SUPPLEMENTAL MATERIAL

Associations of Fitness, Physical Activity, Strength and Genetic Risk with Cardiovascular Disease: Longitudinal Analyses in the UK Biobank Study

Emmi Tikkanen, Stefan Gustafsson, Erik Ingelsson

Supplemental Tables

Supplementary Table 1. Genetic variants included in the genetic risk score for coronary heart disease.

SNP	**Gene**	**Reference allele**	**Weight**
rs10840293	SWAP70	A	1.06
rs10947789	KCNK5	T	1.05
rs10953541	7q22	C	1.05
rs11203042	LIPA	T	1.04
rs1122608	LDLR	G	1.08
rs11556924	ZC3HC1	C	1.08
rs11830157	KSR2	G	1.04
rs12190287	TCF21	C	1.06
rs12413409	CYP17A1-CNNM2-NT5C2	G	1.08
rs12526453	PHACTR1	C	1.10
rs12936587	RAI1-PEMT-RASD1	G	1.03
rs12976411	ZNF507-LOC400684	T	0.95
rs1412444	LIPA	T	1.07
rs1561198	VAMP5-VAMP8-GGCX	T	1.06
rs16986953	AK097927	A	1.09
rs17087335	REST-NOA1	T	1.06
rs17114036	PPAP2B	A	1.13
rs17464857	MIA3	T	1.06
rs17465637	MIA3	C	1.08
rs17514846	FURIN-FES	A	1.05
rs17609940	ANKS1A	G	1.03
rs1878406	EDNRA	T	1.06
rs2023938	HDAC9	C	1.06
rs2047009	CXCL12	G	1.06
rs2048327	SLC22A3-LPAL2-LPA	C	1.06
rs2075650	APOE-APOC1	G	1.07
rs216172	SMG6	C	1.05
rs2252641	ZEB2-ACO74093.1	C	1.03
rs2505083	KIAA1462	C	1.06
rs264	LPL	G	1.06
rs273909	SLC22A4-SLC22A5	G	1.06
rs2895811	HHIPL1	C	1.04
rs2954029	TRIB1	A	1.04
rs3184504	SH2B3	T	1.07
rs3217992	9p21	T	1.14
rs3798220	SLC22A3-LPAL2-LPA	C	1.42

rs3918226	NOS3	T	1.14
rs4252120	PLG	T	1.03
rs445925	APOE-APOC1	G	1.09
rs46522	UBE2Z	T	1.04
rs4773144	COL4A1/A2	G	1.05
rs4845625	IL6R	T	1.05
rs4977574	9p21	G	1.21
rs501120	CXCL12	T	1.08
rs515135	APOB	C	1.07
rs56062135	SMAD3	C	1.07
rs579459	ABO	C	1.08
rs646776	SORT1	T	1.11
rs6544713	ABCG5-ABCG8	T	1.05
rs663129	PMAIP1-MC4R	A	1.06
rs6725887	WDR12	C	1.14
rs6903956	ADTRP-C6orf105	A	1.00
rs7136259	ATP2B1	T	1.04
rs7173743	ADAMTS7	T	1.08
rs7692387	GUCY1A3	G	1.07
rs8042271	MFGE8-ABHD2	G	1.10
rs9319428	FLT1	A	1.04
rs9515203	COL4A1/A2	T	1.07
rs964184	ZNF259-APOA5-APOA1	G	1.05
rs974819	PDGFD	T	1.07
rs9818870	MRAS	T	1.07
rs9982601	KCNE2	T	1.12

Data have been contributed by CARDIoGRAMplusC4D[1].
SNP, single-nucleotide polymorphism.

Supplementary Table 2. Genetic variants included in the genetic risk score for atrial fibrillation.

SNP	Gene	Reference allele	Weight
rs11047543	SOX5	G	1.14
rs11264280	KCNN3	T	1.12
rs1152591	SYNE2	A	1.09
rs11598047	NEURL1	G	1.18
rs11718898	CAND2	C	1.08
rs12664873	GJA1	T	1.08
rs1997572	CAV1/2	G	1.10
rs2106261	ZFHX3	T	1.20
rs2288327	TTN/TTN-AS1	G	1.09
rs2540949	CEP68	A	1.08
rs2967791	KLHL3/WNT8A/FAM13B	T	1.07
rs337711	KCNN2	T	1.07
rs35176054	SH3PXD2A	A	1.14
rs3771537	ANXA4/GMCL1	A	1.09
rs4946333	SLC35F1/PLN	G	1.08
rs520525	PRRX1	A	1.12
rs6800541	SCN10A	T	1.08
rs6843082	PITX2	G	1.45
rs7026071	C9orf3	T	1.09
rs74022964	HCN4	T	1.12
rs7508	ASAH1/PCM1	A	1.09
rs75190942	KCNJ5	A	1.17
rs7915134	SYNPO2L	C	1.12
rs883079	TBX5	T	1.11

Data have been contributed by AFGen Consortium[2].
SNP, single-nucleotide polymorphism.

