

A comprehensive evaluation of the genetic architecture of sudden cardiac arrest

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Aims

Sudden cardiac arrest (SCA) accounts for 10% of adult mortality in Western populations. We aim to identify potential loci associated with SCA and to identify risk factors causally associated with SCA.

Methods and results

We carried out a large genome-wide association study (GWAS) for SCA ($n = 3939$ cases, 25 989 non-cases) to examine common variation genome-wide and in candidate arrhythmia genes. We also exploited Mendelian randomization (MR) methods using cross-trait multi-variant genetic risk score associations (GRSA) to assess causal relationships of 18 risk factors with SCA. No variants were associated with SCA at genome-wide significance, nor were common variants in candidate arrhythmia genes associated with SCA at nominal significance. Using cross-trait GRSA, we established genetic correlation between SCA and (i) coronary artery disease (CAD) and traditional CAD risk factors (blood pressure, lipids, and diabetes), (ii) height and BMI, and (iii) electrical instability traits (QT and atrial fibrillation), suggesting aetiologic roles for these traits in SCA risk.

Conclusions

Our findings show that a comprehensive approach to the genetic architecture of SCA can shed light on the determinants of a complex life-threatening condition with multiple influencing factors in the general population. The results of this genetic analysis, both positive and negative findings, have implications for evaluating the genetic architecture of patients with a family history of SCA, and for efforts to prevent SCA in high-risk populations and the general community.

Keywords

Sudden cardiac arrest • Genome-wide association study • Mendelian randomization

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 (MR) 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-single nucleotide polymorphism (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 genome-wide association study (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 GRSA for each risk factor.

Methods

Study populations and phenotype definition

The overall study design is summarized in [Supplementary material online, Figure S1](#). Briefly, nine studies of European-descent individuals (3939 cases and 25 989 non-cases) comprised a GWAS 'discovery' stage, and 12 studies with individuals of European, African, and Asian descent (4918 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 material online, Appendix](#). All studies were approved by appropriate local institutional review boards.

Genome-wide association study

Genome-wide genotype data was imputed to the HapMap2-CEU reference panel, following study-level quality control checks ([Supplementary material online, Table S1A](#)). Each 'discovery' study performed regression analysis adjusted for age, sex, and study-specific covariates, and results were meta-analysed using inverse-variance meta-analysis implemented in METAL.¹² Meta-analysis was performed with results from 9 GWASs comprising a total of 3939 European-ancestry cases and 25 989 controls ([Supplementary material online, Table S1A](#)), with additional genotyping of 26 SNPs in up to 4918 cases and 21 879 controls of European, African, and Asian descent ([Supplementary material online, Table S1B](#)). For SNP rs1554218, ARIC samples were not included in the discovery data leaving 3815 cases and 17 107 controls for the discovery stage. These ARIC samples were used only in the replication data resulting in 5218 cases and 35 957 controls for the replication stage for analysis involving this SNP only. The replication set included an additional ~120 ARIC cases not present in the discovery set. Therefore, the decision was made to remove the ARIC samples from the discovery dataset to use them in the replication dataset for this SNP. The top 26 SNPs were examined in a 'replication' population ([Supplementary material online, Table S1B](#)). Findings from 'discovery' and 'replication' stages were then meta-analysed ([Supplementary material online, Table S2, Figure S3A](#)). Additionally, exploratory GWASs restricted to men, women, individuals under age 65, and cases with VF/shockable rhythm were performed ([Supplementary material online, Table S3, Figure S3B–E](#)).

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 (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 [Supplementary material online, Appendix](#)). Here, we use a multi-SNP 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

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 (FladjBMI), 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 (WHRadjBMI), and height. [Supplementary material online, Table S4](#) details the 18 traits, and the source published GWAS used to construct the GRSA models for these traits.

To estimate GRSA for each putative SCA risk factor, we examined genome-wide SNPs associated with the risk trait following stringent linkage disequilibrium (LD)-pruning ([Supplementary material online, 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-analysed (over SNPs) estimate of the causal log odds ratio (OR) for SCA associated with a 1 SD higher value of the risk factor from a MR analysis.¹⁵ It is computationally equivalent to the slope estimate from a zero-intercept linear regression with log OR 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) ([Figure 1A](#)) (more details in [Supplementary material online, 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 ([Supplementary material online, Figure 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 ([Supplementary material online, 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 heterogeneity independent instrument (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 ($P < 5 \times 10^{-8}$), GRSA_{GWS}, as SNPs at this significance level likely are true positives and reliable instruments. However, the power for MR 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 ([Supplementary material online, Figure S5](#)). We found that all the traits fell between a 0.2 and 0.4 *P*-value cut-off, but the results within a trait were robust to cut-offs 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

