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Disentangling the association between kidney function and atrial fibrillation: a bidirectional Mendelian randomization study

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ABSTRACT

Background: The potential bidirectional causal association between kidney function and atrial fibrillation (AF) remains unclear.

Methods: We conducted a bidirectional two-sample Mendelian randomization (MR) analysis. From multiple genome-wide association studies (GWAS), we retrieved genetic variants associated with kidney function (estimated glomerular filtration rate based on creatinine (eGFRcreat), blood urea nitrogen (BUN), chronic kidney disease (CKD stage ≥G3): n = 1,045,620, eGFR based on cystatin C: n = 24,063-32,861, urine albumin-to-creatinine ratio (UACR), and microalbuminuria: n = 564,257), and AF (n = 1,030,836). The inverse-variance weighted method was used as our main analysis.

Results: MR analyses supported a causal effect of CKD (n = 9 SNPs, odds ratio (OR): 1.10, 95% confidence interval (CI): 1.04–1.17, p-value = 1.97×10^{-03}), and microalbuminuria (n = 5 SNPs, OR: 1.26, 95% CI: 1.10–1.46, p-value = 1.38×10^{-03}) on AF risk. We also observed a causal effect of AF on eGFRcreat (n = 97 SNPs, OR: 1.00, 95% CI: 1.00–1.00, p-value = 6.78×10^{-03}), CKD (n = 107 SNPs, OR: 1.06, 95% CI: 1.03–1.09, p-value = 2.97×10^{-04}), microalbuminuria (n = 83 SNPs, OR: 1.07, 95% CI: 1.04–1.09, p-value = 2.49×10^{-08}), and a suggestive causal effect on eGFRcys (n = 103 SNPs, OR: 0.99, 95% CI: 0.99–1.00, p-value = 4.61×10^{-02}). Sensitivity analyses, including weighted median estimator, MR-Egger, the MR pleiotropy residual sum and outlier test, and excluding genetic variants associated with possible confounders and/or horizontal mediators (myocardial infarction/coronary artery disease, heart failure) indicated that these findings were robust.

Conclusions: Our results supported a bidirectional causal association between kidney function and AF. The shared genetic architecture between kidney dysfunction and AF might represent potential important therapeutic targets to prevent both conditions in the general population.

1. Introduction

Chronic kidney disease (CKD) and atrial fibrillation (AF) are both common conditions which carry independent risks for cardiovascular morbidity and mortality [1–7]. The public health burden of both diseases is expected to rise as the incidence of CKD and AF increases due to aging of the population [1–7]. Additionally, the increasing incidence of obesity, diabetes mellitus, and hypertension may also contribute to the rise of CKD and AF incidence [7,8].

On the one hand, reduced kidney function may lead to AF through increased activity of the renin-angiotensin-aldosterone system (RAAS) [9–16], hypertension [9,16], left ventricular hypertrophy [9], inflammation [9,17–19] and by promoting cardiovascular diseases such as coronary heart disease, and heart failure [5,9,20]. On the other hand, AF may give rise to kidney dysfunction through activation of RAAS [9], hypoperfusion [9], thromboembolism [9], inflammation [9], and by inducing other cardiovascular diseases [5,9,20]. This complex interplay between the kidneys and the heart may result in a vicious cycle in which each condition promotes initiation and progression of the other condition [5,9,20]. Indeed, unidirectional and bidirectional associations

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between kidney function and AF have been described in several observational studies [8,21–28]. However, observational studies are prone to residual confounding and reverse causality and therefore cannot support a causal association between the two conditions [29].

Mendelian randomization (MR) has emerged as a reliable genetic research method to leverage genetic variation to overcome some of the limitations of observational studies and to estimate causal associations [29,30]. The only previous MR study [28] that assessed the bidirectional causal association between kidney function and AF, described an unidirectional association, identifying AF as a causal risk factor for kidney function, but not vice versa. However, this study used an older trans-ethnic AF genome-wide association study (GWAS) with a smaller sample size and was based on fewer genetic instruments for AF for the MR analyses [31]. Moreover, this study was not comprehensive, as it only investigated the causal association between estimated glomerular filtration rate (eGFR) based on serum creatinine (GFRcreat), CKD and AF [28].

In this study, we performed a comprehensive two-sample MR analysis using summary level data from the largest to date GWAS on kidney function [32–35], CKD [32], and AF [36] to investigate the potential bidirectional causal role of kidney function on AF and vice versa. Assessments of kidney function and CKD included estimated GFR based on serum creatinine (eGFRcreat) [32], blood urea nitrogen (BUN) [32], CKD stage ≥G3 [32], eGFR based on serum cystatin C (eGFRcys) [34,35], urine albumin-to-creatinine ratio (UACR) [33], and microalbuminuria [33].

2. Methods

This study complies with the declaration of Helsinki and has been conducted using publicly available summary statistics from multiple GWAS [32–36]. The summary statistics from four GWAS meta-analyses on kidney function [32–35] are available at URL: https://ckdgen.imbi.uni-freiburg.de/. The summary statistics from the GWAS meta-analysis on AF [36] are available at URL: http://csg.sph.umich.edu/willer/public/afib2018/. No original data were collected for this bidirectional MR study. Ethical approval and informed consent from each participant for each of the studies included in the current investigation can be found in the original publications [32–36]. The analysis of anonymous publicly available summary statistics did not require additional ethical approval, therefore the requirement for informed consent was waived.

