**Supplemental Materials:** **Increasing adiposity prolongs QTc interval and increases risk of ventricular arrhythmias in context of metabolic dysfunction: results from the UK Biobank**

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**Supplemental methods**

**Definitions of co-morbidity and rhythm abnormalities**

Morbidity and rhythm abnormality definitions based on the International Classification of Disease (ICD-10) classification were used in the study analyses. These are listed in **Supplemental Table S1** and encompass the conditions recorded in the primary (main) position in the participants’ hospital inpatient records upon entry to the UK Biobank based on review of past medical records. Participants’ baseline demographic characteristics were collected upon enrolment to the UK Biobank, and includes date of birth, sex and index of deprivation (Townsend deprivation index, TDI). TDI is a census-based index of material deprivation that is widely used in health research to establish whether relationships exist with deprivation. In this study, TDI was used as a surrogate index for lifestyle choices that may associated with adverse health outcomes. It was calculated immediately prior to the participant joining the UK Biobank and was based on preceding national census output areas. Each participant was assigned a score corresponding to the output area in which their postcode was located.

**Supplemental Table S1:**  Definitions of comorbidity based on the main and secondary International Classification of Disease (ICD)-10 summary diagnosis or operative procedures.

|  |  |  |
| --- | --- | --- |
| Comorbidity | ICD Code | Definition |
| Hypertension | I10, I15(Diagnosis) | Essential (primary) hypertension; Secondary hypertension. |
| Diabetes | E10, E11, E13, E14(Diagnosis) | Insulin-dependent diabetes mellitus; Non-insulin-dependent diabetes mellitus; Other specified diabetes mellitus; Unspecified diabetes mellitus. |
| Dyslipidaemia | E78.0, E78.1, E78.2, E78.4, E78.5, E78.6(Diagnosis) | Pure hypercholesterolaemia; Pure hyperglyceridaemia; Mixed hyperlipidaemia; Other hyperlipidaemia; Hyperlipidaemia, unspecified; Lipoprotein deficiency. |
| Coronary artery disease | I20, I21, I22I24, I25(Diagnosis) | Angina pectoris; Acute myocardial infarction; Subsequent myocardial infarction; Other acute ischaemic heart diseases; Chronic ischaemic heart disease. |
| Ventricular Arrhythmias | I47.0, I47.2, I49.0(Diagnosis) | Re-entry ventricular arrhythmia; Ventricular tachycardia; Ventricular fibrillation and flutter;  |
| K57.6(Operative Procedures) | Percutaneous transluminal ablation of ventricular wall;  |

**Derivation of polygenic risk score (PRS) for QTc interval**

To calculate the PRS for QT interval, we use summary statistics from prior genome-wide association studies of 70K individuals(1). P value threshold at genome-wide association level (P≤5×10–8 or –log10P=7.3) was used. 67 SNPs passed the threshold and LD clumping (minimum r2 = 0.05, distance 500kb) are selected and 66 of them were also available in the UK biobank genotyping dataset. **Supplemental Table S2** displays a list of the SNPs for use in the PRS were created based on increasing significance level from −log10P>7.39 (P≤4.07×10–8) to - log10P>212.9 (P≤1.32×10–213). PRS analysis was performed by PRSice (version 2.2.11.b) software using an additive genetic model. PRS score for each UK biobank individual was calculated by β coefficient weighted sum of all 66 selected SNPs and normalized to mean 0 standard deviations 1, as demonstrated by the equation below:

$$PRSj=\frac{∑i(Si×Gij)-Mean(PRS)}{SD(PRS)}$$

Where i is ith selected SNP markers used in PRS, j is jth individual, S is β coefficient, G is genotype (coded as 0, 1, and 2) for an additive genetic model.

This 66-SNP QT-PRS explained a significant degree of variance in 14501 UK biobank Caucasian participants for whom QTc was available, with R2 =0.0308 in a baseline model examining the association of QTc with PRS. Adding sex and age as covariates, they explained 0.0877 variance of QTc. This result is very similar to the result of the previous report of 2%-5% and 7-8% respectively in the European population(2).

