A Comprehensive Evaluation of the Genetic Architecture of Sudden Cardiac Arrest

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INTRODUCTION

Sudden cardiac arrest (SCA) is a major cause of cardiac mortality, affecting over 300,000 people in the US every year(1). Clinical and autopsy studies have demonstrated a predominant, common pathophysiology in Western populations: the most common electrophysiologic mechanism for SCA is ventricular fibrillation (VF) and the most common pathologic substrate is coronary artery disease (CAD). Despite recent increases in SCA survival rates(2), survival remains low, and an important way to impact SCA mortality is through risk stratification and prevention. Although observational studies have identified numerous clinical and subclinical risk factors for SCA, understanding which of these associations are causal will help target prevention strategies.

Family history of SCA is a strong risk factor for SCA in the general population, suggesting that genetic variation may influence SCA risk.(3–5) While patients with inherited arrhythmias (e.g. Long QT Syndrome) are at increased SCA risk(6–8), the vast majority of SCA occurs outside of this high-risk population. Whether common variation in ion channel genes or other genomic regions influences SCA risk and identifies those at higher risk remains largely unknown.

Examining the genomic architecture of SCA allows us not only to examine genomic risk markers for SCA, but also to assess causal relationships of clinical and subclinical risk factors with SCA. Mendelian randomization methods exploit the fact that genetic variants are largely determined at conception and randomly distributed in populations, to determine whether an exposure may be causally associated with the outcome, and to estimate the effect size of that causal association(9–11). Here we use a multi-SNP genetic risk score association (GRSA) model

to compare genetic associations of known SCA risk factors to genetic associations with SCA as an effective way to understand the potential underlying causal pathways and processes that modulate SCA risk.

To determine whether genetic variants are associated with SCA risk, we performed a GWAS for SCA. We additionally examined whether common variation in inherited arrhythmia genes was associated with SCA risk in the general population. We then evaluated the relationships between SCA and multi-SNP GRSAs for each risk factor.

METHODS

Study Populations and Phenotype Definition.

The overall study design is summarized in **Fig. S1**. Briefly, nine studies of European-descent individuals (3,939 cases and 25,989 non-cases) comprised a GWAS 'discovery' stage, and 12 studies with individuals of European, African and Asian descent (4,918 additional cases and 21,873 controls) comprised a 'replication' stage. Study descriptions, along with study-specific SCA definitions and genotyping methods, are detailed in the **Supplementary Appendix**. All studies were approved by appropriate local institutional review boards.

GWAS

Genome-wide genotype data was imputed to the HapMap2-CEU reference panel, following study-level quality control checks (**Table S1A**). Each 'discovery' study performed regression analysis adjusted for age, sex, and study-specific covariates, and results were meta-analyzed using inverse variance meta-analysis implemented in METAL(12). Meta-analysis was performed with results from 9 GWASs comprising a total of 3,939 European-ancestry cases and

25,989 controls (**Table S1A),** with additional genotyping of 26 SNPs in up to 4,918 cases and 21,879 controls of European, African, and Asian descent (**Table S1B**). For SNP rs1554218, ARIC samples were not included in the discovery data leaving 3,815 cases and 17,107 controls for the discovery stage. These ARIC samples were used only in the replication data resulting in 5,218 cases and 35,957 controls for the replication stage for analysis involving this SNP only. The top 26 SNPs were examined in a 'replication' population (**Table S1B**). Findings from 'discovery' and 'replication' stages were then meta-analyzed (**Table S2, Fig. S3A**). Additionally, exploratory GWASs restricted to men; women; individuals under age 65; and cases with VF/shockable rhythm, were performed (**Table S3, Fig. S3B-S3E).**

Candidate genes

Using results from the GWAS meta-analysis, we examined variants in 54 inherited arrhythmia genes using the 'logistic-minsnp-gene-perm' function in FASTv1.8(13). This best single-SNP permutation based p-value is corrected for gene size by performing up to 1 million permutations per gene. Gene boundaries were defined by RefSeq gene coordinates on build GRCh37 with +/-10 kb flanking sequence.

