ESC European Society of Cardiology

European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwab005

FULL RESEARCH PAPER
Blood pressure

The relationship between blood pressure and risk of atrial fibrillation: a Mendelian randomization study

Georgios Georgiopoulos[1,2,*,†], Georgios Ntritsos[3,4,†], Kimon Stamatelopoulos[2], Costas Tsioufis[5], Alberto Aimo[6], Stefano Masi[6,7,8,‡], and Evangelos Evangelou[3,‡]

[1]School of Biomedical Engineering and Imaging Sciences, King's College London, Westminster Bridge Road, London SE1 7EH, UK; [2]Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [3]Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece; [4]Department of Informatics and Telecommunications, School of Informatics and Telecommunications, University of Ioannina, Arta, Greece; [5]First Department of Cardiology, National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [6]Department of Clinical and Experimental Medicine, University of Pisa, 56124 Pisa, Italy; [7]National Centre for Cardiovascular Prevention and Outcomes, Institute of Cardiovascular Science, University College London, London EC1A 4NP, UK; and [8]Department of Twin Research & Genetic Epidemiology, King's College London, London WC2R 2LS, UK

Received 2 November 2020; revised 12 December 2020; editorial decision 24 December 2020; accepted 6 January 2021

Aims Observational studies suggest elevated blood pressure (BP) as the leading risk factor for incident atrial fibrillation (AF), but whether this relationship is causal remains unknown. In this study, we used Mendelian randomization (MR) to investigate the potential causal association of BP levels with the risk of developing AF.

Methods and results Genetic variants associated with the BP traits were retrieved from the International Consortium of Blood Pressure-Genome Wide Association Studies ($N = 299\,024$). From 901 reported variants, 894 were assessed in a dedicated Genome-Wide Association Study of AF genetics, including >1 000 000 subjects of European ancestry. We used two-sample MR analyses to examine the potential causal association of systolic BP (SBP) and diastolic BP (DBP) as well as of pulse pressure (PP) with AF. MR analysis identified a potentially causal association between AF and SBP [odds ratio (OR): 1.018 per 1 mmHg increase, 95% confidence interval (CI): 1.012–1.024, $P < 0.001$], DBP (OR: 1.026, 95% CI: 1.016–1.035, $P < 0.001$), and PP (OR: 1.014, 95% CI: 1.001–1.028, $P = 0.033$). These findings were robust in sensitivity analyses, including the MR-Egger method and the MR pleiotropy residual sum and outlier test (MR-PRESSO). The causal relationship of BP and AF did not change when single-nucleotide polymorphisms associated with possible confounders (i.e. coronary artery disease and obesity) of the causal relationship were excluded.

Conclusions The association between increased BP levels and the risk of AF is likely causal and applies for different BP indices. Independently from other risk factors, optimal BP control might represent an important therapeutic target for AF prevention in the general population.

Keywords Blood pressure • Atrial fibrillation • Mendelian randomization

Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia[1] and is associated with high healthcare system utilization, lower quality of life, and increased risk for hospitalization, heart failure, stroke, and death.[1,2] Thus, prevention of AF is important as it might significantly improve the societal and personal costs related to the disease.

In addition to advancing age, several putative risk factors for incident AF have been identified from large longitudinal cohort studies, including cigarette smoking, alcohol abuse, hypertension, obesity,

* Corresponding author. Tel: +44 747 1551780, Fax: +44 747 1551780, Email: georgios.georgiopoulos@kcl.ac.uk
† The first two authors contributed equally as first authors.
‡ The last two authors contributed equally as senior authors.

diabetes, myocardial infarction, and heart failure.[3–6] Non-genetic risk factors have been recently reported to show a similar impact across different age groups.[7] Notably, the presence of hypertension, its severity and duration have been characterized as important risk factors for new-onset AF, also acting synergistically with other risk factors such as obesity.[7,8] Specifically, a strong relationship between blood pressure (BP) and risk of AF has been described in several observational studies,[6,9] extending to BP values within the normal range.[10] Prolonged exposure to elevated BP values induces remodelling of cardiac chambers, first of all the left atrium,[11] providing an important substrate for the development of AF.[1,12–14] Despite guidelines suggesting that BP lowering treatment might prevent the development of AF, this evidence is based mainly on observational studies, meta-analyses or secondary analyses of randomized clinical trials in patients with hypertension.[15] These study designs, however, are prone to systematic biases and cannot support a causal association between exposure to elevated BP and risk of AF.

Confirmation of a causal association is a challenging task as the relationship between BP and risk of AF might be confounded by several factors. For example, increased BP is commonly associated with ageing, which also represents an important risk factor for AF.[6] This makes difficult deciphering whether BP and AF are causally related each other or they simply represent comorbidities that cluster in old subjects. Mendelian randomization (MR)[16] has emerged as a reliable method to address some of the limitations of observational studies and estimate causality. The random assortment of alleles at conception ensures a balanced distribution of confounders across genotypes, making this approach less prone to conventional confounding issues. The risk of reverse causation is also minimized, since the presence of a disease cannot affect individuals' genotypes.[16]

In this study, we performed large-scale MR analyses using summary-level data from the largest Genome-Wide Association Study (GWAS) on BP and AF up to date to investigate the potential causal role of BP levels on the risk of AF.

