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Estimated GFR Decline is Causally Associated with Acute Pulmonary Embolism: A Nested Case-Control and Mendelian Randomization Study

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Abstract:
Background: Renal dysfunction is highly prevalent among patients with pulmonary embolism (PE). This study combined population-based study and Mendelian randomization to observe the relationship between renal function and PE.
Methods: A nested case-control study were performed using data of PE patients and controls were from two nationwide cohorts, the China pUlmonary thromboembolism REgistry Study (CURES) and China Health and Retirement Longitudinal Survey (CHARLS). Baseline characteristics were balanced using propensity score matching and inverse probability of treatment weighting. Restricted cubic spline models were applied for the relationship between estimated glomerular filtration rate (eGFR) decline and the risk of PE. Bidirectional two-sample Mendelian randomization (MR) analyses were performed using Genome-wide association study summary statistics for eGFR involving 1,201,909 individuals and for PE from the FinnGen consortium.
Results: The nested case-control study including 17,547 participants (6,322 PE patients) found that eGFR distribution was significantly different between PE patients and controls (P<0.001), PE patients had a higher proportion of eGFR<60 mL/min/1·73 m2. eGFR below 88 mL/min/1·73 m2 was associated with a steep elevation in PE risk. MR analyses indicated a potential causal effect of eGFR decline on PE (OR=4·26, 95%CI 2·07-8·79), with no evidence of horizontal pleiotropy and reverse causality.
Conclusions: Our findings support the hypothesis that renal function decline contributes to an elevated PE risk. Together with the high prevalence of chronic kidney diseases globally, there arises the necessity for monitoring and modulation of renal function in effective PE prevention.

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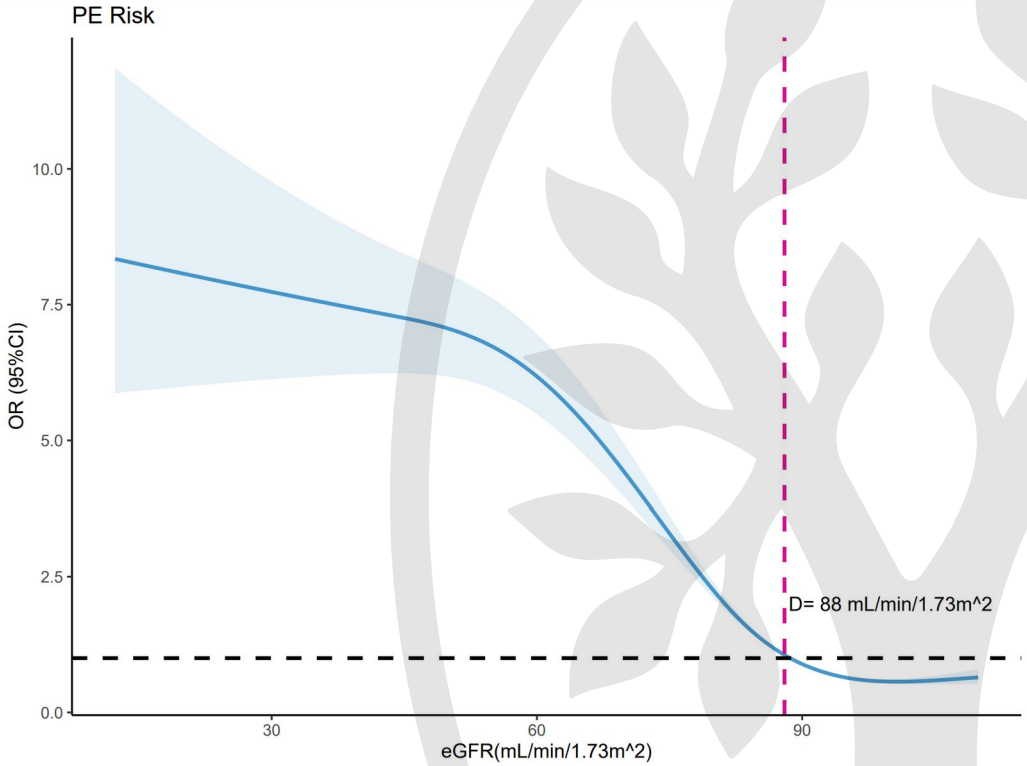
Figure 2 Association between eGFR values and PE risk.



