



Published in final edited form as:

Metabolism. 2010 August ; 59(8): 1084–1091. doi:10.1016/j.metabol.2009.11.005.

Common INSIG2 polymorphisms are associated with age-related changes in body size and HDL-cholesterol from young adulthood to middle-age

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Abstract

Insulin-induced gene 2 (INSIG2) plays an important role in the regulation of cholesterol and fatty acids synthesis. A polymorphism, rs7566605, located 10 kb upstream of the INSIG2 gene was identified in a genome-wide association study of obesity. We conducted an association study of 12 INSIG2 tagSNPs with longitudinal measures of body size (BMI and waist circumference) and lipid metabolism (plasma HDL-, LDL-cholesterol and triglycerides levels). We investigated their interaction with age in 4,304 CARDIA participants (49.5% Blacks; 50.5% Whites) followed prospectively for 20 years. rs7566605 was not associated with variation in body size or lipid metabolism at any age, in either racial group. However, rs1352083 and rs10185316 were associated with age-related decline in HDL-cholesterol in Whites ($P=0.0005$ and 0.04 , respectively). A similar trend was observed in Blacks who consistently maintained a BMI < 25 kg/m² over the study period. These data support a role of INSIG2 sequence variation in the regulation of cholesterol metabolism.

1. Introduction

Insulin-induced gene 2 (INSIG2) encodes a protein of the endoplasmic reticulum that prevents the proteolytic processing of sterol regulatory element-binding proteins (SREBPs)

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Conflict of Interest

None

Institutional Approval

The University of Texas Health Science Center at Houston HSC-MS-03-221 and HSC-IMM-05-0253.

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into active transcription factors, which regulate cholesterol and fatty acid synthesis [1]. A study integrating QTL mapping using a comprehensive single nucleotide polymorphism (SNP) map and gene expression profiling analyses identified INSIG2 as a susceptibility gene influencing plasma cholesterol levels in mice [2]. However, few studies have examined the association between sequence variation in the INSIG2 gene and measures of cholesterol metabolism in humans [3].

In a genome-wide association study, a SNP (rs7566605) upstream of the INSIG2 gene was recently identified, which was associated with increased body mass index (BMI) in 923 individuals from the Framingham Heart study [4]. This association was replicated in several but not all cohorts of varying ethnicity and age [5]. Many additional studies have failed to reproduce this finding [6–11]. Because the functional relevance of the rs7566605 polymorphism is uncertain and linkage disequilibrium (LD) patterns may vary across populations, investigation of additional polymorphisms in the INSIG2 gene may provide further information about the relationship of this gene with metabolic risk factors, including obesity-related phenotypes and plasma lipids. Moreover, it has been suggested that age may play an important role in modifying the association between INSIG2 gene variation and BMI [5]. To address these issues, we conducted an association study of 12 tagSNPs of the INSIG2 gene, selected based on publicly available LD information, with longitudinal measures of body size (waist circumference and BMI) and plasma lipid levels (HDL- and LDL-cholesterol and triglycerides), and we investigated their interaction with age in black and white CARDIA study participants followed prospectively for 20 years.

2. Material and Methods

Study sample and data collection

Participants were from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Details about the study design have been previously published [12]. Briefly, 5,115 black and white men and women, 18–30 years of age, were initially recruited from the total community in Birmingham, AL; from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser-Permanente health plan membership in Oakland, CA. The initial study population was approximately balanced with respect to race, age, gender, and education groups. From the time of initiation of the study in 1985–1986, participants have completed seven sequential examinations in years 0 (baseline), 2, 5, 7, 10, 15 and 20. Retention rates for the follow-up examinations were 90%, 86%, 81%, 79%, 74%, and 72%, respectively. Written informed consent was obtained from the participants at each examination and all study protocols were approved by the institutional review boards of the participating institutions.

Each participant's age, race, and sex were self-reported during the recruitment phase and verified during the baseline clinic visit. Body weight, height, and waist circumference were assessed at each examination. Body weight was measured to the nearest 0.1 kg, using a calibrated scale, with the participant in light clothing without shoes. Height was measured to the nearest 0.5 cm with a vertical ruler. Body mass index (BMI) was computed as body weight/height² (kg/m²). Blood samples were drawn after an overnight fast at each examination. Total plasma cholesterol, HDL-, LDL-cholesterol and triglyceride levels were measured according to standardized methods [13]. Participants eligible for the current study included 4,304 individuals, including 2,129 Blacks and 2,175 Whites, who consented to isolation of genomic DNA from a blood sample obtained at the year 10, 15, or 20 examination. Individuals without genotype data were more likely to be Black, male, and were slightly younger and less educated, but were otherwise similar to those with genotype data (not shown).

Polymorphism selection and genotyping

Single nucleotide polymorphisms (SNPs) were chosen from publicly available genotype data on individuals of African and European ancestry from the HapMap project [14,15]. Within each race, a minimal set of tagSNPs was selected based on pairwise linkage disequilibrium relationships (r^2), as described by Carlson et al. [16] and implemented in the Tagger algorithm [17]. Briefly, bins of SNPs are created based on a specified r^2 threshold, and then one SNP is selected to represent the remainder of SNPs in that bin. In this study, we used an r^2 threshold of 0.8 and minimum allele frequency of 0.05. A total of 12 SNPs spanning a 28 kb region around the INSIG2 gene were genotyped in the sample of CARDIA black and white participants using the TaqMan assay (Applied Biosystems, Foster City, CA) as previously described [18]. Primer and probes are available from the authors upon request. Polymorphism genotyping in the CARDIA study adheres to a rigorous quality control (QC) program, which includes barcode identification of samples, robotic sample handling, and blind replicate genotype assessment on 5% of the total sample (n=219). The overall genotyping rate was 97% and the concordance rate for blind duplicates was greater than 99%.