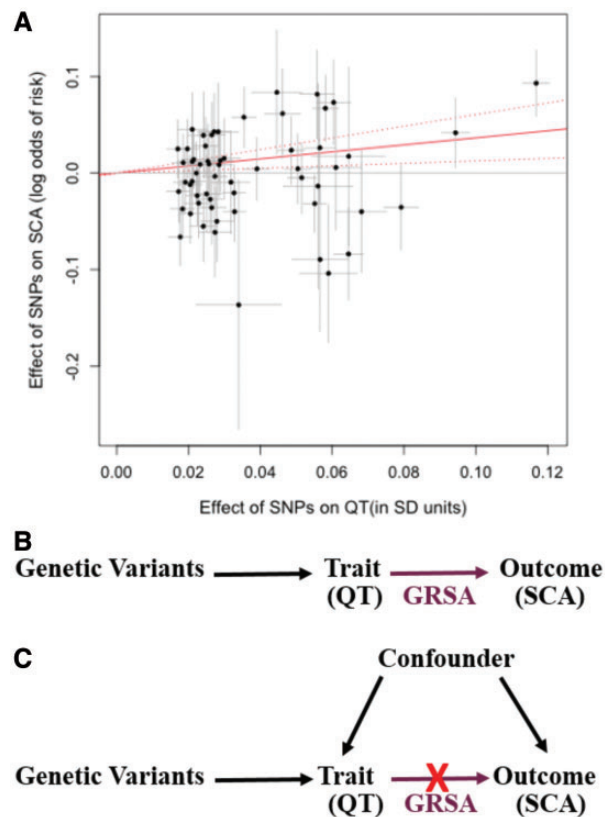


Figure 1 Genetic Risk Score Association (GRSA) estimation. The plot (A) illustrates the process by which the QT-SCA Genetic Risk Score Association is calculated using SNPs associated with QT at $P < 5 \times 10^{-8}$. The points represent the effect of each SNP on QT (in units of standard deviation of QT) on the x-axis and the log odds effect on sudden cardiac arrest 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 Genetic Risk Score Association used in our analyses, the model contains a genome-wide LD-pruned SNP set (details in Methods section). The top directed acyclic graph (B) represents a scenario in which the trait of interest has a causal effect on the outcome. If the Genetic Risk Score Association, comprised of trait-associated variants (e.g. QT), has a significant effect on the outcome (e.g. sudden cardiac arrest), 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 Genetic Risk Score Association 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.

assess the significance of an association. P_{\max} is determined by permutation due to inflated test statistics (Supplementary material online, Figure S6 and Supplementary material online, 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) cut-off of $FDR < 0.05$.

We similarly computed risk factor GRSA 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 GRSA separately by sex. Genetic risk score associations 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 a 1-degree of freedom Wald test.

Results

Genome-wide association study

Meta-analysis was performed with results from 9 GWASs of 3939 European-ancestry cases and 25 989 controls (Supplementary material online, Table S1A, Figure S3A) with additional genotyping of 26 SNPs in up to 4918 cases and 21 879 controls of European, African, and Asian descent (Supplementary material online, Table S1B). No SNPs were associated with SCA ($P < 5 \times 10^{-8}$) (Supplementary material online, 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 (Supplementary material online, Tables S2 and S3, Figure S3B–E).

