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Genetic association analysis of vitamin D pathway with obesity traits

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Abstract

Objective—Observational studies have examined the link between vitamin D deficiency and obesity traits. Some studies have reported associations between vitamin D pathway genes such as *VDR, GC* and *CYP27B1* with body mass index (BMI) and waist circumference (WC); however, the findings have been inconsistent. Hence, we investigated the involvement of vitamin D metabolic pathway genes in obesity-related traits in a large population-based study.

Methods—We undertook a comprehensive analysis between 100 tagging polymorphisms (tagSNPs) in genes encoding for DHCR7, CYP2R1, VDBP, CYP27B1, CYP27A1, CYP24A1, VDR and RXRG and obesity traits in 5,224 participants (aged 45 years) in the 1958 British birth cohort (1958BC). We further extended our analyses to investigate the associations between SNPs and obesity traits using the summary statistics from the GIANT (Genetic Investigation of Anthropometric Traits) consortium (n=123,865).

Results—In the 1958BC (n=5,224), after Bonferroni correction, none of the tagSNPs were associated with obesity traits except for one tagSNP from *CYP24A1* that was associated with waist-hip ratio (WHR) (rs2296239, P=0.001). However, the *CYP24A1* SNP was not associated with BMI-adjusted WHR (WHRadj) in the 1958BC (rs2296239, P=1.00) and GIANT results (n=123,865, P=0.18). There was also no evidence for an interaction between the tagSNPs and obesity on BMI, WC, WHR and WHRadj in the 1958BC. In the GIANT consortium, none of the tagSNPs were associated with obesity traits.

Conclusions—Despite a very large study, our findings suggest that the vitamin D pathway genes are unlikely to have a major role in obesity-related traits in the general population.

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Keywords

Vitamin D pathway; 1958 British birth cohort; tagSNPs; obesity; GIANT; BMI

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Introduction

Obesity is a common multifactorial metabolic disorder that prevalence has been shown to be increasing at an alarming rate.[1, 2] It has been associated with vitamin D deficiency,[3, 4] which is another increasingly prevalent public health concern in developed countries.[5] Several genes from the vitamin D metabolic pathway have been implicated in vitamin D deficiency[6] and genetic variants in some of these genes have been shown to be associated with obesity-related phenotypes[7-9]; however the findings were inconsistent due to the relatively small sample size of several of the studies. Among the most notable, are a study in 1773 healthy Caucasian women which demonstrated a significant association of vitamin D receptor polymorphisms with adiposity phenotypes,[10] and a study in 1,873 Caucasian women reporting an association of vitamin D binding protein gene polymorphisms with percentage of fat mass.[7] However, a recent study in 6,922 Chinese women investigated the association of 198 SNPs in six vitamin D pathway genes with obesity and found that none of the SNPs were associated with BMI after correction for multiple testing.[11] As these studies have been typically small, performed mostly in women and the findings have been inconsistent, there is a need for a replication of these findings in a large well characterised study comprising men and women.

The key genes involved in vitamin D pathway (Table 1) include *DHCR7* (7-dehydrocholesterol reductase), *CYP2R1* (vitamin D-25-hydroxylase), *GC* (vitamin D binding protein, VDBP), *CYP27B1* (25-hydroxyvitamin D-1α-hydroxylase), *CYP27A1* (cytochrome P450, family 27, subfamily A, polypeptide 1), *CYP24A1* (25-hydroxyvitamin D-24-hydroxylase), *VDR* (vitamin D receptor) and *RXRG* (retinoid X receptor gamma).[6, 12] The pathway starts with the conversion of 7-dehydrocholesterol in the skin to a pre-cursor of vitamin D_3 on exposure to sunlight. The DHCR7 converts 7-dehydrocholesterol to cholesterol, thereby removing the cholesterol pathway from the synthetic pathway of vitamin D_3. The previtamin D_3 in turn is converted to vitamin D_3 in a heat-dependent process. The first step in activation, 25-hydroxylation occurring primarily in the liver, is mediated mostly by the microsomal 25-hydroxylase, *CYP2R1*, and possibly to some extent by mitochondrial hydroxylase, *CYP27A1*. 25-hydroxyvitamin D (25(OH)D) is bound to the VDBP, transported to the kidneys and converted by CYP27B1 to the biologically active form 1,25-dihydroxyvitamin D_3 (calcitriol), which further activates the VDR to interact with RXRG leading to the activation/suppression of the target gene expression. Calcitriol can up-regulate the expression of CYP24A1, which catabolises 25(OH)D and calcitriol to water-soluble, biologically inactive metabolites for excretion in the bile.