Methods

Selection of genetic variants and data sources

Genetic variation on blood pressure and atrial fibrillation

The analyses for this study were based on publicly available summary statistics derived from GWAS consortia. Specifically, genetic variants associated with the BP traits were used as instrumental variables for the MR analysis. Novel and previously published confirmed independent variants were retrieved from the largest GWAS of BP traits[17] that used participants of European descent from the UK Biobank[18] ($N = 458\,577$) and the International Consortium of Blood Pressure-Genome Wide Association Studies (ICBP)[19,20] ($N = 299\,024$). The ICBP consortium has been specifically established to investigate BP genetics and represents one of the largest available resource to date. For the 901 reported variants, 894 (266 associated with SBP, 345 with DBP, and 283 with PP) were available on an AF GWAS comprised of six independent cohorts with more than 1 000 000 subjects of European ancestry, including 60 620 cases with AF and 970 216 controls.[21] As UK Biobank participants have been used in the estimation of the genetic risk of AF and to avoid possible sample overlap, we retrieved the effect estimates of the selected variants on BP traits from the summary data derived from the ICBP consortium only. Included variants were independent based on a pre-specified threshold of $r^2 < 0.1$.[17] The definitions of AF are listed in the Supplementary material online, *Table S1*.

Mendelian randomization analyses

We conducted three separate two-sample MR analyses to test the potential causal associations between diastolic BP (DBP), systolic BP (SBP), and pulse pressure (PP) with the risk of AF, estimating the association results in two non-overlapping populations. MR studies typically quantify and compare three associations: (i) biomarker-disease; (ii) genotype-biomarker; and (iii) genotype-disease. Triangulation of the risk estimates provides evidence on causation, with the magnitude of the causal association being estimated by instrumental variables regression.[22] The three key assumptions[16,22] underlying the two-sample MR approach are:

a. The genetic variants must be strongly associated with the exposure;
b. The variants must affect the outcome only through their effect on exposure; and
c. The variants must be independent of any confounders of the association between the exposure and the outcome.[23]

The simplest way to obtain an MR estimate using multiple single-nucleotide polymorphisms (SNPs) is to perform an inverse variance weighted (IVW) meta-analysis of each Wald ratio.[24] Fixed effects IVW assumes that none of the SNPs exhibits horizontal pleiotropy or other violations of assumptions. Random effects IVW relaxes the assumption of no horizontal pleiotropy,[25] and the variance for this model is inflated to take into account the between SNPs heterogeneity.

As a secondary analysis, we used the Maximum Likelihood method, with which the causal effect estimated by the direct maximization of the likelihood given the SNP-exposure and SNP-outcome effects and assuming a linear relationship between the exposure and outcome.[26] Similar to the fixed effects IVW approach, the Maximum Likelihood method assumes that there is no heterogeneity or horizontal pleiotropy. MR results with P-values < 0.05 were considered significant. Effect sizes are provided as odds ratio (OR) alongside 95% confidence intervals (CIs). All MR analyses were performed using R version 3.5.1 (R Core Team).

Sensitivity analyses

MR makes three key assumptions, which, if violated, might lead to biases and wrong estimation of the causal effect. First, the genetic variants must be strongly associated with the exposure. Second, the variants must affect the outcome only through their effect on exposure. The third assumption is that variants must be independent of any confounders of the association between the exposure and the outcome (*Figure 1*). To assess for the presence of pleiotropy, that is each SNP must only modify the

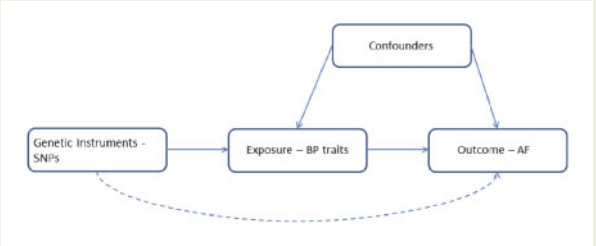

Figure 1 Schematic representation of Mendelian randomization analysis. AF, atrial fibrillation; BP, blood pressure; SNPs, single-nucleotide polymorphisms.

outcome through the exposure and not by any other independent pathways, sensitivity analyses such as MR-Egger, Weighted Median estimator and the MR pleiotropy residual sum and outlier test (MR-PRESSO) were performed.[27–29] Using the MR-Egger method, the SNP's effect on the exposure is plotted against its effect on the outcome and if pleiotropy is absent, the plotted points fall along a line that passes through the origin. Values of the intercept terms away from zero are an indication of pleiotropy. The slope of the MR-Egger regression can provide pleiotropy-corrected causal estimates. This approach assumes that the horizontal pleiotropic effects are not correlated with the SNP-exposure effects (InSIDE assumption).[28] MR-Egger regression requires only the Instrument Strength Independent of Direct Effect (InSIDE) assumption to unbiasedly estimate the causal effect, with no restriction placed on the average value of the pleiotropic effects. Under the InSIDE assumption, the pleiotropic effects are independent of the variant–exposure associations.[28] The weighted median approach orders the MR estimates generated using each instrument separately by the inverse of their variances and report the median.[29] This approach assumes that only half the SNPs need to be valid instruments (i.e. exhibiting no horizontal pleiotropy, no association with confounders and robust association with the exposure). This method improves precision compared to the MR-Egger regression method.[29] MR-PRESSO was used in order to identify horizontal pleiotropic outliers in multi-instrument summary-level MR testing. MR-PRESSO identifies horizontal pleiotropic outlier variants and provides an outlier-corrected estimate.[27] Heterogeneity between genetic variants was estimated using Cochran's *Q* test.[23]

