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Genetic Loci Associated with Ideal Cardiovascular Health: A Meta-Analysis of Genome-wide Association Studies

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None

Abstract

Background—Multiple genetic loci are associated with clinical cardiovascular (CV) disease and individual CV risk factors. Individuals with ideal levels of all major CV risk factors have very low risk for CVD morbidity or mortality. Ideal levels of risk factors can be attained by lifestyle modifications; however, little is known about gene variants associated with ideal CV health. Our objective was to carry out a genome-wide association study (GWAS) on the trait.

Methods and Results—We examined two dichotomous phenotypes of ideal CV health - Clinical (untreated cholesterol < 200 mg/dl; untreated blood pressure (BP) <120/<80; not diabetic) and Clinical+Behavioral (Clinical plus: not a current smoker; BMI <25 kg/m²) -among white participants aged 50 ± 5 years. We performed a meta-analysis of four GWAS (total n=11,708) from the MESA, CARDIA, ARIC and Framingham Heart Study cohorts. We identified a SNP (rs445925) in the *APOC1/APOE* region that was associated with Clinical ideal CV health at genome-wide level of significance ($p < 2.0 \times 10^{-9}$). The significance of this region was validated using exome chip genotyping. The association with ideal CV health was attenuated after adjusting for LDL cholesterol.

Conclusion—A common SNP in the *APOC1/APOE* region, previously found to be associated with protective levels of cholesterol and lower cardiovascular risk, may be associated with ideal health. In future replication studies, larger sample sizes may be needed to detect loci with more modest effects on ideal CV health. In addition to the important impact of lifestyle modifications, we have identified evidence for gene variation that plays a role in ideal CV health.

Keywords

cardiovascular diseases; genetics; epidemiology

INTRODUCTION

The current American Heart Association 2020 Strategic Impact Goals introduce a concept – ideal cardiovascular (CV) health – defined by ideal levels of modifiable major risk factors, with the goal of improving the health of the nation in part by increasing the proportion of Americans who maintain ideal CV health.¹ Individuals having ideal CV health during middle age have been found to have markedly lower risks for cardiovascular and other chronic diseases, lower mortality rates, lower healthcare costs, and improved quality of life in older age.^{2–7} Overall, among participants of Framingham, the lifetime risk for cardiovascular disease after age 50 has been found to be as high as 51% among men and 39% among women; but for individuals with ideal levels of cardiovascular risk factors, the remaining lifetime risk for cardiovascular disease (CVD) is only 5–8%.⁸ The relative contribution of genetic, behavioral and/or environmental factors to achieving or maintaining ideal CV health in middle age remains unclear. Although only about 5% of the U.S. population is in ideal CV health,⁹ understanding how these individuals achieve and maintain ideal cardiovascular health represents an important public health goal that could help reduce the future burden of cardiovascular disease.

Numerous genome-wide association studies (GWAS) have been completed to identify genetic variation underlying clinically apparent CV disease or levels of CVD risk

factors.^{10–13} Two recent GWAS for the clustering of risk factors that comprise the metabolic syndrome have identified multiple loci, mostly near previously known lipid genes, underlying one or two metabolic syndrome components.^{14, 15} However, to date most studies have focused on individual phenotypes of risk and disease; examination of a healthy phenotype defined by the presence of several well defined health factors has not typically been studied. Accordingly, we conducted a meta-analysis of GWAS studies from community-based cohorts to identify common genetic variants associated with ideal CV health. We hypothesized that specific SNPs may be associated with the presence of ideal CV health in middle age.