Mendelian Randomization Instrument

Observational studies examine association of an exposure (e.g., body mass index, or BMI) with an outcome (e.g., SCA) but cannot assess causality. Unobserved variables affecting both exposure and outcome may confound these associations and lead to biased estimates of association. Mendelian randomization is based on the assumption that because genetic variants are determined at conception and are randomly distributed in large populations, they are unassociated with potential confounders. Therefore, under certain assumptions such as the

absence of genetic pleiotropy, genetic variants used as instrumental variables can determine whether an exposure is potentially causally associated with the outcome, and estimate the size of that association (see **Supplemental Appendix**). Here we use a multi-SNP genetic risk score association (GRSA) model to compare genetic associations with SCA with those of known SCA risk factors as an effective way to understand the underlying causal pathways and processes that influence SCA risk.

Genetic Risk Score Association (GRSA)

We estimated a separate GRSA for each of the following: (1) CAD and traditional CAD risk factors, including type 2 diabetes (T2D), fasting glucose adjusted for BMI (FGadjBMI), fasting insulin adjusted for BMI (FIadjBMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), total cholesterol (TCH), and triglycerides (TG); (2) cardiac electrophysiologic factors, including atrial fibrillation (AF), heart rate (HR), QRS interval (QRS), and QT interval (QT); and (3) anthropometric traits, including BMI, waist circumference adjusted for BMI (WCadjBMI), waist to hip ratio adjusted for BMI (WHRadBMI), and height. **Table S4** details the 18 traits, and the source published GWAS used to construct the GRSA models for these traits.

To estimate GRSAs for each putative SCA risk factor, we examined genome-wide SNPs associated with the risk trait following stringent LD-pruning (**Supplementary Appendix**). The associations of these SNPs with the risk factors and the SCA outcome are used to calculate an inverse-variance weighted multi-SNP GRSA as implemented in the R-package 'gtx'(14). This GRSA can be interpreted as an inverse-variance weighted, meta-analyzed (over SNPs) estimate of the causal log odds ratio for SCA associated with a one SD higher value of the risk factor from a Mendelian randomization analysis.(15) It is computationally equivalent to the slope

estimate from a zero-intercept linear regression with log odds ratio for the association of an additional variant allele in SNPs with SCA (β_{SCA}) as the dependent variable and the mean difference associated with one additional variant allele in SNPs on the risk factor trait (β_{trait}) as the independent variable, weighted by the standard error of the β_{SCA} squared (SE_{SCA}^2) (**Fig. 1A**) (more details in **Supplementary Appendix**). We evaluated the use of other MR methods, including MR-Egger, simple median, and median-weighted. However, we found while these produced similar GRSA estimates as the inverse-weighted (IVW) method, these other methods had lower power (**Fig. S4 and Table S5**). We therefore only report the results from the IVW method. We also used the intercept test from the MR-Egger method to evaluate the presence of pleiotropy in our analyses (**Table S5**).

The validity of this analysis requires that SNPs included can only affect the outcome through their effects on the risk factor (i.e. no horizontal pleiotropy). If there is no pleiotropy, the SNPs contributing the GRSA estimate should all estimate the same magnitude causal association between risk factor and SCA. We use the HEIDI-outlier method from the 'gsmr' R package to detect and remove potentially pleiotropic SNPs.(16) Note that we report GRSA estimates from analyses only including SNPs that meet a stringent genome-wide significant (GWS) *P*-value cut-off ($P<5x10^{-8}$), $GRSA_{GWS}$, as SNPs at this significance level likely are true positives and reliable instruments. However, the power for Mendelian randomization is dependent on the variance explained by the SNPs included in the GRSA, and for complex traits, the majority of the true signals may lie in SNPs that do not meet genome-wide significance. Therefore, we identified a somewhat arbitrary *P*-value cut-off based on visual inspection of the variance explained plots that largely maximizes variance explained while minimizing the number of SNPs (**Fig. S5**). We found that all the traits fell between 0.2-0.4 *P*-value cutoff, but the results within a trait were

robust to cutoffs chosen between 0.2 and 0.4. We use a GRSA constructed with this custom *P*-value cut-off ($GRSA_{max}$) to assess only the significance of the GRSA (P_{max}), as this model has the greatest power to assess the significance of an association. P_{max} is determined by permutation due to inflated test statistics (**Fig. S6** and **Supplementary Appendix).** At less stringent *P*-values, false-positive SNPs may be included resulting in a bias of the estimate toward the confounded association level. Therefore, we do not use the $GRSA_{max}$ to determine the magnitude of the GRSA association, only its direction and significance. We performed two analyses, one using $GRSA_{GWS}$ to evaluate significance and effect size, and secondarily using the $GRSA_{max}$ to evaluate potential associations and directions of effect at maximal power (P_{max}). We performed multiple-testing adjustment on all resulting *P*-values (P_{GWS} and P_{max}) using a false discovery rate (FDR) cutoff of FDR<0.05.