Restricted Cubic Spline Model for Risk of Developing Pulmonary Embolism. This figure illustrates the restricted cubic spline model fitted to the relationship between estimated glomerular filtration rate(eGFR) and pulmonary embolism risk. The x-axis represents eGFR in mL/min/1.73m2, while the y-axis depicts the predicted risk of pulmonary embolism. The solid blue line is the estimated odds ratio, and the shaded blue area is the 95% confidence interval, adjusted for covariates including demographic variables (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases). 88/mL/min per 1.73m^2 was identified as the reference value. When the eGFR was lower than 88/mL/min per 1.73m^2, the result showed a marked increase in PE risk as the eGFR decreased, and then the OR of PE reached plateau as eGFR continued to decrease.

Estimated GFR Decline is Causally Associated with Acute Pulmonary Embolism: A Nested Case-Control and Mendelian Randomization Study

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Conclusions: Our findings support the hypothesis that renal function decline contributes to an elevated PE risk. Together with the high prevalence of chronic kidney diseases globally, there arises the necessity for monitoring and modulation of renal function in effective PE prevention.

Key words: Pulmonary Embolism, Glomerular Filtration Rate, Risk Factors, Causal Inference, Nested Case-control Study, Mendelian Randomization Analysis

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Summary Table:

1. **What is known on this topic?**
   (1) Existing studies revealed a high prevalence of renal impairment among pulmonary embolism (PE) patients and the prognosis of PE patients with renal insufficiency.
   (2) Few population-based studies have explored the relationship between renal

function decline and PE and the direction.

2. What does this paper add?

(1) PE patients were associated with a higher prevalence of low eGFR compared to the general population and eGFR levels below 88 mL/min/1·73 m² were associated with a steep increase in PE risk. MR analyses found that renal function decline has the potential to be causally associated with PE, with no evidence of horizontal pleiotropy and reverse causality.

(2) These findings uncovered the connection between the lung and kidneys and provided multi-disciplinary strategies for patient care. The study indicated that monitoring and modulation of renal function could be important and effective measures for reducing PE incidence. This also enhances our understanding of complications arising from CKD and underscores the necessity for monitoring the risk of thrombosis and implementing preventive strategies against PE in patients with CKD to prevent serious complications.

Introduction

Acute pulmonary embolism (PE) refers to a condition in which the pulmonary artery or its branches are obstructed by a thrombus that originated from the deep veins of the pelvis and legs. Together with deep vein thrombosis (DVT), they are commonly known as venous thromboembolism (VTE). With an annual incidence of 39-115/100,000 population, PE is the third most prevalent cardiovascular disease worldwide, after ischemic heart disease and stroke, and is one of the leading causes of

cardiovascular death[1–3]. Nevertheless, in recent years, a steadily increasing global disease burden of PE has been reported, and thus, PE prevention is a priority in global public health[1]. As a multifactorial disease, a series of risk factors for PE have been established, including genetic factors, aging, major trauma and surgery, diabetes mellitus, and a series of non-communicable diseases[1,4–8].

The prevalence of renal insufficiency was reported to be high among PE patients in several large PE registries, ranging between 27% and 49%[9–12]. Also, studies have identified that renal impairment was associated with all-cause death, bleeding and PE recurrence among PE patients [13–16]. Recently, the relationship between impaired renal function and the pulmonary circulation has been observed. Pathophysiological alterations inherent to chronic kidney disease (CKD), such as vascular endothelial damage, play a pivotal role in the pathogenesis of pulmonary embolism (PE) [17]. However, whether renal function decline is an independent risk factor for PE is still poorly understood. Thus, large-scale population-based studies to examine the association between renal function are needed. However, conventional observational studies can likely be affected by reverse causality and confounding, leading to potentially biased results.