Further sensitivity analyses were performed, excluding genetic variants that are strongly associated with the potential confounders of the exposure—outcome relationship (e.g. ischaemic heart disease, and obesity), which would lead to biased causal estimates.[30]

Results

Mendelian randomization estimates

In overall, 894 independent genome-wide significant SNPs associated with BP traits were selected for the construction of the instrumental variable (266 associated with SBP, 345 with DBP, and 283 with PP). The total variance of BP values explained by the genetic instruments was 5.7% for SBP, 5.3% for DBP, and 2.9% for PP.[17] Their effect estimates for the associations with the BP traits and with AF are shown in the Supplementary material online, *Table S2*. *Table 1* reports the MR estimates for BP traits and AF. Based on the IVW method, MR results supported a causal effect of the BP traits on AF risk. Specifically, a 1 unit increase in SBP (mm Hg) was causally associated with a 1.8% relative increase in AF risk ($N = 266$ SNPs, OR: 1.018, 95% CI: 1.012–1.024, $P < 0.001$). For DBP and PP, MR analysis showed that 1 unit increase was causally associated with 2.6% and 1.4% relative increase in AF risk respectively ($N = 345$ SNPs, OR: 1.026, 95% CI: 1.016–1.035, $P < 0.001$ for DBP; $N = 283$ SNPs, OR: 1.014, 95% CI: 1.001–1.028, $P < 0.033$ for PP). These results are also displayed graphically in *Figure 2*.

Sensitivity analyses

Random effect models were used to take into account the substantial heterogeneity that was observed. This heterogeneity did not affect the results, as the weighted median analysis yielded same direction results compared to the IVW and likelihood-based approach (*Table 1*). Moreover, MR-Egger intercept did not provide evidence for the

Table 1 Mendelian randomization estimates between blood pressure traits and atrial fibrillation

		Inverse-variance weighted method				Maximum likelihood			MR-Egger regression						Median-based method		
									Intercept			Slope					
BP trait	*N*	OR	95% CI	*P*-value	*P*-value for heterogeneity	OR	95% CI	*P*-value	*P*-value for heterogeneity	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
SBP	266	1.018	1.012–1.024	1E-08	<0.0001	1.019	1.012–1.025	<0.001	<0.0001	1.006	1.002–1.010	0.006	0.998	0.982–0.013	0.763	1.016	1.009–1.023	<0.001
DBP	345	1.026	1.016–1.035	1.5E-<0	<0.0001	1.027	1.016–1.037	<0.001	<0.0001	1.001	0.997–1.005	0.597	1.02	0.997–1.043	0.083	1.021	1.012–1.030	<0.001
PP	283	1.014	1.001–1.028	0.033	<0.0001	1.016	1.000–1.031	0.05	<0.0001	0.998	0.993–1.004	0.533	1.024	0.991–1.058	0.158	1.015	1.005–1.025	0.004

BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; MR, mendelian randomization; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SNPs, single-nucleotide polymorphisms; N, # of SNPs used in MR.

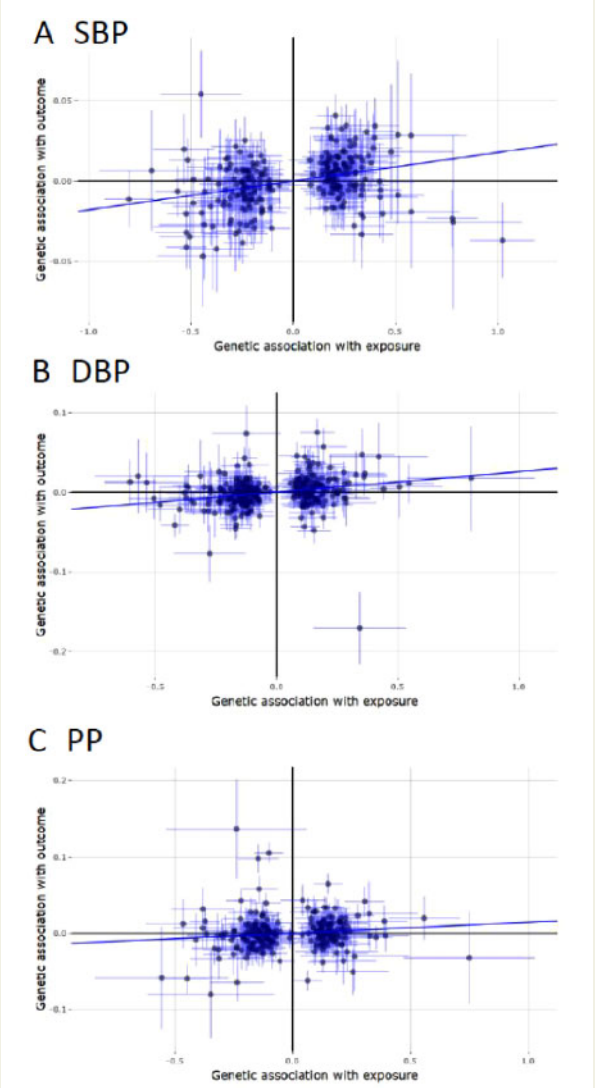

Figure 2 Association between SNPs associated with (*A*) SBP, (*B*) DBP, (*C*) PP and risk of atrial fibrillation. Per allele associations with exposure plotted against per allele associations with outcome (vertical and horizontal black lines around points show 95% confidence interval for each polymorphism). DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; SNPs, single-nucleotide polymorphisms.