We similarly computed risk factor GRSAs on the outcome of CAD. We use a 1-degree of freedom Wald test to test for difference in $GRSA_{GWS}$ magnitudes between SCA and CAD.

Sex-specific analyses

We performed sex-specific SCA GWAS analyses to construct trait GRSAs separately by sex. GRSAs were constructed from the same set of LD-pruned SNPs used for overall $GRSA_{GWS}$ analyses. *P*-values for difference in $GRSA_{GWS}$ between sexes were obtained from 1-degree of freedom Wald test.

RESULTS

GWAS

Meta-analysis was performed with results from 9 GWASs of 3,939 European-ancestry cases and 25,989 controls (**Table S1A, Fig. S3A**) with additional genotyping of 26 SNPs in up to 4,918 cases and 21,879 controls of European, African, and Asian descent (**Table S1B**). No SNPs were associated with SCA ($P<5x10^{-8}$) (**Table S2**) in the main analysis or in subgroup analyses limited to European-descent individuals, men, women, younger participants (≤65 years), or cases with documented VF/shockable rhythm (**Tables S2** and **S3, Fig. S3B-S3E**).

Candidate Gene and Candidate SNP Analyses

Despite sufficient power to detect relative risks of 1.15 (80% power, allele frequency 0.30, at alpha=0.05, after Bonferroni correction for multiple-testing; more details in the **Supplementary Appendix**) in a candidate gene analysis**,** we did not find common variants in inherited arrhythmia genes associated with SCA in the general population (**Table S6)**. Examining SNPs previously associated with SCA in smaller studies, no SNP was found to be associated with SCA at the genome-wide significance threshold. **Table S7)**.

Genetic Risk Scores Associations (GRSAs)

To explore whether clinical and subclinical risk factors are causally linked with SCA, we examined genetic risk score associations (GRSA) between SCA and: (1) CAD and traditional CAD risk factors; (2) cardiac electrophysiologic factors; and (3) anthropometric traits. While the results reported below were computed using the IVW method, we used the intercept test of the MR-Egger method to evaluate the possible presence of pleiotropy. While HDL was nominally significant (P=0.02), all other traits were not found to be significantly influenced by pleiotropy.

CAD and CAD risk factors

Prevalent CAD is an important SCA risk factor with ~80% of male SCA survivors having underlying CAD(17). From $GRSA_{GWS}$ analysis we show that the difference in CAD status is causally associated with SCA (odds ratio in SCA risk per log odds difference in CAD, 1.36; 95% CI, 1.19-1.55; $P_{GWS}=9.29x10^{-5}$) (**Fig. 2, Table S8**). While traditional CAD risk factors (blood pressure, lipids and diabetes) were not significantly associated with SCA at the more restrictive $GRSA_{GWS}$ threshold, using $GRSA_{max}$ to maximize power, several additional associations were detected, including type 2 diabetes ($P_{max}<0.001$), LDL ($P_{max=}0.005$), total cholesterol ($P_{max}<0.001$), triglycerides ($P_{max}<0.001$), diastolic blood pressure ($P_{max}=0.0170$), and systolic blood pressure ($P_{max}=0.0230$) (**Table S9)**. In the $GRSA_{max}$ analysis, variants associated with higher diabetes risk, higher cholesterol and triglyceride levels, and higher systolic and diastolic blood pressure were all associated with higher SCA risk.