Mendelian randomization (MR) is an important approach to estimating the causal relationship between exposure and outcome, employing genetic variants associated with specific exposure as instruments to compare two genetically defined groups with

different average levels of exposure (glossary seen in the Supplementary Table 1)[18]. Since naturally occurring genetic variants associated with phenotypes are distributed randomly in the population at conception, these two genetically defined groups are considered not to be systematically different in terms of confounding variables. Since these genetic variants are generally not linked to confounders, any differences in the outcome between individuals who carry the variant and those who do not can be attributed to variations in the associated risk factor (detailed description of several statistical methods seen in the Supplementary Table 1). Thus, MR provides a powerful tool for identifying causal relationships between risk factors and outcome. Previous MR studies have provided evidence on the causal relationship between PE and a series factors like uric acid, smoking [19,20]. However, until now, no MR studies have focused on the bidirectional relationship between renal function and PE.

In this study, we firstly conducted a nested case-control study from two nationwide cohorts to characterize the observational association between renal function (measured by creatinine-based estimated glomerular filtration rate) and PE, followed by bidirectional MR analyses to estimate the causal relationship between them (Figure 1).

Methods

Data source and study population of observational study

PE patient data were collected from the China pUlmonary thromboembolism REgistry

Study (CURES) , an ongoing nationwide registry that recruited patients aged>18 with acute symptomatic PE from 100 medical centers across China between 2009 and 2015[21,22]. The PE patients were diagnosed by helical computed tomographic pulmonary angiography (CTPA), ventilation-perfusion lung scintigraphy (V/Q scan) or pulmonary angiography. Meanwhile, data on controls were collected from the China Health and Retirement Longitudinal Survey (CHARLS, Wave 3, 2015), a national survey of Chinese adults over 45 years old [23]. Renal function for both cohorts was defined using creatinine-based eGFR (Supplementary Method), calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[24]. Definition of comorbidities were shown in the Supplementary Method[22]. Then, the eGFR value was converted to categorical variables according to the cutoff value of 30,60,90 mL/min/1·73 m^2.

Propensity score matching and cubic-spline model analyses.

In order to balance baseline characteristics of the PE and control populations, propensity score-matching (PSM) was employed, followed by inverse probability of treatment weighting (IPTW). The individual propensity to the presence of PE was estimated using a logistic regression model incorporating confounding variables as covariates, including variables that were significantly different between groups in univariable analyses and were known to be associated with renal function.. Then, 1:1 PSM was performed between two groups, followed by IPTW performed as previously described [25]. A restricted cubic spline with four knots to examine the association

between eGFR and risk of PE was performed, adjusting for covariates including demographic variables (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases). P-values were two-tailed, and the significance level was set at P-value < 0.05. Statistical analyses were performed using R software (version 4·3·0), and the PSM and IPTW were performed using the R package"*Matching*", cubic-spline models were generated using the R package "*rms*".

GWAS data of renal function

Trans-ethnic GWAS data for estimated glomerular filtration rate (eGFR) were obtained from the largest meta-analysis on eGFR to date, which pooled data of the Chronic Kidney Disease Genetics Consortium (CKDGen, encompassing European (n = 567,460), East Asian (n = 165,726), African-American (n = 13,842), South Asian (n = 13,359) and Hispanic ancestry (n = 4,961) and the UK Biobank (European ancestry, n = 436,581)), collectively including 1,201,909 participants (Supplementary Table S1) [26]. Four hundred twenty-four significant (*P-value* $\leq 5 \times 10^{-8}$) eGFR-associated single nucleotide polymorphisms (SNPs), explaining ~10% of eGFR variance, were identified from the dataset and SNPs meeting the selection criteria described below were proposed as primary instrumental variables (IVs) for creatinine-based eGFR(eGFRcrea)[27]. Also, eGFRcrea-associated SNPs derived from European ancestry (100% European ancestry from CKDGen and UKB, n = 1,004,040), uncovered by the CKDGen meta-analysis, were employed as supplement IVs to assess the robustness of