Supplementary Table 3. Hazard ratios with 95% confidence intervals for CHD according to tertiles of genetic risk and grip strength, physical activity and cardiorespiratory fitness.

	HR (95% CI)		
GRS	**Strength**		
	Low	**Intermediate**	**High**
Low	1 (ref)	0.74 (0.66 , 0.83)	0.57 (0.51 , 0.65)
Intermediate	1 (ref)	0.81 (0.73 , 0.90)	0.64 (0.58 , 0.72)
High	1 (ref)	0.80 (0.73 , 0.88)	0.69 (0.62 , 0.75)
	Physical activity		
Low	1 (ref)	0.91 (0.82 , 1.01)	0.86 (0.78 , 0.96)
Intermediate	1 (ref)	0.83 (0.76 , 0.92)	0.95 (0.87 , 1.04)
High	1 (ref)	0.85 (0.78 , 0.92)	0.89 (0.82 , 0.96)
	Cardiorespiratory fitness		
Low	1 (ref)	0.70 (0.50 , 0.98)	0.43 (0.28 , 0.67)
Intermediate	1 (ref)	0.71 (0.52 , 0.96)	0.45 (0.30 , 0.65)
High	1 (ref)	0.65 (0.50 , 0.86)	0.51 (0.38 , 0.69)

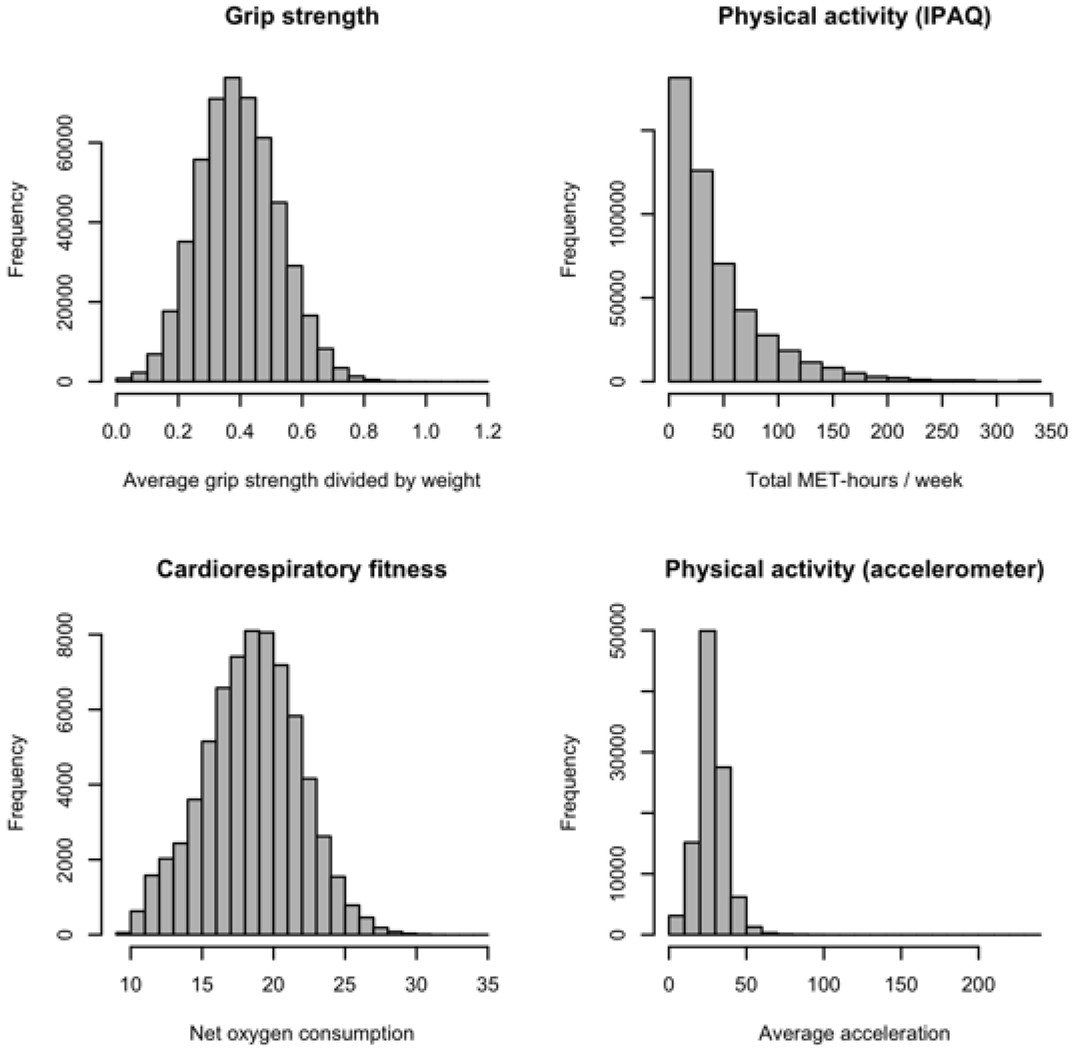
Abbreviations: CHD, coronary heart disease; HR, hazard ratio; CI, confidence interval; GRS, genetic risk score.