2.1. Genome-wide association study meta-analysis for kidney function

The four GWAS meta-analyses that were used for this study were part of the CKDGen Consortium and have investigated different assessments of kidney function (eGFRcreat, BUN, eGFRcys, UACR, and microalbuminuria) and CKD (CKD stage ≥G3; in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) classification) [37]. The study characteristics of the four GWAS meta-analyses are extensively discussed in the Methods S1–3 [32–35].

The kidney function genetic variants that were reported in the various GWAS involved genes that are expressed in renal tissues, such as the kidneys and urinary tract, and may thereby affect eGFR, kidney physiology or kidney morphology [32–35]. We implemented these genetic variants as instrumental variables for eGFRcreat, BUN, CKD, eGFRcys, UACR, and microalbuminuria as an exposure. Additionally, we also used the summary statistics of eGFRcreat, BUN, CKD, eGFRcys, UACR, and microalbuminuria as an outcome in our bidirectional MR analyses.

2.2. Genome-wide association study meta-analysis for atrial fibrillation

The study characteristics of the GWAS meta-analysis of AF are shown in Methods S4. The AF genetic variants implicated genes that are expressed within the heart and have been suggested to affect cardiac development, cardiac ion channels, cardiac calcium signaling, structural integrity of the heart, and skeletal muscles [36]. We also utilized these genetic variants as instrumental variables for AF as an exposure. In addition, the summary statistics of AF were also used as an outcome in our bidirectional MR analyses.

2.3. Mendelian randomization analyses

Multiple bidirectional two-sample MR analyses were conducted to examine the causality between kidney function and AF. Three assumptions should be fulfilled for MR analyses to provide valid causal estimates. The first assumption is that the genetic variant is strongly associated with the exposure. The second assumption is that the genetic variant only affects the outcome through its effect on the exposure. Finally, the third assumption is that the genetic variant is not associated with any confounders of the exposure-outcome relationship. We selected genetic variants that were genome-wide significantly associated with the trait of interest. We next clumped the genetic variants to ensure that the instrumental variables for the exposure were independent (p-value $<5.0 \times 10^{-08}$ for genome-wide significance and $r^2 <0.1$) to avoid the use of correlated genetic variants that are in linkage disequilibrium [29,30]. In addition, palindromic genetic variants were removed during the harmonization of the genetic variants. Moreover, European ancestry genetic variants and summary statistics were selected in the subsequent MR analyses, if available, to avoid possible bias due to population stratification [29,30].

We calculated the F-statistic of each genetic instrument, as a strength measure for the genetic instruments, to limit weak instrument bias. We included genetic variants with sufficient strength and considered $F >10$ as sufficient strength [38]. We used the "TwoSampleMR" package [38,39] to combine the effects of the individual genetic variants on the exposure and outcome using the inverse-variance weighted (IVW) method [40]. The IVW method was our main MR method and it includes a meta-analysis of all the Wald ratios from the individual genetic variants on the exposure and outcome. In other words, the IVW method represents a weighted mean estimate of the effect of genetically determined kidney function on AF risk and vice versa. In addition, we used the random effect IVW method to account for possible heterogeneity between genetic variants and to relax the assumption of no horizontal pleiotropy.

MR estimates are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Statistical significance was considered at a two-sided p-value <0.05. All MR analyses and data management were done using R statistical software (R 4.0.2: R Foundation for Statistical Computing, Vienna, Austria).

2.4. Mendelian randomization sensitivity analyses

The rationale, assumptions, and sensitivity analyses of the MR analyses are depicted in detail in Methods S5 and S6 [41–46].

3. Results

3.1. Mendelian randomization analyses

Within the European study sample, a total of 256 genome-wide significant index genetic variants were associated with eGFRcreat of which 19 were also genome-wide significantly associated with CKD stage ≥G3. A total of 111 and 5 genome-wide significant genetic variants were associated with BUN and eGFRcys, respectively. A total of 59 genome-wide significant index genetic variants were associated with UACR of which 17 were genome-wide significantly associated with microalbuminuria. The genetic variants associated with BUN, UACR, and microalbuminuria were retrieved from a trans-ethnic study sample, because no summary statistics were available from an European study

sample. The AF GWAS identified 111 genome-wide significant genetic variants that were associated with AF.

As aforementioned, we clumped all genetic variants and removed palindromes. In addition, we removed potential outliers by using the MR pleiotropy residual sum and outlier (MR-PRESSO) test and examined sensitivity plots to select our genetic variants. This provided a total of 218 genetic variants for eGFRcreat, 91 for BUN, 9 for CKD, 4 for eGFRcys, 43 for UACR, and 5 for microalbuminuria, which were available in the AF GWAS and were subsequently used as instrumental variables in the MR analyses. In addition, from the 111 genetic variants for AF, a total of 97 genetic variants for eGFRcreat, 99 for BUN, 107 for CKD, 103 for eGFRcys, 100 for UACR, and 83 for microalbuminuria were available in the kidney function GWAS and were subsequently used in the MR analyses (Fig. 1).