Based on the vitamin D pathway (Table 1), we conducted a candidate gene association study examining the association of 100 tagging single nucleotide polymorphisms (tagSNPs) from the eight vitamin D metabolism genes,[6] namely *DHCR7, CYP2R1, GC, CYP27B1, CYP27A1, CYP24A1, VDR* and *RXRG* with obesity traits, specifically BMI, waist circumference (WC), waist-hip ratio (WHR) and BMI-adjusted WHR (WHRadj) and also testing for gender specific effects of the genetic variations on obesity traits in 5,224 individuals from the 1958 British Birth Cohort. We further extended our analyses to investigate the association between SNPs and obesity traits using summary results from the GIANT (Genetic Investigation of Anthropometric Traits) (n=123,865) consortium.[13, 14]

Methods

Study population

Detailed description of the 1958 British birth cohort (1958BC) has been published previously.[15] In brief, study participants were born in England, Scotland or Wales during one week in March 1958 (n=17,638).[16] At age 45 years, 11,971 participants were invited to attend a biomedical survey: 9,377 (78%) completed at least one questionnaire. The 1958BC is almost entirely a white European population (98%),[17] and for these analyses, 158 individuals of other ethnic groups and one pregnant participant were excluded. The main analyses were conducted on 5,224 participants of European ancestry with information on the 100 tagSNPs, BMI, and WC (Table 2). The 45-year biomedical survey was approved by the South-East Multi-Centre Research Ethics Committee (ref. 01/1/44), and written consent [for use of information in medical research studies] was obtained from the participants.

Data collection

Weight and standing height, at 45 years of age, were measured without shoes and in light clothing by a trained nurse using standardized protocol and equipment; WC was measured by the nurse midway between the costal margin and iliac crest.

TagSNP selection and genotyping

TagSNPs in the genes, *DHCR7, CYP2R1, GC, CYP27B1, CYP27A1, CYP24A1, VDR* and *RXRG*, were selected using genotype data from the International HapMap collected in individuals of Northern and Western European ancestry (CEU) (HapMap data release 24/ phase II Nov08, on NCBI B36 assembly, dbSNP b126). The Haploview software V3.3 (http://www.broadinstitute.org/haploview/haploview-downloads) was used to assess the linkage disequilibrium (LD) structure between SNPs.[18] Tagger software was used to select tagSNPs with the 'pairwise tagging only' option and an r^2 threshold of >0.8 (±10kb upstream and downstream of the genes). In the tagSNP selection, we force included the functional SNPs previously studied (rs2276360, rs12794714, rs4588, rs7041, rs2296239, rs6068816, rs2296241, rs731236, rs2228570, rs2134095) before running tagger. There were 122 tagSNPs; however, 22 SNPs were excluded from the analysis either because of their very low call rate (<90%) or low minor allele frequency (<5%). In total, there were 100 tagSNPs (4 tagSNPs in the *DHCR7*, 8 in the *CYP2R1*, 13 in the *GC*, 22 in the *CYP24A1*, 2 in the *CYP27B1*, 2 in the *CYP27A1*, 26 in the *VDR* and 23 in the *RXRG*) representing the common genetic variations across the eight genes (Table 1).

Genome-wide data for the 1958BC were obtained through two sub-studies, both using the 1958BC members as population controls. The first sub-study included 3,000 DNA samples randomly selected as part of the Wellcome Trust Case Control Consortium (WTCCC2) and genotyped on the Affymetrix 6.0 platform.[19] The second sub-study was the Type 1 diabetes case-control study (T1DGC) which used 2,500 DNA samples and genotyped using the Illumina Infinium 550K chip through the JDRF/WT Diabetes and Inflammation Laboratory.[20] All SNPs included in the analysis had call rate >95%, imputation quality >0.9, MAF >0.05, and were in Hardy-Weinberg equilibrium (p>0.01).

Associations between the 100 tagSNPs and obesity traits (BMI and WHRadj) were further investigated using summary statistics from the GIANT consortium,[13, 14] which currently encompasses 46 studies with up to 123,865 genotyped adult individuals of European ancestry associations. The samples from 46 studies were genotyped using Affymetrix and Illumina whole genome genotyping arrays.[13] Imputation of polymorphic HapMap European CEU SNPs was done to allow for meta-analysis across different marker sets from 46 studies.[13]

Statistical analysis

The natural logarithm was used to transform slightly skewed variables (BMI and WC) to an improved approximation of the normal distribution. All the SNPs were coded additively for the minor allele. The genetic associations with the continuous outcomes were examined using linear regression models, adjusted for gender and region (coded as Scotland, North of England, Middle of England including Wales, and South of England) because of their contribution to the model fit. World Health Organization recommendations for BMI (≥30 kg/m^2) was used to define obesity.[21] Differences in the genotype frequencies among underweight (BMI <18.5 kg/m^2), healthy weight (BMI ≥18.5, < 25 kg/m^2) and overweight/obese (BMI ≥25 kg/m^2) were tested using the Fisher's exact test. Results from the two sub-studies were meta-analysed using a fixed effects model. Because of the differing body composition in men and women, we also tested for the interaction between the tagSNPs and gender on the obesity traits in the 1958BC. In order to assess whether the results varied between obese and non-obese individuals, interactions between tagSNPs and obesity were also tested. Interactions were tested by conducting a 1-df test on the interaction term. All P values are from likelihood ratio tests (LRT). Bonferroni correction was used to adjust for multiple testing, with a corrected P value <0.05/(No. of SNPs tested) being considered statistically significant (100 SNPs tested in the 1958BC and 98 SNPs with BMI and 96 SNPs with WHRadj in GIANT). The analyses were conducted using STATA, version 12.

