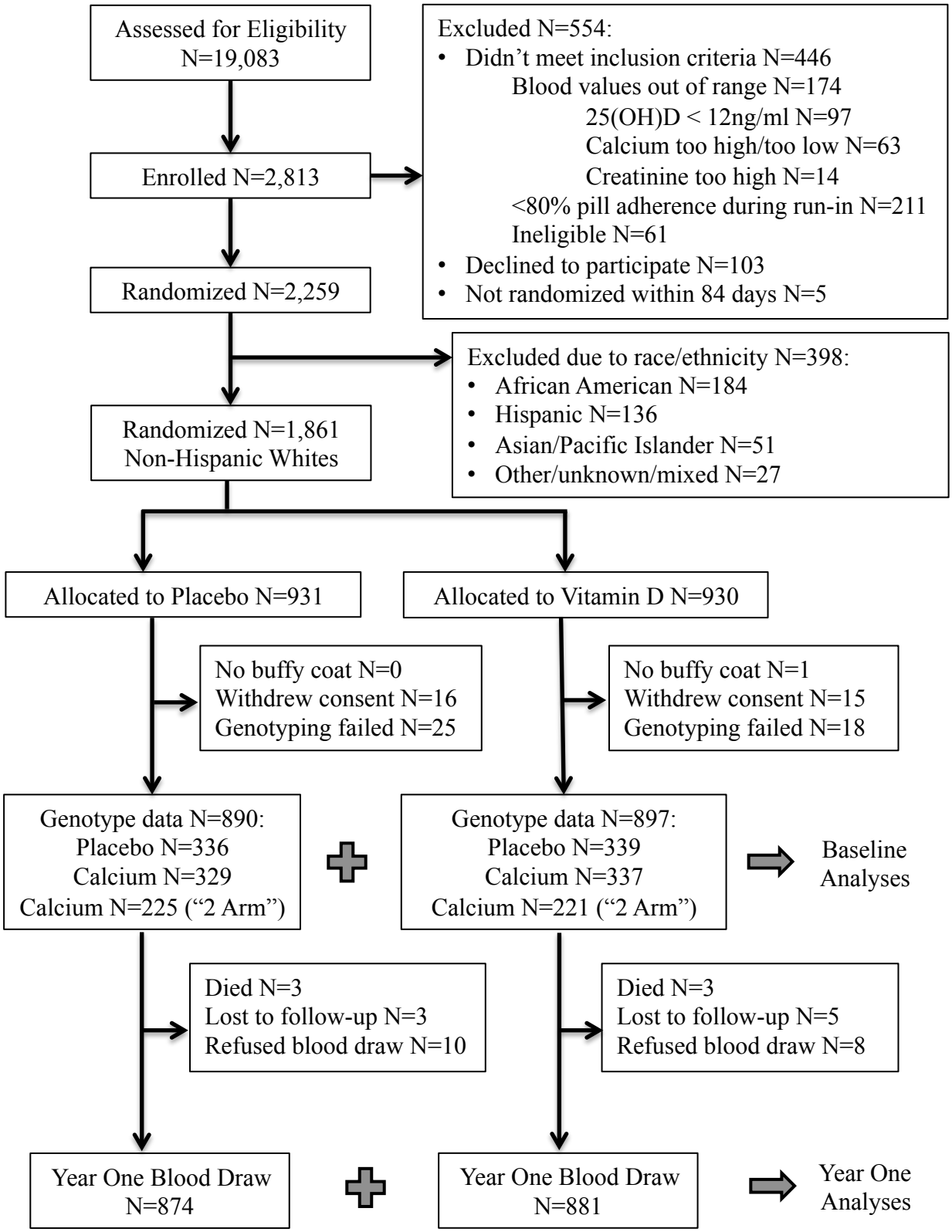
Supplemental Figure 1. Participant Flow Diagram for Genetic Association Analyses