Statistical analyses

Genotype frequencies were estimated in each racial group by direct counting. Agreement of the genotype frequencies with Hardy Weinberg equilibrium expectations was tested using a X^2 goodness-of-fit test.

To examine the association of INSIG2 polymorphisms with 20-year measures of body size (BMI) and lipid metabolism (plasma HDL-cholesterol, LDL cholesterol, and triglycerides levels), we first performed serial cross-sectional analyses on the subset of the CARDIA participants who completed all 7 examinations from year 0 to year 20. In each racial group, associations between each phenotype and individual tagSNPs were assessed using multiple linear regression models adjusting for baseline age, sex, and field center. Additional models adjusting for baseline BMI and current use of lipid lowering medication were estimated in the analyses of plasma lipid levels. Triglyceride levels were log-transformed to reduce skewness. For each polymorphism, genotypes were coded as the number of copies (0, 1, or 2) of the reference allele. Additive models have been shown to perform well even when the underlying inheritance model is recessive or dominant.[19,20] Significance of allelic effects on each trait was determined empirically by permutation-derived P values. Both point-wise and family-wise (i.e., corrected for multiple tests) permutation-derived P values were estimated.

To examine the age-dependent effects of INSIG2 polymorphisms on measures of body size and lipid metabolism independently from secular trends or other age-unrelated changes in the phenotypes, we performed longitudinal analyses using Generalized Estimating Equations (GEE). In each racial group, models were estimated with INSIG2 genotype (coded as previously), time-dependent age, and genotype x time-dependent age interaction as independent variables and adjusting for sex, field center, and examination. Additional models adjusting for time-dependent BMI and lipid-lowering medication use were estimated for the analyses of plasma lipids.

3. Results

Baseline characteristics of the CARDIA participants included in this study are shown in Table 1. Of the 4,304 CARDIA participants with available DNA, there were 2,705 individuals who participated in all 7 exams. Compared to the total cohort, individuals in the constant cohort were more likely to be female, white, and slightly better educated, and less

likely to smoke. Allele frequencies of the 12 INSIG2 polymorphisms are shown in Table 2 by race. Genotype frequency distributions of all polymorphisms were in agreement with Hardy-Weinberg equilibrium expectations in each racial group. Pairwise linkage disequilibrium (LD) between the INSIG2 SNPs is shown in Figure 1. As expected based on our tagSNP selection strategy, there was little LD between the selected SNPs, with the exception of rs10185316 and rs1352083 in Blacks ($r^2=0.83$).

We first performed serial cross-sectional analyses of association between each INSIG2 SNP and lipid levels and measures of body size in the constant cohort by race. In Blacks, rs13409050 was associated with variation in BMI at all exams and both significance of association and magnitude of the effect tended to increase over time. At baseline, individuals carrying the common rs13409050_G allele had a 0.60 kg/m² higher BMI per copy (P=0.03). At Year 20, these individuals had a 1.1 kg/m² higher BMI per copy (P=0.01) (Table 3a). Similar results were obtained in the association of the rs13409050 polymorphism with waist circumference. At baseline, individuals carrying the common rs13409050_G allele had a 1.1 cm higher waist circumference per copy (P=0.05). At Year 20, these individuals had a 2.1 cm higher waist circumference per copy (P=0.01). In Blacks from the CARDIA study, there was no significant association of INSIG2 polymorphisms with plasma HDL-cholesterol levels (Table 3b) at any of the 7 examinations; similarly for plasma LDL-cholesterol and triglyceride levels (not shown).

In Whites, none of the INSIG2 polymorphisms were significantly associated with variation in body size at any of the 7 examinations (Table 3a). However, two polymorphisms in moderate LD ($r^2=0.7$), rs10185316 and rs1352083, showed similar associations with variation in HDL cholesterol (Table 3b). At baseline, individuals carrying the variant allele rs10185316_G had a 0.84 mg/dL lower plasma HDL-cholesterol level per copy (P=0.05) compared to those who did not carry this allele. The magnitude and statistical significance of this difference increased over time. At year 20, these individuals had a 1.8 mg/dL lower plasma HDL-cholesterol per copy (P=0.003). A similar trend was observed for the rs1352083_T variant, although both the magnitude and statistical significance of the difference in plasma HDL-cholesterol between variant and wild-type allele were slightly less than for rs10185316. Adjusting for BMI and current use of lipid-lowering medication did not significantly affect these associations (Table 3b). There was no significant association of INSIG2 polymorphisms with plasma LDL-cholesterol or triglycerides levels at any of the 7 examinations (not shown).