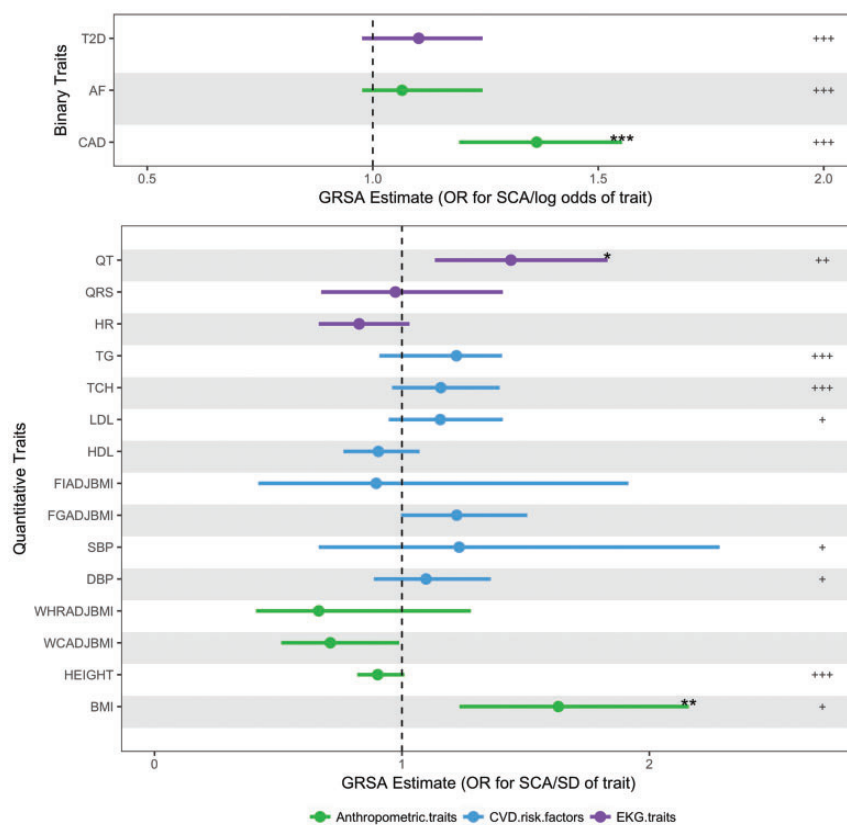


Figure 2 Genetic Risk Scores Association (GRSA) estimates for sudden cardiac arrest. These data points represent the exponentiated Genetic Risk Score Association estimates of 18 traits on sudden cardiac arrest (SCA) and corresponding 95% confidence interval values. The Genetic Risk Score Association 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. Genetic Risk Score Association estimates and significance are derived from SNPs associated with each trait at $P < 5 \times 10^{-8}$. The significance of the $GRSA_{GWS}$ estimates (false discovery rate 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 (false discovery rate 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 Genetic Risk Score Association estimates and P -values, see [Supplementary material online, Tables S8 and S9](#). AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; FGadjBMI, fasting glucose adjusted for BMI; FIadjBMI, fasting insulin adjusted for BMI; HDL, high-density lipoproteins; HR, heart rate; LDL, low-density lipoproteins; QRS, QRS interval; QT, QT interval; SBP, systolic blood pressure; TCH, total cholesterol; TG, triglycerides; T2D, type 2 diabetes; WCadjBMI, waist circumference adjusted for BMI; WHRadBMI, waist-to-hip ratio adjusted for BMI.

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 material online, Appendix](#)) in a candidate gene analysis, we did not find common variants in inherited arrhythmia genes associated with SCA in the general population ([Supplementary material online, 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. ([Supplementary material online, Table S7](#)).

Genetic Risk Scores Associations

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 high-density lipoprotein (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 (OR in SCA risk per log odds difference in CAD, 1.36; 95% CI 1.19–1.55; $P_{GWS} = 9.29 \times 10^{-5}$) ([Figure 2, Supplementary material online, 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 ($P_{max} < 0.001$), low-density lipoprotein ($P_{max} = 0.005$), total cholesterol ($P_{max} < 0.001$), triglycerides ($P_{max} < 0.001$), DBP ($P_{max} = 0.0170$), and SBP ($P_{max} = 0.0230$) (Supplementary material online, Table S9). In the $GRSA_{max}$ analysis, variants associated with higher diabetes risk, higher cholesterol and triglyceride levels, and higher SBP and DBP 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 (OR in SCA risk per SD increase in QT, 1.44; 95% CI 1.13–1.83; $P_{GWS} = 0.018$) (Figure 2, Supplementary material online, 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) (Supplementary material online, Table S9). Variants associated with longer QT interval and higher AF risk were associated with higher SCA risk. In 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 (OR for SCA risk per SD higher BMI 1.63; 95% CI 1.23–2.15; $P_{GWS} = 0.005$) (Figure 2, Supplementary material online, Table S8). Using $GRSA_{max}$, we found a significant negative association between height and SCA ($P_{max} < 0.001$) (Supplementary material online, 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 sudden cardiac arrest and coronary artery disease Genetic Risk Score Associations

Given the strong association of CAD with SCA, we compared the magnitudes of risk factor $GRSA_{GWS}$ on the outcomes of SCA (Figure 2) and CAD (Supplementary material online, Figure 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 (Figure 3, Supplementary material online, 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. 0.021 for men, P for difference = 0.05) and HDL (-0.417 for women vs. 0.026 for men, P for difference = 0.04) (Supplementary material online, 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 vs. correlational associations. Using MR, 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 AF.

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 electrophysiologic 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 vs. SCA in the general population. In 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 (Figure 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.