METHODS

Discovery GWAS Studies

To identify common genetic variants associated with ideal CV health, we conducted a GWAS meta-analysis of a total of 11,708 white participants aged 50 ± 5 years at the time of an examination from four prospective cardiovascular cohort studies participating in the CHARGE (Cohorts for Heart and Aging Research in Genome Epidemiology) consortium.¹⁶ The four cohorts included the Multi-Ethnic Study of Atherosclerosis (MESA) (with examination cycles between 2000–2011), Coronary Artery Risk in Young Adults (CARDIA) Study (1985–2011), FHS Original Cohort and Offspring Cohorts (1948–2010) and Atherosclerosis Risk in Communities (ARIC) Study (1987–1998). Details about genome-wide genotyping in each cohort are found in Table 1. If participants were within the age range of 50 ± 5 years during multiple exams, the first/earliest exam within the age window was chosen and included in the analyses.

Assessment of Cardiovascular Risk Factors

Methods for the measurement of CV health factor levels for each study have been published.^{17–20} In each of the studies, blood pressure was determined as the average of two measurements performed by trained study personnel with the participant seated. Fasting blood draws were used when possible to obtain total cholesterol and fasting glucose levels; however, casual glucose was used if no fasting sample was available. Medication use and current smoking status were assessed by self-report. Physical exams were conducted by trained study personnel in which height and weight were determined and used to calculate body mass index (BMI), defined as the weight in kg divided by the square of the height in meters.

Ideal Cardiovascular Health

Ideal CV health definitions were created based on the AHA 2020 goals.¹ In this study, we examined the presence of two dichotomous phenotypes of ideal CV health at ages 50 ± 5 years: (1) Clinical, defined by the simultaneous presence of untreated serum cholesterol levels < 200 mg/dl (< 5.16 mmol/l); untreated blood pressure of $< 120/ < 80$ mm Hg; and not diabetic (fasting glucose < 126 mg/dL or casual glucose < 201 mg/dL and no reported use of any anti-diabetic medications). (2) Clinical+Behavioral, defined using the same criteria as the Clinical definition plus: not being a current smoker and having BMI < 25 kg/m².

Genome-Wide Association Analyses

We performed meta-analysis of four existing GWAS (n=11,708). For each of the four GWAS, genotypes were imputed using HapMap 2 data. Details about HapMap2 imputation in each cohort are found in Table 1. We filtered SNPs with MAF<0.05. Each study conducted logistic regression analyses for the approximately 2.5 million imputed SNPs using an additive SNP model for each of the two ideal CV health phenotypes. Models were adjusted for age, sex, site and study-specific principal components of ancestry. Study-specific results were combined using inverse-variance weighted meta-analysis implemented in METAL²¹ and corrected for residual inflation using genomic control. The genome-wide level of significance threshold was set at $P < 5 \times 10^{-8}$. There was no evidence of p-value inflation upon examination of the quantile-quantile plots. The genomic control inflation factor (λ_{GC}) was 1.019 for the Clinical ideal health phenotype and 1.017 for the Clinical +Behavioral phenotype.

Genetic determinants of ideal CV health, if observed, could be related to one or more of the individual cardiovascular health factors which together constitute the ideal CV health phenotype. In order to investigate this question, we examined the association of any SNPs that reached genome-wide significance for ideal CV health with each of the five individual dichotomous components included within either definition of ideal CV health: (1) ideal cholesterol, (2) ideal blood pressure, (3) not diabetic, (4) ideal BMI, and (5) non-smoker.

In order to determine whether the effect of the identified SNPs which reached genome-wide significance on ideal CV health were due to their association with LDL levels, we conducted logistic regression models in each of the cohorts after conditioning on continuous LDL in addition to the original covariates of age, sex, site and principal components of ancestry. Study-specific results of the conditional analyses were meta-analyzed in METAL using the same methods as the GWAS described above.

Validation Analysis

After completion of the GWAS, we conducted a validation analysis. Because the single SNP rs445925 that reached genome-wide significance in the GWAS meta-analysis was a low frequency variant with low imputation quality in some cohorts, we replicated the association of this SNP and of SNPs in the same region using directly genotyped SNPs from exome chip data from each of the same four cohorts. Exome chip data for participants of CARDIA, MESA, ARIC and FHS was obtained from the Illumina HumanExome Beadchip, after common genotype calling in these four cohorts and other cohorts in the CHARGE Consortium, as previously described.²² Details about genomewide exome chip genotyping in each cohort are found in Table 1.