All genetic instruments/instrumental variables had a F-statistic >10 and were, therefore considered of sufficient strength to be used in the MR analyses (range 23–2648) [38]. Our MR analyses based on the IVW method supported a causal effect of CKD and microalbuminuria on AF risk (CKD: $n = 9$ SNPs, OR: 1.10, per 1 unit increase in the odds for CKD, 95% CI: 1.04–1.17, p-value $= 1.97 \times 10^{-03}$; microalbuminuria: $n = 5$ SNPs, OR: 1.26, per 1 unit increase in the odds for microalbuminuria, 95% CI: 1.10–1.46, p-value $= 1.38 \times 10^{-03}$) (Table 1). Moreover, we observed causal effects of AF on eGFRcreat ($n = 97$ SNPs, OR: 1.00, per 1 unit increase in the odds for AF, 95% CI: 1.00–1.00, p-value $= 6.78 \times 10^{-03}$), CKD risk ($n = 107$ SNPs, OR: 1.06, per 1 unit increase in the odds for AF, 95% CI: 1.03–1.09, p-value $= 2.97 \times 10^{-04}$), and microalbuminuria risk ($n = 83$ SNPs, OR: 1.07, per 1 unit increase in the odds for AF, 95% CI: 1.04–1.09, p-value $= 2.49 \times 10^{-08}$) (Table 1, Figs. 2 and 3). We found a suggestive causal effect of AF on eGFRcys ($n = 103$ SNPs, OR: 0.99, per 1 unit increase in the odds for AF, 95% CI: 0.99–1.00, p-value $= 4.61 \times 10^{-02}$). MR analyses did not support a significant causal effect of the other kidney function assessments (eGFRcreat, BUN, eGFRcys, and UACR) on AF risk (Table 1, Figs. 2 and 3). The effect estimates of the genetic variants associated with eGFRcreat, BUN, CKD, eGFRcys, UACR, microalbuminuria, and AF that were used in our bidirectional MR analyses are extensively presented in Tables S1–12.

3.2. Mendelian randomization sensitivity analyses

Our MR sensitivity analyses based on the WME and MR-Egger slope method were in general concordant with the results of the IVW method (Table 1, Figs. 2 and 3). More specifically, the WME sensitivity analyses also supported a causal effect of CKD, and microalbuminuria on AF risk (CKD: $n = 9$ SNPs, OR: 1.08, per 1 unit increase in the odds for CKD, 95% CI: 1.00–1.16, p-value $= 4.43 \times 10^{-02}$; microalbuminuria: 5 SNPs, OR: 1.23, per 1 unit increase in the odds for microalbuminuria, 95% CI:

