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APOA5 genotype influences the association between 25-hydroxyvitamin D and high density lipoprotein cholesterol

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ABSTRACT

Objective: Circulating levels of 25-hydroxyvitamin D (25OHD) are positively associated with high density lipoprotein (HDL) cholesterol. We sought to replicate a previously reported interaction between *APOA5* genotype and vitamin D, and to examine whether HDL-associated genetic loci modify the association between serum 25OHD and HDL cholesterol.

Methods: We examined whether 42 single nucleotide polymorphisms (SNPs) modify the association between serum 25OHD and HDL cholesterol in the 1958 British Birth cohort (aged 45 years, $n = 4978$).

Results: We identified a borderline interaction between the SNP rs12272004 (near the *APOA5*) and serum 25OHD on HDL cholesterol ($P_{interaction} = 0.05$). The interaction was particularly prominent among the samples collected during winter ($P_{interaction} = 0.001$). None of the other loci showed an interaction with serum 25OHD concentrations on HDL cholesterol.

Conclusions: Our study in 4978 British Whites provides further support that *APOA5* genotype modifies the association between vitamin D metabolites and HDL cholesterol.

1. Introduction

Cardiovascular disease is one of the leading causes of mortality in the world [1]. Epidemiological studies have shown an inverse association between circulating levels of 25-hydroxyvitamin D (25OHD) and cardiovascular risk factors including lipid profile, in particular, high density lipoprotein (HDL) cholesterol [2,3]. However, it is still unclear whether 25OHD concentrations are causally related to the disease or are just a marker of health or lifestyle [4]. Placebo-controlled randomized trials that examined the effect of vitamin D supplementation on serum lipids have provided divergent results, with some showing a positive effect while others were negative [5]. These inconsistencies could possibly be due to unidentified interactions between the genes that contribute to variation in HDL cholesterol and 25OHD concentrations.

A recent genome-wide association study has identified nearly 95 loci that have been shown to contribute to the normal variation in lipid traits and also to extreme lipid phenotypes [6]. Of these 95 loci, 47 were shown to contribute to the variation in the HDL cholesterol. A recent study in 1060 individuals from Utah families used 14 of the most significant and replicated lipid loci [6] to identify possible interactions with dietary vitamin D on lipid levels. They reported a significant interaction between dietary vitamin D intake and *APOA5* SNP rs3135506 on HDL cholesterol levels and found that the interaction was more significant among the winter-collected samples as compared to the entire sample ($p = 0.0004$) [7]. They observed a similar interaction in the replication sample ($n = 2890$) [7], where the interaction between dietary vitamin D and *APOA5* on HDL cholesterol was stronger among the winter-collected samples as compared to the entire sample ($p = 0.002$). However, in another replication sample ($n = 1552$) [7], where serum 25OHD concentrations were used instead of dietary vitamin D, interaction was not observed.

In line with the hypothesis that genes influence HDL cholesterol levels in response to vitamin D intake, we expanded the study to investigate gene–environment interaction using data from 4978 individuals from the 1958 British Birth Cohort. The two main objectives of the study include (i) to test whether the *APOA5* SNP rs3135506 interacts with serum 25OHD on HDL cholesterol, and (ii) to perform explorative evaluation of all other possible interactions between the other established HDL-related loci [6] and serum 25OHD concentrations on HDL cholesterol levels.

Abbreviations: HDL, high density lipoprotein; SNP, single nucleotide polymorphism; 25OHD, 25-hydroxyvitamin D; 1958BC, 1958 British Birth Cohort.