We next examined the association of INSIG2 polymorphisms with age-related changes in measures of body size and plasma lipid levels using GEE models in the total cohort. Consistent with results of the serial cross-sectional analyses, we observed a significant association of rs13409050 with variation in BMI in Blacks and this association was age-dependent. At age 18, individuals carrying the common allele of rs13409050 (G) had a slightly higher BMI per copy (0.4 kg/m²; P=0.07) (Table 4a) and slightly larger waist circumference (0.7 cm; P=0.09), compared to individuals who did not carry this allele. However, with increasing age, these individuals had a significant increase in BMI (0.02 kg/m² per year of age and per copy of the allele; P=0.02) (Table 4a) and waist circumference (0.05 cm per year of age and per copy of the allele). In Whites, we also observed an age-dependent association between INSIG2 SNPs and HDL-cholesterol levels, consistent with results from the serial cross-sectional analyses (Table 4b). At age 18, individuals carrying the variant allele rs10185316_G had a slightly lower plasma HDL-cholesterol level per copy (0.7 mg/dL; P=0.05) compared to those who did not carry this allele. With increasing age, these individuals tended to have increasingly lower plasma HDL-cholesterol levels (0.03 mg/dl per year of age and per copy of the allele; P=0.08). Similarly for rs1352083, individuals aged 18 years carrying the variant rs1352083_T allele had slightly, although not

significantly, lower HDL-cholesterol levels than those who did not carry this allele. However, as they got older, carriers of the rs1352083_T allele had a greater decline in HDL-cholesterol levels (0.07 mg/dl per year of age and per copy of the allele; $P=0.002$). Further adjusting for BMI and use of lipid-lowering medication did not significantly modify these age-dependent associations (Table 4b).

We also examined the association of INSIG2 sequence variants with plasma lipid levels in a subset of the CARDIA participants who consistently maintained their BMI below 25 kg/m² over the 20 year study period (N=246 Blacks; 615 Whites). In Whites who were consistently lean, rs1352083_T and rs10185316_G were significantly associated with a greater age-related decrease in HDL-cholesterol (0.13 and 0.11 mg/dl per year of age and per copy of the allele, $P=0.0004$ and 0.003, respectively). In Blacks, a similar trend was observed although statistical significance was not reached (0.08 and 0.10 mg/dl per year of age and per copy of the allele, $P=0.10$ and 0.12, respectively).

In an effort to determine whether the identified SNPs had potential functional consequences, we screened the 2 tagSNPs against a set of previously reported expression-associated SNPs (eSNPs) in lymphoblastoid cell lines [21]. Neither polymorphism (or their proxy) was associated with variation in INSIG2 gene expression levels in cell lines.

4. Discussion

In the CARDIA cohort of young adults of African and European ancestry, sequence variants of the INSIG2 gene were significantly associated with BMI and HDL-cholesterol and these associations were age-dependent.

We failed to reproduce an association of rs7566605 with measures of body size, including BMI at any age, in either Blacks or Whites, consistent with our previous report [11] and similar to many studies [7–10]. Although it was previously suggested this polymorphism was associated with an increased BMI in overweight individuals [10], additional analyses of a subgroup of CARDIA participants who were consistently overweight over the 20-year study period (N=537 Black, 475 Whites), did not reveal a significant association of rs7566605 with body size (not shown). Our results also did not support an earlier suggestion of an interaction of this polymorphism with age, namely a stronger effect on BMI in younger individuals and a decreasing effect size with increasing age [5]. A recent report also showed suggestive evidence of an association of this polymorphism with BMI in children [22]. Nonetheless, we report a significant association of the common allele of rs13409050 – a tagSNP located in intron 3 of the INSIG2 gene – with a greater BMI and waist circumference in Blacks. We also provide evidence of an interaction of this polymorphism with age on body size, specifically an increasing effect size with increasing age. These associations were not observed in Whites, possibly due to differences in allele frequency, in linkage disequilibrium patterns, or in genetic or environmental contexts. The mechanisms that underlie the association of INSIG2 variants and increased BMI remain unclear. INSIG2 is ubiquitously expressed and adipocyte differentiation is characterized by an enhanced INSIG2 expression [23]. It has been recently suggested that INSIG2 may regulate adipogenesis via the sterol regulatory element-binding protein 1 (SREBP1) [23,24]. A recent study in Hispanic individuals also reported an association of INSIG2 gene variants with computed tomography (CT)-measured adiposity [25]. Future characterization of functional variation in the INSIG2 gene may shed light on the relationship of this gene with obesity-related traits.

We provide evidence of an association of two INSIG2 variants, rs1352083 and rs10185316, with age-dependent decline in HDL cholesterol in the 20-year period from young adulthood

to middle age. This association was observed in both black and white individuals who maintained a normal weight ($BMI < 25 \text{ kg/m}^2$) over the study period, although statistical significance was reached only for Whites. rs10185316 is located in the promoter region of the gene and rs1352083 is located in intron 1. These variants have similar allele frequencies in the 2 racial groups and are in linkage disequilibrium. The relationship between INSIG2 and cholesterol metabolism has been well documented in experimental studies. In the presence of sterols, INSIG2 prevents the proteolytic activation of SREBPs by Golgi enzymes and, hence, blocks cholesterol metabolism [1]. Moreover, INSIG2 has been shown to regulate the degradation of HMG-CoA reductase, a rate-limiting enzyme in cholesterol synthesis [26,27]. However, few studies have investigated the association of INSIG2 polymorphism with plasma lipid levels. No significant association of rs7566605 was reported with plasma levels of either total, HDL-, or LDL-cholesterol in middle-aged individuals from European ancestry [3] or Japanese ancestry [28]. However, none of these studies examined the relationship of other INSIG2 gene variants with longitudinal profiles of plasma lipid levels.

Despite the clear strengths of our study, including a well-characterized bi-racial sample of young adults followed prospectively for 20 years, and a more comprehensive tagSNP strategy in the INSIG2 gene, some limitations must be acknowledged. First, we have not examined possible interactions of INSIG2 polymorphisms with environmental or other genetic factors known to influence body size and plasma lipid levels. Therefore, we cannot exclude that the associations (or lack thereof) reported here may vary in different environmental contexts, such as physical activity or dietary fat intake, or in the presence of other susceptibility genes [29]. Second, association studies cannot distinguish the causal SNP (or combination of SNPs), among those in linkage disequilibrium (LD). Therefore, as the functional relevance of the identified SNPs is uncertain, we cannot exclude that a polymorphism(s) unrelated to INSIG2 function may be responsible for the effects observed in this study. Finally, the novel SNP associations reported here require validation through analysis in other cohorts. In particular, replication in other African-American cohorts taking into account genetic measures of ancestry is warranted to rule out any spurious findings due to population stratification.