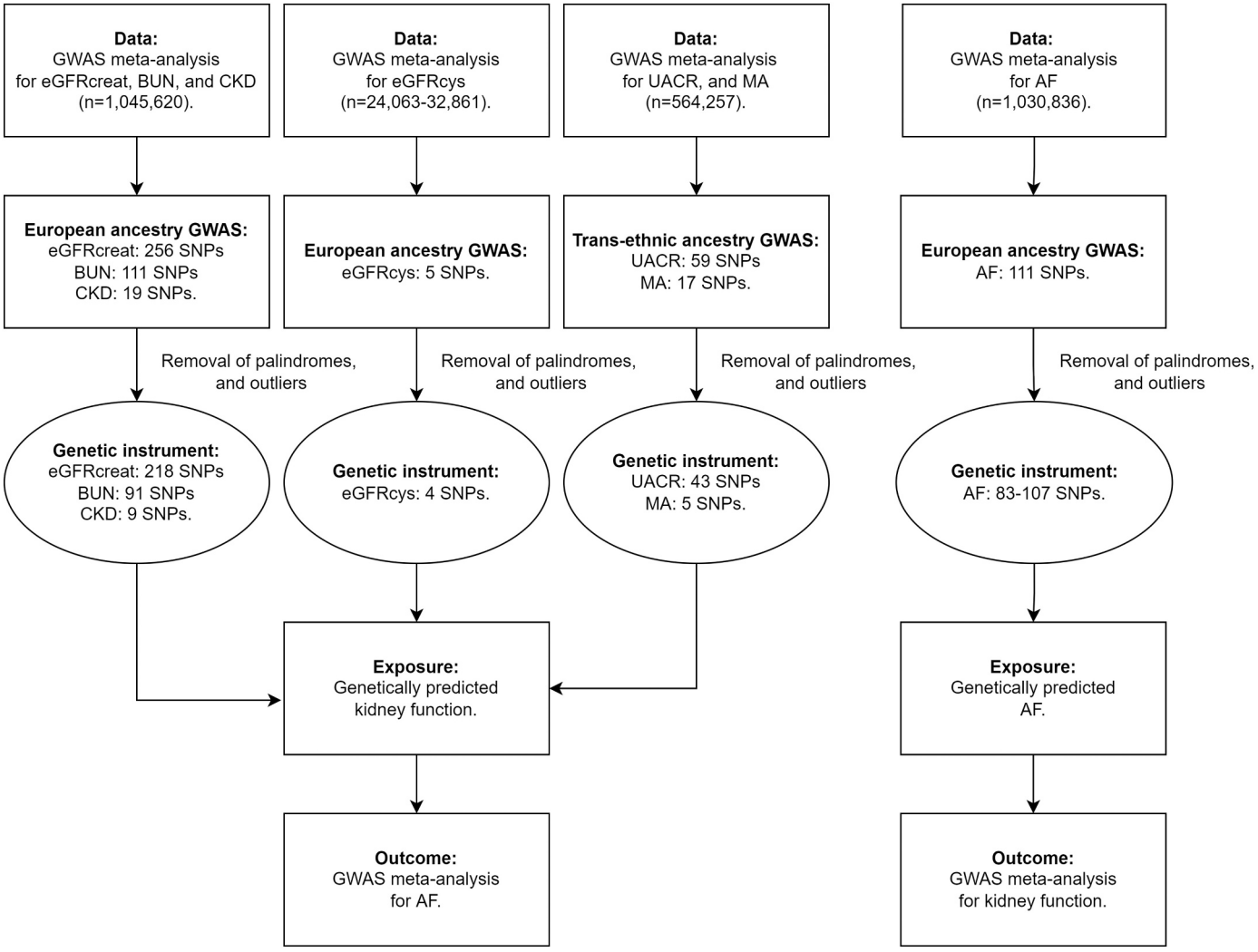

Fig. 1. Flow chart for the selection of genetic variants.
Abbreviations: AF, atrial fibrillation; BUN, blood urea nitrogen; CKD, chronic kidney disease; creat, creatinine; cys, cystatin; eGFR, estimated glomerular filtration rate; GWAS, genome-wide association study; MA, microalbuminuria; n, number; SNP, single nucleotide polymorphism; UACR, urine albumin-to-creatinine ratio.

Table 1
Mendelian randomization analyses between kidney function and atrial fibrillation.

			IVW			WME		MR-Egger slope		MR-Egger intercept
Exposure	Outcome	n of SNPs	OR (95% CI) *	P-value	P-value for heterogeneity	OR (95% CI) *	P-value	OR (95% CI) *	P-value	P-value
eGFRcreat	**AF**	218	0.88 (0.58–1.34)	5.54×10^{-01}	4.17×10^{-12}	0.70 (0.42–1.17)	1.71×10^{-01}	0.80 (0.28–2.34)	6.86×10^{-01}	8.49×10^{-01}
BUN	**AF**	91	1.22 (0.92–1.62)	1.71×10^{-01}	4.16×10^{-05}	1.29 (0.89–1.86)	1.78×10^{-01}	1.25 (0.62–2.53)	5.30×10^{-01}	9.35×10^{-01}
CKD	**AF**	9	**1.10 (1.04–1.17)**	**1.97×10^{-03}**	9.62×10^{-01}	**1.08 (1.00–1.16)**	**4.43×10^{-02}**	1.07 (0.84–1.37)	6.04×10^{-01}	8.18×10^{-01}
eGFRcys	**AF**	4	0.86 (0.69–1.08)	1.99×10^{-01}	6.52×10^{-01}	0.85 (0.67–1.08)	1.88×10^{-01}	0.88 (0.63–1.21)	5.10×10^{-01}	9.15×10^{-01}
UACR	**AF**	43	1.16 (0.97–1.40)	1.07×10^{-01}	7.76×10^{-03}	1.03 (0.83–1.27)	8.02×10^{-01}	1.06 (0.51–2.20)	8.82×10^{-01}	7.94×10^{-01}
MA	**AF**	5	**1.26 (1.10–1.46)**	**1.38×10^{-03}**	4.72×10^{-01}	**1.23 (1.03–1.47)**	**2.57×10^{-02}**	0.94 (0.45–1.97)	8.84×10^{-01}	4.85×10^{-01}
AF	**eGFRcreat**	97	**1.00 (1.00–1.00)**	**6.78×10^{-03}**	3.28×10^{-06}	**1.00 (1.00–1.00)**	**9.26×10^{-03}**	1.00 (1.00–1.00)	3.50×10^{-01}	5.98×10^{-01}
AF	**BUN**	99	1.00 (1.00–1.00)	7.06×10^{-01}	1.15×10^{-02}	1.00 (1.00–1.01)	4.97×10^{-01}	1.00 (1.00–1.01)	6.12×10^{-01}	4.05×10^{-01}
AF	**CKD**	107	**1.06 (1.03–1.09)**	**2.97×10^{-04}**	1.50×10^{-01}	**1.07 (1.02–1.13)**	**5.03×10^{-03}**	**1.08 (1.02–1.15)**	**1.14×10^{-02}**	4.13×10^{-01}
AF	**eGFRcys**	103	**0.99 (0.99–1.00)**	**4.61×10^{-02}**	6.94×10^{-01}	0.99 (0.98–1.01)	2.92×10^{-01}	0.99 (0.98–1.01)	2.99×10^{-01}	9.96×10^{-01}
AF	**UACR**	100	1.00 (0.99–1.01)	9.28×10^{-01}	6.36×10^{-08}	1.00 (0.99–1.01)	7.98×10^{-01}	1.00 (0.98–1.01)	5.47×10^{-01}	4.49×10^{-01}
AF	**MA**	83	**1.07 (1.04–1.09)**	**2.49×10^{-08}**	5.67×10^{-01}	**1.04 (1.00–1.08)**	**4.34×10^{-02}**	1.04 (1.00–1.09)	7.50×10^{-02}	1.92×10^{-01}