the primary genetic instruments and minimize population stratification bias [27]. GWASs incorporated in the meta-analyses were adjusted for age, sex, principal components by the developers[28]. Detailed information on the two sets of genetic instruments for eGFR is presented in Supplementary Table S1. Full GWAS summary statistics were obtained from CKDGen (https://CKDGen.imbi.uni-freiburg.de/).

GWAS data of PE

We further obtained the PE summary statistics from the FinnGen consortium(https://www.finngen.fi/en/access_results). The FinnGen consortium (R10 release) includes 10,046 PE cases and 401,128 controls. Population of GWAS of PE exhibits no overlap with the participants of the eGFR GWAS. FinnGen excluded subjects who have ambiguous gender, heterozygosity (± 4 standard deviation), high genotype missingness (> 5%), excess and non-Finnish ancestry. Also, the SNPs with high missingness (> 2%), low Hardy–Weinberg equilibrium p-value ($P < 5 \times 10-6$) and minor allele count, minor allele counts < 3 were excluded. GWASs were adjusted for sex, age, principal components as previously described[29]. More detailed methods, including information on the included study, fine-mapping and analytic codes can be accessed on the websites(https:// www. finngen.fi/) (https:// www. finngen.fi/). In the reverse MR, SNPs meeting the selection criteria shown below were retrieved as IVs from the FinnGen summary statistics. Falsification tests were performed to examine the specificity of the study. Dementia and Actinic keratosis, which have not been explicitly reported to be associated with kidney function, were selected to conduct a

falsification test and examine the causal relationship between kidney function and these variables. The summary statistics for Dementia (20,338 PE cases and 391,843 controls) and Actinic keratosis (12,094 PE cases and 398,605 controls) were obtained from the FinnGen consortium (R10 release).

Selection of instrumental variables

Mendelian Randomization (MR) uses genetic variants, mainly SNPs, as instrumental variables (IVs) to explore the genetic link between an exposure and an outcome. MR relies on three core assumptions: (1) the genetic variants must be strongly associated with the exposure; (2) the genetic variants must be independent of any confounding factors; (3) the genetic variants must influence the outcome only through their effect on the exposure (the glossary and detailed description of statistical methods seen in the Supplementary Table 1).. These assumptions must be satisfied for the IVs to be considered valid

A 3-step filtering process was employed to select IVs (Supplementary Tables S3-4)[30]. First, the IV were clumped with 1000 genomes of European ancestry sample data as a reference to ensure independence between SNP markers (linkage disequilibrium - LD - $R^2 < 0.001$, window size = 1000 kb). Second, IVs associated with confounders (ie. risk factors of exposure including cancer, obesity, hypertension, diabetes, inflammatory bowel diseases) were identified by PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) and excluded. Thirdly, the outcome

GWAS summary results of the retained IVs were obtained, except if 1) the IV and were not included in the outcome GWAS 2) the IVs were palindromic and their minimum allele frequency was >0.40, in which case they were defined as directionally ambiguous. Pleiotropy was then examined by MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO), MR-Egger. “Weak instrument” was tested by calculating individual the F statistics for IVs as previously described[20]. An F-statistics exceeding a threshold of 10 was considered as a non-weak instrument.

Bidirectional two-sample MR analyses

Bidirectional two-sample MR analyses to estimate the causal relationship between eGFR exposure and PE outcome was performed and the random-effects of inverse variance weighted (IVW) method was used for the main MR estimate[31]. The STROBE-MR checklist for the reporting of MR studies was used in this study (Supplementary Table S2).