In the GIANT consortium, each study performed the association of the SNPs with BMI using an additive genetic model adjusted for age, age^2 and other appropriate covariates such as principal components.[13] Meta-analysis was performed using the inverse-variance method, which is based on beta coefficients and standard errors from each individual genome-wide association study. We used the GIANT consortium summary statistics for the outcomes, BMI and WHRadj, which are publicly available to download from the link: (http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files)

Results

In the 1958BC (n=5,224), of the 100 tagSNPs, only one tagSNP from *CYP24A1* was associated with WHR (rs2296239, P=0.01), after correction for multiple testing (Table 3). However, when the *CYP24A1* SNP rs2296239 was tested for its association with WHRadj, the association was not significant after correction for multiple testing (Table 3). None of the other tagSNPs showed an association with BMI, WC, and WHR in the 1958BC (Table 3). There was no difference in the genotype frequencies of the 100 tagSNPs among the underweight, healthy weight and overweight/obese (P>0.05, for all comparisons). We found no evidence for effect modification by gender affecting associations between the tagSNPs and BMI, WC or WHR in the 1958BC (uncorrected p-interaction >0.05 for all comparisons, data not shown). Also, there were no statistically significant interactions between the tagSNPs and obesity on BMI, WC, WHR and WHRadj, after correction for multiple testing (p>0.05). As the interaction analysis were likely to have low statistical power, we tested for the association between the tagSNPs and the obesity related outcomes such as BMI, WC and WHR among obese individuals only and found that none of the associations were significant after correction for multiple testing (corrected P>0.11 for all outcomes).

In the GIANT consortium (n=123,865), the *CYP24A1* tagSNP rs927651 (r^2=1 with rs2296239, that showed an association with WHR in the 1958BC) was not associated with WHRadj (P=0.18) (Table 3).Two tagSNPs from *CYP27A1*, that did not show an association with BMI in the 1958BC, were associated with BMI (rs17470271, P=0.002; rs6436089, P=0.0005) in the GIANT; however, after correction for multiple testing, SNP rs6436089 showed a borderline association with BMI (P=0.05) and the SNP rs17470271 did not show

an association with BMI (P=0.22). None of the other tagSNPs were associated with BMI or WHRadj in the GIANT consortium.

Discussion

Our analyses, using 100 tagSNPs in the eight vitamin D pathway genes provided very little support for an association with obesity-related traits including BMI, WC and WHR. Analyses in the 1958BC (n=5,224) did not support gender specific effects, despite some evidence from previous smaller samples. In addition, the summary data from the GIANT consortium (n=123,865) show that the vitamin D pathway genes are unlikely to have a major contribution to obesity-related outcomes.

For the evaluation of a possible causal association between vitamin D and adiposity outcomes using an approach of genetic proxy markers,[22] associations between genes known to affect 25(OH)D concentrations are of great interest. In particular, *CYP2R1* and *DHCR7* both of which are located on the same chromosome 11 function upstream (synthesis) of the 25(OH)D production, while *GC, CYP24A1* and *CYP27B1* function downstream (metabolism) of the 25(OH)D production.[23] *DHCR7* was identified as a novel locus for association with vitamin D status in a recent genome-wide association study;[24] and this is the first large study to comprehensively analyse related genetic variants in association with obesity outcomes. However, none of the *DHCR7* or *CYP2R1* tagSNPs were associated with BMI, WC and WHR/WHRadj in the 1958BC or GIANT. These data also provided no support for previously reported association between genetic variants in the *GC* and BMI.[7] The other downstream regulator, *CYP27B1*, had been shown to be a candidate for hypoleptinemia and hyperphagia based on the knock-out mice studies.[25] However, again *CYP27B1* tagSNPs were not associated with obesity traits in our analyses, confirming the findings from the recent study in 6,922 Chinese women.[11]

In our analyses, also none of the *VDR* and *RXRG* tagSNPs were associated with obesity traits. This is in contrast to several smaller genetic association studies that demonstrated an association between *VDR* and obesity phenotypes.[10, 26-29] However, negative findings have also been reported by a handful of studies.[11, 30] The reported associations between *VDR* and adiposity phenotypes could be a result of publication bias, which is known to be a problem with genetic association studies,[31] with our data strongly suggesting that if true associations were to exist they are likely to be negligible. This highlights the need for caution in the interpretation of individual studies that lack adequate statistical power or replication.

The observed lack of association was very convincing, with the exception for the marginal association observed for *CYP27A1* SNP rs6436089 in the GIANT consortium even after accounting for multiple testing. *CYP27A1* was not identified as a genome-wide significant locus for 25(OH)D concentrations in the large meta-analyses by the SUNLIGHT consortium.[24] Compared to CYP2R1, which has been shown to be highly specific for 25-hydroxylation, the affinity of CYP27A1 is low.[32] Hence, it is not known whether the two 25-hydroxylases (Table 1), CYP2R1 and CYP27A1, represent an example of biological redundancy in the vitamin D metabolic pathway or whether *CYP2R1* alone or some unidentified enzyme compensates this essential role. It seems possible that the observed association of *CYP27A1* variant with BMI in the GIANT meta-analysis represents a chance finding, and certainly before firm statements about a presence of true association, this finding warrants replication in larger studies.