Supplementary Table 4. Hazard ratios with 95% confidence intervals for AF according to tertiles of genetic risk and grip strength, physical activity and cardiorespiratory fitness.

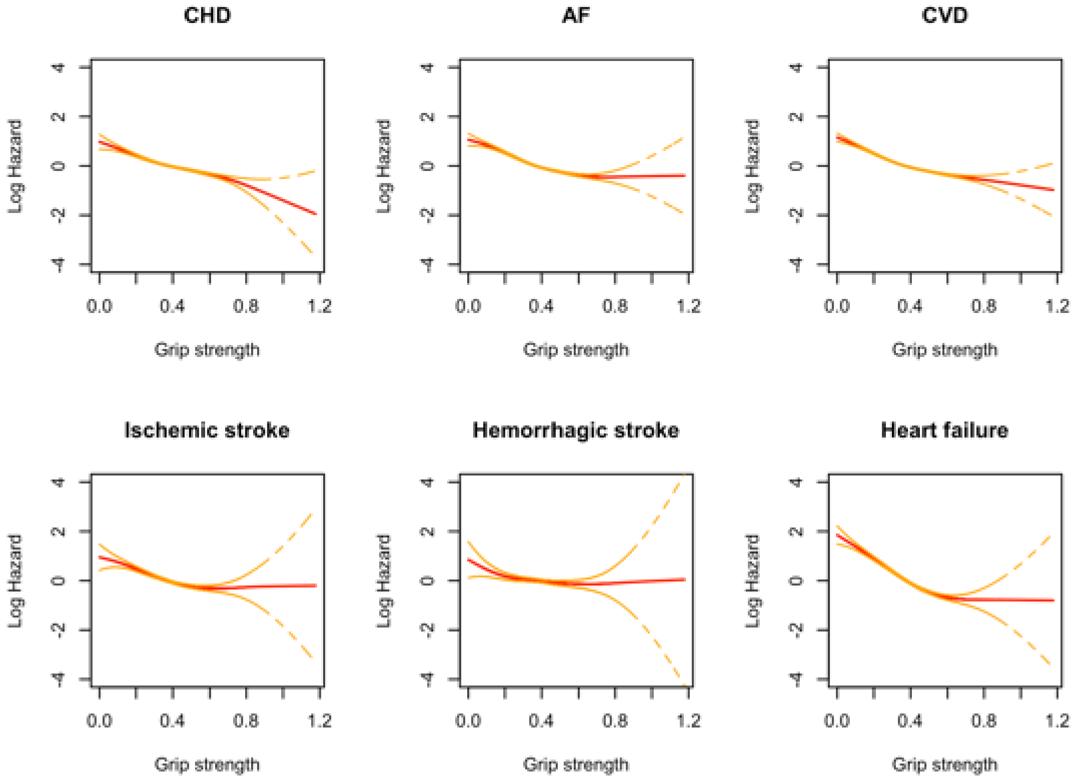
	HR (95% CI)		
GRS	**Strength**		
	Low	**Intermediate**	**High**
Low	1 (ref)	0.67 (0.60 , 0.74)	0.51 (0.45 , 0.57)
Intermediate	1 (ref)	0.65 (0.60 , 0.72)	0.54 (0.49 , 0.60)
High	1 (ref)	0.71 (0.66 , 0.77)	0.61 (0.56 , 0.67)
	Physical activity		
Low	1 (ref)	0.98 (0.89 , 1.09)	0.91 (0.82 , 1.00)
Intermediate	1 (ref)	0.89 (0.82 , 0.97)	0.82 (0.75 , 0.89)
High	1 (ref)	0.90 (0.83 , 0.97)	0.90 (0.83 , 0.97)
	Cardiorespiratory fitness		
Low	1 (ref)	0.68 (0.49 , 0.94)	0.46 (0.30 , 0.71)
Intermediate	1 (ref)	0.51 (0.39 , 0.68)	0.38 (0.26 , 0.54)
High	1 (ref)	0.51 (0.40 , 0.65)	0.40 (0.30 , 0.55)