Additional MR estimators, including the weighted median, MR-PRESSO, MR-Egger approaches, were used as complementary analyses to ensure that the causal estimates were robust to heterogeneity and the “no pleiotropy” assumption was not violated[32,33] (Supplementary Table 5). Leave-one-out analyses were performed to assess the reliance of the MR analyses. The I^2 (%) statistic and P-value were generated to examine the heterogeneity among estimates across individual SNPs. Odds ratios (OR) and corresponding confidence intervals (CI) of PE were scaled to one-unit decrease in

log-transformed eGFR. Reverse MR analyses was also conducted to examine the reverse causal effect of PE on eGFR. The R packages *"TwosampleMR"*, *"MRPRESSO"* were used to conduct MR analyses with R software (version 4·3·0) and a two-sided P-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the nested case-control study

In total, 17,547 participants available for calculation of eGFR were included in this study, including 6,322 PE patients from CURES and 11,225 controls from CHARLS. Baseline characteristics were significantly different between these two groups in terms of demographic variables and comorbidities. PE groups were older, with higher BMI, more likely to comorbid cardiovascular diseases, diabetes mellitus, chronic pulmonary diseases, and kidney diseases, (Table 1).

Observational association of eGFR with PE

Demographic variables (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases, kidney diseases) were used to calculate individual propensity score. After PSM and IPTW, the demographic variables and comorbidities of the two groups were well-balanced, (Table 1). The distribution of eGFR was significantly different between PE and controls *(P*<0.001): more PE patients present in the <30, 30~60,60~90 quantiles, suggesting that PE was associated with declined renal function. Then, the restricted

cubic spline showed that 88/mL/min per 1·73m^2 was identified as the reference value. Overall, a Z-shape association was observed for PE risk and eGFR (Figure 2). When the eGFR was lower than 88/mL/min per 1·73m^2, a marked increase in PE risk as the eGFR decreased, and then the OR of PE reached plateau as eGFR continued to decrease (non-linear relationship: P<0.001).

Evidence for causal effects of renal function decline on PE

After IVs selection procedures, 370 independent SNPs reaching genome-wide significance ($P < 5 \times 10^{-8}$) were identified as primary instruments for the dataset of trans-ethnic GWAS of eGFR (Supplementary Table S3). At the same time, 324 independent SNPs derived from the eGFR dataset restricted to the European ancestry were identified as supplementary instruments, to assess the robustness and minimize the population stratification bias (Supplementary Table S4). Importantly, less than 1/3 of the SNPs were overlapping between these two sets of IVs, suggesting that IVs of these two datasets were independent (Supplementary Figure S1). The strength of the IVs in the two datasets used was evaluated by the F statistics, which were all over 10 (Supplementary Table S3-4). Funnel plots showed a symmetric distribution of the SNPs from primary and supplementary sets of IVs (Supplementary Figure S2).

Various methods for MR estimates were employed to assess the causal effect of renal function on PE. The IVW method showed that genetically predicted decline of eGFR was associated with the risk of PE (Figure 2), suggesting that poorer renal function was probablycausally associated with PE (OR=4·26, 95%CI 2·07-8·79). Significant