Our results are negative; however, this study is important given the several previous reports, where conclusions for an association between vitamin D related genetic variants and obesity outcomes have been done based on notably smaller samples. Given the large size of our

study, and that results from the large meta-analyses carried out by the GIANT consortium (n=123,865) further confirmed our findings, it appears unlikely that our null findings will be false-negatives. We corrected for multiple testing by applying a Bonferroni correction for the number of SNPs tested, both in the 1958BC and in the GIANT consortium. An alternative approach would have been to include the GIANT results purely as replication rather than reporting all the SNPs. However, the only SNP, rs2296239, that showed association with WHR in 1958BC after correction for multiple testing, did not show any evidence for association even without any corrections in the GIANT data, which suggests that the selection of statistical strategy did not affect our conclusions.

None of the previous studies have conducted a replication to confirm their findings, which is one of the main drawbacks of genetic association studies.[33] We have also confirmed in the 1958BC that the lack of association between vitamin D pathway gene polymorphisms and obesity traits does not appear to be due to gender-specific effects, given the lack of any evidence for interaction between gender and tagSNPs on obesity-related traits. In addition, there was no evidence for effect modification by obesity affecting associations between the tagSNPs and BMI, WC, WHR and WHRadj in the 1958BC.

One of the limitations of our study is that we were able to capture only ~82% of the common genetic variations across the eight genes as we had to exclude 22 SNPs because of their low minor allele frequency (<5%) and low call rate (<95%). Of these 22 tagSNPs, 20 SNPs were from the non-coding regions and two SNPs were from the coding regions (rs760242 from *DHCR7* gene and rs10735810 from *VDR* gene). Although there is a possibility that the remaining 18% might contribute to the variation in the BMI, the previous large-scale study has also failed to demonstrate an association of the vitamin D pathway genes with obesity traits[11]. However, functional characterization of the two SNPs from the *DHCR7* and *VDR* genes is warranted to confirm their role in obesity. Another limitation is the lack of more refined indicators for adiposity or fat mass in the 1958BC and GIANT consortium. Although animal studies have convincingly illustrated the role of some of the vitamin D genes in contributing to adiposity phenotypes, it is possible that there is, indeed, no effect in humans, either because the gene is not necessary for the regulation of these phenotypes or because functional variation is absent.

In conclusion, our findings show that the vitamin D pathway genes are unlikely to have an important impact on the obesity outcomes.

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Abbreviations

1958BC 1958 British birth cohort

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SNP	single nucleotide polymorphism
GIANT	Genetic investigation of anthropometric traits
BMI	Body mass index
WC	waist circumference
WHR	waist hip ratio

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Table 1
Vitamin D pathway candidate genes and their functions

Gene name	Gene symbol	Gene function in relation to vitamin D pathway	Chromosome location	Number of tagSNPs
7-dehydrocholesterol reductase	*DHCR7*	Encodes the enzyme that converts 7-dehydrocholesterol to cholesterol, thereby removing the substrate from the synthetic pathway of vitamin D_3	11q13.4	4
Vitamin D-25-hydroxylase	*CYP2R1*	Encodes the microsomal 25-hydroxylase that catalyses the C-25 hydroxylation of vitamin D_3	11p15.2	8
Cytochrome P450, family 27, subfamily A, polypeptide 1	*CYP27A1*	Encodes the mitochondrial 25-hydroxylase that catalyses the C-25 hydroxylation of vitamin D_3	2q33-qter	2
Group-specific component (Vitamin D binding protein)	*GC*	Encodes the serum glycoprotein that binds to 25-hydroxyvitamin D and other vitamin D sterol metabolites and transports them in circulation to target organs	4q12-q13	13
25-hydroxyvitamin D-1α-hydroxylase	*CYP27B1*	Encodes a member of the cytochrome P450 superfamily of enzymes that catalyses the synthesis of active 1, 25-dihydroxyvitamin D_3	12q13.1-q13.3	2
25-hydroxyvitamin D-24-hydroxylase	*CYP24A1*	Encodes the enzyme that catabolises 1,25-dihydroxyvitamin D_3 to the water-soluble, biologically inactive calcitroic acid	20q13	22
Vitamin D receptor	*VDR*	Encodes the nuclear hormone receptor for vitamin D_3	12q13.11	26
Retinoid X receptor, gamma	*RXRG*	As homo- or heterodimers, binds to the VDR and regulates transcription	1q22-q23	23