Gene Expression Analysis

We queried over 90 datasets from multiple tissues for evidence of an expression quantitative trait locus (QTL) as well as 11 methylation QTL datasets to search for associations with our top SNP, rs445925, and 4 European ancestry LD proxies with $r^2 > 0.5$ identified using SNAP.²³

Multi-SNP Genetic Risk Scores

To further explore the role of genetic variation previously known to underlie lipids and CV disease with ideal CV health, including the contributory role of our top SNP, rs445925, we created 4 separate genetic risk scores (GRS) that were associated with coronary artery disease (CAD), LDL, HDL, and triglycerides (TG). The SNPs included in each of the Genetic Risk Scores can be found in Supplemental Table 1. Each GRS was calculated using single SNP meta-analysis association statistics from the meta-analysis described above and implemented using the *gtx* package in R as developed by Toby Johnson.²⁴ The CAD GRS included 45 SNPs identified by DeLoukas et al.¹⁰ The lipid GRS included 144 lipid GWAS SNPs (n=57 for LDL, n=71 for HDL, n=39 for triglycerides).²⁵ We examined the association of each GRS with ideal CV health with and without inclusion of our top SNP in the GRS, rs445925. Additionally, as a sensitivity analysis, we recalculated the CAD GRS, excluding SNPs known to be associated with LDL and TG (these eight loci are *APOB*, *ABCG5-ABCG8*, *PCSK9*, *SORT1*, *ABO*, *LDLR*, *APOE* and *LPA*),¹⁰ and examined its association with ideal CV health.

All studies included in this research have been supported by the National Institutes of Health. The authors are solely responsible for the design and conduct of this study, all analyses, the drafting and editing of the paper and its final contents.

RESULTS

Characteristics of Discovery GWAS Studies

Table 2 lists the characteristics of the four cohorts included in the GWAS meta-analysis for participants aged 50 years. Among our sample of 11,708 participants, the prevalence of Clinical ideal CV health was 19.2% (range: 10% to 29% among cohorts) and the prevalence of Clinical+Behavioral ideal CV health was 7.6% (range: 5% to 13% among cohorts). The mean age was just under 50 years and slightly more than half of the participants were female.

Meta-Analysis of GWAS

The Manhattan plots from the GWAS meta-analysis are shown in Figures 1A and 1B for the Clinical ideal CV health and Clinical+Behavioral ideal CV health, respectively. QQ plots for both analyses are shown in Supplemental Figures 1A and 1B. We identified one SNP (rs445925, range of MAF 0.13– 0.14) on chromosome 19 located between *APOC1* and *APOE* for which the A (minor) allele was associated with Clinical ideal CV health at a genome-wide level of significance ($p < 1.97 \times 10^{-9}$, OR= 1.72). These results were consistent across cohorts (Supplemental Table 2); however, the imputation quality was low (~ 0.3) across the cohorts and there were no other significant associations in this region (regional association plot in Figure 2). There was evidence for a nominally significant ($p = 0.0042$) association for rs445925 with the Clinical+Behavioral ideal CV health phenotype. There were no SNPs associated at a genome-wide significance level with Clinical+Behavioral ideal CV health.

When the association between rs445925 and the individual dichotomous components of ideal CV health was examined, the only significant association for rs445925 was with ideal cholesterol levels ($p=8.5 \times 10^{-23}$) and not with the other clinical or behavioral components of ideal CV health (Table 3).

When adjusted for continuous LDL, the association of SNP rs445925 was attenuated and no longer significantly associated with either Clinical ideal CV health or with Clinical +Behavioral ideal CV health (in the meta-analysis, $p=0.15$ for Clinical ideal CV health and $p=0.91$ for Clinical+Behavioral ideal CV health, respectively). These results were consistent across cohorts.