In summary, common variants of the INSIG2 gene are associated with age-dependent increase in body size and decrease in plasma HDL cholesterol in the period of young adulthood to early middle-age. The molecular mechanisms that mediate these relationships remain to be investigated. In particular, characterization of functional variants in the INSIG2 gene will contribute toward a better understanding of the role of this gene in susceptibility to metabolic and cardiovascular dysfunction.

Acknowledgments

This study is supported by grant R01-HL69126 to MF and by contracts N01-HC-48047, N01-HC-48048, N01-HC-48049, N01-HC-48050 and N01-HC-95095 from the National Heart, Lung, and Blood Institute to the CARDIA investigators. The authors thank the staff and participants of the CARDIA study for their important contributions.

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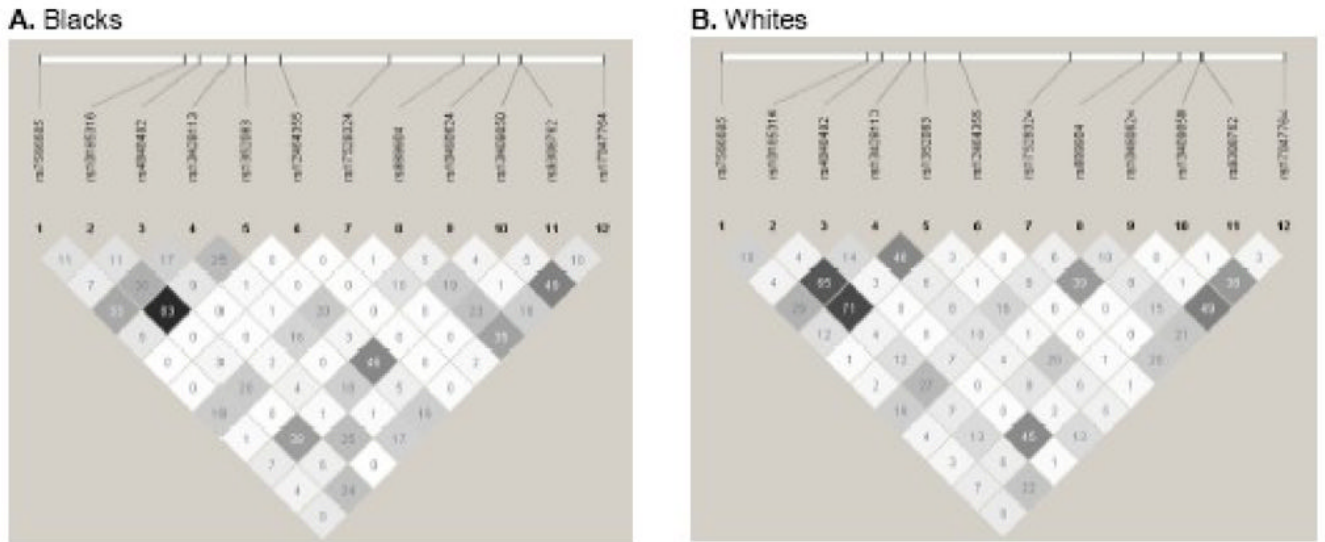


Figure 1. Pairwise linkage disequilibrium (r^2) among 12 INSIG2 tagSNPs by racial group

Table 1

Baseline characteristics of the CARDIA participants genotyped for INSIG2 tagSNPs

Characteristic	Total cohort (N=4,304)	Constant cohort (N=2,705)
Age (years)	25.0 (3.6)	25.3 (3.5)
Male (%)	44.3	43.4
Black (%)	49.5	42.5
Education (years)	13.9 (2.2)	14.2 (2.2)
Current smoking (%)	29.1	24.1
Body mass index (kg/m ²)	24.5 (5.1)	24.4 (4.8)
LDL-cholesterol (mg/dL)	109.5 (31.1)	109.8 (30.6)
HDL-cholesterol (mg/dL)	53.1 (13.1)	53.3 (12.7)
Log-triglycerides (mg/dL)	4.15 (0.48)	4.14 (0.47)
Diabetes (%)	0.6%	0.6%

Table 2

Allele frequencies and P-value for test of significance of departure from Hardy-Weinberg equilibrium expectations for 12 INSIG2 tagSNPs in each racial group.

Polymorphism	Chromosomal position	Gene Location	Allele 1	Allele 2	Blacks (N=2, 129)		Whites (N=2,175)	
					Freq (allele 1)	HWE P	Freq (allele 1)	HWE P
rs7566605	118552495	5' flanking	C	G	0.26	0.15	0.33	0.32
rs10185316	118560948	5' flanking	G	C	0.30	0.40	0.32	0.66
rs4848492	118561741	5' flanking	C	T	0.20	0.59	0.10	0.61
rs13428113	118563355	Intron 1	C	T	0.41	0.24	0.58	0.65
rs1352083	118564311	Intron 1	T	C	0.27	0.70	0.25	0.82
rs12464355	118566320	Intron 1	G	A	0.01	1.00	0.09	0.11
rs17528324	118572626	Intron 2	A	G	0.01	1.00	0.05	0.67
rs889904	118576941	Intron 2	G	A	0.40	0.96	0.52	0.28
rs10490624	118578962	Intron 3	G	A	0.11	0.14	0.09	0.59
rs13409050	118580240	Intron 3	A	G	0.25	0.48	0.07	0.63
rs9308762	118580344	Intron 3	C	T	0.14	0.06	0.17	0.75
rs17047764	118585051	3' flanking	C	G	0.39	0.37	0.16	0.81

Table 3

Table 3a. Serial cross-sectional association of INSIG2 tagSNPs with BMI in the constant cohort by race.