heterogeneity was detected across the estimates (Cochrane's Q = 478; $P < 0.001$, Supplementary Table S7). The MR-Egger intercept indicated the absence of significant pleiotropy ($P = 0.6$, Table 3). Several outliers were identified by MR-PRESSO, but the distortion test showed that the results were not significantly different before and after removal of the outliers (P=0.9). These together suggested the current results were less likely to be biased by horizontal pleiotropy (Table 3). The scatter plots suggested a positive causal relationship of the SNP effects on eGFR decline against SNP effects on PE (Supplementary Figure S3). Leave-one-out analyses indicated that the results were robust and not driven by any single SNP (Supplementary Figure S4-5). The results of MR analyses using the IVs of genetic data of eGFR restricted in European ancestry were presented in Figure 2. Consistently, the associations of genetically predicted decline of eGFR with PE risk based on the random-effect IVW method were significant (OR=4·69, 95%CI 2·43-9·08, Figure 2), although significant heterogeneity among used SNPs existed (Cochrane's Q = 381; P= 0.01, Supplementary Table S7). Horizontal pleiotropy in MR-Egger regression ($P = 0.17$) and MR-PRESSO was not detected (Table 3). Dataset of two diseases from the Finngen, Dementia and Actinic keratosis, which have not been explicitly reported to be associated with kidney function, were selected to conduct a falsification test and examine the causal relationship between kidney function and these variables. The results showed no significant causal relationship between eGFR and dementia (P IVW = 0.76), eGFR and Actinic keratosis (P IVW = 0.17), thereby supporting the specificity of our original findings.

No evidence suggesting that PE has the potential to be the cause of eGFR decline

In the reverse MR, PE was the exposure to examine its causal effect on renal function. Here, none of the methods (IVW, MR-Egger, MR-PRESSO, Weighted median) showed significant results, suggesting no evidence that PE could affect creatinine-based eGFR (OR=1·00, 95%CI 0.99-1·00, Table 4). Sensitivity analyses and test for horizonal pleiotropy indicated that the results were robust (Supplementary Tables S9)

DISCUSSION

In this study, we provided the evidence that renal function decline was probably causally associated with PE. The nested case-control study based on two large-scale cohorts suggested that low eGFR was associated with PE prevalence, followed by MR analyses using the largest eGFR GWAS to date, confirmed that genetically predicted eGFR decline was associated with the development of PE. This is the first study combining large-scale observational analyses and MR that reveals the association between declined renal function and the occurrence of PE.

Previously, studies have demonstrated high incidence of VTE in CKD or end stage renal disease (ESRD) populations confirmed by MR analysis[34,35] . However, these VTE studies did not explore the breakdown of the association between PE and DVT despite significant differences between PE and DVT in treatment, clinical outcomes and risk factors[36]. Our study is the first one that focus on the causal association between renal function and PE development. Although PE and deep vein thrombosis

(DVT) have been considered as a same disease with different presentation, recent studies provided evidence that there are differences between the two diseases. Several risk factors, such as pneumonia, chronic obstructive pulmonary disease, and atrial fibrillation are associated with higher risk of PE, but seem to have a much smaller effect on DVT, which may be because some risk factors mainly have an effect on pulmonary vasculature[36,37,38]. More importantly, a large-scale study comparing PE and DVT patients highlighted that renal insufficiency were more common in PE patients compared to those with DVT, suggesting that renal insufficiency may play a unique role in the pulmonary vasculature beyond its general effects on the vascular endothelium, and thus the association of renal function on PE need to be studied separately[37]. Several large PE registries have reported that up to one third of PE patients were comorbid with renal insufficiency suggesting an association between them, but none of them clearly illustrated the association between renal function and PE risks[9–12]. A study with limited representativeness showed that ESRD patients receiving chronic dialysis were associated with a higher risk of developing PE, compared with general population, which was consistent with current findings indicating renal function decline could cause PE[39]. Thus, our study provided robust association between renal function and PE, more specifically.