presence of directional pleiotropy for the analysis of DBP and PP with AF and the results of the regression slope were consistent with those from the IVW and likelihood-based approach (*Table 1*). Despite the fact that the pleiotropy-corrected estimate of the MR-Egger regression slope does not support a causal effect of the SBP with AF risk, both raw and outlier corrected estimates (excluding 11, 19, 22 SNPs for SBP, DBP, PP, respectively) from MR-PRESSO are identical to IVW and likelihood-based results, establishing the causal association of the BP traits with AF (*Table 2*).

Similar results were observed in sensitivity analyses. As reported in the Supplementary material online, *Table S3*, MR estimates obtained after excluding SNPs that were associated with ischaemic heart disease and obesity did not differ from the main MR analyses including all SNPs (SBP: $N = 251$, OR: 1.020, 95% CI: 1.014–1.026; DBP: $N = 332$, OR: 1.029, 95% CI: 1.019–1.039; PP: $N = 272$, OR: 1.015, 95% CI: 1.001–1.029).

Discussion

Epidemiological studies have highlighted the strong associations between several cardiovascular risk factors and the risk of developing AF. Hypertension represents one of the most common and strongest risk factor associated with the risk of AF. Despite this evidence, the association between hypertension and AF might be subject to several confounding factors, as they are both diseases of ageing and commonly cluster with other cardiovascular risk factors, including obesity, diabetes, inflammation and dyslipidaemia. Using MR, we now provide the first evidence that the relationship between elevated BP and the risk of AF is likely to be causal. Importantly, the association between BP values and the risk of AF was not limited to SBP but also involved DBP and PP. Sensitivity analysis documented that the potential causal relationship between BP and AF is not driven by the presence of other well-established risk factors associated to both conditions, including ischaemic heart disease and obesity. Together with other MR studies, our findings confirm the hypothesis that AF is preventable. Given that AF remains the leading cardiac arrhythmia and one of the major causes of invalidating diseases in the world, including stroke, heart failure, sudden death, and cardiovascular morbidity, our results advocate the need of public health strategies aimed to emphasizing the importance of an adequate control of BP to reduce the global burden of AF and its severe complications.

Several different mechanisms may be involved in the pathogenesis of AF in hypertensive patients. Haemodynamic and non-haemodynamic

Table 2 MR-PRESSO estimates between blood pressure traits and atrial fibrillation

	Raw estimates				Outlier corrected estimates			
BP trait	***N***	**OR**	**95% CI**	***P*-value**	***N***	**OR**	**95% CI**	***P*-value**
SBP	266	1.018	1.016–1.019	<0.001	255	1.018	1.017–1.019	<0.001
DBP	345	1.026	1.024–1.027	<0.001	326	1.023	1.022–1.024	<0.001
PP	283	1.044	1.035–1.053	0.034	261	1.016	1.015–1.017	0.0004

BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; MR-PRESSO, Mendelian Randomization pleiotropy residual sum and outlier; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SNPs, single-nucleotide polymorphisms.

mechanisms are thought to promote complex changes of the atrial structure, architecture, contraction, and electrophysiology with the potential to produce clinically relevant manifestations.[31] Haemodynamic mechanisms involve the development of hypertensive cardiomyopathy characterized by increased left ventricular (LV) wall thickness, raised LV stiffness, and impaired LV diastolic function. These processes may lead to a rise in left atrial stretch and pressure, with subsequent remodelling and dysfunction that predispose to AF. Among the non-haemodynamic mechanisms, there are histological changes in the atria such as the proliferation of fibroblasts, alterations of the extracellular matrix, and hypertrophy of myocytes that can alter interconnections between muscle bundles and lead to electrophysiological remodelling.[9] Effect sizes for increasing BP values on the risk of AF in our MR analysis was smaller compared with those obtained using observational data. This might be related to several factors. Firstly, AF is difficult to document when paroxysmal and might remain silent in clinically stable patients. Therefore, cohort studies with more stringent follow up of the participants might have had the opportunity to capture more cases of AF than those observed in our large population, where we cannot exclude undiagnosed or silent cases of AF. Another potential explanation is related to the influence of confounding factors on the relationship between AF and elevated BP described in observational studies. This highlights the inherent limitations of observational analyses that are prone to several biases, such as confounding, reverse causality, and multicollinearity. Instead, MR utilizes genetic variants as proxies for risk factors, which are free from these biases. Another advantage of using MR to explore causality in the relationship between BP and risk of AF is related to the difficulties in designing and conducting clinical trials assessing the impact of an intensive control of BP on the risk of subsequent risk of AF, as they would require elevated costs for the large number of patients to be recruited and the very long follow-up.