Abbreviations: AF, atrial fibrillation; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; creat, creatinine; cys, cystatin; eGFR, estimated glomerular filtration rate; IVW, inverse variance weighted; MA, microalbuminuria; n, number; OR, odds ratio; SNP, single nucleotide polymorphism; UACR, urine albumin-to-creatinine ratio; WME, weighted median estimator.
The associations with a *p*-value <0.05 are highlighted in bold.
* Odds ratios represent a genetically determined 1 unit increase of ln(eGFRcreat), 1 unit increase of BUN, 1 unit increase in the odds of CKD, 1 unit increase of ln (eGFRcys), 1 unit increase of ln(UACR), and 1 unit increase in the odds of MA, respectively (kidney function as exposure) with the odds of atrial fibrillation (atrial fibrillation as outcome). Alternatively, the odds ratios represent a genetically determined 1 unit increase in the odds of atrial fibrillation (atrial fibrillation as exposure) with a lower ln(eGFRcreat), higher BUN, higher odds of CKD, lower ln(eGFRcys), higher ln(UACR), higher odds of MA, respectively (kidney function as outcome).

1.03–1.47, p-value = 2.57×10^{-03}). The point estimates of the MR-Egger slope method were also in general in line with the point estimates of the IVW method. This is reassuring, because valid MR estimates rely on sensitivity analyses that are concordant with its main analysis (i.e. the IVW method). In addition, the MR-Egger intercept and MR-PRESSO did not provide evidence for the presence of directional pleiotropy after clumping, removal of palindromes, and removal of potential outliers (Table 1, Figs. 2 and 3). Similar results were observed when we excluded genetic variants that were also associated with potential confounders and/or horizontal mediators such as myocardial infarction/coronary artery disease, [44] and heart failure [45] (data not shown). The exact extent of sample overlap could not be determined due to unavailability of individual level data. The potential overlap could be estimated based on the description of the individual studies included within the different GWAS. There was potential overlap between eGFRcreat and AF for 291,146 individuals and between CKD and AF for 296,258 individuals. Potential overlap was present between eGFRcys from Gorski et al. [35] and AF for 15,470 individuals, between eGFRcys from Li et al. [34] and AF for 16,335 individuals. Potential overlap was present between UACR and AF for 439,298 individuals, and between microalbuminuria and AF for 290,249 individuals (Methods S1–4).

4. Discussion

Our study sheds light on the complex bidirectional interplay between kidney function and AF by leveraging genetic variants to infer causality. In this comprehensive bidirectional MR analysis, we found evidence to support the bidirectional causal relationship between kidney function and AF. Specifically, our MR analysis supports a causal effect of CKD stage ≥G3 and microalbuminuria on AF risk. Moreover, we found causal effects of AF on various kidney function assessments and CKD including eGFRcreat, CKD stage ≥G3 and microalbuminuria, and a suggestive causal effect of AF on eGFRcys. Our study therefore extends our knowledge about the unidirectional and bidirectional association that has been suggested by previous observational studies [8,21–27]. Our results confirm that CKD, in particular its more severe forms such as CKD stage ≥G3 and increased urinary albumin excretion defined as microalbuminuria, are independent risk factors for AF and vice versa. The shared genetic architecture between kidney dysfunction and AF could be used to identify therapeutic targets to prevent both diseases, as well as their complications, in the general population.

Several mechanisms potentially underlie the bidirectional causal relationship between kidney function and AF. One mechanism could be the presence of shared cardiovascular risk factors such as obesity, hypertension, myocardial infarction, heart failure, and diabetes mellitus which all have been suggested as risk factors for CKD and AF [8]. Another possible link between kidney function and AF is sodium retention [5,20]. Kidney dysfunction increases the risk of sodium retention which may lead to extracellular volume expansion, hypertension, left ventricular hypertrophy, and cardiac dilation [5,20]. This cardiac remodeling that occurs due to left ventricular hypertrophy and cardiac dilation may then increase the myocardial oxygen demand and potentially create myocardial ischemia [5,20]. In addition, cardiac dilation may also cause mitral insufficiency which may further impair left and right ventricular function [5,8]. These aforementioned mechanisms thereby increase the risk of AF [5,20]. AF may cause thromboembolism which could lead to renal infarction and a decline in cardiac function. Both thromboembolism and a decline in cardiac function may then have deleterious effects on the kidneys [8]. Further, it has been suggested that AF induces angiotensin II type 1 receptor-mediated