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2. Materials and methods

2.1. Study participants

Study participants are from the 1958 British birth cohort (1958BC), which initially included all births in England, Scotland, and Wales during 1 week in March 1958 ($n = 16,751$) [8]. At age 45 years, 11,971 participants were invited to attend a biomedical survey: 9377 (78%) completed at least one questionnaire. The 1958BC is largely a white European population (98%) and despite some data attrition, it has been evaluated to be broadly representative of the surviving cohort [9]. The main analyses were conducted on 4978 participants of European Ancestry with information on the single nucleotide polymorphisms (SNPs), 25OHD concentrations, and HDL cholesterol. The 45-year biomedical survey and genetic studies were approved by the South-East Multi-Centre Research Ethics Committee (Ref: 01/1/44) and the joint UCL/UCLH Committees on the Ethics of Human Research (Ref: 08/H0714/40).

2.2. Clinical data collection

Venous blood samples were drawn without prior fasting and posted to the collaborating laboratory. HDL cholesterol was measured by standard autoanalyzer methodology. As in a previous study of lipid measures in the 1958BC [10], HDL cholesterol levels were corrected to allow for treatment effects amongst those taking lipid medications ($n = 74$) prior to the analysis. This was based on the assumption that commonly prescribed lipid-lowering medications increase HDL cholesterol by an average of 5%. The 25OHD was measured using automated application of an enzyme-linked immunosorbent assay (IDS OCTEIA ELISA; IDS, Bolton, United Kingdom) and an analyser (BEP2000; Dade-Behring, Milton Keynes, United Kingdom) with sensitivity of 5.0 nmol/L, linearity $\leq$155 nmol/L, and intraassay CV 5.5–7.2%. The 25OHD concentrations were standardized according to the mean of the values found by the Vitamin D External Quality Assurance survey (DEQAS) [11].

2.3. SNP selection and genotyping

We selected 47 loci that have been shown to be associated with HDL cholesterol based on the recently published GWAS [6]. In addition, we selected the *APOA5* SNP rs3135506 based on the study by Shirts et al., 2012 [7]. The *APOA5* SNP rs3135506 was not available and hence, we used the SNP rs12272004 (near the *APOA5*), which is in high linkage disequilibrium (LD, $r^2 = 1$) [7] with the SNP rs3135506.

The genotype data for the SNPs were obtained from the genome-wide platforms through two sub-studies [12,13], both using the 1958BC participants as population controls. The first sub-study included 3000 DNA samples randomly selected as part of the Welcome Trust Case Control Consortium (WTCCC2) and genotyped on the Affymetrix 6.0 platform [12]. The second sub-study was the Type 1 diabetes case–control study (T1DGC) which used 2500 DNA samples and genotyped using the Illumina Infinium 550K chip through the JDRF/WT Diabetes and Inflammation Laboratory [13]. For SNPs not included in the genome-wide platforms, a proxy ($r^2 = 1$) or imputed SNP was used for analysis where available. "Best-guess" genotypes were inferred from the imputed SNP probabilities using a call threshold of 0.9 [14]. All SNPs included in the analysis had call rate >95%, imputation quality >0.9, MAF >0.05, and were in Hardy–Weinberg equilibrium ($p > 0.01$). Six SNPs (rs13107325, rs581080, rs1883025, rs4759375, rs4420638 and rs2652834) were excluded from the analysis because of low call rate (<95%) and unavailability of proxy or imputed SNPs. In total, we used 42 SNPs (41 SNPs selected from Teslovich et al. [6] and 1 SNP chosen from Shirts et al. [7]) for the present study.

2.4. Statistical analyses

The natural logarithm was used to transform the skewed HDL cholesterol levels to an improved approximation of the normal distribution. All models were adjusted for sex and region (Scotland or South, Middle or North of England). Owing to the complex inheritance pattern of HDL cholesterol, different genetic models that could be compatible with the data were tested. Interactions between each SNP and 25OHD were assessed using linear regression and the likelihood ratio test. For calculating the percentage of variation in HDL cholesterol explained by the interaction effect, we used the adjusted *R*-squared (R^2) from the regression model. A chi-square goodness of fit test was used to assess deviation from Hardy–Weinberg equilibrium ($P > 0.01$ for all SNPs). All *P* values were derived from two-sided tests. Multiple testing was corrected for in the exploratory interaction analyses using Bonferroni method [$P_{interaction} < 0.00122$ (= 0.05/41 SNPs) were considered to be significant]. The correction for multiple testing was not applied for the *APOA5* interaction analysis, as it was an independent test for replication. Due to the postulated effect of season on the strength of the genetic interaction suggested by the earlier study [7], interactions were also investigated by the time of sample collection (winter vs summer). Winter was defined as November–March (Shirts et al.) [7] and summer was defined as May–September (samples collected during April and October were excluded