A major strength of our study is related to the large study sample used in the analyses, which allowed us to perform comprehensive analysis for incident AF and well-powered GWAS to obtain genetic instruments for MR analyses. Indeed, we used hundreds of genetic variants for each component of BP. Our study also has some limitations. The use of a genetic instrument including hundreds of genetic variants for each component of BP increases the risk of including pleiotropic SNPs. In fact, there was evidence for horizontal pleiotropy that was addressed through current best practices for MR sensitivity analysis. However, as with all MR studies, we could not address unobserved pleiotropy. In addition, it should be acknowledged that IVW effect estimates are liable to be biased when some of the instrumental SNPs exhibit horizontal pleiotropy e.g., when we have genetically determined factors which are associated with AF and we have not taken them into account such as diabetes, alcohol consumption habits and valvular heart disease. The European ancestry of the samples also limits generalizability of our results to other ancestries. Finally, information on baseline treatment with drugs affecting BP levels was not available.

In summary, despite its potential limitations, our study provides the first evidence that the relationship between BP and risk of AF may be causal, suggesting that strict control of BP might represent a long-term effective strategy to reduce the burden of AF and its associated complications. Future studies should clarify whether the relationship between increased risk of AF and elevated BP is linear or threshold and whether there are specific classes of antihypertensive drugs that, independently from the elevation of BP values might attenuate the risk of developing AF in patients with arterial hypertension.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Conflict of interest: none declared.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
2. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Hear Rhythm* 2019;**16**:e66–e93.
3. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kääb S, Couper D, Harris TB, Soliman EZ, Stricker BH, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF Consortium. *J Am Heart Assoc* 2013;**18**:e000102.
4. Chamberlain AM, Alonso A, Gersh BJ, Manemann SM, Killian JM, Weston SA, Byrne M, Roger VL. Multimorbidity and the risk of hospitalization and death in atrial fibrillation: a population-based study. *Am Heart J* 2017;**185**:74–84.
5. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;**373**:739–745.
6. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154–162.
7. Kim YG, Han K, Choi JI, Choi YY, Choi HY, Boo KY, Kim DY, Lee KN, Shim J, Kim JS, Park YG, Kim YH. Non-genetic risk factors for atrial fibrillation are equally important in both young and old age: a nationwide population-based study. *Eur J Prev Cardiol* 2020;doi:10.1177/2047487320915664.
8. Kim YG, Han K-D, Choi J-I, Yung Boo K, Kim DY, Oh S-K, Lee K-N, Shim J, Kim JS, Kim Y-H. Impact of the duration and degree of hypertension and body weight on new-onset atrial fibrillation: a nationwide population-based study. *Hypertens (Dallas, Tex 1979)* 2019;**74**:e45–e51.
9. Verdecchia P, Angeli F, Reboldi G. Hypertension and atrial fibrillation. *Circ Res* 2018;**122**:352–368.
10. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE, Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;**119**:2146–2152.
11. Przewłocka-Kosmala M, Jasic-Szpak E, Rojek A, Kabaj M, Sharman JE, Kosmala W. Association of central blood pressure with left atrial structural and functional abnormalities in hypertensive patients: implications for atrial fibrillation prevention. *Eur J Prev Cardiol* 2019;**26**:1018–1027.