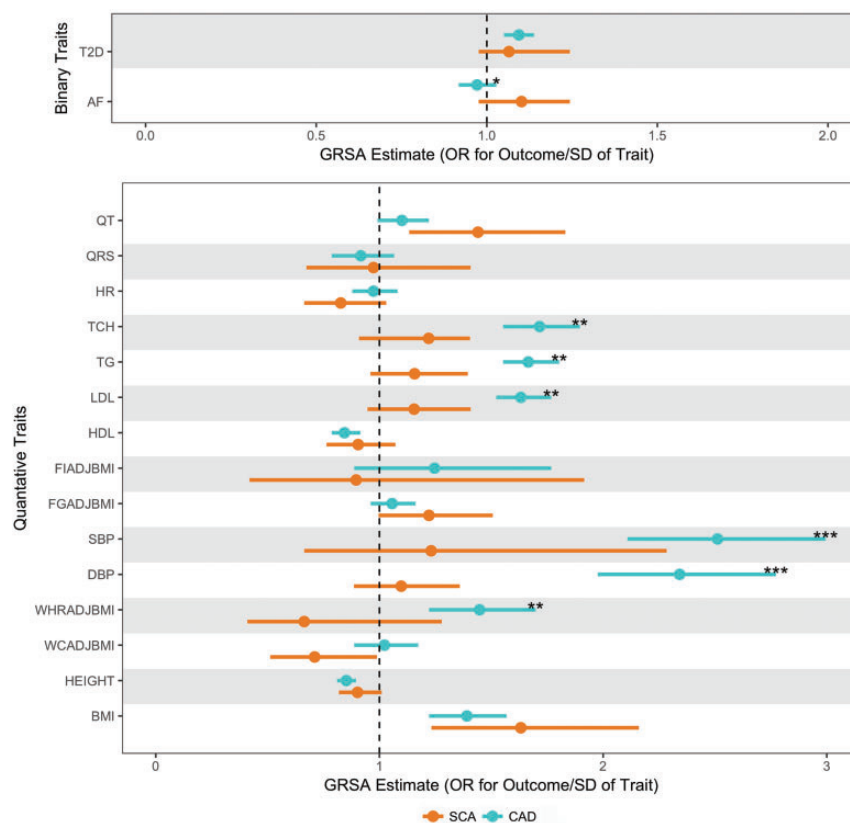


Figure 3 Comparison of Genetic Risk Score Association for sudden cardiac arrest and coronary artery disease. These data represent exponentiated Genetic Risk Score Associations of all 17 traits. Genetic Risk Score Association estimates for sudden cardiac arrest and coronary artery disease, are plotted in orange and teal, respectively. Bars around the estimates represent the 95% confidence interval. The Genetic Risk Score Association 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 sudden cardiac arrest and coronary artery disease is represented * for $P < 0.05$, ** for $P < 0.01$, and *** for $P < 0.001$. AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; FGadjBMI, fasting glucose adjusted for BMI; FladjBMI, fasting insulin adjusted for BMI; HDL, high-density lipoproteins; HR, heart rate; LDL, low-density lipoproteins; QRS, QRS interval; QT, QT interval; SBP, systolic blood pressure; TCH, total cholesterol; TG, triglycerides; T2D, type 2 diabetes; WCadjBMI, waist circumference adjusted for BMI; WHRadBMI, waist-to-hip ratio adjusted for BMI.

Coronary artery disease 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 there is a different biological process underlying BMI and central obesity.^{28,29}