Cardiac electrophysiologic factors

To explore the influence of cardiac electrophysiology on SCA, we examined genetics of electrophysiologic traits associated with SCA: (1) atrial fibrillation, (2) QT interval (ventricular repolarization), (3) QRS interval (ventricular conduction), and (4) heart rate. In the $GRSA_{GWS}$ analysis, we show that longer QT interval, a risk factor for SCA in the general population, is significantly associated with SCA (odds ratio in SCA risk per SD increase in QT, 1.44; 95% CI, 1.13-1.83; $P_{GWS}=0.018$) **(Fig. 2, Table S8)**.(18) Using $GRSA_{max}$, in addition to QT, we also identified a significant association of AF with SCA ($P_{max}<0.001$ for both QT and AF) (**Table S9**). Variants associated with longer QT interval and higher AF risk were associated with higher SCA risk. By contrast, no significant association was seen with QRS or heart rate, even at the more permissive and statistically powerful $GRSA_{max.}$

Anthropometric Measures

The BMI $GRSA_{GWS}$ was significantly associated with SCA (odds ratio for SCA risk per SD higher BMI, 1.63; 95% CI, 1.23-2.15; P_{GWS}=0.005) (**Fig. 2, Table S8).** Using $GRSA_{max}$, we found a significant negative association between height and SCA (P_{max}<0.001) **(Table S9)**. Variants associated with greater height are associated with lower CAD risk(19), and we correspondingly observed a negative GRSA between SCA and height. No significant association was seen with GRSAs composed of variants associated with measures of central/abdominal adiposity, such as waist-to-hip ratio or waist circumference.

Contrasting SCA and CAD GRSAs

Given the strong association of CAD with SCA, we compared the magnitudes of risk factor $GRSA_{GWS}$ on the outcomes of SCA (**Fig. 2**) and CAD (**Fig. S7**) to identify traits where risk factors may be more strongly causally associated with SCA than CAD. While the $GRSA_{GWS}$ for traditional CAD risk factors (blood pressure and lipid traits) are larger for CAD risk than SCA risk, we find that $GRSA_{GWS}$ for electrophysiologic traits of QT interval (0.34 for SCA vs. 0.096 for CAD, *P* for difference = 0.06) and AF (0.097 for SCA vs. -0.029 for CAD, *P* for difference=0.017), there was a suggestion of a larger association with SCA than CAD risk (**Fig. 3, Table S8**).

Sex differences

Sex differences in SCA incidence, underlying SCA pathophysiology, and prevalence of certain risk factors have been well documented(20), yet little is known about whether the effect of risk factors on SCA differs by sex. Among $GRSAs_{GWS}$ where a main effect association was identified, we found a nominally significant difference in association between women and men

for diabetes (0.240 for women vs. 0.0205 for men, *P* for difference = 0.05) and HDL (-0.417 for women vs. 0.0256 for men, *P* for difference = 0.04) (**Table S10**).

DISCUSSION

Our SCA GWAS demonstrates that while SCA is a complex disease with multiple risk factors, a comprehensive genetic approach can shed light on causal versus correlational associations. Using Mendelian randomization, we establish that differences in CAD, BMI, and QT interval are causally associated with SCA. Secondary analyses further implicate type 2 diabetes, additional traditional CAD risk factors such as lipids and blood pressure, as well as height and atrial fibrillation.

Despite adequate power to identify relatively modest associations (OR > 1.3), our study did not find evidence that common variation in Mendelian arrhythmia genes is associated with SCA risk in the general population. Since underlying electrical instability is an important cause of SCA, prior smaller studies have examined inherited arrhythmia genes or variants associated with electrophysiological traits to identify genetic variants that influence SCA risk (21–23). While rare private mutations in ion-channel and other electrophysiology-related genes increase arrhythmia risk in high-risk families and may also increase SCA risk in the general population(24), our study suggests that common variants in these genes are not significant contributors to SCA in the general population. This may be due to differing underlying genetics between inherited arrhythmias versus SCA in the general population. By contrast, we do find that GRSA estimates of phenotypes associated with electrical instability (AF and QT) are causally associated with SCA risk, more so than they are causally associated with CAD. This confirms

our understanding of the pathophysiology of SCA—SCA is not simply fatal CAD, but rather, electrical instability also plays a prominent role in influencing SCA risk.