Supplemental Table 1. Description of Candidate SNPs Genotyped

LD[a]	SNP[b,c]	Gene	SNP location or coding change	Alleles	N[d]	MAF	References
	rs12512631	*GC*	3'	T/C	1759	0.37	(1)
*	(rs2282679)	(vitamin D-binding	intron	T/G	1762	0.27	(1-5)
*	(rs3755967)	protein)	intron	C/T	1738	0.27	(2)
*	rs4588		missense	C/A	1737	0.27	(1, 5, 6)
	rs7041		missense	C/A	1748	0.43	(1, 2, 5, 6)
	rs222020		intron	T/C	1755	0.15	(7, 8)
	rs16847015		intron	G/T	1771	0.06	(6)
	rs1155563		intron	T/C	1742	0.27	(1, 2, 5, 6)
	rs2298849		intron	T/C	1771	0.19	(4, 6, 7)
	rs12785878	*DHCR7*[e] (7-dehydro-	5'	T/G	1763	0.26	(2, 7)
	rs3829251	cholesterol reductase)	5'	G/A	1754	0.16	(3, 5, 7)
	rs12794714	*CYP2R1*	synonymous	G/A	1768	0.44	(2, 6-8)
*	rs10741657	(25-hydroxylase)	5'	G/A	1764	0.40	(1-3, 6-8)
*	(rs2060793)		5'	C/T	1756	0.40	(3)
	rs1562902		5'	A/G	1768	0.45	(7)
	rs10766197		5'	G/A	1755	0.46	(7, 8)
*	(rs4646536)	*CYP27B1*	intron	T/C	1760	0.33	(1, 9)
*	(rs10877012)	(1-hydroxylase)	5'	G/T	1759	0.33	(1, 4)
*	rs703842		5'	A/G	1763	0.33	(1)
	rs6013897	*CYP24A1*	3'	T/A	1766	0.20	(2)
	rs2209314	(24-hydroxylase)	intron	T/C	1745	0.24	(10)
	rs2762939		intron	G/C	1757	0.25	(11)
	rs4809958		intron	T/G	1751	0.16	(9)
	rs2244719		intron	T/C	1756	0.47	(12)
	rs2296241		synonymous	A/G	1735	0.47	(12)
	rs17219315		5'	A/G	1768	0.03	(12)
	rs7968585	*VDR*	3'	A/G	1784	0.50	(13)
	rs11574143	(vitamin D receptor)	3'	G/A	1758	0.09	(14, 15)
*	rs731236		synonymous	T/C	1768	0.38	(16)
	rs7975232		intron	A/C	1769	0.49	(16)
*	(rs1544410)		intron	G/A	1757	0.39	(17)
	rs2239179		intron	A/G	1752	0.41	(13)
	rs2228570		start codon[f]	G/A	1777	0.37	(1)
	rs10783219		intron	A/T	1769	0.35	(1)
^	(rs4516035)		intron	T/C	1771	0.43	(1)
^	rs7139166		intron	C/G	1772	0.43	(1)
	rs11568820		intron	C/T	1730	0.20	(16)
*	(rs17251221)	*CASR*	intron	A/G	1768	0.13	(18, 19)
*	rs1801725	(calcium-sensing	missense	G/T	1761	0.13	(18-20)
	rs1042636	receptor)	missense	A/G	1739	0.07	(19-23)
	rs1801726		missense	C/G	1766	0.04	(20, 24)

Abbreviations: LD, linkage disequilibrium; SNP, single nucleotide polymorphism; MAF, minor allele frequency.
[a] Within each gene, * (or ^) indicates SNPs in high LD with each other (r^2>95%).
[b] *VDR* restriction fragment length polymorphisms: rs731236 (taq1), rs7975232 (apa1), rs1544410 (bsm1), rs2228570 (fok 1), rs11568820 (cdx2).
[c] SNPs in parentheses are not included in Table 2 due to high LD (r^2>95%).
[d] Number of participants with genotype data available for analysis.
[e] *DHCR7* SNPs (rs12785878 and rs3829251) are located within introns in the upstream *NADSYN1* gene.
[f] SNP rs2228570 (fok1) leads to new start site 9 bp upstream and VDR protein longer by 3 amino acids.