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Table 2

Characteristics of the study participants

Characteristics	Median [IQR] or N (%)
Gender	
Men	2,625 (50.25)
Women	2,599 (49.75)
Region	
South of England (including London)	1,961 (37.54)
Middle of England (including Wales)	1,372 (26.26)
North of England	1,374 (26.30)
Scotland	517 (9.90)
Waist circumference (cm)	91.90 [82.15, 100.80]
Waist-Hip ratio	0.87 [0.80, 0.93]
Weight (kg)	77.4 [66.4, 89.2]
Body mass index (kg/m^2)	26.66 [24.03, 29.85]
Underweight (BMI<18.5)	27 (0.52)
Healthy weight (BMI ≥18.5, <25)	1,757 (33.63)
Overweight (BMI ≥25, <30)	2,173 (41.60)
Obese (BMI ≥30)	1,267 (24.25)

IQR, Interquartile range

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Table 3

Association of the 100 tagging polymorphisms in the Vitamin D pathway genes with obesity-related traits in the 1958 British Birth cohort (n= 5,224) and GIANT Consortium (n= 123,865)

Vitamin D pathway Genes	1958 British Birth cohort								GIANT consortium	
	BMI* (kg/m^2)		Waist Circumference* (cm)		Waist-Hip ratio		Waist-Hip ratio (adjusted for BMI)		BMI (kg/m^2)	Waist-Hip ratio$^{\psi}$
	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)
7-dehydrocholesterol reductase (*DHCR7*)										
rs1790349	−0.006±0.005	0.23	−0.004±0.004	0.26	−0.001±0.002	0.64	0.001±0.001	0.48	0.16	0.80
rs2002064	−0.003±0.004	0.56	−0.002±0.003	0.51	0.001±0.001	0.72	0.001±0.001	0.48	0.87	0.51
rs2276360	−0.001±0.004	0.91	−0.001±0.003	0.69	0.001±0.001	0.72	0.001±0.001	0.72	0.81	0.33
rs4316537	0.0±0.008	0.99	−0.001±0.006	0.83	0.0±0.003	1.00	0.0±0.002	0.88	0.09	0.68
Vitamin D-25-hydroxylase (*CYP2R1*)										
rs10832312	0.004±0.005	0.46	0.003±0.004	0.37	0.0±0.002	0.85	−0.001±0.001	0.72	0.05 (1.00)	0.76
rs11023374	0.003±0.004	0.39	0.0±0.003	1.00	0.001±0.001	0.72	0.001±0.001	0.72	0.36	0.73
rs11819875	0.003±0.005	0.47	0.005±0.003	0.14	0.003±0.001	0.03 (1.00)	0.003±0.001	0.08	0.10	0.08
rs12794714	−0.002±0.004	0.57	−0.003±0.002	0.27	0.001±0.001	0.72	0.0±0.001	0.65	0.06	0.61
rs1562902	0.003±0.004	0.48	0.002±0.002	0.34	−0.001±0.001	0.48	−0.001±0.001	0.12	0.06	0.97
rs16930625	0.001±0.006	0.93	0.004±0.004	0.41	0.003±0.002	0.16	0.003±0.002	0.11	0.98	0.39
rs1868997	0.001±0.004	0.89	0.001±0.003	0.86	−0.002±0.001	0.29	−0.001±0.001	0.18	0.42	0.92
rs7129781	0.007±0.006	0.31	0.005±0.005	0.29	0.004±0.002	0.09	0.002±0.002	0.35	0.06	0.54
Vitamin D binding protein (*GC*)										
rs1155563	0.003±0.004	0.39	0.0±0.003	1.00	0.0±0.001	1.00	−0.001±0.001	0.72	0.89	0.35
rs12512631	0.002±0.004	0.57	0.003±0.003	0.29	0.002±0.001	0.29	0.0±0.001	0.82	0.08	0.33
rs12640179	−0.005±0.006	0.48	−0.005±0.005	0.31	−0.001±0.002	0.81	0.001±0.002	0.81	0.54	0.81
rs1352844	−0.01±0.005	0.06	−0.005±0.004	0.22	−0.001±0.002	0.55	0.001±0.001	0.48	0.57	0.74
rs1491718	0.009±0.006	0.13	−0.006±0.004	0.16	−0.003±0.002	0.24	−0.001±0.001	0.72	0.29	0.96
rs222020	−0.01±0.005	0.02 (1.00)	−0.009±0.004	0.02 (1.00)	−0.002±0.001	0.16	0.0±0.001	1.00	0.15	0.44
rs2298849	−0.01±0.004	0.01 (1.00)	−0.007±0.003	0.01 (1.00)	−0.002±0.001	0.16	0.0±0.001	1.00	0.51	0.97