Validation Analysis

In our GWAS meta-analysis we identified a significant association of rs445925 with Clinical ideal CV health. This SNP is in high LD ($r^2=0.588$) with rs7412, known to be one of two SNPs defining the APOE2 allele. In order to determine whether rs7412 was driving the association between rs445925 and ideal CVD health, we used exome chip data from each of the cohorts to examine the associations between rs7412 and ideal CV health while adjusting for rs445925. Among cohort participants with exome chip data ($n=12,230$), rs445925 and rs7412 were both significantly associated with Clinical ideal CV health ($p=8.6 \times 10^{-10}$ and $0.1.45 \times 10^{-8}$, respectively) and Clinical+Behavioral ideal health ($p=0.00019$), and ($p=9.2 \times 10^{-16}$) respectively. The association of rs445925 with ideal CV health was attenuated after adjustment for rs7412, such that the p-values for Clinical ideal CV health and Clinical+Behavioral ideal CV health were 0.017 and 0.078, respectively.

eQTL Gene Expression Analysis

We identified an eQTL of modest strength for this SNP in subcutaneous adipose tissue from the MuTHER consortium in which rs445925 is associated with increased APOE expression ($p<3.85E-6$, beta 0.28, SE 0.06 which exceeds a 1% FDR threshold in the dataset).²⁶ The strongest eQTL SNP for APOE in this tissue is rs439401 ($P<2.38E-9$), but the correlation is low between rs439401 and rs445925 (r^2 0.02, $D'=0.51$).

Multi-SNP Genetic Risk Scores

When we examined associations with genetic risk scores for lipid subfractions and CHD, the LDL GRS had the strongest association with ideal CV health (p-values were 5.04×10^{-25} and <0.001 , for the Clinical and Clinical+Behavioral ideal CV health outcomes, respectively); these associations were only slightly attenuated with addition of rs445925. The TG GRS was also significantly associated with both ideal CV health outcomes ($p=6.6 \times 10^{-6}$ and 0.002, respectively), although these associations were not altered by the addition of rs445925. The CAD GRS was also significantly associated with ideal CV health. However, in sensitivity analysis after removal of eight SNPs in lipid loci known to be associated with LDL or triglycerides, the remaining CAD GRS was no longer significantly associated with ideal CV health ($p=0.8$). The HDL GRS was not associated with ideal CV health without or with inclusion of rs445925.

Funding for each of the cohort studies involved in the study is provided by the National Institutes of Health. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

DISCUSSION

To our knowledge, this is the first study to examine genetic determinants of ideal CV health and one of the few to examine a state of optimal health as opposed to a diseased state or shortened lifespan. In our results, we found that a common SNP in the APOC1/APOE region (rs445925) is associated with Clinical ideal CV health although this association appears to be driven largely by lipid levels. This specific SNP has been identified in previous GWAS to be associated with higher risk of coronary heart disease,^{10, 27} greater common carotid IMT and carotid plaque,²⁸ and long-term higher LDL levels in older adults²⁹ as well as in childhood through young adulthood.³⁰ Additionally, SNPs in the APOC1/APOE region have been associated with Alzheimer's disease,^{31, 32} longevity,³³ lipids³⁴ and metabolic syndrome.¹⁴ In our study we found that the A (minor) allele was associated with an increase in the odds of being in Ideal CV Health; this is consistent with the prior studies of CHD, carotid IMT and LDL cholesterol, in which the A (minor) allele was associated with a negative beta or decreased odds of disease. Our findings suggest that the effect of rs445925 on ideal CV health is likely mediated by its impact on LDL cholesterol levels. The SNP rs445925 remained significantly associated with ideal CV health in exome chip analyses even after adjustment for SNP rs7412 in the APOE region. Although adjustment for rs7412 attenuated the relationship, rs445925 remained significantly related to Clinical ideal CV health suggesting that this SNP (or a related variant) may have some independent effect on the trait above and beyond its direct effect on the APOE E2 allele. In analyses conditioning on LDL, rs445925 was no longer associated with ideal CV health. Beyond the finding that a lower prevalence of LDL raising risk loci are strongly and significantly associated with ideal health, we did not find strong evidence to support the association of other major gene loci.