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Statistical Methods for Haplotype Analyses (see Supplement Table 2)

For haplotype analyses, linkage disequilibrium (LD) blocks were defined with Haploview using the standard algorithm (https://www.broadinstitute.org). Phased haplotype pairs and probabilities were estimated with PLINK using the standard EM algorithm (http://pngu.mgh.harvard.edu). The most common haplotype was used as the reference and was omitted from the regression models. Haplotype was modeled additively according to the number of non-referent variant haplotypes of each common type. Rare haplotypes (<1% frequency) were pooled. Wald test P values were calculated for individual haplotypes, and a likelihood ratio test used for the joint contribution of all haplotypes to the model.

Supplemental Table 2: Associations of Haplotypes with Baseline 25(OH)D Level and Modification of the Increase in 25(OH)D Level Due to Randomized Vitamin D_3 Supplementation (1,000 IU/day) for One Year

Haplotype	Baseline 25(OH)D			Year One Increase in 25(OH)D		
	Frequency (%)	Estimated % difference (95% CI)[a]	P Value[b]	Frequency (%)	Estimated % difference (95% CI)[c]	P Value[d]
GC Block 1: rs12512631, rs2282679, rs3755967, rs4588			**<0.0001**			0.73
CTCC	37	reference		36	reference	
TTCC	36	**-9.34 (-11.63, -6.99)**	**<0.0001**	36	-1.11 (-4.95, 2.90)	0.58
TGTA	26	-0.86 (-3.15, 1.49)	0.47	26	1.30 (-3.00, 5.79)	0.56
rare	0.62	7.30 (-5.24, 21.49)	0.27	0.63	-2.50 (-21.05, 20.41)	0.81
GC Block 2: rs222020, rs16847015, rs1155563			**<0.0001**			0.42
TGT	58	reference		58	reference	
TGC	27	**-8.44 (-10.55, -6.28)**	**<0.0001**	27	1.29 (-2.63, 5.36)	0.53
CGT	11	0.96 (-2.43, 4.47)	0.58	11	-3.96 (-9.33, 1.73)	0.17
CTT	4.6	-0.60 (-5.41, 4.46)	0.81	4.6	-0.38 (-8.41, 8.36)	0.93
DHCR7 Block: rs12785878, rs3829251			0.25			0.06
TG	73	reference		73	reference	
GA	15	-2.39 (-5.63, 0.97)	0.16	15	-1.20 (-5.81, 3.64)	0.62
GG	11	-2.21 (-4.99, 0.66)	0.13	11	5.50 (-0.27, 11.60)	0.06
TA	0.43	-5.51 (-19.40, 10.78)	0.49	0.44	-22.26 (-41.08, 2.57)	0.08
CYP2R1 Block 1: rs12794714, rs10741657, rs2060793			**<0.0001**			**0.01**
AGC	44	reference		44	reference	
GAT	40	**5.82 (3.49, 8.20)**	**<0.0001**	40	1.25 (-2.47, 5.11)	0.52
GGC	16	**2.95 (-0.05, 6.03)**	**0.05**	16.	**7.54 (2.39, 12.94)**	**0.004**
rare	0.06	6.43 (-30.77, 63.61)	0.78	0.06	Data too thin	
CYP2R1 Block 2: rs1562902, rs10766197			**0.002**			**0.02**
AA	46	reference		46	reference	
GG	45	**4.29 (0.56, 8.15)**	**0.02**	45	3.34 (-0.31, 7.13)	0.07
AG	9.2	**3.89 (1.67, 6.15)**	**0.001**	9.3	**8.64 (2.29, 15.39)**	**0.007**
GA	0.06	31.36 (-14.65, 102.18)	0.22	0.06	Data too thin	
CYP27B1 Block: rs4646536, rs10877012, rs703842			0.85			0.61
TGA	67	reference		67	reference	
CTG	33	0.58 (-1.60, 2.81)	0.60	33	-0.23 (-3.83, 3.50)	0.90
rare	0.48	-1.54 (-15.19, 14.30)	0.84	0.46	15.79 (-13.64, 55.25)	0.33
CYP24A1 Block: rs2762939, rs4809958, rs2244719			0.05			0.37
GTC	47	reference		47	reference	
CTT	25	0.25 (-2.68, 3.27)	0.87	25	-3.54 (-7.58, 0.68)	0.10
GGT	16	**3.11 (0.50, 5.79)**	**0.02**	16	1.17 (-3.75, 6.33)	0.65
GTT	12	2.24 (-1.19, 5.79)	0.20	12	-2.55 (-7.93, 3.16)	0.38
rare	0.08	-25.08 (-47.39, 6.68)	0.11	0.09	-1.59 (-47.08, 83.01)	0.96
VDR Block 1: rs11574143, rs731236, rs7975232, rs1544410			0.30			**0.05**
GTCG	49	reference		49	reference	
GCAA	38	1.37 (-0.83, 3.62)	0.22	38	-1.53 (-5.06, 2.14)	0.41
ATAG	8.9	**6.56 (-0.05, 13.61)**	**0.05**	8.8	-3.54 (-9.49, 2.81)	0.27
GTAG	2.8	0.21 (-3.54, 4.09)	0.92	2.9	**-13.87 (-22.52, -4.27)**	**0.006**
rare	1.1	-0.44 (-9.35, 9.34)	0.93	1.1	-9.49 (-23.05, 6.46)	0.23
VDR Block 2: rs10783219, rs4516035, rs7139166, rs11568820			0.76			0.33