Abbreviations: AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval; GRS, genetic risk score.

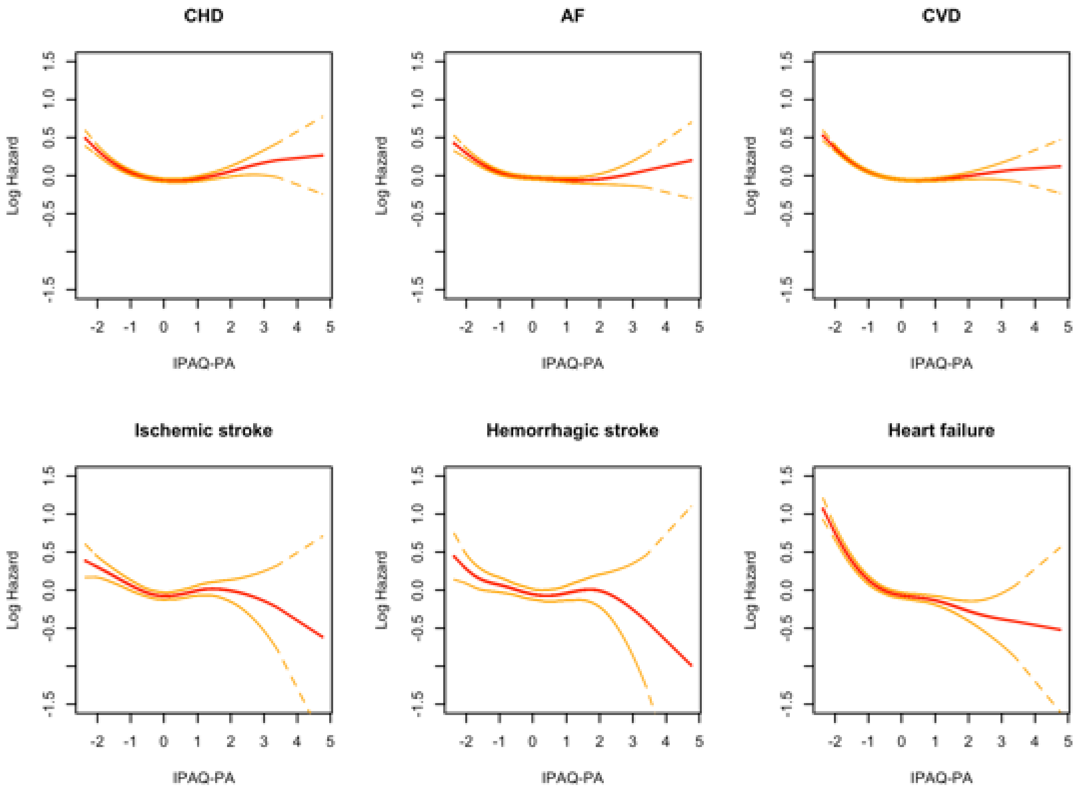
Supplemental Figures



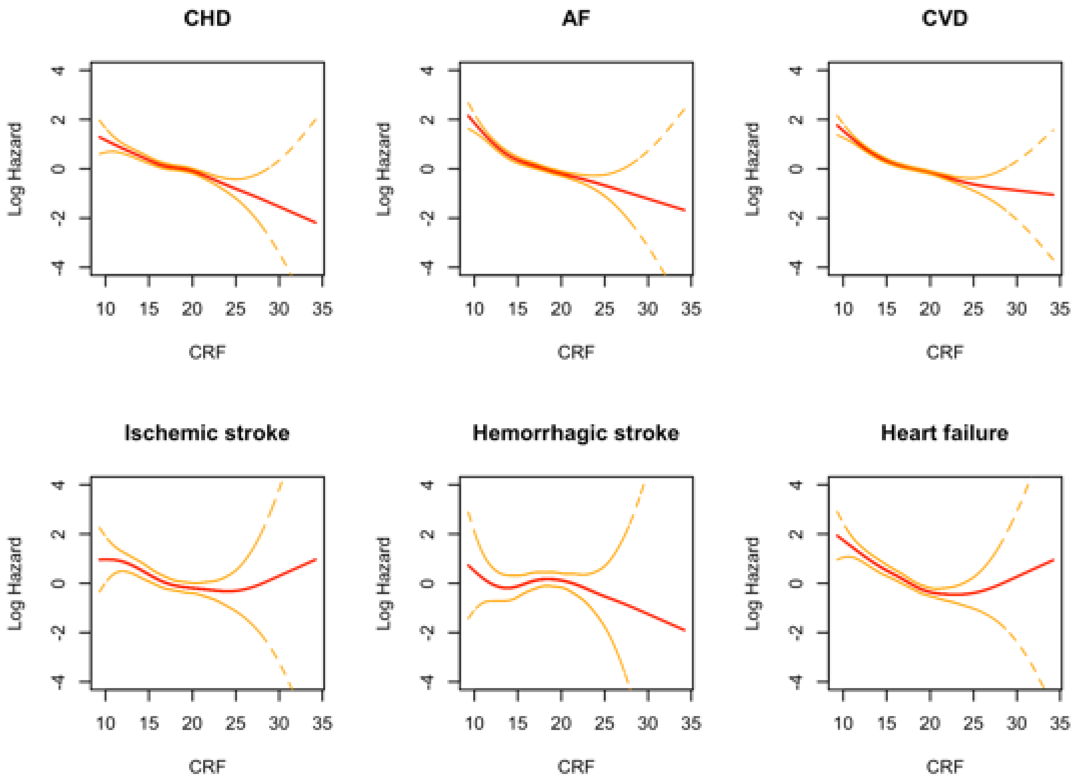
Supplementary Figure 1. Distributions of fitness and physical activity variables.



