Research Letter

Resting Heart Rate and Cardiovascular Disease: Mendelian Randomization Analysis

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An increase in resting heart rate (RHR) is associated with increased risk of mortality,[1,2] but the causal role of RHR for cardiovascular disease (CVD) remains unclear. Meta-analyses of observational studies have shown that RHR is positively associated with risk of coronary heart disease, heart failure, and stroke but not atrial fibrillation (AF).[2] However, residual confounding and reverse causality may have influenced the results.

Genetic variants with an explicit association with a potential risk factor, such as RHR, can be used as proxy indicators for the risk factor to determine causality, a method known as Mendelian randomization (MR). This technique decreases bias due to confounding because genetic variants are unlikely associated with lifestyle behaviors and environmental factors. Additionally, because disease cannot modify genotype, reverse causality is prevented.

We used the MR study design to determine the associations of RHR with coronary artery disease (CAD), AF and ischemic stroke using summary-level data from the Coronary ARtery DIsease Genome wide Replication and Meta-analysis plus The Coronary Artery Disease consortium's 1000 Genomes-based genome-wide association study (n=184 305 individuals of mainly European ancestry),[3] Atrial Fibrillation Consortium (n=537 409 European-descent individuals),[4] and MEGASTROKE consortium (n=438 847 European-descent individuals).[5] A secondary aim was to assess the association between RHR and 13 CVD outcomes in UK Biobank[6] (application number 29202). We restricted the UK Biobank cohort to European-descent individuals and excluded related individuals, low call rate and excess heterozygosity, leaving 367 703 participants for analyses. The UK Biobank study received ethics approval from the North West Multicenter Research Ethics Committee. All studies participating in the consortia received ethics approval from relevant institutional review boards. All participants provided informed consent.

The hitherto largest genome-wide association study of RHR in up to 265 046 individuals identified 64 single-nucleotide polymorphisms (SNPs) associated with RHR (at $P < 5 \times 10^{-8}$),

explaining 2.5% of the variance in RHR.[1] Four of the SNPs were unavailable in the outcome datasets, leaving 60 SNPs for analysis.

The inverse-variance weighted and weighted median methods were used to obtain odds ratios of each CVD per 10 beats per minute (about 1 SD) increase in genetically predicted RHR. The I^2 statistic was used to assess heterogeneity among SNPs. The possible presence of directional pleiotropy was tested with the MR-Egger method. All statistical tests are 2-sided and considered statistically significant at a Bonferroni-corrected P value of ≤0.003, adjusting for 16 distinct outcomes. P values between 0.003 and 0.05 were deemed suggestive evidence of possible associations.

Genetically predicted RHR was inversely associated with AF, ischemic stroke as a whole, cardioembolic stroke and large-artery stroke in analyses based on the random-effects inverse-variance weighted or weighted median method, but only the association between RHR and AF in the weighted median analysis was statistically significant at the Bonferroni-adjusted significance level (Figure 1). There was moderate to substantial heterogeneity between SNPs in analyses of AF (I^2=92%), CAD (I^2=60%) and cardioembolic stroke (I^2=48%) but not large-artery (I^2=13%) and small vessel (I^2=17%) stroke. There was no evidence of directional pleiotropy for any outcome (MR-Egger intercept $P > 0.05$ for all). In secondary analyses using data from UK Biobank, genetically predicted RHR was inversely associated with AF in the weighted median analysis, and there was suggestive evidence of a positive association between RHR and subarachnoid hemorrhage (Table 1).

In conclusion, this MR study found suggestive evidence of possible inverse associations of genetically predicted RHR with AF and ischemic stroke, particularly cardioembolic stroke, and suggestive evidence of a possible positive association of genetically predicted RHR with subarachnoid hemorrhage. Genetically predicted RHR was not significantly associated with other CVD outcomes but weak associations cannot be ruled out.

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Data on genetic associations with coronary artery disease have been contributed by the Coronary Artery Disease consortium's 1000 Genomes-based genome-wide association study and can be downloaded from www.cardiogramplusc4d.org/. Data on genetic associations with atrial fibrillation have been contributed by the Atrial Fibrillation Consortium and can be downloaded from http://www.broadcvdi.org/. Data on genetic associations with ischemic stroke have been contributed by the International Stroke Genetics Consortium and can be downloaded at www.cerebrovascularportal.org/. The MEGASTROKE project received funding from sources specified at http://megastroke.org/acknowledgements.html.

Conflict of interest

None.