**Supplemental Table S2:** 66 SNPs identified to modulate QT and available in the UK Biobank were used to generate a polygenic risk score as an indicator of repolarisation reserve. Summary statistics from Arking et al (1) were used to derive polygenic risk score. SNP, single nucleotide variants (with corresponding rs identification); CHR, chromosome number; POS: position of each SNP in hg19 reference genome; A1, allele 1; A2, allele 2; HAPMAP\_A1\_FREQ: A1 allele frequency in Hapmap project; Beta, beta co-efficients from GWAS identifying allele with QT prolongation(1).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **CHR** | **POS** | **A1** | **A2** | **HAPMAP\_A1\_FREQ** | **Beta** | **P** |
| rs12143842 | 1 | 162033890 | T | C | 0.1892 | 3.5009 | 1.32E-213 |
| rs3934467 | 1 | 162182677 | T | C | 0.1525 | 2.7435 | 2.76E-129 |
| rs880296 | 1 | 162128446 | G | C | 0.2009 | 2.2456 | 1.27E-81 |
| rs11153730 | 6 | 118667522 | T | C | 0.4914 | -1.6491 | 2.23E-67 |
| rs16857031 | 1 | 1162112910 | G | C | 0.1525 | 2.3653 | 6.45E-61 |
| rs37055 | 16 | 58560775 | T | C | 0.2895 | -1.7297 | 2.20E-57 |
| rs7122937 | 11 | 2486550 | T | C | 0.2105 | 1.9273 | 1.24E-54 |
| rs2072413 | 7 | 150647969 | T | C | 0.2931 | -1.6757 | 1.32E-49 |
| rs6676438 | 1 | 161983089 | T | C | 0.2902 | 1.5168 | 2.59E-45 |
| rs846111 | 1 | 6279370 | C | G | 0.2917 | 1.7317 | 7.39E-40 |
| rs347273 | 1 | 162317513 | G | A | 0.07589 | 1.8041 | 1.87E-38 |
| rs3807375 | 7 | 150667210 | T | C | 0.3795 | 1.2227 | 2.88E-33 |
| rs1805120 | 7 | 150649531 | A | G | 0.2054 | 1.5387 | 3.55E-33 |
| rs10919070 | 1 | 169099037 | C | A | 0.1417 | -1.6781 | 1.11E-31 |
| rs735951 | 16 | 11693536 | A | G | 0.4688 | -1.1529 | 2.29E-28 |
| rs12271931 | 11 | 2478519 | G | A | 0.1116 | -2.7657 | 8.94E-28 |
| rs6793245 | 3 | 38599037 | A | G | 0.2857 | -1.1163 | 4.43E-27 |
| rs1052536 | 17 | 33331575 | C | T | 0.4955 | 0.98 | 6.21E-25 |
| rs12210733 | 6 | 118653075 | A | G | 0.03704 | -2.051 | 1.13E-22 |
| rs12061601 | 1 | 169070450 | C | T | 0.1071 | -1.4096 | 3.10E-21 |
| rs4656345 | 1 | 1619912378 | A | G | 0.1 | -4.7305 | 1.03E-19 |
| rs457162 | 6 | 118535983 | T | A | 0.01887 | -1.8493 | 2.49E-18 |
| rs545833 | 1 | 168689940 | T | C | 0.2679 | 0.8975 | 3.89E-17 |
| rs17460657 | 1 | 162261826 | C | A | 0.03333 | -4.6017 | 2.72E-16 |
| rs3902035 | 6 | 119000232 | C | T | 0.1698 | -0.8519 | 8.00E-16 |
| rs1983546 | 1 | 139446183 | G | A | 0.35 | -0.8069 | 9.74E-16 |
| rs2298632 | 1 | 23710475 | T | C | 0.4955 | 0.6998 | 1.38E-14 |
| rs9892651 | 17 | 64303793 | C | T | 0.4688 | -0.7441 | 2.71E-14 |