Table 1
Interaction between SNP rs12272004 near the *APOA5* gene and 25-hydroxyvitamin D concentrations on high density lipoprotein cholesterol levels[a] in the 1958 British Birth Cohort ($n = 4936$).

Season	Genotype	*N*	% change in HDL (SE)[b]	*P* values for % change in HDL	Interaction *P*-value (LRT)	Percentage (%) of variation in the HDL cholesterol explained[c]
All	CC	4295	0.12 (0.01)	1.2×10^{-17}	0.05	Interaction term: 0.07
	AC	616	0.08 (0.04)	0.03		Genetic main effect: 0.11
	AA	25	0.44 (0.15)	0.004		25OHD main effect: 1.48
Winter-collected samples[d]	CC	1615	0.09 (0.03)	1.7×10^{-4}	0.004	Interaction term: 0.41
	AC	236	0.11 (0.06)	0.06		Genetic main effect: 0.08
	AA	12	0.79 (0.21)	1.6×10^{-4}		25OHD main effect: 1.21
Summer-collected samples[d]	CC	1850	0.14 (0.02)	1.8×10^{-11}	0.13	Interaction term: 0.09
	AC	270	0.03 (0.05)	0.58		Genetic main effect: 0.18
	AA	12	−0.07 (0.26)	0.80		25OHD main effect: 1.70

LRT, Likelihood ratio test.
[a] The natural logarithm was used to transform the skewed HDL cholesterol levels to an improved approximation of the normal distribution. All models adjusted for geographical region and gender.
[b] Percentage change in HDL cholesterol for a 1 nmol/L increase in 25-hydroxyvitamin D concentration.
[c] Based on difference in adjusted R^2 between nested models; R^2 for interaction obtained from comparison with a model including both main terms.
[d] Winter is defined as November–March (Shirts et al.) [7] and Summer is defined as May–September.

Table 2
Interaction between HDL-associated loci and 25-hydroxyvitamin D (25OHD) concentrations on high density lipoprotein cholesterol levels in the 1958 British Birth Cohort ($n = 4978$).