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Vitamin D pathway Genes	1958 British Birth cohort								GIANT consortium	
	BMI* (kg/m^2)		Waist Circumference* (cm)		Waist-Hip ratio		Waist-Hip ratio (adjusted for BMI)		BMI (kg/m^2)	Waist-Hip ratio$^{\Psi}$
	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)
rs4364228	0.001±0.007	0.94	0.003±0.005	0.58	0.0±0.002	0.91	−0.001±0.002	0.81	0.92	0.28
rs4588	0.004±0.004	0.32	−0.001±0.003	0.72	−0.001±0.001	0.72	−0.001±0.001	0.48	–	–
rs6817912	−0.009±0.007	0.23	−0.008±0.005	0.11	−0.001±0.002	0.64	0.001±0.002	0.64	0.92	0.51
rs6837549	0.004±0.004	0.32	0.005±0.002	0.05	0.001±0.001	0.48	−0.001±0.001	0.18	0.42	0.47
rs7041	0.001±0.004	0.89	−0.003±0.002	0.24	0.0±0.001	1.00	0.0±0.001	0.82	0.66	0.43
rs705117	−0.003±0.005	0.53	−0.001±0.004	0.78	−0.001±0.001	0.72	0.0±0.001	1.00	0.51	0.65
25-hydroxyvitamin D-1α-hydroxylase (*CYP27B1*)										
rs1048691	−0.001±0.004	0.81	−0.002±0.003	0.59	−0.001±0.001	0.72	−0.001±0.001	0.72	0.09	0.28
rs10877012	0.001±0.004	0.89	0.001±0.003	0.72	0.001±0.001	0.72	0.001±0.001	0.72	–	–
Cytochrome P450, family 27, subfamily A, polypeptide 1 (*CYP27A1*)										
rs17470271	0.002±0.004	0.57	−0.001±0.002	0.59	−0.001±0.001	0.72	−0.001±0.001	0.37	0.002 (0.22)	0.85
rs6436089	−0.004±0.004	0.26	0.0±0.002	0.97	0.001±0.001	0.48	0.001±0.001	0.04 (1.00)	0.0005 (0.05)	0.88
25-hydroxyvitamin D-24-hydroxylase (*CYP24A1*)										
rs1570669	0.008±0.004	0.02 (1.00)	0.008±0.003	0.005 (0.47)	0.004±0.001	0.005 (0.47)	0.002±0.001	0.01 (1.00)	0.41	0.27
rs2245153	0.011±0.004	0.01 (0.952)	0.008±0.003	0.01 (1.00)	0.003±0.001	0.03 (1.00)	0.002±0.001	0.29	0.62	0.42
rs2248359	0.004±0.004	0.26	0.004±0.003	0.16	0.001±0.001	0.48	0.001±0.001	0.37	0.29	0.86
rs2296239	0.011±0.004	0.01(1.00)	0.009±0.003	0.003 (0.15)	0.006±0.001	0.0001 (0.01)	0.003±0.001	0.03 (1.00)	0.31	0.18$^{\$}$
rs2426498	0.006±0.005	0.26	0.003±0.004	0.47	0.002±0.002	0.15	0.001±0.002	0.41	0.63	0.78
rs2585413	−0.003±0.004	0.39	−0.001±0.003	0.86	0.001±0.001	0.72	0.001±0.001	0.72	0.35	0.90
rs2585424	0.012±0.007	0.09	0.011±0.006	0.06	0.004±0.003	0.16	0.002±0.002	0.48	0.16	0.63
rs2762926	0.001±0.004	0.89	0.003±0.002	0.29	0.003±0.001	0.08	0.002±0.001	0.07	0.79	0.45
rs2762927	0.001±0.004	0.89	0.003±0.003	0.38	0.002±0.001	0.16	0.001±0.001	0.18	0.53	0.54
rs2762932	−0.004±0.005	0.42	−0.002±0.004	0.67	−0.001±0.001	0.48	0.0±0.001	1.00	0.36	0.72
rs2762934	−0.006±0.004	0.16	−0.002±0.003	0.53	−0.001±0.001	0.72	0.001±0.001	0.72	0.69	–
rs3787555	0.005±0.004	0.24	0.004±0.003	0.11	0.002±0.001	0.29	0.002±0.001	0.29	0.32	0.14