12. Dzeshka MS, Shahid F, Shantsila A, Lip GYH. Hypertension and atrial fibrillation: an intimate association of epidemiology, pathophysiology, and outcomes. *Am J Hypertens* 2017;**30**:733–755.
13. Xu J, Cui G, Esmailian F, Plunkett M, Marelli D, Ardehali A, Odim J, Laks H, Sen L. Atrial extracellular matrix remodeling and the maintenance of atrial fibrillation. *Circulation* 2004;**109**:363–368.
14. Pluteanu F, Heß J, Plackic J, Nikonova Y, Preisenberger J, Bukowska A, Schotten U, Rinne A, Kienitz M-C, Schäfer MK-H, Weihe E, Goette A, Kockskämper J. Early subcellular Ca2+ remodelling and increased propensity for Ca2+ alternans in left atrial myocytes from hypertensive rats. *Cardiovasc Res* 2015;**106**:87–97.
15. Emdin CA, Callender T, Cao J, Rahimi K. Effect of antihypertensive agents on risk of atrial fibrillation: a meta-analysis of large-scale randomized trials. *Europace* 2015;**17**:701–710.
16. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003;**32**:1–22.
17. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, Ntritsos G, Dimou N, Cabrera CP, Karaman I, Ng FL, Evangelou M, Witkowska K, Tzanis E, Hellwege JN, Giri A, Velez Edwards DR, Sun YV, Cho K, Gaziano JM, Wilson PWF, Tsao PS, Kovesdy CP, Esko T, Mägi R, Milani L, Almgren P, Boutin T, Debette S, Ding J, Giulianini F, Holliday EG, Jackson AU, Li-Gao R, Lin W-Y, Luan J, Mangino M, Oldmeadow C, Prins BP, Qian Y, Sargurupremraj M, Shah N, Surendran P, Thériault S, Verweij N, Willems SM, Zhao J-H, Amouyel P, Connell J, de Mutsert R, Doney ASF, Farrall M, Menni C, Morris AD, Noordam R, Paré G, Poulter NR, Shields DC, Stanton A, Thom S, Abecasis G, Amin N, Arking DE, Ayers KL, Barbieri CM, Batini C, Bis JC, Blake T, Bochud M, Boehnke M, Boerwinkle E, Boomsma DI, Bottinger EP, Braund PS, Brumat M, Campbell A, Campbell H, Chakravarti A, Chambers JC, Chauhan G, Ciullo M, Cocca M, Collins F, Cordell HJ, Davies G, de Borst MH, de Geus EJ, Deary IJ, Deelen J, Del Greco M F, Demirkale CY, Dörr M, Ehret GB, Elosua R, Enroth S, Erzurumluoglu AM, Ferreira T, Frånberg M, Franco OH, Gandin I, Gasparini P, Giedraitis V, Gieger C, Girotto G, Goel A, Gow AJ, Gudnason V, Guo X, Gyllensten U, Hamsten A, Harris TB, Harris SE, Hartman CA, Havulinna AS, Hicks AA, Hofer E, Hofman A, Hottenga J-J, Huffman JE, Hwang S-J, Ingelsson E, James A, Jansen R, Jarvelin M-R, Joehanes R, Johansson Å, Johnson AD, Joshi PK, Jousilahti P, Jukema JW, Jula A, Kähönen M, Kathiresan S, Keavney BD, Khaw K-T, Knekt P, Knight J, Kolcic I, Kooner JS, Koskinen S, Kristiansson K, Kutalik Z, Laan M, Larson M, Launer LJ, Lehne B, Lehtimäki T, Liewald DCM, Lin L, Lind L, Lindgren CM, Liu YMei, Loos RJF, Lopez LM, Lu Y, Lyytikäinen L-P, Mahajan A, Mamasoula C, Marrugat J, Marten J, Milaneschi Y, Morgan A, Morris AP, Morrison AC, Munson PJ, Nalls MA, Nandakumar P, Nelson CP, Niiranen T, Nolte IM, Nutile T, Oldehinkel AJ, Oostra BA, O'Reilly PF, Org E, Padmanabhan S, Palmas W, Palotie A, Pattie A, Penninx BWJH, Perola M, Peters A, Polasek O, Pramstaller PP, Nguyen QT, Raitakari OT, Ren M, Rettig R, Rice K, Ridker PM, Ried JS, Riese H, Ripatti S, Robino A, Rose LM, Rotter JI, Rudan I, Ruggiero D, Saba Y, Sala CF, Salomaa V, Samani NJ, Sarin A-P, Schmidt R, Schmidt H, Shrine N, Siscovick D, Smith AV, Snieder H, Sõber S, Sorice R, Starr JM, Stott DJ, Strachan DP, Strawbridge RJ, Sundström J, Swertz MA, Taylor KD, Teumer A, Tobin MD, Tomaszewski M, Toniolo D, Traglia M, Trompet S, Tuomilehto J, Tzourio C, Uitterlinden AG, Vaez A, van der Most PJ, van Duijn CM, Vergnaud A-C, Verweort GC, Vitart V, Völker U, Vollenweider P, Vuckovic D, Watkins H, Wild SH, Willemsen G, Wilson JF, Wright AF, Yao J, Zemunik T, Zhang W, Attia JR, Butterworth AS, Chasman DI, Conen D, Cucca F, Danesh J, Hayward C, Howson JMM, Laakso M, Lakatta EG, Langenberg C, Melander O, Mook-Kanamori DO, Palmer CNA, Risch L, Scott RA, Scott RJ, Sever P, Spector TD, van der Harst P, Wareham NJ, Zeggini E, Levy D, Munroe PB, Newton-Cheh C, Brown MJ, Metspalu A, Hung AM, O'Donnell CJ, Edwards TL, Psaty BM, Tzoulaki I, Barnes MR, Wain LV, Elliott P, Caulfield MJ; the Million Veteran Program. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* 2018;**50**:1412–1425.
18. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;**12**:e1001779.
19. International Consortium for Blood Pressure Genome-Wide Association Studies; Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, Smith AV, Tobin MD, Verwoert GC, Hwang S-J, Pihur V, Vollenweider P, O'Reilly PF, Amin N, Bragg-Gresham JL, Teumer A, Glazer NL, Launer L, Zhao JH, Aulchenko Y, Heath S, Sõber S, Parsa A, Luan J, Arora P, Dehghan A, Zhang F, Lucas G, Hicks AA, Jackson AU, Peden JF, Tanaka T, Wild SH, Rudan I, Igl W, Milaneschi Y, Parker AN, Fava C, Chambers JC, Fox ER, Kumari M, Go MJ, van der Harst P, Kao WHL, Sjögren M, Vinay DG, Alexander M, Tabara Y, Shaw-Hawkins S, Whincup PH, Liu Y, Shi G, Kuusisto J, Tayo B, Seielstad M, Sim X, Nguyen K-DH, Lehtimäki T, Matullo G, Wu Y, Gaunt TR, Onland-Moret NC, Cooper MN, Platou CGP, Org E, Hardy R, Dahgam S, Palmen J, Vitart V, Braund PS, Kuznetsova T, Uiterwaal CSPM, Adeyemo A, Palmas W, Campbell H, Ludwig B, Tomaszewski M, Tzoulaki I, Palmer ND, Aspelund T, Garcia M, Chang Y-PC, O'Connell JR, Steinle NI, Grobbee DE, Arking DE, Kardia SL, Morrison AC, Hernandez D, Najjar S, McArdle WL, Hadley D, Brown MJ, Connell