Finally, of the traits associated with SCA, we found that GRSA 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 aetiology 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 ~4000 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 MR 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.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2014;CIR.0000000000000152.
- Blom MT, Beesems SG, Homma PCM, Zijlstra JA, Hulleman M, van Hoeijen DA, Bardai A, Tijssen JGP, Tan HL, Koster RW. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. *Circulation* 2014;130:1868–1875.
- Friedlander Y, Siscovick DS, Weinmann S, Austin MA, Psaty BM, Lemaitre RN, Arbogast P, Raghunathan TE, Cobb LA. Family history as a risk factor for primary cardiac arrest. *Circulation* 1998;97:155–160.
- Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation* 1999;99:1978–1983.
- Dekker LRC, Bezzina CR, Henriques JPS, Tanck MW, Koch KT, Alings MW, Arnold AER, Boer M-J, D, Gorgels APM, Michels HR, Verkerk A, Verheugt FWA, Zijlstra F, Wilde AAM. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation* 2006;114:1140–1145.
- Ackerman MJ. Genotype-phenotype relationships in congenital long QT syndrome. *J Electrocardiol* 2005;38:64–68.
- Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP, Burashnikov E, Wu Y, Sargent JD, Schickel S, Oberheiden R, Bhatia A, Hsu L-F, Haissaguerre M, Schimpf R, Borggrete M, Wolpert C. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 2007;115:442–449.
- Mohamed U, Napolitano C, Priori SG. Molecular and electrophysiological bases of catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol* 2007;18:791–797.
- Jansen H, Samani NJ, Schunkert H. Mendelian randomization studies in coronary artery disease. *Eur Heart J* 2014;35:1917–1924.
- Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol* 2004;33:30–42.
- Voight B, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hölm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijnenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buyschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. *Lancet* 2012;380:572–580.
- Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genome-wide association scans. *Bioinformatics* 2010;26:2190–2191.
- Chanda P, Huang H, Arking DE, Bader JS. Fast association tests for genes with FAST. *PLoS One* 2013;8:e68585.
- Johnson T, gtx: Genetics ToolboX [Internet]. 2013. Available from: <http://CRAN.R-project.org/package=gtx>.
- Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol* 2013;37:658–665.
- Causal associations between risk factors and common diseases inferred from GWAS summary data | bioRxiv [Internet]. [cited 2017 Oct 5]. Available from: <https://www.biorxiv.org/content/early/2017/07/26/168674>.
- Albert CM, McGovern BA, Newell JB, Ruskin JN. Sex differences in cardiac arrest survivors. *Circulation* 1996;93:1170–1176.
- Straus SMJM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MCJM, Stricker BHC, Witteman JCM. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol* 2006;47:362–367.
- Nelson CP, Hamby SE, Saleheen D, Hopewell JC, Zeng L, Assimes TL, Kanoni S, Willenborg C, Burgess S, Amouyel P, Anand S, Blankenberg S, Boehm BO, Clarke RJ, Collins R, Dedoussis G, Farrall M, Franks PW, Groop L, Hall AS, Hamsten A, Hengstenberg C, Hovingh GK, Ingelsson E, Kathiresan S, Kee F, König IR, Koener J, Lehtimäki T, März W, McPherson R, Metspalu A, Nieminen MS, O'Donnell CJ, Palmer CNA, Peters A, Perola M, Reilly MP, Ripatti S, Roberts R, Salomaa V, Shah SH, Schreiber S, Siegbahn A, Thorsteinsdottir U, Veronesi G, Wareham N, Willer CJ, Zalloua PA, Erdmann J, Deloukas P, Watkins H, Schunkert H, Danesh J, Thompson JR, Samani NJ. Genetically determined height and coronary artery disease. *N Engl J Med* 2015;372:1608–1618.
- Cupples LA, Gagnon DR, Kannel WB. Long- and short-term risk of sudden coronary death. *Circulation* 1992;85:111–118.
- Arking DE, Junttila MJ, Goyette P, Huertas-Vazquez A, Eijgelsheim M, Blom MT, Newton-Cheh C, Reinier K, Teodoroescu C, Uy-Evanado A, Carter-Monroe N, Kaikkonen KS, Kortelainen M-L, Boucher G, Lagacé C, Moes A, Zhao XQing, Kolodjiev F, Rivadeneira F, Hofman A, Witteman JCM, Uitterlinden AG, Marsman RF, Pazoki R, Bardai A, Koster RW, Dehghan A, Hwang S-J, Bhatnagar P, Post W, Hilton G, Prineas RJ, Li M, Köttgen A, Ehret G, Boerwinkle E, Coresh J, Kao WHL, Psaty BM, Tomaselli GF, Sotoodehnia N, Siscovick DS, Burke GL, Marbán E, Spooner PM, Cupples LA, Jui J, Gunson K, Kesäniemi YA, Wilde AAM, Tardif J-C, O'Donnell CJ, Bezzina CR, Virmani R, Stricker B, H C h, Tan HL, Albert CM, Chakravarti A, Rioux JD, Huikuri HV, Chugh SS. Identification of a sudden cardiac death susceptibility locus at 2q24.2 through genome-wide association in European ancestry individuals. *PLoS Genet* 2011;7:e1002158.
- Noseworthy PA, Havulinna AS, Porthan K, Lahtinen AM, Jula A, Karhunen PJ, Perola M, Oikarinen L, Kontula KK, Salomaa V, Newton-Cheh C. Common genetic variants, QT interval, and sudden cardiac death in a Finnish population-based study/clinical perspective. *Circ Cardiovasc Genet* 2011;4:305–311.
- Albert CM, MacRae CA, Chasman DI, VanDenburgh M, Buring JE, Manson JE, Cook NR, Newton-Cheh C. Common variants in cardiac ion channel genes are associated with sudden cardiac death. *Circ Arrhythm Electrophysiol* 2010;3:222–229.