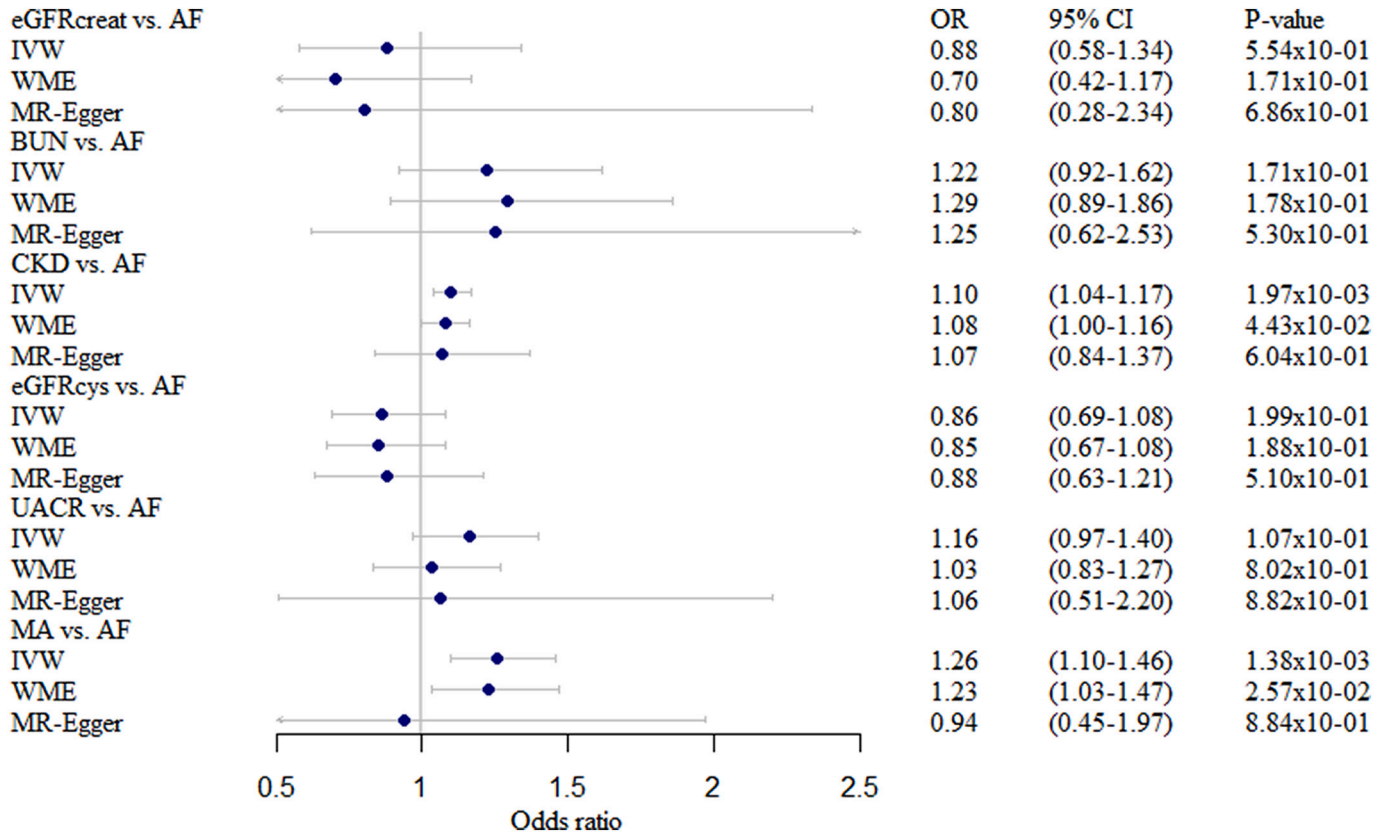

Fig. 2. Forest plot which visualizes the Mendelian randomization analyses between kidney function and atrial fibrillation.
Abbreviations: AF, atrial fibrillation; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; creat, creatinine; cys, cystatin; eGFR, estimated glomerular filtration rate; IVW, inverse variance weighted; MA, microalbuminuria; n, number; OR, odds ratio; SNP, single nucleotide polymorphism; UACR, urine albumin-to-creatinine ratio; WME, weighted median estimator.

oxidative stress and impairs microvascular blood flow of the ventricles [47]. This mechanism was also extended to the renal microvasculature as AF also affects renal microvascular blood flow, down-regulates renal neutral endopeptidase expression, induces renal profibrotic structural changes, and ultimately may impact renal function over time [48]. In addition, the application of aldosterone, atrial natriuretic peptide, asymmetric dimethylarginine, and angiotensin peptides during AF did not prevent the down-regulation of renal neutral endopeptidase expression. This could imply that the irregularly irregular rhythm caused by AF is the direct effect that induces structural renal changes rather than indirect humoral changes that may be induced during this process [48,49]. Other possible links that could link kidney dysfunction to AF is inflammation [16–19,50]. Kidney dysfunction and AF are both associated with a pro-inflammatory state through increased levels of pro-inflammatory cytokines, which further cause a decline in kidney and cardiac function, respectively and thereby may increase the risk of one another [16–19,50]. The increased activity of the RAAS is also among the suggested mechanisms. On the one hand, activation of the RAAS caused by CKD could lead to atrial remodeling through hypertension, increased atrial pressure, atrial enlargement, cardiac fibrosis, and by modulation of cardiac ion channels. On the other hand, activation of RAAS caused by AF could also have a detrimental effect on the kidneys [9–15].

We did not find evidence for a causal role of eGFRcreat and eGFRcys on AF, although the effect estimates of both assessments were in line with each other. However, we did find a causal effect of CKD stage ≥G3 and microalbuminuria on AF risk. This could be due to the fact that the presence of CKD stage ≥G3 and microalbuminuria represent a greater level of impaired kidney function and therefore may be more strongly associated with AF risk. A possible explanation for these discrepancies could be that indeed only more pathological levels of eGFR (CKD stage ≥G3, defined as eGFRcreat <60 ml/min per 1.73 m^2) and UACR (microalbuminuria is defined as UACR >30 mg/g) may lead to AF and vice versa. This hypothesis is supported by previous studies that reported a J-shaped or graded relationship between impaired kidney function and incident AF [9,21,26]. Participants with CKD stage ≥G3 were shown to have a significant graded increasing risk of incident AF while such a significant increased risk for AF was not observed in participants with CKD stage G2 (eGFRcreat levels of 60-89 ml/min per 1.73 m^2) or with CKD stage G1 (>90 ml/min per 1.73 m^2) [9,21,26]. Similarly, the presence of microalbuminuria (30-299 mg/g) or macroalbuminuria (≥300 mg/g) also showed a significant graded association with increased incident AF risk with increasing levels of albuminuria [9,21,26,27]. These findings indeed suggest that there is a pathological kidney function threshold that has to be surpassed. Subsequently, surpassing this threshold would then trigger the pathological cascades that are set in motion by reduced kidney function such as activation of the RAAS, hypertension, ischemia, heart failure, and inflammation which may then lead to incident AF. Moreover, we found that both CKD and microalbuminuria were significantly associated with AF and vice versa, which further supports the idea that both markers represent independent risk factors for AF and vice versa [27]. Reason for this might be that albuminuria is a reflection of microvascular damage, endothelial dysfunction, or cardiometabolic syndrome whereas CKD may be a better representation of intrinsically impaired kidney function [27].