SNP	Ref. allele	Year 0		Year 2		Year 5		Year 7		Year 10		Year 15		Year 2	
		Difference ^a (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b
African-Americans (N=1,149)															
rs756605	C	0.05 (0.27)	0.86	0.02 (0.30)	0.96	0.04 (0.31)	0.89	-0.05 (0.32)	0.87	0.04 (0.33)	0.90	0.38 (0.35)	0.28	0.20 (0.36)	0.56
rs10885316	G	-0.46 (0.25)	0.07	-0.50 (0.27)	0.07	-0.6 (0.28)	0.03	-0.60 (0.30)	0.04	-0.54 (0.31)	0.08	-0.57 (0.33)	0.08	-0.58 (0.33)	0.09
rs4848492	C	0.30 (0.29)	0.32	0.32 (0.32)	0.32	0.34 (0.34)	0.33	0.30 (0.35)	0.39	0.36 (0.36)	0.32	0.09 (0.38)	0.80	0.15 (0.39)	0.69
rs1328113	C	-0.07 (0.23)	0.75	0.002 (0.25)	0.98	0.01 (0.26)	0.96	0.004 (0.28)	0.99	-0.03 (0.28)	0.90	0.21 (0.30)	0.48	0.20 (0.31)	0.49
rs132083	T	-0.45 (0.26)	0.07	-0.56 (0.29)	0.05	-0.64 (0.30)	0.04	-0.70 (0.31)	0.02	-0.62 (0.32)	0.06	-0.66 (0.34)	0.05	-0.73 (0.35)	0.05
rs1264355	G	0.05 (0.97)	0.95	0.19 (1.06)	0.85	0.21 (1.13)	0.85	0.12 (1.16)	0.91	-0.70 (1.21)	0.59	-0.63 (1.28)	0.63	-0.58 (1.30)	0.66
rs1228324	A	-1.71 (0.96)	0.08	-1.20 (1.07)	0.23	-1.81 (1.11)	0.08	-1.17 (1.15)	0.33	-0.96 (1.19)	0.40	-1.38 (1.27)	0.27	-0.75 (1.31)	0.57
rs889904	G	0.12 (0.24)	0.61	0.13 (0.26)	0.63	0.07 (0.27)	0.81	-0.07 (0.28)	0.83	0.03 (0.30)	0.89	0.01 (0.31)	0.95	0.18 (0.32)	0.58
rs1290624	G	0.02 (0.37)	0.95	0.12 (0.41)	0.78	0.43 (0.43)	0.31	0.55 (0.45)	0.22	0.66 (0.46)	0.15	0.22 (0.49)	0.65	0.66 (0.50)	0.21
rs13409050	G	0.60 (0.27)	0.03	0.68 (0.30)	0.02	0.80 (0.31)	0.02	0.83 (0.33)	0.01*	0.81 (0.34)	0.02	1.0 (0.36)	0.005**	0.95 (0.34)	0.01*
rs938762	C	0.19 (0.34)	0.58	0.24 (0.37)	0.51	0.07 (0.39)	0.87	0.04 (0.41)	0.93	-0.04 (0.42)	0.93	-0.08 (0.45)	0.87	-0.17 (0.46)	0.70
Whites (N=1,556)															
rs756605	C	-0.12 (0.15)	0.43	-0.10 (0.16)	0.46	-0.03 (0.17)	0.86	0.02 (0.19)	0.90	0.002 (0.20)	0.99	-0.08 (0.22)	0.72	-0.21 (0.26)	0.43
rs10885316	G	0.14 (0.15)	0.33	0.11 (0.16)	0.48	0.17 (0.17)	0.33	0.09 (0.19)	0.66	0.17 (0.20)	0.37	0.14 (0.22)	0.54	-0.06 (0.25)	0.82
rs4848492	C	0.17 (0.23)	0.47	0.09 (0.25)	0.74	0.01 (0.27)	0.97	-0.01 (0.30)	0.96	-0.05 (0.32)	0.83	-0.26 (0.36)	0.50	-0.13 (0.40)	0.73
rs13428113	T	0.19 (0.14)	0.15	0.15 (0.15)	0.32	0.17 (0.17)	0.30	0.08 (0.18)	0.64	0.14 (0.19)	0.46	0.05 (0.22)	0.81	-0.09 (0.25)	0.73
rs1352083	T	-0.001 (0.16)	0.99	-0.04 (0.17)	0.81	0.11 (0.19)	0.53	0.07 (0.21)	0.72	0.09 (0.22)	0.65	0.08 (0.24)	0.75	-0.19 (0.28)	0.50
rs12464355	G	-0.03 (0.25)	0.90	-0.01 (0.27)	0.96	-0.03 (0.29)	0.90	0.13 (0.32)	0.66	0.07 (0.34)	0.84	0.33 (0.38)	0.38	0.38 (0.44)	0.36
rs17528324	A	0.32 (0.30)	0.28	0.33 (0.32)	0.32	-0.001 (0.35)	0.99	-0.11 (0.39)	0.79	0.16 (0.41)	0.67	0.25 (0.46)	0.60	0.26 (0.53)	0.61
rs889904	A	0.22 (0.14)	0.12	0.22 (0.15)	0.12	0.26 (0.16)	0.10	0.24 (0.18)	0.19	0.30 (0.19)	0.10	0.41 (0.21)	0.06	0.35 (0.24)	0.15
rs104906624	G	0.07 (0.24)	0.77	0.06 (0.26)	0.80	-0.02 (0.26)	0.94	-0.11 (0.31)	0.75	0.04 (0.33)	0.89	0.11 (0.37)	0.76	0.06 (0.42)	0.87
rs13409050	G	-0.46 (0.27)	0.09	-0.30 (0.30)	0.31	-0.74 (0.32)	0.02	-0.70 (0.35)	0.05	-0.81 (0.38)	0.04	-0.91 (0.41)	0.03	-0.74 (0.48)	0.14