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Vitamin D pathway Genes	1958 British Birth cohort								GIANT consortium	
	BMI* (kg/m^2)		Waist Circumference* (cm)		Waist-Hip ratio		Waist-Hip ratio (adjusted for BMI)		BMI (kg/m^2)	Waist-Hip ratio$^{\psi}$
	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)
rs3787557	0.009±0.005	0.09	0.006±0.004	0.07	0.002±0.002	0.18	0.002±0.001	0.29	0.32	0.14
rs4809956	0.005±0.004	0.29	0.005±0.003	0.13	0.004±0.001	0.01 (1.00)	0.002±0.001	0.16	0.87	0.27
rs4809958	0.004±0.005	0.37	0.003±0.004	0.39	0.002±0.001	0.29	0.002±0.001	0.29	0.69	0.04 (1.00)
rs4809959	−0.005±0.004	0.16	−0.005±0.003	0.05 (1.00)	−0.003±0.001	0.08	−0.002±0.001	0.03 (1.00)	0.54	0.93
rs4809960	0.011±0.004	0.004 (0.42)	0.009±0.003	0.001 (0.15)	0.004±0.001	0.005 (0.47)	0.002±0.001	0.29	0.59	0.47
rs6068816	0.001±0.006	0.93	0.001±0.004	0.81	0.001±0.002	0.81	0.001±0.001	0.72	0.81	0.04 (1.00)
rs6068821	0.006±0.004	0.12	0.006±0.003	0.03 (1.00)	0.003±0.001	0.08	0.001±0.001	0.50	0.25	0.69
rs6097797	−0.001±0.005	0.92	0.002±0.004	0.57	0.001±0.002	0.46	0.002±0.001	0.29	0.83	0.60
rs8124792	0.014±0.007	0.07	0.012±0.006	0.03 (1.00)	0.006±0.003	0.05	0.003±0.002	0.16	0.51	0.25
rs927650	−0.003±0.004	0.39	−0.005±0.002	0.04 (1.00)	−0.003±0.001	0.03 (1.00)	−0.002±0.001	0.01 (1.00)	0.70	0.56
Vitamin D receptor (*VDR*)										
rs11568820	−0.006±0.004	0.16	−0.003±0.003	0.31	−0.003±0.001	0.08	−0.002±0.001	0.29	0.57	0.72
rs11574143	−0.004±0.006	0.48	−0.006±0.004	0.19	−0.002±0.002	0.35	−0.002±0.002	0.48	0.98	0.94
rs12721364	0.003±0.005	0.51	−0.001±0.004	0.89	−0.001±0.001	0.72	−0.001±0.001	0.72	0.81	0.56
rs1540339	0.003±0.004	0.48	−0.002±0.003	0.48	−0.002±0.001	0.16	−0.002±0.001	0.07	0.25	0.54
rs2107301	−0.002±0.004	0.57	−0.005±0.003	0.08	−0.004±0.001	0.01 (1.00)	−0.003±0.001	0.03 (1.00)	0.21	0.73
rs2189480	0.0±0.004	1.00	−0.005±0.003	0.11	−0.003±0.001	0.08	−0.001±0.001	0.12	0.61	0.70
rs2238136	0.006±0.004	0.12	0.005±0.003	0.11	0.003±0.001	0.08	0.002±0.001	0.29	0.90	0.91
rs2239179	−0.003±0.004	0.48	−0.001±0.002	0.70	0.002±0.001	0.29	0.001±0.001	0.50	0.47	0.64
rs2239182	0.002±0.004	0.67	0.0±0.002	0.93	−0.002±0.001	0.29	−0.001±0.001	0.50	0.88	0.92
rs2239186	0.002±0.004	0.64	−0.003±0.003	0.37	−0.002±0.001	0.29	−0.002±0.001	0.16	0.73	0.85
rs2254210	0.001±0.004	0.89	0.001±0.003	0.86	0.001±0.001	0.72	0.0±0.001	0.82	0.04 (1.00)	0.99
rs2283342	0.0±0.005	1.00	−0.004±0.004	0.26	−0.003±0.001	0.03 (1.00)	−0.003±0.001	0.03 (1.00)	0.37	0.39
rs2853564	0.006±0.004	0.12	0.004±0.003	0.22	0.001±0.001	0.48	0.0±0.001	1.00	0.09	0.70
rs3819545	0.002±0.004	0.67	−0.002±0.003	0.59	−0.001±0.001	0.48	−0.001±0.001	0.18	0.65	0.55