There is substantial evidence demonstrating the benefits of the ideal cardiovascular health phenotype during middle age, and these benefits extend beyond the avoidance of incident cardiovascular disease. Prior research has shown that individuals who are able to achieve or maintain ideal CV health into middle age have greater longevity, lower morbidity from multiple chronic diseases, greater health-related quality of life, and lower healthcare costs in older age.^{2-7, 35} Similar to the findings in this study, the prevalence of Clinical (and Clinical + Behavioral) ideal CV health is low across the United States.^{7, 9} Given the demonstrated benefits, the American Heart Association recently published their goal to improve the CV health of all Americans by 2020.¹

We have identified a GWAS finding of a common SNP with potential biologic relevance and a consistent clinical impact. rs445925 is in the ApoC1/ApoE region. Apolipoprotein E (encoded by *APOE*) is primarily found in chylomicron and intermediate-density lipoproteins. In peripheral tissues, APOE mediates cholesterol metabolism while in the central nervous system it is involved in cholesterol transport. The APOE E2 allele (characterized by two SNPs including rs7412 in high LD with our top SNP rs445925) binds poorly to the cell surface receptors and has been shown to be associated with lower LDL-C

levels, type III hyperlipoproteinemia and Parkinson's disease.³⁶ In more recent GWAS studies, SNPs in the APOE locus appear to have pleiotropic effects beyond simply lipid metabolism.^{36,37} Among African Americans of the PAGE study, variants in the APOE region were found to be associated with multiple components of metabolic syndrome.³⁸ In addition to its effect on the functional form of APOE, rs445925 may also play a role in APOE expression. There is an eQTL of modest strength for this SNP in subcutaneous adipose tissue in which rs445925 is associated with increased APOE expression ($p < 3.85E-6$, beta 0.28, SE 0.06 which exceeds a 1% FDR threshold in the dataset). This same SNP, rs445925, is also associated with levels of subclinical and clinical atherosclerosis with results consistently pointing to the A allele as being associated with greater health. In the CHARGE Consortium, the A (minor) allele of rs445925 is associated with lower common carotid cIMT (discovery $p = 5.2 \times 10^{-8}$) as well as with decreased risk of carotid plaque.²⁸ Similarly, using data from the CHARGE Consortium, the A (minor) allele was associated with lower levels of coronary artery calcification (CAC) ($p = 6.99 \times 10^{-5}$).³⁹ Using data from CardioGram, rs445925 was found to be associated with coronary artery disease ($p = 0.019$), such that the G (major) allele was associated with increased risk of coronary artery disease. In a more recent meta-analysis of 41,513 cases and 65,919 controls in the second stage of the CardioGramPlusC4D Consortium, the G (major) allele of rs445925 was associated with increased risk of coronary artery disease (OR 1.13, $p = 8.76 \times 10^{-9}$).¹⁰ Thus, there is consistent evidence that this particular SNP provides strong protective effects on a range of traits related to cardiovascular health.

In this study, we found that rs445925 was primarily associated with Ideal Cardiovascular Health through an association with lipid levels; however, its impact may extend beyond simply lipid levels. There are data to suggest that lipid levels are prospectively associated with the development of other cardiovascular risk factors. For example, dyslipidemia is an independent predictor for the incidence of hypertension and diabetes.⁴⁰⁻⁴² In addition, hypercholesterolemia tends to precede the development of other risk factors more often than would be expected by chance.⁴³ These findings generate the hypothesis that persons with low lipid levels may be less likely to manifest other risk factors, and thus that individuals with the affected allele who are more likely to have ideal lipid levels may thus maintain ideal levels of the other risk factors as well (a.k.a. Ideal CV Health). Although lifestyle factors likely play an important role in ideal CV health, our GRS analyses reinforce the role that genetic predisposition to low LDL and possibly low triglycerides is an important contributor to ideal CV health and suggest that certain individuals with a beneficial genetic background (e.g. to lower LDL) are more likely to achieve ideal CV health. Given the association with ideal CV health of SNPs associated with both lower levels of lipids and lower CAD risk, future studies are warranted in larger populations to identify the protective genetic variants underlying ideal health.