The causal effect estimates that we obtained from the MR analysis were different than the effect estimates that were obtained from previous observational epidemiological studies [8,21–27]. This could be due to the differences in the time window between MR studies and traditional observational studies. MR studies calculate a risk estimate from a

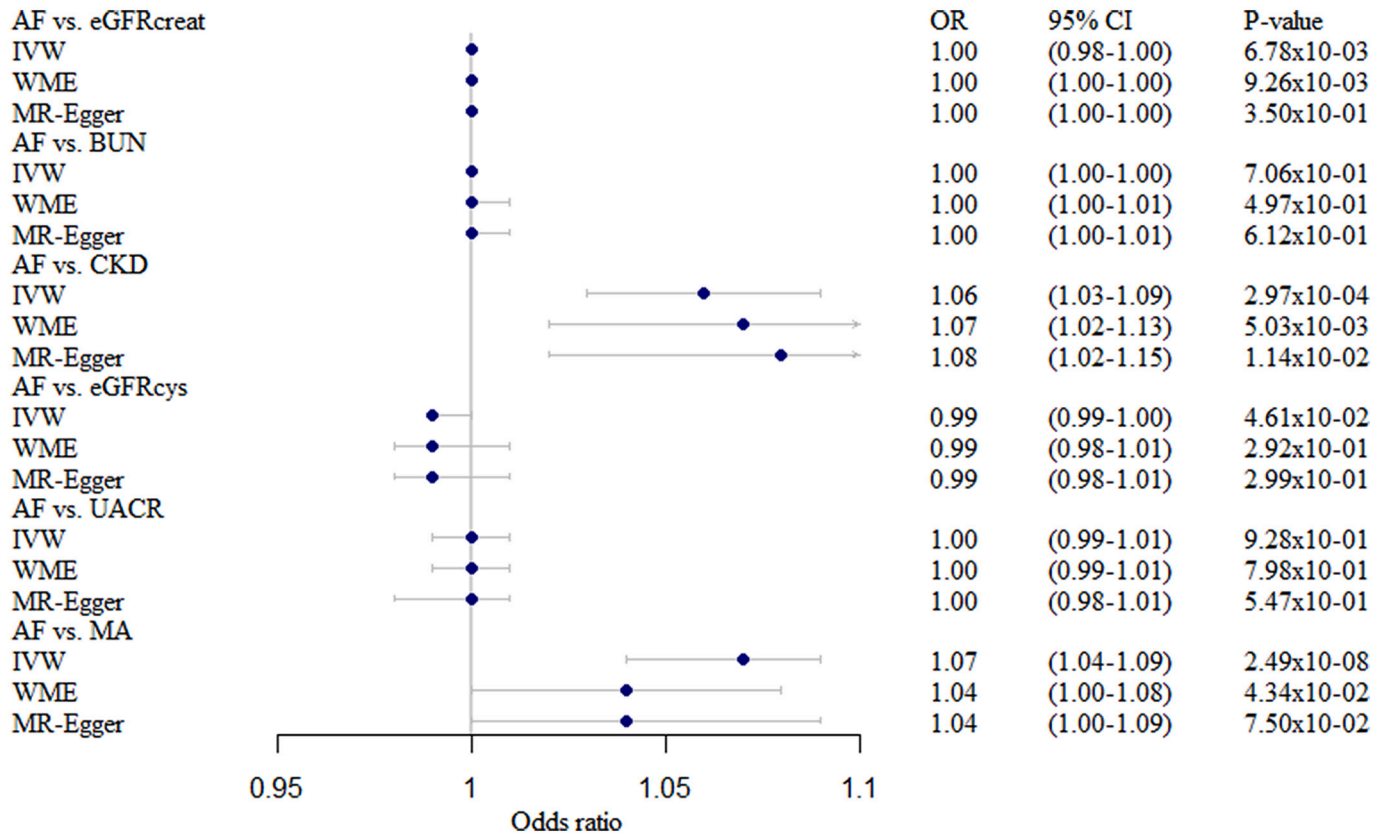

Fig. 3. Forest plot which visualizes the Mendelian randomization analyses between atrial fibrillation and kidney function.
Abbreviations: AF, atrial fibrillation; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; creat, creatinine; cys, cystatin; eGFR, estimated glomerular filtration rate; IVW, inverse variance weighted; MA, microalbuminuria; n, number; OR, odds ratio; SNP, single nucleotide polymorphism; UACR, urine albumin-to-creatinine ratio; WME, weighted median estimator.