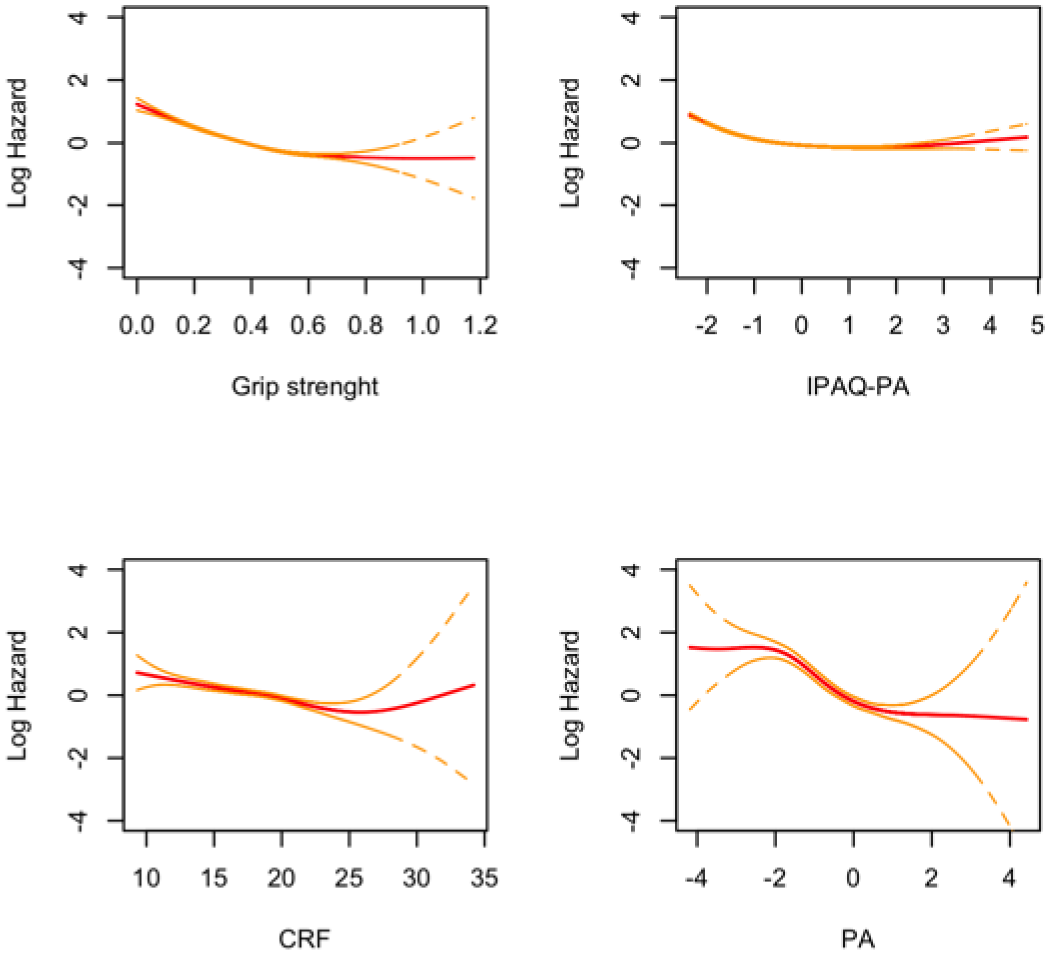
Supplementary Figure 2. Relations of grip strength and cardiovascular disease (CVD) events. Lines are based on a regression spline of Cox proportional hazards. CHD, coronary heart disease; AF, atrial fibrillation.