This study took advantage of a several large, prospective cohorts with detailed risk factor information to conduct a collaborative meta-analysis of GWAS data. The findings in this study were generated in studies of Caucasians and are not necessarily applicable to racial/ethnic minorities. We examined genetic determinants of being in ideal health in middle-age (50 years of age); however, relatively few cardiovascular cohorts included participants within this age range. In addition, ideal CV health is a relatively low prevalence phenotype.

In future replication studies, larger sample sizes may be needed to replicate and extend these findings as we are likely to have been underpowered to detect a more complete repertoire of loci with more modest effects on ideal CV health. In addition to the known important impact of lifestyle modifications, we here have identified evidence for lipid gene variation that underlies ideal CV health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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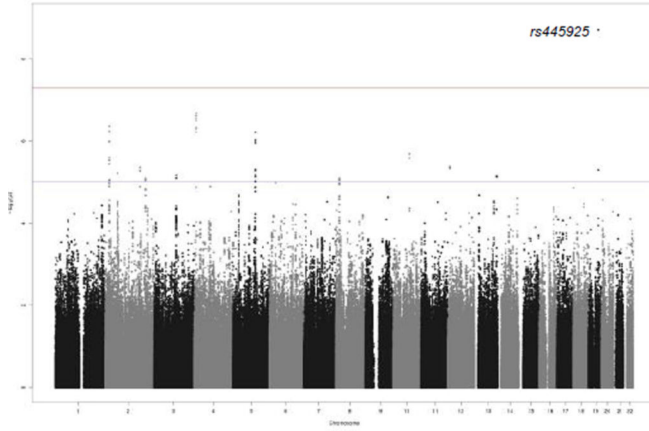
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A. Clinical Ideal CV Health