Table 3a. Serial cross-sectional association of INSIG2 tagSNPs with BMI in the constant cohort by race.

SNP	Ref. allele	Year 0		Year 2		Year 5		Year 7		Year 10		Year 15		Year 20	
		Difference ^a (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b
rs9308762	C	0.17 (0.19)	0.36	0.07 (0.20)	0.72	0.02 (0.22)	0.92	-0.02 (0.25)	0.91	-0.08 (0.26)	0.73	-0.07 (0.29)	0.83	0.21 (0.33)	0.54

Table 3b. Serial cross-sectional association of INSIG2 tagSNPs with HDL-cholesterol levels in the constant cohort by race.

SNP	Ref. allele	Year 0		Year 2		Year 5		Year 7		Year 10		Year 15		Year 20	
		Difference ^a (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b	Difference (SE) In trait value per copy of ref. allele	p ^b
African-Americans (N=1,149)															
rs756605	C	0.41 (0.61)	0.53	0.52 (0.69)	0.44	0.01 (0.68)	0.98	-0.08 (0.68)	0.90	0.27 (0.66)	0.68	0.11 (0.66)	0.87	0.84 (0.76)	0.29
rs10185316	G	0.65 (0.57)	0.26	0.77 (0.64)	0.24	0.56 (0.64)	0.39	0.93 (0.63)	0.14	0.42 (0.62)	0.49	0.18 (0.62)	0.77	0.05 (0.72)	0.95
rs4848492	C	1.12 (0.66)	0.10	-0.76 (0.76)	0.31	0.93 (0.76)	0.21	0.57 (0.74)	0.44	0.76 (0.72)	0.31	0.67 (0.73)	0.38	0.47 (0.84)	0.56
rs1328113	C	-0.98 (0.52)	0.06	-0.21 (0.59)	0.71	-1.22 (0.59)	0.03	-0.95 (0.58)	0.10	-0.70 (0.57)	0.22	-0.40 (0.57)	0.47	-0.24 (0.66)	0.73
rs1322083	T	0.50 (0.60)	0.41	0.58 (0.67)	0.38	0.54 (0.67)	0.39	1.15 (0.66)	0.08	0.44 (0.64)	0.47	0.36 (0.65)	0.58	-0.15 (0.75)	0.81
rs1264355	G	1.91 (2.21)	0.38	1.75 (2.45)	0.45	-2.97 (2.52)	0.22	-1.25 (2.45)	0.61	-1.19 (2.39)	0.63	1.50 (2.40)	0.51	-0.46 (2.79)	0.87
rs1728324	A	0.57 (2.23)	0.80	-0.38 (2.52)	0.87	0.52 (2.49)	0.84	-0.78 (2.46)	0.75	-0.23 (2.44)	0.93	-0.70 (2.46)	0.77	1.17 (2.81)	0.66
rs882904*	G	-0.57 (0.54)	0.29	-0.57 (0.61)	0.34	-0.73 (0.62)	0.21	-0.54 (0.61)	0.37	0.18 (0.59)	0.76	-0.15 (0.59)	0.81	0.46 (0.69)	0.51
rs13290624	G	0.75 (0.85)	0.36	0.21 (0.96)	0.83	0.52 (0.96)	0.57	-0.19 (0.93)	0.83	0.11 (0.92)	0.91	0.25 (0.93)	0.79	0.02 (1.0)	0.98
rs13209050	G	-0.84 (0.62)	0.19	-0.90 (0.70)	0.20	-1.12 (0.71)	0.11	-1.81 (0.69)	0.01*	-1.07 (0.68)	0.11	-1.20 (0.68)	0.08	-0.91 (0.79)	0.24
rs9308762	C	0.56 (0.77)	0.45	-1.27 (0.89)	0.15	0.16 (0.88)	0.85	0.28 (0.86)	0.74	0.49 (0.85)	0.55	0.28 (0.84)	0.75	0.60 (0.99)	0.53
Whites (N=1,556)															
rs7566605	C	0.06 (0.45)	0.90	0.21 (0.49)	0.66	0.12 (0.49)	0.81	-0.03 (0.49)	0.96	0.25 (0.48)	0.62	0.15 (0.50)	0.77	0.28 (0.58)	0.60
rs10185316	G	-0.84 (0.45) -0.71 (0.43)	0.05 0.09	-1.1 (0.40) 0.80 (0.47)	0.04 0.10	-1.1 (0.49) -0.72 (0.46)	0.030 0.10	-1.2 (0.49) -0.91 (0.47)	0.02 0.05	-1.6 (0.48) -1.3 (0.46)	0.004 0.005	-1.5 (0.51) -1.3 (0.49)	0.005 0.005	-1.8 (0.58) -1.6 (0.56)	0.003 0.004
rs4848492	C	0.04 (0.71)	0.96	-0.21 (0.78)	0.79	0.33 (0.77)	0.64	0.89 (0.78)	0.27	0.74 (0.77)	0.33	1.33 (0.81)	0.10	1.3 (0.92)	0.17
rs13428113	T	-0.71 (0.43)	0.10	-0.94 (0.47)	0.05	-0.60 (0.46)	0.19	-0.91 (0.47)	0.19	-1.0 (0.46)	0.04	-0.85 (0.48)	0.07	-1.07 (0.55)	0.06

Metabolism. Author manuscript; available in PMC on August 1, 2014.

