the African-ancestry cohort and 22% in the European-ancestry cohort (standard errors 17.8 and 5.2, respectively). In those of European ancestry, the PGS accounts for 17.1% (3.7/21.6) of the SNP heritability of 25(OH)D concentrations and previous replicated GWAS findings (i.e., SNPs from *CYP2R1*, *CYP24A1*, *DHCR7* and *GC*) account for 6.9% (1.5/21.6) of the total SNP heritability (Ahn et al. 2010; Hong et al. 2018; Wang et al. 2010). In those of African ancestry, these same top GWAS findings accounted for only 1.6% (0.5/32.2) of the total SNP heritability. Heritability accounted for by previous GWAS findings remained unchanged when ancestry-specific novel findings were included in the heritability estimations (3.7% for European ancestry, and 0.5% for African ancestry) (Ahn et al. 2010; Hong et al. 2018; Jiang et al. 2018; Wang et al. 2010). African-ancestry sample size was too small to calculate heritability accounted for by the PGS.

Discussion

Vitamin D inadequacy is a pervasive health problem, with a strong genetic basis. However, to date, much of the heritability of 25(OH)D remains unexplained. Furthermore, there is a tremendous gap in the research carried out in minority ancestries compared to European ancestry. Filling these knowledge gaps is critical in preventive care to

manage 25(OH)D concentration, especially as we move towards precision medicine, and development of an ancestry-specific PGS is one way to address these gaps. To date, across all phenotypes, most PGS have been calculated in those of European ancestry. A handful of studies have begun to explore ancestry-specific PGS, however, none of these approaches utilize an entirely ancestry-specific approach as was undertaken here (Coram et al. 2017; Márquez-Luna et al. 2017; Vassos et al. 2017). Given the underlying genetic difference between ancestries (i.e., different LD patterns and allele frequencies), an ancestry-specific approach is more appropriate. Calculating PGSs using GWAS summary statistics from an ancestry-matched population accounts for differences in linkage disequilibrium (LD) and allele frequencies that exist between ancestral groups leading to differences in allele effect sizes, which are used as weights in the PGS calculation. Here, optimal PGSs were discerned and validated in an ancestry-specific manner. Heritability explained by the PGS and previous GWAS findings was compared to overall SNP heritability.

The relationship between the PGS and 25(OH)D concentrations was consistent across ancestries in the validation cohorts, albeit modest variance was explained by the PGS; those with the lowest PGS (most risk) had the lowest 25(OH)D concentrations. Moving from the highest to lowest quantile changed 25(OH)D concentrations by 2.8–3.0 ng/mL, a statistically significant and clinically meaningful difference. One study reported that for each additional 100 IU of vitamin D consumed, serum 25(OH)D levels increased by 0.6 ng/mL (Cranney et al. 2007). Using this conversion, compared to those with lowest genetic risk, those with highest genetic risk could require an additional 467–500 IU of vitamin D to maintain comparable levels. While the small sample used to determine the p value cutoff in those of African ancestry could have led to overfitting of the model, the consistent direction of effect between PGS quantile and 25(OH)D concentrations suggests clinical utility for a 25(OH)D PGS to inform vitamin D supplementation in those with high genetic risk for 25(OH)D inadequacy.

The portion of phenotypic variance explained by the PGS was modest due to many concurrent influences. First, the PGS did not include rare variants (MAF < 0.01) as they were removed from the base set (TRANSCEN-D). Common SNPs account for only a small proportion of genetic variance in complex traits (Manolio et al. 2009). Future PGSs that include rare variants will likely account for a greater portion of the variance. Additionally, the variance that the PGS can capture is limited by the input SNPs. In the best-case scenarios (i.e., densest chips), the overlap between the SNPs in the base and target datasets was 3,520,049 and 1,026,643 SNPs, for African and European ancestries, respectively. While over 1 million SNPs can be very informative, much of the genome was not included. Third, PRSice implements clumping which keeps only the SNP with the strongest association for SNPs in LD ($r^2 > 0.5$ used here) in any given 500-kb window, thus reducing the maximum variability that could be captured by a PGS.