B. Clinical+Behavioral Ideal CV Health

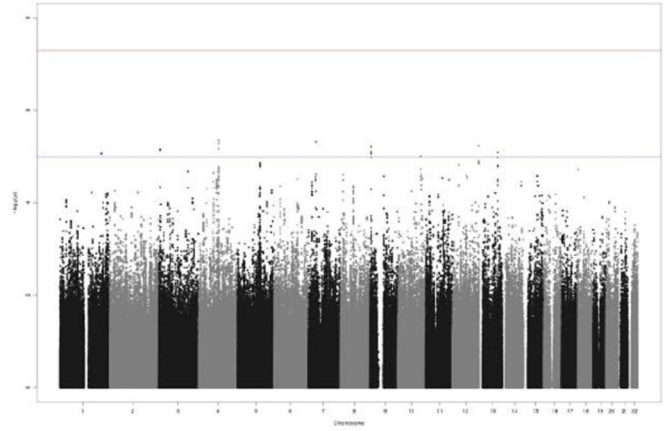


Figure 1.
Manhattan Plots

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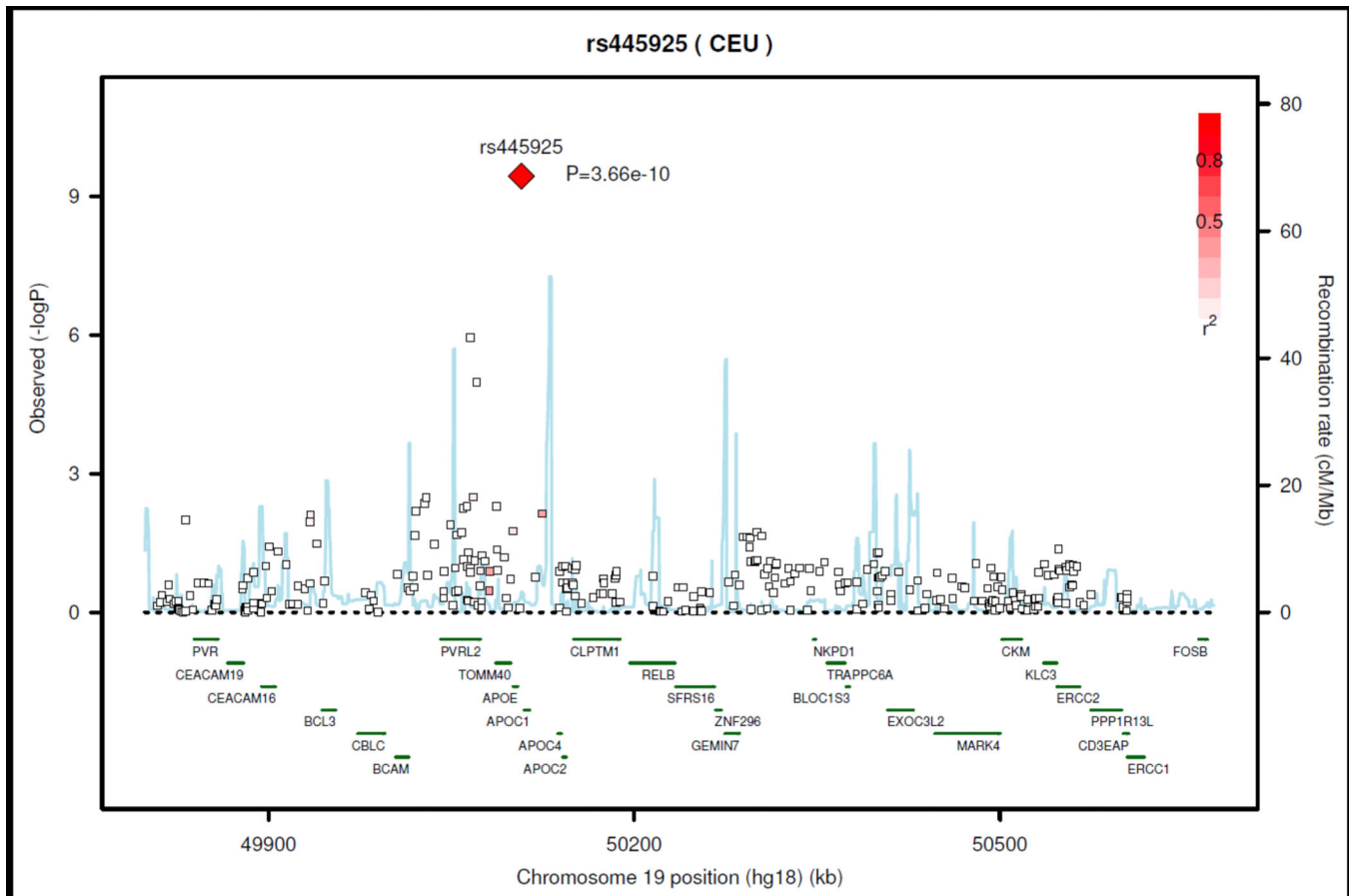