24. Milano A, Blom MT, Lodder EM, van Hoeijen DA, Barc J, Koopmann TT, Bardai A, Beekman L, Lichtner P, van den Berg MP, Wilde AAM, Bezzina CR, Tan HL. Sudden cardiac arrest and rare genetic variants in the community. *Circ Cardiovasc Genet* 2016;**9**:147–153.
25. Jouven X, Zureik M, Desnos M, Guérot C, Ducimetière P. Resting heart rate as a predictive risk factor for sudden death in middle-aged men. *Cardiovasc Res* 2001;**50**:373–378.
26. Laukkanen JA, Di Angelantonio E, Khan H, Kurl S, Ronkainen K, Rautaharju P. T-wave inversion, QRS duration, and QRS/T angle as electrocardiographic predictors of the risk for sudden cardiac death. *Am J Cardiol* 2014;**113**:1178–1183.
27. Adabag S, Huxley RR, Lopez FL, Chen LY, Sotoodehnia N, Siscovick D, Deo R, Konety S, Alonso A, Folsom AR. Obesity related risk of sudden cardiac death in the atherosclerosis risk in communities study. *Heart Br Card Soc* 2015;**101**:215–221.
28. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, Croteau-Chonka DC, Esko T, Fall T, Ferreira T, Gustafsson S, Kutalik Z, Luan J, Mägi R, Randall JC, Winkler TW, Wood AR, Workalemahu T, Faul JD, Smith JA, Zhao JH, Zhao W, Chen J, Fehrmann R, Hedman ÖK, Karjalainen J, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bolton JL, Bragg-Gresham JL, Buyske S, Demirkan A, Deng G, Ehret GB, Feenstra B, Feitosa MF, Fischer K, Goel A, Gong J, Jackson AU, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Mangino M, Leach IM, Medina-Gomez C, Medland SE, Nalls MA, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Shungin D, Stančáková A, Strawbridge RJ, Sung YJ, Tanaka T, Teumer A, Trompet S, van der Laan SW, van Setten J, Van Vliet-Ostaptchouk JV, Wang Z, Yengo L, Zhang W, Isaacs A, Albrecht E, Ärnlöv J, Arscott GM, Attwood AP, Bandinelli S, Barrett A, Bas IN, Bellis C, Bennett AJ, Berne C, Blagieva R, Blüher M, Böhringer S, Bonnycastle LL, Böttcher Y, Boyd HA, Bruinenberg M, Caspersen IH, Chen YI, Clarke R, Daw EW, de Craen AJM, Delgado G, Dimitriou M, Doney ASF, Eklund N, Estrada K, Eury E, Folkersen L, Fraser RM, Garcia ME, Geller F, Giedraitis V, Gigante B, Go AS, Golay A, Goodall AH, Gordon SD, Gorski M, Grabe HJ, Grallert H, Grammer TB, Gräßler J, Grönberg H, Groves CJ, Gusto G, Haessler J, Hall P, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q, Hengstenberg C, Holmen O, Hottenga JJ, James AL, Jeff JM, Johansson Ö, Jolley J, Juliusdottir T, Kinnunen L, Koenig W, Koskenvuo M, Kratzer W, Laitinen J, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, Lindström J, Lo KS, Lobbens S, Lorbeer R, Lu Y, Mach F, Magnusson PKE, Mahajan A, McArdle WL, McLachlan S, Menni C, Merger S, Mihailov E, Milani L, Moayyeri A, Monda KL, Morken MA, Mulas A, Müller G, Müller-Nurasyid M, Musk AW, Nagaraja R, Nöthen MM, Nolte IM, Pilz S, Rayner NW, Renstrom F, Rettig R, Ried JS, Ripke S, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Scott WR, Seufferlein T, Shi J, Smith AV, Smolonska J, Stanton AV, Steinthorsdottir V, Stirrups K, Stringham HM, Sundström J, Swertz MA, Swift AJ, Svänen AC, Tan ST, Tayo BO, Thorand B, Thorleifsson G, Tyrer JP, Uhl HW, Vandenput L, Verhulst FC, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Warren HR, Waterworth D, Weedon MN, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A, Wright AF, Zhang Q; LifeLines Cohort Study, Brennan EP, Choi M, Dastani Z, Drong AW, Eriksson P, Franco-Cereceda A, Gådin JR, Gharavi AG, Goddard ME, Handsaker RE, Huang J, Karpe F, Kathiresan S, Keildson S, Kiryluk K, Kubo M, Lee JY, Liang L, Lifton RP, Ma B, McCarroll SA, McKnight AJ, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Okada Y, Perry JRB, Dorajoo R, Reinmaa E, Salem RM, Sandholm N, Scott RA, Stolk L, Takahashi A, Tanaka T, van't Hooft FM, Vinkhuyzen AAE, Westra HJ, Zheng W, Zondervan KT; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MIGen Consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium; Heath AC, Arveiler D, Bakker SJL, Beilby J, Bergman RN, Blangero J, Bovet P, Campbell H, Caulfield MJ, Cesana G, Chakravarti A, Chasman DI, Chines PS, Collins FS, Crawford DC, Cupples LA, Cusi D, Danesh J, de Faire U, den Ruijter HM, Dominiczak AF, Erbel R, Erdmann J, Eriksson JG, Farrall M, Felix SB, Ferrannini E, Ferrières J, Ford I, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gejman PV, Gieger C, Gottesman O, Gudnason V, Gyllenstein U, Hall AS, Harris TB, Hattersley AT, Hicks AA, Hindorf LA, Hingorani AD, Hofman A, Homuth G, Hovingh GK, Humphries SE, Hunt SC, Hyppönen E, Illig T, Jacobs KB, Jarvelin MR, Jöckel KH, Johansen B, Jousilahti P, Jukema JW, Julia AM, Kaprio J, Kastelein JJP, Keinanen-Kiukkaanniemi SM, Kiemenev LA, Knekt P, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Marchand LL, Lehtimäki T, Lyssenko V, Männistö S, Marette A, Matise TC, McKenzie CA, McKnight B, Musk AW, Möhlenkamp S, Morris AD, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Palmer LJ, Penninx BW, Peters A, Pramstaller PP, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Rioux JD, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schunkert H, Schwarz PEH, Sever P, Shuldiner AR, Sinisalo J, Stolk RP, Strauch K, Tönjes A, Trégouët DA, Tremblay A, Tremoli E, Virtamo J, Vohl MC, Völker U, Waeber G, Willemsen