Intriguingly, not all electrophysiologic phenotypes observationally linked to SCA are causally associated with SCA in our analyses. QRS interval and heart rate, two traits observationally associated with SCA(25,26), failed to show significant evidence of a shared genetic basis with SCA. This lack of association may be due to inadequate power to identify more modest correlations. Alternatively, it may be that the associations from observational studies are confounded by other factors, and not causative **(Fig. 1B-C)**. For instance, underlying CAD can lead to both longer QRS interval and increased SCA risk; thus, while observational studies show an association between SCA and both traits (CAD and QRS interval), the association between SCA and QRS interval may not be causal. Similarly, the observational association of higher heart rate with SCA risk may be confounded by higher adrenergic state due to underlying heart disease and not itself be causal. Thus, the GRSA approach to examining observational risk factors assists in differentiating causative factors from confounded associations.

CAD is the most common underlying pathologic substrate for SCA. It is reassuring, therefore, that we find significant estimated causal associations with SCA risk using GRSA models constructed from CAD and traditional CAD risk factors, including blood pressure, diabetes and cholesterol traits.

Anthropometric measures appear to be causally associated with SCA. Shorter stature is associated with increased SCA risk in observational studies; our findings support the conclusion that this observational association is causal. Observational data on BMI and SCA risk have been

conflicting, perhaps due to confounding from smoking status and frailty. Previously(27), we have shown that increased BMI is associated with increased SCA risk in non-smokers, but not smokers. In this study, we find that differences in BMI, but not central/abdominal obesity, were causally associated with SCA risk. This finding is especially interesting in the context of recent data that imply different biological process underlying BMI and central obesity.(28,29)

Finally, of the traits associated with SCA, we found that GRSAs for diabetes and HDL were nominally significantly different between men and women. While diabetes is a SCA risk factor among both sexes, previous observational studies have consistently suggested a stronger, albeit not statistically different, association among women than men(30,31). These findings may reflect different underlying SCA pathophysiology between men and women. While these differences may be due to chance as they do not remain significant after multiple test correction, it is also likely that our study is underpowered to detect these differences.

Several limitations deserve consideration. First, without detailed autopsy information, rhythm monitoring, and information on circumstances surrounding the cardiac arrest, the underlying etiology and mechanism of death may be heterogeneous and genetic associations are likely to be diluted. Nonetheless, clinical and autopsy studies have demonstrated a predominant, common pathophysiology of SCA in Western populations: VF in the setting of CAD. Hence, it is reassuring that our genetic studies suggest an important role for both CAD and electrical instability in SCA. Second, despite ours being the largest exploration of SCA genomics to date, the discovery sample size of only ~4,000 cases, in addition to the heterogeneity of the phenotype, limited our ability to find genetic associations with low frequency variants or variants of modest effect. Hence, while our data do not support screening individuals with a family history of SCA for common variation in inherited arrhythmia genes, much larger samples sizes are needed to

address whether rare variation of modest effect in these genes influence SCA risk. Third, the validity of the GRSA method as a Mendelian randomization instrument rests on the assumption that the variant causes differences in the outcome only by its effects on the risk factor of interest, and not directly or by influencing other risk factors. Although we did not explicitly exclude SNPs associated with multiple risk factors (genetic pleiotropy), we did utilize a goodness-of-fit approach to exclude putative "pleiotropic" effects from all GRSAs. Furthermore, we performed a sensitivity analysis using the MR-Egger method, which tests for the presence of pleiotropy. Only HDL was found to be significantly influenced by pleiotropy (P=0.02). Lastly, while genetic pleiotropy can bias our conclusions, important influence is less likely when using multiple SNPs aggregated in a genetic risk score(32). Finally, the lack of common variants exhibiting large effect sizes associated with SCA limits the potential clinical utility for risk prediction.

In conclusion, while we were not able to identify any common genetic variants significantly associated with SCA risk through the GWAS, as well as any common variation in specific inherited arrhythmia genes associated with SCA risk, we have provided evidence for causal associations between some, but not all, observational risk factors for SCA. We show that differences in CAD status, BMI, and QT interval are causally associated with SCA risk. While SCA is a complex disease with multiple influencing factors, a comprehensive genetic approach can untangle risk factor relationships, enhancing our understanding of SCA pathophysiology. Ultimately, genetic studies will enhance efforts to prevent SCA in high-risk populations and the general community.