Gene	Gene name	SNPs	Chromosome location	Call rate for genotyping (%)	HWE *P* value	MAF	*P* values[a] for the interaction between SNPs and 25OHD on HDL cholesterol[b]		
							All seasons	Winter	Summer
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	rs1883025[d]	9q31.1	91.9	0.01	0.24	–	–	–
ABCA8	ATP-binding cassette, sub-family A (ABC1), member 8	rs4148008	17q24	99.2	0.28	0.32	0.72	0.19	0.55
AMPD3	Adenosine monophosphate deaminase 3	rs2923084	11p15	100.0	0.15	0.17	0.88	0.58	0.87
ANGPTL4	Angiopoietin-like 4	rs7255436	19p13.3	99.8	0.56	0.49	0.78	0.68	0.54
APOA1	Apolipoprotein A-I	rs964184	11q23-q24	99.8	1.00	0.13	0.78	0.23	0.26
APOB	Apolipoprotein B	rs1042034	2p24-p23	99.2	0.61	0.21	0.82	0.38	0.34
APOE	Apolipoprotein E	rs4420638[d]	19q13.2	57.7	0.50	0.18	–	–	–
ARL15	ADP-ribosylation factor-like 15	rs6450176	5p15.2	97.5	0.55	0.25	0.89	0.89	0.71
C6orf106	Chromosome 6 open reading frame 106	rs2814944	6p21.31	100.0	0.25	0.15	0.15	0.02 (0.66)[c]	0.97
CETP	Cholesteryl ester transfer protein, plasma	rs3764261	16q21	99.2	0.73	0.33	0.35	0.53	0.36
CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	rs605066	6q23.3	99.7	0.36	0.41	0.84	0.69	0.79
CMIP	c-Maf inducing protein	rs2925979	16q23	98.9	0.60	0.31	0.94	0.87	0.44
COBLL1	COBL-like 1	rs12328675	2q24.3	99.2	0.69	0.12	0.82	0.65	0.53
FADS1-2-3	Fatty acid desaturase 1	rs174546	11q12.2-q13.1	100.0	0.16	0.34	0.21	0.01 (0.57)[c]	0.83
GALNT2	UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyltransferase 2 (GalNAc-T2)	rs4846914	1q41-q42	98.6	0.15	0.38	0.46	0.16	0.95
HNF4A	Hepatocyte nuclear factor 4, alpha	rs1800961	20q13.12	100.0	1.00	0.03	0.02 (0.62)[c]	0.009 (0.37)[c]	0.42
IRS1	Insulin receptor substrate 1	rs2972146	2q36	99.7	0.23	0.36	0.70	0.75	0.50
KLF14	Kruppel-like factor 14	rs4731702	7q32.3	99.6	0.14	0.49	0.47	0.76	0.69
LACTB	Lactamase, beta	rs2652834[d]	15q22.1	92.8	0.28	0.17	–	–	–
LCAT	Lecithin-cholesterol acyltransferase	rs16942887	16q22.1	100.0	0.22	0.12	0.93	0.56	0.94
LIPC	Lipase, hepatic	rs1532085	15q21-q23	98.2	1.00	0.39	0.11	0.25	0.45
LIPG	Lipase, endothelial	rs7241918	18q21.1	99.3	0.36	0.18	0.82	0.38	0.35
LOC55908	Chromosome 19 open reading frame 80	rs737337	19p13.2	98.1	0.40	0.07	0.78	0.25	0.53
LPA	Lipoprotein, Lp(a)	rs1084651	6q26	95.9	0.67	0.16	0.26	0.97	0.20
LPL	Lipoprotein lipase	rs12678919	8p22	100.0	0.88	0.10	0.60	0.90	0.29
LRP1	Low density lipoprotein receptor-related protein 1	rs11613352	12q13-q14	100.0	0.06	0.24	0.48	0.44	0.96
LRP4	Low density lipoprotein receptor-related protein 4	rs3136441	11p11.2	99.7	0.18	0.15	0.68	0.89	0.12
MC4R	Melanocortin 4 receptor	rs12967135	18q22	99.4	0.88	0.23	0.16	0.21	0.33
MLXIPL	MLX interacting protein-like	rs17145738	7q11.23	99.6	0.95	0.13	0.90	0.95	0.79
MVK	Mevalonate kinase	rs7134594	12q24	99.1	0.33	0.47	0.28	0.61	0.18
PABPC4	Poly(A) binding protein, cytoplasmic 4 (inducible form)	rs4660293	1p34.2	100.0	0.40	0.24	0.27	0.03 (1.00)[c]	0.21
PDE3A	Phosphodiesterase 3A, cGMP-inhibited	rs7134375	12p12	95.2	0.31	0.41	0.04 (1.00)[c]	0.62	0.12
PGS1	Phosphatidylglycerophosphase synthase 1	rs4129767	17q25.3	100.0	0.44	0.49	0.13	0.90	0.35
PLTP	Phospholipid transfer protein	rs6065906	20q13.12	100.0	0.04	0.18	0.46	0.27	0.43
PPP1R3B	Protein phosphatase 1, regulatory subunit 3B	rs9987289	8p23.1	99.5	0.86	0.09	0.86	0.26	0.64
SBNO1	Strawberry notch homolog 1 (Drosophila)	rs4759375[d]	12q24.31	94.5	0.02	0.05	–	–	–
SCARB1	Scavenger receptor class B, member 1	rs838880	12q24.31	99.2	0.43	0.31	0.22	0.18	0.04 (1.00)[c]
SLC39A8	Solute carrier family 39 (zinc transporter), member 8	rs13107325[d]	4q22-q24	88.1	0.79	0.06	–	–	–
STARD3	StAR-related lipid transfer (START) domain containing 3	rs11869286	17q11-q12	100.0	0.90	0.33	0.42	0.56	0.51
TRIB1	Tribbles homolog 1 (Drosophila)	rs2954029	8q24.13	99.1	0.11	0.47	0.43	0.33	0.16
TRPS1	Trichorhinophalangeal syndrome I	rs2293889	8q24.12	99.6	0.61	0.43	0.18	0.87	0.18
TTC39B	Tetratricopeptide repeat domain 39B	rs581080[d]	9p22.3	87.1	0.52	0.15	–	–	–
UBASH3B	Ubiquitin associated and SH3 domain containing B	rs7941030	11q24.1	98.6	0.98	0.38	0.43	0.52	0.28
UBE2L3	Ubiquitin-conjugating enzyme E2L 3	rs181362	22q11.21	100.0	0.78	0.19	0.12	0.60	0.01 (0.39)[c]
ZNF664	Zinc finger protein 664	rs4765127	12q24.31	100.0	0.02	0.34	0.74	0.29	0.09
ZNF648	Zinc finger protein 648	rs1689803	1q25.3	100.0	0.81	0.36	0.06	0.36	0.02 (0.90)[c]
LILRA3	Leukocyte immunoglobulin-like receptor, subfamily A (without TM domain), member 3	rs398217	19q13.4	98.6	0.94	0.23	0.78	0.07	0.06