G, Witteman JC, Zillikens MC, Adair LS, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bornstein SR, Botttinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker PIW, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hui J, Hunter DJ, Hveem K, Kaplan RC, Kivimäki M, Kuh D, Laakso M, Liu Y, Martin NG, März W, Melbye M, Metspalu A, Moebus S, Munroe PB, Njølstad I, Oostra BA, Palmer CNA, Pedersen NL, Perola M, Pérusse L, Peters U, Power C, Quertemous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sattar N, Schadt EE, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Walker M, Wallaschofski H, Wareham NJ, Watkins H, Weir DR, Wichmann HE, Wilson JF, Zanan P, Borecki IB, Deloukas P, Fox CS, Heid IM, O'Connell JR, Strachan DP, Stefansson K, van Duijn CM, Abecasis GR, Franke L, Frayling TM, McCarthy MI, Visscher PM, Scherag A, Willer CJ, Boehnke M, Mohlke KL, Lindgren CM, Beckmann JS, Barroso I, North KE, Ingelsson E, Hirschhorn JN, Loos RJF, Speliotes EK. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;**518**:197–206.
29. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Mägi R, Strawbridge RJ, Pers TH, Fischer K, Justice AE, Workalemahu T, Wu JMW, Buchkovich ML, Heard-Costa NL, Roman TS, Drong AW, Song C, Gustafsson S, Day FR, Esko T, Fall T, Kutalik Z, Luan J, Randall JC, Scherag A, Vedantam S, Wood AR, Chen J, Fehrmann R, Karjalainen J, Kahali B, Liu CT, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bragg-Gresham JL, Buyske S, Demirkan A, Ehret GB, Feitosa MF, Goel A, Jackson AU, Johnson T, Kleber ME, Kristiansson K, Mangino M, Leach IM, Medina-Gomez C, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Stančáková A, Sung YJ, Tanaka T, Teumer A, Van Vliet-Ostaptchouk JV, Yengo L, Zhang W, Albrecht E, Ärnlöv J, Arscott GM, Bandinelli S, Barrett A, Bellis C, Bennett AJ, Berne C, Blüher M, Böhringer S, Bonnet F, Böttcher Y, Bruinenberg M, Carba DB, Caspersen IH, Clarke R, Daw EW, Deelen J, Deelman E, Delgado G, Doney AS, Eklund N, Erdos MR, Estrada K, Eury E, Friedrich N, Garcia ME, Giedraitis V, Gigante B, Go AS, Golay A, Grallert H, Grammer TB, Gräßler J, Grewal J, Groves CJ, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heikkilä K, Herzig KH, Helmer Q, Hillege HL, Holmen O, Hunt SC, Isaacs A, Ittermann T, James AL, Johansson I, Juliusdottir T, Kalafati IP, Kinnunen L, Koenig W, Kooner IK, Kratzer W, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, Lindström J, Lobbens S, Lorentzon M, Mach F, Magnusson PK, Mahajan A, McArdle WL, Menni C, Merger S, Mihailov E, Milani L, Mills R, Moayyeri A, Monda KL, Mooijaart SP, Mühleisen TW, Mulas A, Müller G, Müller-Nurasyid M, Nagaraja R, Nalls MA, Narisu N, Glorioso N, Nolte IM, Olden M, Rayner NW, Renstrom F, Ried JS, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Sennblad B, Seufferlein T, Sitali CM, Smith AV, Stirrups K, Stringham HM, Sundström J, Swertz MA, Swift AJ, Svänen AC, Tayo BO, Thorand B, Thorleifsson G, Tomaschitz A, Troffa C, van Oort FV, Verweij N, Vonk JM, Waite LL, Wennauer R, Wilsgaard T, Wojczynski MK, Wong A, Zhang Q, Zhao JH, Brennan EP, Choi M, Eriksson P, Folkersen L, Franco-Cereceda A, Gharavi AG, Hedman ÖK, Hivert MF, Huang J, Kanoni S, Karpe F, Keildson S, Kiryluk K, Liang L, Lifton RP, Ma B, McKnight AJ, McPherson R, Metspalu A, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Olsson C, Perry JR, Reinmaa E, Salem RM, Sandholm N, Schadt EE, Scott RA, Stolk L, Vallejo EE, Westra HJ, Zondervan KT; ADIPOGen Consortium; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GEFOS Consortium; GENIE Consortium; GLGC; ICBP; International Endogene Consortium; LifeLines Cohort Study; MAGIC Investigators; MuTHER Consortium; PAGE Consortium; ReproGen Consortium; Amouyel P, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Blangero J, Brown MJ, Burnier M, Campbell H, Chakravarti A, Chines PS, Claudi-Boehm S, Collins FS, Crawford DC, Danesh J, de Faire U, de Geus EJ, Dörr M, Erbel R, Eriksson JG, Farrall M, Ferrannini E, Ferrières J, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gieger C, Gudnason V, Haiman CA, Harris TB, Hattersley AT, Heliövaara M, Hicks AA, Hingorani AD, Hoffmann W, Hofman A, Homuth G, Humphries SE, Hyppönen E, Illig T, Jarvelin MR, Johansen B, Jousilahti P, Julia AM, Kaprio J, Kee F, Keinanen-Kiukkaanniemi SM, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuulasmaa K, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimäki T, Lyssenko V, Männistö S, Marette A, Matise TC, McKenzie CA, McKnight B, Musk AW, Möhlenkamp S, Morris AD, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Palmer LJ, Penninx BW, Peters A, Pramstaller PP, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schwarz PE, Shuldiner AR, Staessen JA, Steinthorsdottir V, Stolk RP, Strauch K, Tönjes A, Tremblay A, Tremoli E, Vohl MC, Völker U, Vollenweider P, Wilson JF, Witteman JC, Adair LS, Bochud M, Boehm BO, Bornstein SR, Bouchard C, Cauchi S, Caulfield MJ, Chambers JC, Chasman DI, Cooper RS, Dedoussis G, Ferrucci L, Froguel P, Grabe HJ, Hamsten A, Hui J, Hveem K, Jöckel KH, Kivimäki M, Kuh D, Laakso M, Liu Y, März W, Munroe PB, Njølstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Pérusse L, Peters U, Power C, Quertemous T, Rauramaa R, Rivadeneira