| rs12997023 | 2 | 40752982 | C | T | 0.05085 | -1.6892 | 4.67E-14 |
| rs7545047 | 1 | 162191103 | A | G | 0.025 | -1.7784 | 8.89E-14 |
| rs12927050 | 16 | 11673488 | A | C | 0.12 | -0.973 | 1.17E-13 |
| rs1811815 | 11 | 2475150 | A | G | 0.2273 | -0.9 | 1.18E-13 |
| rs11710077 | 3 | 38657899 | T | A | 0.1964 | 0.9224 | 1.42E-13 |
| rs10775360 | 17 | 68325868 | T | C | 0.3051 | -0.7551 | 1.07E-12 |
| rs12444261 | 16 | 11734642 | T | G | 0.2857 | -0.7915 | 2.14E-12 |
| rs3105593 | 15 | 50845018 | T | C | 0.4732 | 0.6643 | 3.06E-12 |
| rs6599234 | 3 | 38715300 | A | T | 0.3 | 0.6986 | 2.22E-11 |
| rs11708996 | 3 | 38633923 | C | G | 0.2 | -0.9238 | 2.27E-11 |
| rs164133 | 1 | 162381288 | C | G | 0.1833 | 0.7195 | 2.99E-11 |
| rs2273905 | 14 | 102974999 | T | C | 0.2946 | 0.6102 | 4.04E-11 |
| rs236523 | 17 | 68212642 | C | A | 0.4955 | 0.6377 | 4.77E-11 |
| rs1659127 | 16 | 14388305 | A | G | 0.3 | 0.7068 | 6.38E-11 |
| rs13355516 | 5 | 137380603 | G | A | 0.175 | -0.8306 | 6.97E-11 |
| rs6800541 | 3 | 38774832 | C | T | 0.4196 | -0.6249 | 8.14E-11 |
| rs12079745 | 1 | 139101060 | A | G | 0.02586 | -1.3408 | 1.22E-10 |
| rs174577 | 11 | 61604814 | A | C | 0.3393 | -0.6523 | 1.30E-10 |
| rs6544311 | 2 | 40353277 | A | C | 0.3776 | 0.6457 | 1.79E-10 |
| rs1296720 | 16 | 3873642 | C | A | 0.2455 | 0.8297 | 3.57E-10 |
| rs4716056 | 6 | 16278390 | G | A | 0.3646 | 0.648 | 3.95E-10 |
| rs2301696 | 11 | 2426984 | G | C | 0.4 | -1.1423 | 4.26E-10 |
| rs2363719 | 4 | 72138216 | A | G | 0.09375 | 0.9677 | 7.84E-10 |
| rs12675772 | 8 | 71213705 | G | C | 0.1 | 0.9447 | 1.76E-09 |
| rs11888462 | 2 | 201160499 | T | G | 0.4153 | 0.5605 | 4.95E-09 |
| rs183993 | 4 | 95130025 | G | A | 0.35 | 0.5662 | 5.19E-09 |
| rs13002675 | 2 | 174739352 | A | C | 0.1937 | 0.7217 | 5.38E-09 |
| rs4784934 | 16 | 58459926 | A | G | 0.2091 | 0.6748 | 5.55E-09 |
| rs2273042 | 1 | 6149122 | A | G | 0.1308 | 0.9375 | 6.80E-09 |
| rs4630352 | 12 | 110747419 | A | G | 0.3227 | 0.5675 | 1.09E-08 |
| rs4657172 | 1 | 162179632 | C | G | 0.1583 | -0.8141 | 1.27E-08 |
| rs9489510 | 6 | 119043898 | G | A | 0.3036 | 0.6085 | 1.36E-08 |
| rs728926 | 13 | 74513122 | T | C | 0.3438 | 0.5746 | 2.06E-08 |
| rs9920 | 7 | 116200092 | C | T | 0.07658 | 0.7899 | 2.60E-08 |
| rs2485376 | 10 | 104050006 | A | G | 0.4286 | -0.5629 | 2.69E-08 |
| rs3789530 | 1 | 6153406 | T | C | 0.1205 | 0.9171 | 3.29E-08 |
| rs295449 | 3 | 47375955 | G | A | 0.433 | -0.549 | 3.83E-08 |
| rs2916558 | 8 | 103847399 | A | C | 0.3833 | 0.5563 | 4.07E-08 |

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