SNP, Single nucleotide polymorphism; MAF, Minor allele frequency; HWE, Hardy–Weinberg equilibrium, HDL, High density lipoprotein.
[a] Results are for the additive models, and all are adjusted for sex and region.
[b] The natural logarithm was used to transform the skewed HDL cholesterol levels to an improved approximation of the normal distribution.
[c] *P* values in brackets are corrected for multiple testing.
[d] SNPs with an overall call rate <95% were excluded from the analyses ($n = 6$).

from this analysis). All analyses were carried out using STATA, version 12.

3. Results

3.1. Replication of the interaction between the SNP rs12272004 near the APOA5 gene and 25OHD on HDL cholesterol

In the 1958BC, 25OHD concentrations were associated with HDL cholesterol (% change in HDL: 0.15, 95%CI: 0.12–0.18, $P = 1.39 \times 10^{-23}$, adjusted for sex, region and month of measurement) while there was no evidence for an association between the SNP rs12272004 near the *APOA5* gene and HDL cholesterol ($P = 0.13$, adjusted for sex, region, and 25OHD).

The SNP rs12272004 showed an interaction ($P_{interaction} = 0.05$) with 25OHD on HDL cholesterol under an additive model (Table 1). For every 1 nmol/L increase in 25OHD concentrations, the change in HDL cholesterol levels was larger amongst those with two minor ("A") alleles of the *APOA5* SNP (0.44% increase in HDL, $p = 0.004$) compared to individuals with either no minor alleles or one minor allele (0.12% increase in HDL, $p = 1.2 \times 10^{-17}$ and 0.08% increase in HDL, $p = 0.03$, respectively). The evidence for interaction was slightly stronger when tested under a recessive model (taking *CC* + *AC* as reference, $P_{interaction} = 0.03$). We also tested for the interaction based on the stratification of the samples by the month of sample collection, as performed in the study by Shirts et al., 2012 [7], and found that the evidence for an interaction was predominantly seen when restricted to samples collected during winter ($P_{interaction} = 0.004$) (Table 1). Among the winter-collected samples, for every 1 nmol/L increase in 25OHD concentrations, the change in HDL cholesterol level was larger amongst those with two minor alleles of the SNP (0.79% increase in HDL, $P = 1.6 \times 10^{-4}$) compared to those with either no minor alleles or one minor allele (0.09% increase in HDL, $p = 1.7 \times 10^{-4}$ and 0.11% increase in HDL, $P = 0.06$, respectively).