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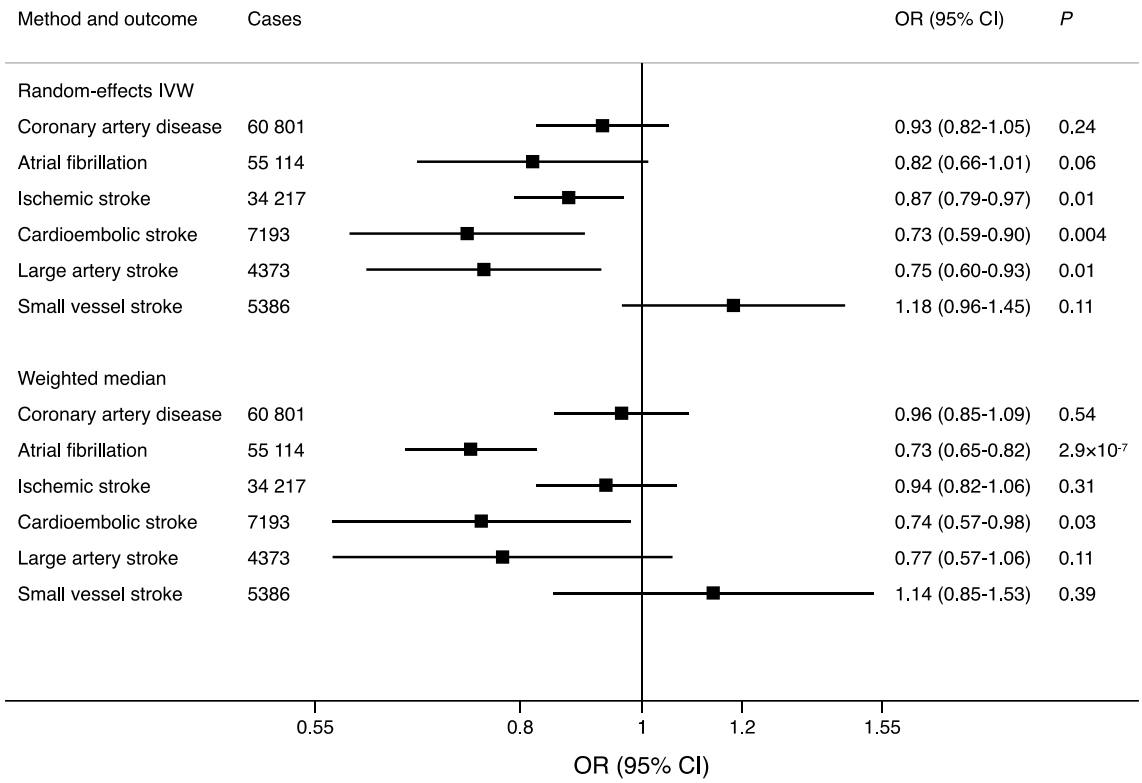


Figure 1. Associations of genetically predicted 10 beats per minute (about 1 SD) increase of resting heart rate and coronary artery disease, atrial fibrillation, and ischemic stroke and its subtypes from two-sample Mendelian randomization analyses using summarized data. Summarized data on coronary artery disease are from the Coronary Artery Disease consortium's 1000 Genomes-based genome-wide association study, atrial fibrillation from the Atrial Fibrillation Consortium and ischemic stroke from the MEGASTROKE consortium. CI, confidence interval; IVW, inverse-variance weighted; OR, odds ratio.

Table 1. Associations of genetically predicted 10 beats per minute (about 1 SD) increase of resting heart rate with cardiovascular disease outcomes in UK Biobank (n=367 703)

		Random-effects IVW			Weighted median		
Outcome	**Cases**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Coronary artery disease	24 531	0.97	0.87-1.09	0.62	1.02	0.91-1.15	0.71
Atrial fibrillation	13 538†	0.80	0.64-1.00	0.06	0.73	0.61-0.87	3.2×10^{-4}
Heart failure	4803	0.96	0.82-1.13	0.65	0.94	0.74-1.20	0.63
Aortic valve stenosis	1252	1.09	0.83-1.43	0.55	1.09	0.82-1.45	0.54
Abdominal aortic aneurysm	758	0.75	0.48-1.18	0.21	0.78	0.41-1.47	0.44
Thoracic aortic aneurysm	231	0.88	0.41-1.87	0.74	1.18	0.40-3.54	0.76
Ischemic stroke	3554	0.98	0.80-1.20	0.85	0.86	0.65-1.13	0.28
Intracerebral hemorrhage	1655	1.26	0.95-1.66	0.10	1.12	0.73-1.73	0.59
Subarachnoid hemorrhage	1834	1.31	1.01-1.71	0.04	1.34	0.90-2.00	0.15
Deep vein thrombosis	8891	1.00	0.86-1.16	0.99	1.13	0.94-1.37	0.20
Pulmonary embolism	5097	0.98	0.84-1.15	0.82	1.01	0.80-1.28	0.92
Peripheral arterial disease	3514	0.83	0.67-1.01	0.07	0.80	0.59-1.08	0.15
Hypertension	119 500	1.06	0.99-1.14	0.09	1.06	0.99-1.14	0.12

Abbreviations: CI, confidence interval; IVW, inverse-variance weighted; OR, odds ratio.
*****These cases overlap with those in the Atrial Fibrillation Consortium.