Supplementary Figure 3. Relations of questionnaire-based physical activity (IPAQ-PA) and cardiovascular disease (CVD) events. Lines are based on a regression spline of Cox proportional hazards. CHD, coronary heart disease; AF, atrial fibrillation.



Supplementary Figure 4. Relations of cardiorespiratory fitness (CRF) and cardiovascular disease (CVD) events. Lines are based on a regression spline of Cox proportional hazards. CHD, coronary heart disease; AF, atrial fibrillation.



Supplementary Figure 5. Relations of grip strength, questionnaire-based (IPAQ-PA) and objective (PA) physical activity, and cardiorespiratory fitness (CRF), and all-cause death. Lines are based on a regression spline of Cox proportional hazards.

Supplemental References

1. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjonnes A, Chasman DI, Chen S, Ford I, Franceschini N, Gieger C, Grace C, Gustafsson S, Huang J, Hwang SJ, Kim YK, Kleber ME, Lau KW, Lu X, Lu Y, Lyytikainen LP, Mihailov E, Morrison AC, Pervjakova N, Qu L, Rose LM, Salfati E, Saxena R, Scholz M, Smith AV, Tikkanen E, Uitterlinden A, Yang X, Zhang W, Zhao W, de Andrade M, de Vries PS, van Zuydam NR, Anand SS, Bertram L, Beutner F, Dedoussis G, Frossard P, Gauguier D, Goodall AH, Gottesman O, Haber M, Han BG, Huang J, Jalilzadeh S, Kessler T, Konig IR, Lannfelt L, Lieb W, Lind L, Lindgren CM, Lokki ML, Magnusson PK, Mallick NH, Mehra N, Meitinger T, Memon FU, Morris AP, Nieminen MS, Pedersen NL, Peters A, Rallidis LS, Rasheed A, Samuel M, Shah SH, Sinisalo J, Stirrups KE, Trompet S, Wang L, Zaman KS, Ardissino D, Boerwinkle E, Borecki IB, Bottinger EP, Buring JE, Chambers JC, Collins R, Cupples LA, Danesh J, Demuth I, Elosua R, Epstein SE, Esko T, Feitosa MF, Franco OH, Franzosi MG, Granger CB, Gu D, Gudnason V, Hall AS, Hamsten A, Harris TB, Hazen SL, Hengstenberg C, Hofman A, Ingelsson E, Iribarren C, Jukema JW, Karhunen PJ, Kim BJ, Kooner JS, Kullo IJ, Lehtimaki T, Loos RJ, Melander O, Metspalu A, Marz W, Palmer CN, Perola M, Quertermous T, Rader DJ, Ridker PM, Ripatti S, Roberts R, Salomaa V, Sanghera DK, Schwartz SM, Seedorf U, Stewart AF, Stott DJ, Thiery J, Zalloua PA, O'Donnell CJ, Reilly MP, Assimes TL, Thompson JR, Erdmann J, Clarke R, Watkins H, Kathiresan S, McPherson R, Deloukas P, Schunkert H, Samani NJ, Farrall M, Consortium CAD. A comprehensive 1,000 genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015; 47:1121-1130. doi: 10.1038/ng.3396.
2. AFGen Consortium, Metastroke Consortium of the ISGC, Neurology Working Group of the Charge Consortium. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat Genet*. 2017; doi: 10.1038/ng.3843.