- F, Saaristo TE, Saleheen D, Sinisalo J, Slagboom PE, Snieder H, Spector TD, Stefansson K, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Veronesi G, Walker M, Wareham NJ, Watkins H, Wichmann HE, Abecasis GR, Assimes TL, Berndt SI, Boehnke M, Borecki IB, Deloukas P, Franke L, Frayling TM, Groop LC, Hunter DJ, Kaplan RC, O'Connell JR, Qi L, Schlessinger D, Strachan DP, Thorsteinsdottir U, van Duijn CM, Willer CJ, Visscher PM, Yang J, Hirschhorn JN, Zillikens MC, McCarthy MI, Speliotes EK, North KE, Fox CS, Barroso I, Franks PW, Ingelsson E, Heid IM, Loos RJ, Cupples LA, Morris AP, Lindgren CM, Mohlke KL. New genetic loci link adipose and insulin biology to body fat distribution. *Nature* 2015;**518**:187–196.
30. Chen LY, Sotoodehnia N, Bůžková P, Lopex LF, Yee LM, Heckbert SR, Prineas R, Soliman EZ, Adabag S, Konety S, Folsom AR, Siscovick D, Alonso A. Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. *JAMA Intern Med* 2013;**173**:29–35.
31. Jouven X, Lemaître RN, Rea TD, Sotoodehnia N, Empana J-P, Siscovick DS. Diabetes, glucose level, and risk of sudden cardiac death. *Eur Heart J* 2005;**26**:2142–2147.
32. Brion M, Benyamin B, Visscher P, Smith G. Beyond the single SNP: emerging developments in Mendelian randomization in the “Omics” era. *Curr Epidemiol Rep* 2014;**1**:228–236.