Table 3a. Serial cross-sectional association of INSIG2 tagSNPs with BMI in the constant cohort by race.

SNP	Ref. allele	Year 0		Year 2		Year 5		Year 7		Year 10		Year 15		Year 2	
		Difference ^a (SE) In trait value per copy of ref. allele	P ^b	Difference (SE) In trait value per copy of ref. allele	P ^b	Difference (SE) In trait value per copy of ref. allele	P ^b	Difference (SE) In trait value per copy of ref. allele	P ^b	Difference (SE) In trait value per copy of ref. allele	P ^b	Difference (SE) In trait value per copy of ref. allele	P ^b	Difference (SE) In trait value per copy of ref. allele	P ^b
rs1352083	T	-0.3 (0.48) -0.15 (0.46)	0.74 0.74	-0.3 (0.53) -0.16 (0.51)	0.74 0.75	-0.6 (0.52) -0.34 (0.50)	0.27 0.49	-0.7 (0.53) -0.54 (0.51)	0.27 0.29	-1.2 (0.53) -1.0 (0.50)	0.03 0.04	-1.3 (0.55) -1.1 (0.53)	0.02 0.03	-1.8 (0.62) -1.6 (0.60)	0.007*** 0.01*
rs12464356	G	-1.0 (0.76)	0.19	0.85 (0.83)	0.32	-0.15 (0.81)	0.85	0.34 (0.82)	0.66	0.05 (0.82)	0.93	-0.57 (0.85)	0.52	-1.0 (0.97)	0.30
rs17228324	A	-1.9 (0.92)	0.05	-2.44 (1.0)	0.01	-1.71 (0.99)	0.10	-1.6 (1.0)	0.10	-1.7 (0.99)	0.09	-1.67 (1.04)	0.12	-0.99 (1.19)	0.41
rs88904	A	-0.71 (0.43)	0.10	-0.51 (0.47)	0.27	-0.52 (0.46)	0.24	-0.36 (0.47)	0.45	-0.58 (0.46)	0.22	-1.10 (0.48)	0.02	-1.21 (0.55)	0.03
rs10290624	G	-0.82 (0.73)	0.27	-0.93 (0.81)	0.25	-0.67 (0.79)	0.38i	-0.23 (0.81)	0.76	-0.87 (0.79)	0.28	-1.08 (0.83)	0.20	-0.23 (0.95)	0.79
rs1109050	G	-0.71 (0.83)	0.40	0.64 (0.91)	0.49	0.06 (0.89)	0.95	1.04 (0.91)	0.25	0.85 (0.89)	0.34	0.95 (0.93)	0.32	1.18 (1.06)	0.24
rs9388762	C	0.21 (0.58)	0.71	0.16 (0.63)	0.79	0.28 (0.62)	0.66	0.65 (0.63)	0.32	0.53 (0.63)	0.41	1.33 (0.65)	0.05	1.10 (0.74)	0.15

^a expressed in kg/m²;

^b point-wise empirical P-value derived from permutation;

* family-wise empirical P value < 0.10;

** family-wise empirical P value < 0.05; Models were adjusted for age, sex, and field center; Ref.: Reference; SE: standard error

^a expressed in mg/dL;

^b point-wise empirical P-value derived from permutation;

* family-wise empirical P value < 0.10;

** family-wise empirical P value < 0.05; Models were adjusted for age, sex, and field center;

^c model further adjusted for baseline BMI and current use of lipid lowering medication; Ref.: Reference; SE: standard error