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CONFLICT OF INTEREST

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None to disclose: FNA, RNM, CN-C, JAB, MM-N, AM, TM, ACYM, HH, MJJ, PG, SLP, RP, MWT, MTB, XQZ, ASH, RJ, CG, VT, SAE, AC, GE, JC, ML, RJP, PYK, FD, CJOD, S-JH, AGU, AH, BHCS, PDB, PWF, JHJ, FWA, MKH, JJM, JT-H, VS, RV, FK, AAMW, HLT, CRB, ME, JDR, XJ, SK, DSS, NS.

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Figure Legends.

Figure 1. Genetic Risk Score Association (GRSA) Estimation. The plot (A) illustrates the process by which the QT-SCA GRSA is calculated using SNPs associated with QT at $P<5x10^{-8}$. The points represent the effect of each SNP on QT (in units of standard deviation of QT) on the x-axis, and the log odds effect on SCA risk (corresponding 95% confidence intervals in grey) on the y-axis. The estimate of the genetic risk score association is the slope of the zero-intercept weighted regression line (solid red line). For the GRSA used in our analyses, the model contains a genome-wide LD-pruned SNP set (details in Methods). The top directed acyclic graph (B) represents a scenario in which the trait of interest has a causal effect on the outcome. If the GRSA, comprised of trait-associated variants (e.g., QT), has a significant effect on the outcome (e.g., SCA), it supports a causal role for the trait on the outcome. The bottom directed acyl graph (C) presents the case where an association is observed between the trait and outcome, but the GRSA comprised of trait-associated variants is not significantly associated with the outcome, suggesting that the observational association is likely being mediated by a confounding variable and the trait does not have a causal impact on the outcome.

Figure 2. Genetic Risk Scores Association (GRSA) Estimates for SCA. These data points represent the exponentiated GRSA estimates of 18 traits on sudden cardiac arrest (SCA) and corresponding 95% confidence interval values. The GRSA estimates in the top panel for the binary traits are in log odds units. Values in bottom panel are in SD units of the quantitative traits. GRSA estimates and significance are derived from SNPs associated with each trait at $P<5x10^{-8}$.

The significance of the $GRSA_{GWS}$ estimates (FDR adjusted P_{GWS}) are represented as "*" for $P<0.05$, "**" for $P<0.01$, and "***" for $P<0.001$. The significance of the secondary analysis using $GRSA_{max}$ estimates (FDR adjusted permuted P_{max}) are represented as "+" for $P<0.05$, "++" for $P<0.01$ and "+++" for $P<0.001$. For details on values of GRSA estimates and *P*-values, see **Table S8-S9.** CAD = coronary artery disease; T2D = type 2 diabetes; AF = atrial fibrillation; BMI = body mass index; WCadjBMI = waist circumference adjusted for BMI; WHRadBMI = waist to hip ratio adjusted for BMI; DBP = diastolic blood pressure; SBP = systolic blood pressure; FGadjBMI = fasting glucose adjusted for BMI; FIadjBMI = fasting insulin adjusted for BMI; HR = heart rate; QRS = QRS interval; QT = QT interval; HDL = high-density lipoproteins; LDL = low-density lipoproteins; TCH = total cholesterol; TG = triglycerides.

Figure 3. Comparison of GRSA for SCA and CAD. These data represent exponentiated GRSAs of all 17 traits. GRSA estimates for SCA and CAD, are plotted in orange and teal respectively. Bars around the estimates represent the 95% confidence interval. The GRSA estimates in the top panel for the binary traits are in log odds units. Values in bottom panel are in SD units of the quantitative traits. The level of significance for 1 degree of freedom Wald test of difference in $GRSA_{GWS}$ estimates between SCA and CAD is represented "*" for $P<0.05$, "**" for $P<0.01$, and "***" for $P<0.001$. T2D = type 2 diabetes; AF = atrial fibrillation; BMI = body mass index; WCadjBMI = waist circumference adjusted for BMI; WHRadBMI = waist to hip ratio adjusted for BMI; DBP = diastolic blood pressure; SBP = systolic blood pressure; FGadjBMI = fasting glucose adjusted for BMI; FIadjBMI = fasting insulin adjusted for BMI; HR = heart rate; QRS = QRS interval; QT = QT interval; HDL = high-density lipoproteins; LDL = low-density lipoproteins; TCH = total cholesterol; TG = triglycerides.