ACGC	42	reference		42	reference	
TTCC	35	4.06 (-3.70, 12.43)	0.31	35	-2.96 (-6.70, 0.94)	0.14
ATCT	20	-0.94 (-3.62, 1.82)	0.50	20	0.47 (-4.02, 5.17)	0.84
ATCC	1.9	-0.003 (-2.33, 2.38)	1.00	1.8	0.36 (-12.00, 14.44)	0.96
rare	0.96	-2.52 (-12.40, 8.47)	0.64	0.92	10.85 (-7.71, 33.15)	0.27
CASR Block: rs17251221, rs1801725, rs1042636			0.26			0.51
AGA	79	reference		80	reference	
GTA	13	-1.68 (-4.59, 1.32)	0.27	13	-1.61 (-6.43, 3.45)	0.53
AGG	7.2	0.10 (-3.85, 4.21)	0.96	7.2	-3.50 (-9.77, 3.21)	0.30
GGG	0.03	67.02 (-9.36, 207.75)	0.10	0.03	Data too thin	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval.
Bold numbers indicate P≤0.05.
[a] Estimated % difference in baseline 25(OH)D level per haplotype compared to reference haplotype using linear regression of log-transformed 25(OH)D, adjusting for age, sex, and season of baseline blood draw.
[b] Wald test P-values for individual haplotypes. Likelihood ratio test P-values for joint contribution of all haplotypes in a block (first row).
[c] Estimated % difference in year one 25(OH)D level due to vitamin D_3 supplementation per haplotype compared to the reference haplotype using linear regression of log-transformed year one 25(OH)D, adjusting for log-transformed baseline 25(OH)D, age, sex, season of year one blood draw, haplotype and vitamin D_3 treatment assignment. Estimate is for the interaction between haplotype and vitamin D_3 treatment (haplotype*vitamin D_3 treatment) and indicates how haplotype modifies the effect of vitamin D_3 treatment on year one 25(OH)D level.
[d] Wald test P-values for the interaction term (haplotype*vitamin D_3 treatment). Likelihood ratio test P-values for the joint contribution of all interaction terms for all haplotypes in the block (first row).