lifetime exposure to a certain risk factor where traditional observational studies estimate a risk estimate of an exposure with a certain follow-up time, for example a 10-years risk. Another possible explanation could be the unmeasured confounding and reverse causation that could still be present in traditional observational studies. MR analysis avoids these biases by using genetic proxies of risk factors that are not prone to these biases, because of the random distribution of genetic variants at conception. In addition, MR analysis is a helpful and insightful research method to assess causality of associations which are not possible or feasible to be investigated with randomized clinical trials due to limitations such as being unethical, unpractical and/or too expensive. Furthermore, our results also differ from the results of a previous bidirectional MR [28]. Park et al. [28] found that AF is a causal risk factor for kidney function impairment, however a causal effect of kidney function on AF was not observed. Specifically, there are several noteworthy differences between the study of Park et al. [28] and our study. First, Park et al. [28] used fewer assessments of kidney function (eGFRcreat and CKD) while we used a more comprehensive kidney function panel (eGFRcreat, BUN, CKD, eGFRcys, UACR, and microalbuminuria) to assess the bidirectional association. Second, in contrast to Park et al. [28], we used the most recent available GWAS for AF. The GWAS for AF that was used by Park et al. [28] was trans-ethnic, had a smaller sample size (n = 588,190), and had fewer genetic variants (n = 94 SNPs) that could be used for the MR analyses. Park et al. [28] focused primarily on trans-ethnic ancestry while we focused on European ancestry, when available.

Unravelling the bidirectional casual association between kidney function and AF could have some clinical implications. As kidney dysfunction and AF are causal risk factors for one another, appropriate management of kidney dysfunction may lead to a reduced risk of AF and the other way around. On the one hand, appropriate management of kidney dysfunction includes managing CKD-related risk factors such as obesity, dyslipidemia, hypertension, and lifestyle advice [37]. On the other hand, management of AF is based on the ABC pathway as suggested by the ESC guidelines which consists of: (A) avoid stroke (anticoagulation), (B) better symptom management with patient-centered, symptom directed decisions on rate or rhythm control, and (C) cardiovascular and comorbidity risk optimization [4]. Future randomized clinical trials could support our findings by evaluating kidney dysfunction outcomes when performing AF-targeted interventions and evaluating AF outcomes when performing interventions that target kidney dysfunction. Moreover, early screening for kidney dysfunction and monitoring of kidney function in AF patients or early screening for AF and monitoring of AF in patients with kidney dysfunction is warranted.

Major strengths of this study include the use of summary statistics from the largest to date GWAS meta-analyses. With these large study samples we were able to extract a substantial amount of genetic instruments that we could use for the subsequent MR analyses. By using a bidirectional MR approach, we were also able to disentangle the complex interplay between the kidneys and the heart. In addition, by using MR, we were more likely to avoid certain biases that are more common in traditional observational epidemiological studies such as residual confounding and reverse causation. However, our study also has some limitations. First, we cannot rule out unobserved horizontal pleiotropy, although we tried to address horizontal pleiotropy through current best practices for MR sensitivity analyses. We used the WME, MR-Egger, MR-PRESSO, and sensitivity plots to identify and correct for horizontal pleiotropy. Additionally, we excluded genetic variants that were associated with potential confounders and/or horizontal mediators such as myocardial infarction/coronary artery disease, and heart failure.

Second, there was a potential partial overlap in the samples that were used to obtain the genetic instruments which may cause bias towards the observational findings [43]. However, this bias is difficult to avoid with the ongoing collaborations between large scale genetic consortia which combine their study samples in an attempt to increase their sample sizes. Additionally, to what extent this might have led to weak instrument bias is uncertain, although considerable weak instrument bias may be of less concern given the aforementioned range of the F-statistic of the included genetic instruments used in our analyses [43]. Third, we were unable to perform MR analyses for BUN, UACR, and microalbuminuria with European summary statistics due to unavailability of these statistics, which may have caused some stratification bias in those analyses, nonetheless the GWAS of Wuttke et al. [32] (BUN) and Teumer et al. [33] (UACR, and microalbuminuria) both included mainly European participants (74% and 97%, respectively). Fourth, mostly single assessments of eGFRcreat, BUN, CKD, eGFRcys, UACR, microalbuminuria and AF were used in the various GWAS from which we derived the genetic variants. This may have caused misclassification bias to some extent, although this would have probably led to an underestimation of the true association. Fifth, our results may not be generalizable to younger populations and other ethnicities, because our analysis included older participants mostly from European descent. Lastly, it is also worth noting that the limited amount of genetic variants that we were able to use for some of the analyses to evaluate the associations could have led to insufficient power to detect some significant associations. Future GWAS with even larger sample sizes could aid in identification of additional genetic variants to further increase the power of future MR studies.

In summary, our study confirms a bidirectional causal relationship between kidney function and AF that has been suggested by previous observational studies. The shared genetic architecture between kidney dysfunction and AF might represent important therapeutic targets to prevent both diseases, as well as their complications, in the general population.

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Authors contributions

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Writing – original draft: SG, ACvdB, LC, MK.
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Declaration of Competing Interest

Ikram reports consulting fees from BioGen Inc. The remaining authors have no disclosures to report.

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Appendix A. Supplementary data

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