JM, Hingorani AD, Day INM, Lawlor DA, Beilby JP, Lawrence RW, Clarke R, Hopewell JC, Ongen H, Dreisbach AW, Li Y, Young JH, Bis JC, Kähönen M, Viikari J, Adair LS, Lee NR, Chen M-H, Olden M, Pattaro C, Bolton JAH, Köttgen A, Bergmann S, Mooser V, Chaturvedi N, Frayling TM, Islam M, Jafar TH, Erdmann J, Kulkarni SR, Bornstein SR, Grässler J, Groop L, Voight BF, Kettunen J, Howard P, Taylor A, Guarrera S, Ricceri F, Emilsson V, Plump A, Barroso I, Khaw K-T, Weder AB, Hunt SC, Sun YV, Bergman RN, Collins FS, Bonnycastle LL, Scott LJ, Stringham HM, Peltonen L, Perola M, Vartiainen E, Brand S-M, Staessen JA, Wang TJ, Burton PR, Soler Artigas M, Dong Y, Snieder H, Wang X, Zhu H, Lohman KK, Rudock ME, Heckbert SR, Smith NL, Wiggins KL, Doumatey A, Shriner D, Veldre G, Viigimaa M, Kinra S, Prabhakaran D, Tripathy V, Langefeld CD, Rosengren A, Thelle DS, Corsi AM, Singleton A, Forrester T, Hilton G, McKenzie CA, Salako T, Iwai N, Kita Y, Ogihara T, Ohkubo T, Okamura T, Ueshima H, Umemura S, Eyheramendy S, Meitinger T, Wichmann H-E, Cho YS, Kim H-L, Lee J-Y, Scott J, Sehmi JS, Zhang W, Hedblad B, Nilsson P, Smith GD, Wong A, Narisu N, Stančáková A, Raffel LJ, Yao J, Kathiresan S, O'Donnell CJ, Schwartz SM, Ikram MA, Longstreth WT, Mosley TH, Seshadri S, Shrine NRG, Wain LV, Morken MA, Swift AJ, Laitinen J, Prokopenko I, Zitting P, Cooper JA, Humphries SE, Danesh J, Rasheed A, Goel A, Hamsten A, Watkins H, Bakker SJL, van Gilst WH, Janipalli CS, Mani KR, Yajnik CS, Hofman A, Mattace-Raso FUS, Oostra BA, Demirkan A, Isaacs A, Rivadeneira F, Lakatta EG, Orru M, Scuteri A, Ala-Korpela M, Kangas AJ, Lyytikäinen L-P, Soininen P, Tukiainen T, Würtz P, Ong RT-H, Dörr M, Kroemer HK, Völker U, Völzke H, Galan P, Hercberg S, Lathrop M, Zelenika D, Deloukas P, Mangino M, Spector TD, Zhai G, Meschia JF, Nalls MA, Sharma P, Terzic J, Kumar MVK, Denniff M, Zukowska-Szczechowska E, Wagenknecht LE, Fowkes FGR, Charchar FJ, Schwarz PEH, Hayward C, Guo X, Rotimi C, Bots ML, Brand E, Samani NJ, Polasek O, Talmud PJ, Nyberg F, Kuh D, Laan M, Hveem K, Palmer LJ, van der Schouw YT, Casas JP, Mohlke KL, Vineis P, Raitakari O, Ganesh SK, Wong TY, Tai ES, Cooper RS, Laakso M, Rao DC, Harris TB, Morris RW, Dominiczak AF, Kivimaki M, Marmot MG, Miki T, Saleheen D, Chandak GR, Coresh J, Navis G, Salomaa V, Han B-G, Zhu X, Kooner JS, Melander O, Ridker PM, Bandinelli S, Gyllensten UB, Wright AF, Wilson JF, Ferrucci L, Farrall M, Tuomilehto J, Pramstaller PP, Elosua R, Soranzo N, Sijbrands EJG, Altshuler D, Loos RJF, Shuldiner AR, Gieger C, Meneton P, Uitterlinden AG, Wareham NJ, Gudnason V, Rotter JI, Rettig R, Uda M, Strachan DP, Witteman JCM, Hartikainen A-L, Beckmann JS, Boerwinkle E, Vasan RS, Boehnke M, Larson MG, Järvelin M-R, Psaty BM, Abecasis GR, Chakravarti A, Elliott P, van Duijn CM, Newton-Cheh C, Levy D, Caulfield MJ, Johnson T. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* 2011;**478**:103–109.
20. Wain LV, Vaez A, Jansen R, Joehanes R, van der Most PJ, Erzurumluoglu AM, O'Reilly PF, Cabrera CP, Warren HR, Rose LM, Verwoert GC, Hottenga J-J, Strawbridge RJ, Esko T, Arking DE, Hwang S-J, Guo X, Kutalik Z, Trompet S, Shrine N, Teumer A, Ried JS, Bis JC, Smith AV, Amin N, Nolte IM, Lyytikäinen L-P, Mahajan A, Wareham NJ, Hofer E, Joshi PK, Kristiansson K, Traglia M, Havulinna AS, Goel A, Nalls MA, Sõber S, Vuckovic D, Luan J, Del Greco M F, Ayers KL, Marrugat J, Ruggiero D, Lopez LM, Niiranen T, Enroth S, Jackson AU, Nelson CP, Huffman JE, Zhang W, Marten J, Gandin I, Harris SE, Zemunik T, Lu Y, Evangelou E, Shah N, de Borst MH, Mangino M, Prins BP, Campbell A, Li-Gao R, Chauhan G, Oldmeadow C, Abecasis G, Abedi M, Barbieri CM, Barnes MR, Batini C, Beilby J, Blake T, Boehnke M, Bottinger EP, Braund PS, Brown M, Brumat M, Campbell H, Chambers JC, Cocca M, Collins F, Connell J, Cordell HJ, Damman JJ, Davies G, de Geus EJ, de Mutsert R, Deelen J, Demirkale Y, Doney ASF, Dörr M, Farrall M, Ferreira T, Frånberg M, Gao H, Giedraitis V, Gieger C, Giulianini F, Gow AJ, Hamsten A, Harris TB, Hofman A, Holliday EG, Hui J, Jarvelin M-R, Johansson Å, Johnson AD, Jousilahti P, Jula A, Kähönen M, Kathiresan S, Khaw K-T, Kolcic I, Koskinen S, Langenberg C, Larson M, Launer LJ, Lehne B, Liewald DCM, Lin L, Lind L, Mach F, Mamasoula C, Menni C, Mifsud B, Milaneschi Y, Morgan A, Morris AD, Morrison AC, Munson PJ, Nandakumar P, Nguyen QT, Nutile T, Oldehinkel AJ, Oostra BA, Org E, Padmanabhan S, Palotie A, Paré G, Pattie A, Penninx BWJH, Poulter N, Pramstaller PP, Raitakari OT, Ren M, Rice K, Ridker PM, Riese H, Ripatti S, Robino A, Rotter JI, Rudan I, Saba Y, Saint Pierre A, Sala CF, Sarin A-P, Schmidt R, Scott R, Seelen MA, Shields DC, Siscovick D, Sorice R, Stanton A, Stott DJ, Sundström J, Swertz M, Taylor KD, Thom S, Tzoulaki I, Tzourio C, Uitterlinden AG, Völker U, Vollenweider P, Wild S, Willemsen G, Wright AF, Yao J, Thériault S, Conen D, Attia J, Sever P, Debette S, Mook-Kanamori DO, Zeggini E, Spector TD, van der Harst P, Palmer CNA, Vergnaud A-C, Loos RJF, Polasek O, Starr JM, Girotto G, Hayward C, Kooner JS, Lindgren CM, Vitart V, Samani NJ, Tuomilehto J, Gyllensten U, Knekt P, Deary IJ, Ciullo M, Elosua R, Keavney BD, Hicks AA, Scott RA, Gasparini P, Laan M, Liu YMei, Watkins H, Hartman CA, Salomaa V, Toniolo D, Perola M, Wilson JF, Schmidt H, Zhao JH, Lehtimäki T, van Duijn CM, Gudnason V, Psaty