3.2. Interaction between the 41 HDL-associated loci and 25OHD on HDL cholesterol

Before correction for multiple testing, two SNPs, namely *PDE3A* SNP rs7134375 and *HNF4A* SNP rs1800961, showed some evidence for interaction with 25OHD concentrations on HDL cholesterol under an additive model (rs7134375, $P_{interaction} = 0.04$; rs1800961, $P_{interaction} = 0.02$) (Table 2). For *HNF4A* SNP rs1800961, there was also evidence for an interaction that was predominantly seen during the winter ($p = 0.009$). However, after correction for multiple testing, none of the interactions were significant. Similarly, under a recessive model, none of the interactions were significant after correction for multiple testing (data not shown).

4. Discussion

Extending from the findings on earlier study on vitamin D intake [7], these data suggest that the association between 25OHD concentrations and HDL cholesterol levels is stronger amongst those with two minor alleles of the *APOA5* SNP compared to those with one or less minor allele. Low 25OHD concentrations have been associated with lipid traits in several studies [5] and are also associated with metabolic syndrome, with proposed adverse influences on the risk of cardiovascular disease [15]. These findings suggest that the associations between vitamin D status and metabolic conditions are likely to be complex and that, along with other proposed mechanisms [5], effects that operate via influences on HDL cholesterol deserve consideration.

Our data on 4978 individuals from the 1958BC support the findings of Shirts et al. [7] suggesting that *APOA5* SNP 3135506 (Ser → Trp), that is in high LD with rs12272004, might have a functional effect on the APOA5 protein by interacting with 25OHD, which is likely to contribute to the variation in the HDL cholesterol levels. Another finding from Shirts et al., [7] which was further confirmed in our study, was the stronger interaction effect seen in the winter-collected samples as compared to the entire sample. The interaction term explained a relatively large proportion of variation (0.41%) among the winter-collected samples, especially when compared to values seen for genetic main effects (0.08–0.18%). One explanation for seeing a stronger effect during winter could be because of the fact that people are more prone to be vitamin D deficient in the winter and the deleterious effects of the risk alleles on HDL cholesterol could be pronounced in those with very low vitamin D. Also, the use of serum 25OHD concentrations in our analysis, in contrast to dietary vitamin D that was considered in the previous study [7], adds importance to our study in extending the previous findings.

In addition, we have performed an explorative evaluation of all possible interactions of the 41 HDL-associated loci with 25OHD concentrations on HDL cholesterol and have shown that none of the loci showed a significant interaction after correction for multiple testing. Overall there was very little evidence for further genetic influences on the 25OHD association with HDL. Somewhat intriguingly, also, *HNF4A* appeared to influence the association only in samples collected during winter, which is suggestive of the need to consider seasonal variation in the studies involving vitamin D. Our sample size was relatively large, however, in the context of our exploratory testing of a large number of variants, we may have been underpowered to detect the association and hence, additional replication might be of interest. Furthermore, we cannot rule out the possible interactions that could have been seen with the six HDL-associated loci, for which the genotype data was not available due to low call rate.

5. Conclusions

There are still very few studies examining gene–environmental interaction, and replicated findings suggesting modification by diet-related factors (such as 25OHD) and genes are even sparser. Together with the previous study on vitamin D intake [7], these data suggest that genetic influences may modify the strength of the beneficial effect of vitamin D nutrition on HDL cholesterol, which illustrates the likely complexity of mechanisms underlying the pathogenesis of cardiovascular- related traits.

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Conflict of interest

None of the authors have declared a conflict of interest.

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