Supplementary analyses performed in the full independent sample of African-ancestry participants ($n = 1099$) demonstrated (1) the importance of a large tuning sample and (2) the importance of ancestrally matched base and target sets. Comparing the results from the small tuning sample ($n = 57$) and the analysis using the full independent sample of African-ancestry participants ($n = 1099$), more variance, 0.3% compared to 0.2%, was accounted for, and the association between PGS and 25(OH)D was stronger ($p = 0.0545$ vs 0.15) using the PGS developed in the full sample ($n = 1099$). Additionally, variance accounted for dropped to 0.14% (compared to 0.31%) and the PGS-25(OH)D association became non-significant ($p = 0.19$) when using mismatched summary statistics, reiterating the importance of ancestry-specific analyses as to not exacerbate health disparities (Martin et al. 2019).

Not surprisingly, the heritability investigation provided further evidence that PGSs using a less stringent p value threshold account for a higher portion of the heritability than genome-wide significant SNPs from previous GWAS. Here, the PGS explained more of the SNP heritability than did previous GWAS findings, 17.1% compared to 6.9% in those of European ancestry (sample size was too small for PGS heritability calculations in those of African ancestry). However, neither the PGS nor previous GWAS findings explain a large portion of total SNP heritability, promoting the need for genetic studies with larger sample sizes and more dense SNP data that include low-frequency variants to fully understand the genetic determinants of 25(OH)D concentrations and, therefore, inform the most effective vitamin D supplementation practices. Additionally, there was higher missing heritability in the African ancestry compared to the European ancestry. A possible mechanism behind this is the difference in LD structure between the ancestries. Given that the African-ancestry population is older than the European-ancestry population, with more generations for recombination to occur and break up the genome, the African-ancestry population has more and smaller LD regions. Therefore, it is plausible that each GWAS tagging SNP captures large regions and more functional variants in individuals of European ancestry, but captures fewer small regions, missing additional regions with functional variants, in those of African ancestry.

This study calculated a PGS with a moderate R^2, a consistent relationship to 25(OH)D concentrations and that explained more heritability of 25(OH)D than previous GWAS findings, reiterating the importance of capturing genetic risk by PGS which can be used for clinical predictions. Additionally, this study contributes in-depth

multi-ethnic investigation into 25(OH)D heritability by ancestry, teasing apart genetic underpinnings of 25(OH)D concentrations. However, the study does come with some limitations. To maintain independence from TRANSCEN-D, which provided ancestry-specific weights for the PGSs, the sample size used in this analysis was relatively small, especially for the African-ancestry cohort. The sample size issues experienced for the African-ancestry cohort emphasize the importance of obtaining more diverse samples (i.e., in initiatives like All of Us) (Haskins 2018). Through the TRANSCEN-D GWAS meta-analysis and the analysis here, nearly all the publicly available African-ancestry samples with relevant data have been exhausted and sample sizes for other racial/ethnic groups remain limited. The limited amount of diverse data led to a small African-ancestry training set. A small training set limits discrimination of risk groups which could explain the less significant findings for those of African ancestry (Dudbridge 2013). Furthermore, the genotyping performed did not capture rare variants, limiting the variance that could be captured by the PGS. While GCTA allows for the calculation of heritability in non-related participants, which avoids overestimation due to shared environment, it only accounts for additive SNP effects, potentially underestimating total heritability which also could include gene-by-gene interactions. Finally, while adjusting for available UV radiation is more precise than season, it is not a perfect proxy for time spent outside and does not consider the amount of skin exposed, sunscreen use or skin pigmentation. These limitations leave room for future studies and replication that should be performed. For example, future PGSs could be developed implementing the recent cross-prediction method developed by Mak et al.; this method allows and corrects for overlap between the base and target dataset that would have allowed for a much larger African-ancestry sample (Mak et al. 2018). Additionally, in the future, the PGS could be utilized as an independent variable to predict health outcomes.

In conclusion, this study showed that PGSs are a powerful predictive tool for determining 25(OH)D concentrations. Given the association between the optimal PGS and 25(OH)D concentrations, PGSs could be leveraged for personalized vitamin D supplementation, which could prevent the negative downstream effects of 25(OH)D inadequacy. Additionally, through an in-depth investigation of 25(OH)D SNP heritability, it was shown that the PGS explains more heritability than do GWAS findings to date. This provides additional evidence that many SNPs that function through small effect sizes influence 25(OH)D concentrations, yielding further understanding of the genetic architecture of 25(OH)D. However, much of the heritability remains to be explained, therefore, more research is warranted along the quest to effectively and efficiently preventing 25(OH)D inadequacy through personalized supplementation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Wisconsin-Madison IRVB 2017-0332 and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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