BM, Peters A, Rettig R, James A, Jukema JW, Strachan DP, Palmas W, Metspalu A, Ingelsson E, Boomsma DI, Franco OH, Bochud M, Newton-Cheh C, Munroe PB, Elliott P, Chasman DI, Chakravarti A, Knight J, Morris AP, Levy D, Tobin MD, Snieder H, Caulfield MJ, Ehret GB; BIOS Consortium. Novel blood pressure locus and gene discovery using genome-wide association study and expression data sets from blood and the kidney. *Hypertension* 2017;doi: 10.1161/HYPERTENSIONAHA.117.09438.

21. Nielsen JB, Thorolfsdottir RB, Fritsche LG, Zhou W, Skov MW, Graham SE, Herron TJ, McCarthy S, Schmidt EM, Sveinbjornsson G, Surakka I, Mathis MR, Yamazaki M, Crawford RD, Gabrielsen ME, Skogholt AH, Holmen OL, Lin M, Wolford BN, Dey R, Dalen H, Sulem P, Chung JH, Backman JD, Arnar DO, Thorsteinsdottir U, Baras A, O'Dushlaine C, Holst AG, Wen X, Hornsby W, Dewey FE, Boehnke M, Kheterpal S, Mukherjee B, Lee S, Kang HM, Holm H, Kitzman J, Shavit JA, Jalife J, Brummett CM, Teslovich TM, Carey DJ, Gudbjartsson DF, Stefansson K, Abecasis GR, Hveem K, Willer CJ. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet* 2018;**50**:1234–1239.
22. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. *Stat Med* 2008;**27**:1133–1163.
23. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *Bmj* 1997;**315**:1533–1537.
24. Yang J, Ferreira T, Morris AP, Medland SE, Madden PAF, Heath AC, Martin NG, Montgomery GW, Weedon MN, Loos RJ, Frayling TM, McCarthy MI, Hirschhorn JN, Goddard ME, Visscher PM; Genetic Investigation of ANthropometric Traits (GIANT) Consortium. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat Genet* 2012;**44**:369–375.
25. Bowden J, Del Greco M F, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med* 2017;**36**:1783–1802.
26. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. *Am J Epidemiol* 2013;**178**: 1177–1184.
27. Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* 2018;**50**:693–698.
28. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015;**44**:512–525.
29. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol* 2016;**40**:304–314.
30. Gkatzionis A, Burgess S. Contextualizing selection bias in Mendelian randomization: how bad is it likely to be? *Int J Epidemiol* 2019;**48**:691–701.
31. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim Y-H, Lip GYH, Ma C-S, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR, Nattel S. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Hear Rhythm* 2017;**14**: e3–e40.