Figure 2.
Chrom 19 Regional Association Plot: Clinical Ideal CV Health

Table 1

Study Characteristics

COHORT	ARIC	CARDIA	FHS	MESA
Name	Atherosclerosis Risk in Communities Study (ARIC)	Coronary Artery Risk Development in Young Adults (CARDIA)	Framingham Heart Study (FHS)	Multi-Ethnic Study of Atherosclerosis (MESA)
Ethnicity	European descent	European descent	European descent	European-American
Country	United States	United States	United States	United States
Collection type	Population-based	Cohort	Population-based	Population-based (6 recruitment centers)
Genotyping platform	Illumina Exome Chip v1.0	Illumina Exome Chip v1.0	Illumina Exome Chip v1.0	Illumina Exome Chip v1.0
Genotyping centre	UT Houston, Human Genetics Center	UT Houston, Human Genetics Center	Illumina FastTrack Genotyping facility	Cedars Sinai
Genotyping calling algorithm	Illumina GenomStudio20 1.1.1	Illumina GenomStudio20 1.1.1	Illumina GenomStudio20 1.1.1	Illumina GenomStudio20 1.1.1
Joint calling performed?	Yes	Yes	Yes	Yes
Call rate by variant	mean 99.7%, range 0–100%	> 95%	97%	mean 99.7%, range 0–100%
HWE for MAF >5% & p < 10⁻⁶	Yes	Yes	Yes	No
Call rate by sample	Cutoff > 95%, mean 99.77%, range 95–99.84%	> 95%	-	-
Genotyping platform	Affymetrix Exome SNP Wide Hi-C Array 6.0	Affymetrix Exome SNP Wide Hi-C Array 6.0	Affymetrix 50K (50K Nip & 250K Sip), MIP5 50K	Affymetrix Exome SNP Wide Hi-C Array 6.0
Genotyping centre	Broad Institute	Broad Institute	Affymetrix	Affymetrix
Genotyping calling algorithm	BRLMM	Beaglecall	BRLMM	Birdseed v2
Call rate by variant	>95%	95%	>97%	95%
Imputation Software	Mach (version 1.0.16)	Mach (version 1.0.16)	Mach (version 1.0.1.5)	IMPUTE (version 2)
Reference Panel	BRLMM to Hapmap V1 CEU backbone (build 35)	HapMap Phase II, Build 36, Release 22	HapMap CEU, Build 36, Release 22	HapMap Phase I and II, Build 36, Release 24
Pre-Imputation MAF Filter	<0.01	<0.02	<0.01	<0.01
Pre-Imputation HWE Filter	< 1 × 10 ⁻⁶	< 1 × 10 ⁻⁴	< 1 × 10 ⁻⁶	< 1 × 10 ⁻⁵

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	Pre-Imputation Call Rate by Sample	>95%	95%	>97%	95%
ANALYSIS AND REFERENCES	Adjustments	Principal Components, Age, Sex, Center	Principal Components, Age, Sex, Center	Principal Components, Age, Sex, Center	Principal Components, Age, Sex, Center
	Software for analysis	PLINK, ProbABEL, SAS	PLINK, ProbABEL, SAS	PLINK, ProbABEL, SAS	PLINK, SNPTst, SAS
	Reference GWAS (PMID)	20031568	20400780, 20091798	-	23966861
	Website	http://www2.cse.cornell.edu/artc/	http://www.cardia.dopm.uab.edu/	http://www.acbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v2.p1	http://www.mesa-nhlbi.org/

Table 2

GWAS Cohort Characteristics

	ARIC	CARDIA	MESA	Framingham
N	4,751	1,311	757	4,889
Mean Age (yr range)	50.0 (45–55)	48.3 (45–55)	50.4 (45–55)	48.2 (45–55)
% Female	56.1%	53.3%	53.7%	53.2%
BMI, mean (SD)	26.7 (4.9)	28.0 (6.1)	27.9 (5.7)	26.6 (4.9)
% Clinical Ideal CV Health	24.3%	28.4%	29.3%	10.1%
% Clinical+Behavioral Ideal CV Health	9.2%	12.9%	6.9%	4.6%

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Table 3

P-values for rs445925 associations with components of Ideal Health

Component of Ideal CV Health	ARIC	CARDIA	MESA	Framingham	Meta-Analysis
Cholesterol	4.75E-11	0.08	0.004	2.26E-11	8.50E-23
Blood Pressure	0.73	0.45	0.28	0.004	0.09
Glucose	0.76	0.28	0.54	0.22	0.13
Smoking	0.47	0.75	0.87	0.93	0.71
BMI	0.40	0.25	0.52	0.28	0.96

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