Table 4

Table 4a. Age-dependent association of selected INSIG2 tagSNPs with BMI in the total cohort by race.					
African-Americans (N=2,129)		Difference ^d in trait value (95% CI) at age 18 per copy of reference allele	P	Change ^d in trait value (95% CI) per year of age per copy of reference allele	P
SNP	Reference				
rs7566605	C	-0.03 (-0.46; 0.39)	0.88	0.004 (-0.018; 0.023)	0.65
rs10185316	G	0.02 (-0.37; 0.41)	0.92	-0.006 (-0.024; 0.011)	0.49
rs4848492	C	0.01 (-0.48; 0.51)	0.95	-0.008 (-0.029; 0.013)	0.44
rs13428113	C	-0.003 (-0.36; 0.36)	0.99	0.009 (-0.008; 0.025)	0.32
rs1352083	T	-0.06 (-0.45; 0.34)	0.77	-0.011 (-0.020; 0.007)	0.23
rs12464355	G	0.47 (-1.44; 2.39)	0.62	-0.03 (-0.11; 0.05)	0.51
rs17528324	A	-0.16 (-1.83; 1.50)	0.85	0.003 (-0.063; 0.069)	0.92
rs889904	G	0.10 (-0.27; 0.47)	0.6	0.001 (-0.016; 0.018)	0.93
rs10490624	G	-0.04 (-0.62; 0.54)	0.89	0.011 (-0.017; 0.039)	0.44
rs13409050	G	0.4 (0.03; 0.80)	0.07	0.02 (0.01; 0.03)	0.02
rs9308762	C	0.12 (-0.43; 0.68)	0.66	-0.006 (-0.031; 0.018)	0.61
Whites (N=2,175)					
rs7566605	C	0.19 (-0.09; 0.47)	0.2	-0.003 (-0.019; 0.012)	0.69
rs10185316	G	0.10 (-0.17; 0.37)	0.48	-0.005 (-0.019; 0.010)	0.51
rs4848492	C	0.20 (-0.30; 0.69)	0.44	-0.014 (-0.043; 0.015)	0.35
rs13428113	C	-0.18 (-0.45; 0.08)	0.17	0.009 (-0.005; 0.023)	0.18
rs1352083	T	0.07 (-0.22; 0.37)	0.62	-0.003 (-0.018; 0.013)	0.75
rs12464355	G	-0.26 (-0.68; 0.16)	0.23	0.017 (-0.010; 0.044)	0.22
rs17528324	A	-0.07 (-0.56; 0.42)	0.77	-0.005 (-0.032; 0.023)	0.74
rs889904	G	-0.004 (-0.26; 0.26)	0.98	-0.008 (-0.021; 0.006)	0.26
rs10490624	G	-0.15 (-0.54; 0.23)	0.44	0.004 (-0.018; 0.027)	0.7
rs13409050	G	0.002 (-0.47; 0.48)	0.99	0.023 (-0.002; 0.048)	0.08
rs9308762	C	0.08 (-0.31; 0.46)	0.69	-0.006 (-0.027; 0.014)	0.55
Table 4b. Age-dependent association of selected INSIG2 tagSNPs with HDL-cholesterol levels in the total cohort by race.					
African-Americans (N=2,129)					

Table 4a. Age-dependent association of selected INSIG2 tagSNPs with BMI in the total cohort by race.

African-Americans (N=2,129)					
SNP	Reference	Difference ^d in trait value (95% CI) at age 18 per copy of reference allele	P	Change ^d in trait value (95% CI) per year of age per copy of reference allele	P
SNP	Reference allele	Difference ^d in trait value (95% CI) at age 18 per copy of reference allele	P	Change ^d in trait value (95% CI) per year of age per copy of reference allele	P
rs7566605	C	-0.07 (-0.93; 0.80)	0.88	0.006 (-0.043; 0.055)	0.81
rs10185316	G	0.27 (-0.53; 1.08)	0.51	-0.024 (-0.068; 0.020)	0.29
rs4848492	C	0.21 (-0.76; 1.18)	0.67	0.02 (-0.03; 0.07)	0.43
rs13428113	C	-0.47 (-1.22; 0.28)	0.22	0.008 (-0.030; 0.047)	0.66
rs1352083	T	-0.05 (-0.79; 0.88)	0.91	-0.015 (-0.061; 0.030)	0.5
rs12464355	G	-0.48 (-3.84; 2.87)	0.78	0.02 (-0.12; 0.16)	0.78
rs17528324	A	1.01 (-1.63; 3.65)	0.45	0.03 (-0.14; 0.20)	0.76
rs889904	G	-0.65 (-1.43; 0.13)	0.1	0.025 (-0.017; 0.066)	0.24
rs10490624	G	0.50 (-0.76; 1.77)	0.44	-0.012 (-0.076; 0.051)	0.7
rs13409050	G	0.72 (-0.16; 1.60)	0.11	0.014 (-0.036; 0.063)	0.59
rs9308762	C	-0.41 (-1.48; 0.67)	0.46	-0.012 (-0.068; 0.043)	0.66
Whites (N=2,175)					
rs7566605	C	0.20 (-0.93; 0.53)	0.59	-0.002 (-0.042; 0.037)	0.9
rs10185316	G	-0.7 (-1.4; 0.01) -0.6 (-1.3; 0.06)*	0.05 0.07	-0.03 (-0.07; 0.01) -0.04 (-0.07; 0.00)*	0.09 0.05
rs4848492	C	0.22 (-1.03; 1.47)	0.73	0.06 (-0.005; 0.118)	0.07
rs13428113	C	0.56 (-0.14; 1.28)	0.11	0.013 (-0.025; 0.051)	0.49
rs1352083	T	-0.19 (-0.98; 0.59) -0.14 (-0.88; 0.60)*	0.62 0.71	-0.07 (-0.11; -0.02) -0.07 (-0.11; -0.03)*	0.002 0.0007
rs12464355	G	-0.99 (-0.46; 2.43)	0.18	-0.046 (-0.115; 0.023)	0.19
rs17528324	A	-1.48 (-3.06; 0.10)	0.06	0.07 (-0.01; 0.15)	0.09
rs889904	G	0.11 (-0.56; 0.80)	0.74	0.02 (-0.01; 0.06)	0.27
rs10490624	G	-0.74 (-1.91; 0.44)	0.22	0.012 (-0.051; 0.076)	0.7
rs13409050	G	0.13 (-1.28; 1.54)	0.85	-0.09 (-0.16; -0.02)	0.01
rs9308762	C	0.09 (-0.83; 1.02)	0.84	0.053 (0.004; 0.103)	0.03

Models were adjusted for examination, sex, and field center.

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^a expressed in kg/m²

Models were adjusted for examination, sex, end field center.

* also adjusted for time-dependent BMI and use of lipid-lowering medication;

^a expressed in mg/dL