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Vitamin D pathway Genes	1958 British Birth cohort								GIANT consortium	
	BMI* (kg/m^2)		Waist Circumference* (cm)		Waist-Hip ratio		Waist-Hip ratio (adjusted for BMI)		BMI (kg/m^2)	Waist-Hip ratio$^{\psi}$
	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)
rs3847987	−0.002±0.005	0.76	−0.003±0.004	0.48	−0.002±0.002	0.35	−0.002±0.001	0.29	0.94	0.94
rs3890733	0.005±0.004	0.16	0.004±0.003	0.16	0.002±0.001	0.16	0.002±0.001	0.07	0.41	0.50
rs4237855	−0.002±0.004	0.55	−0.002±0.003	0.58	−0.001±0.001	0.72	0.002±0.001	0.07	0.04 (1.00)	0.53
rs4328262	−0.003±0.004	0.47	−0.002±0.003	0.48	0.001±0.001	0.72	0.001±0.001	0.26	0.69	0.45
rs4516035	0.003±0.004	0.39	0.002±0.002	0.49	0.001±0.001	0.48	0.0±0.001	1.00	0.19	0.11
rs4760648	−0.009±0.004	0.02 (1.00)	−0.006±0.002	0.01 (0.98)	−0.002±0.001	0.16	−0.001±0.001	0.37	0.09	0.58
rs7132324	0.003±0.004	0.48	0.002±0.003	0.59	0.002±0.001	0.29	0.001±0.001	0.48	0.16	0.53
rs7136534	−0.005±0.004	0.21	−0.003±0.003	0.29	−0.003±0.001	0.08	−0.002±0.001	0.16	0.44	0.77
rs7299460	−0.007±0.004	0.048 (1.00)	−0.005±0.003	0.08	−0.003±0.001	0.03 (1.00)	−0.002±0.001	0.16	0.59	0.91
rs731236	−0.003±0.004	0.39	−0.001±0.002	0.70	0.001±0.001	0.72	0.0±0.001	0.65	0.10	–
rs739837	0.004±0.004	0.26	0.003±0.002	0.29	0.001±0.001	0.72	0.0±0.001	0.82	0.94	0.28
rs886441	0.001±0.004	0.81	0.003±0.003	0.34	0.002±0.001	0.48	0.001±0.001	0.72	0.02 (1.00)	0.23
Retinoid X receptor gamma (*RXRG*)										
rs10489745	−0.006±0.006	0.28	−0.005±0.005	0.28	0.0±0.002	1.00	0.001±0.002	0.71	0.10	0.52
rs10800098	−0.004±0.007	0.56	0.0±0.005	0.99	0.003±0.003	0.37	0.003±0.002	0.16	0.48	0.52
rs10918172	−0.005±0.004	0.24	−0.004±0.004	0.32	−0.003±0.001	0.08	−0.002±0.001	0.29	0.91	0.76
rs12069160	−0.004±0.007	0.54	−0.002±0.005	0.65	0.001±0.002	0.57	0.002±0.002	0.35	0.34	0.19
rs12739596	−0.011±0.004	0.006 (0.58)	−0.007±0.003	0.01 (1.00)	−0.003±0.001	0.08	−0.001±0.001	0.72	0.29	0.91
rs157861	0.002±0.004	0.74	0.001±0.003	0.72	−0.001±0.001	0.72	−0.002±0.001	0.29	0.13	0.22
rs157864	0.002±0.005	0.71	0.004±0.004	0.26	0.001±0.001	0.48	0.0±0.001	1.00	0.18	0.29
rs157871	0.006±0.005	0.27	−0.001±0.004	0.89	−0.001±0.002	0.58	−0.003±0.001	0.08	0.68	0.07
rs157872	−0.004±0.004	0.32	−0.005±0.002	0.05 (1.00)	−0.003±0.001	0.03 (1.00)	−0.002±0.001	0.01 (1.00)	0.82	0.33
rs17429123	−0.009±0.004	0.045 (1.00)	−0.005±0.003	0.09	−0.003±0.001	0.08	−0.001±0.001	0.48	0.76	0.64
rs2134095	0.002±0.004	0.57	−0.001±0.003	0.72	−0.002±0.001	0.16	−0.001±0.001	0.12	0.17	0.02 (1.00)
rs2281985	−0.004±0.003	0.18	−0.006±0.002	0.01 (1.00)	−0.003±0.001	0.08	−0.002±0.001	0.03 (1.00)	0.49	0.30

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Vitamin D pathway Genes	1958 British Birth cohort								GIANT consortium	
	BMI* (kg/m^2)		Waist Circumference* (cm)		Waist-Hip ratio		Waist-Hip ratio (adjusted for BMI)		BMI (kg/m^2)	Waist-Hip ratio$^{\psi}$
	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Beta ± SE	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)	Unadjusted *P* (Adjusted *P***)
rs283694	0.001±0.004	0.89	0.0±0.003	1.00	−0.001±0.001	0.72	−0.001±0.001	0.72	0.76	0.30
rs283695	0.001±0.004	0.78	−0.002±0.002	0.49	−0.002±0.001	0.29	−0.001±0.001	0.12	0.65	0.02 (1.00)
rs285429	0.004±0.005	0.42	−0.003±0.004	0.48	−0.003±0.001	0.08	−0.003±0.001	0.03 (1.00)	0.57	0.07
rs285480	0.0±0.004	0.93	0.001±0.003	0.72	0.0±0.001	1.00	0.0±0.001	1.00	0.19	0.29
rs285482	0.004±0.004	0.25	0.003±0.003	0.29	0.001±0.001	0.72	−0.001±0.001	0.72	0.13	0.02 (1.00)
rs3753898	−0.002±0.004	0.64	0.007±0.003	0.02 (1.00)	0.005±0.001	0.001 (0.15)	0.005±0.001	0.001 (0.15)	0.96	0.84
rs3767333	−0.005±0.004	0.24	−0.005±0.003	0.08	−0.003±0.001	0.03 (1.00)	−0.002±0.001	0.16	0.60	0.87
rs380518	0.003±0.005	0.47	0.002±0.004	0.67	0.001±0.002	0.52	0.0±0.001	1.00	0.75	0.58
rs466639	0.0±0.005	0.99	0.005±0.004	0.17	0.001±0.002	0.58	0.002±0.001	0.29	0.08	0.59
rs6669441	0.002±0.004	0.64	−0.004±0.003	0.25	−0.003±0.001	0.03 (0.78)	−0.003±0.001	0.03 (1.00)	0.62	0.19
rs746332	0.001±0.005	0.84	−0.004±0.004	0.26	−0.002±0.002	0.17	−0.003±0.001	0.03 (1.00)	0.61	0.03 (1.00)

*Log transformed to get normal distribution

**P value after correction for multiple testing using bonferroni correction

$P value for the proxy SNP rs927651 (r^2=1 with rs2296239)