The mechanism under the relationship between renal insufficiency and PE contain several pathways: nephrotic syndrome is the most recognized condition of high risk of VTE, with clear mechanisms of the urinary loss of antithrombin and higher level of

platelet activation. Moreover, studies showed endogenous anticoagulants such as antithrombin, were lower than general population in patients with nephrotic syndrome. But inconsistent results were reported by another study using renal impaired population caused by various reasons, suggesting that loss of antithrombin might only exist in patients with damaged glomerular filtration barriers[40,41]. For CKD or renal impairment caused by underlying disease other than nephrotic syndrome, the mechanisms include activation of procoagulant markers, decreased endogenous anticoagulants, enhanced platelet activation and aggregation, and decreased activity of the fibrinolytic system [35]. A series of clinical studies showed coagulating factors including D-dimer, fibrinogen, factor VII, and factor VIII and von Willebrand factor were increased in patients with renal insufficiency[42,43]. Besides, CKD patients were associated with an increased level of plasminogen activator inhibitor-1, suggesting that endothelial damage. Furthermore, a study found an inverse correlation between circulating levels of plasmin-antiplasmin complex and creatinine clearance rate, suggesting fibrinolytic activity may be compromised as renal function decreases[44]. Moreover, there were studies showing that patients with nephrotic syndrome had higher levels of P-selectin, suggesting platelet activation in patients with chronic kidney diseases[45]. Both the above are components of Virchow's triad and could be secondary to CKD[43,46]. PE could be caused by procoagulant status and endothelial damage resulting from renal function decline. However, the pathogenesis likely differs depending on the cause of the kidney disease (nephrotic syndrome, non-nephrotic and ESRD) but there lacks clear experimental research for further

explanation of those mechanisms.

We innovatively quantify the decrease of eGFR that lower than 88mL /min per 1·73m^2 would be a cut-off point indicating increasing risk of PE. Consistent with our finding, the risk of different degree of CKD on VTE had also been investigated by other clinical studies and they found that VTE risk increased with worsening CKD stage (the adjusted risk ratio of VTE in Stage 2 and 3/4 CKD was 1.28 and 1.71)[47]. Another study showed that the relative risks for developing VTE were gradually increased as renal function decline, from 1·28 for those with mildly decreased renal function to 2·09 for those with eGFR between 15 and 59 mL/min/1·73 m^2 [48]. The understanding of the relationship between renal function decline and PE risk could be of great significance in clinical practice. It is reported that the global prevalence of CKD is around 8~12%[49,50]. Thus, the findings of a potential causal relationship between renal function decline and PE highlighted the importance of preventing thrombosis in patients with impaired renal function. Thus, preventative measures on thrombosis may be warranted since the study found that PE risk was steeply increased when the eGFR was lower than 88 mL/min per 1·73m^2. Since renal insufficiency could affect the use of anticoagulants and was associated with poor prognosis of PE, mechanistic and clinical studies to provide evidence of the PE prevention strategies in patients with renal insufficiency were also justified. Furthermore, the modification effects of various renal disease etiologies on the association between renal function decline and PE risk warrants further investigation. Lastly, the findings of the current

observational study indicated modulation of renal function could be an effective measure to reduce the incidence of PE and in turn the interventional studies to validate the findings are warranted.

The primary strength of the current study is combining the nested case-control study and MR study with large population, which minimized bias from confounding and reverse causality. Moreover, unlike previous studies focusing on VTE, the research for the first time uncovered the potential causal relationship between renal function and PE. Furthermore, the MR analyses employed genetic instruments of eGFR from the most recent and largest GWAS studies, and findings were reinforced by the consistent results observed using two independent sets of IVs and several analytical approaches for MR estimates. However, several limitations of the current study are necessary to be discussed. Firstly, a major limitation of the MR design is horizontal pleiotropy, However, in this study, biases induced by pleiotropic effects are likely minimal. There was no indications of horizontal pleiotropy in the MR-Egger test and consistent results were drawn from several sensitivity analyses. Secondly, the results of the nested case-control study could be potentially biased since cases and controls came from two cohorts employing different technical specifications. Nevertheless, both cohorts employed the same and standardized test for serum creatinine (Supplementary Methods). Also, unmeasured or unknown confounders may influence the observed associations. Atrial fibrillation, although discussed as a potential factor associated with pulmonary embolism, could not be included as a covariate in the propensity

score matching due to the absence of relevant data in the database. Lastly, the result of eGFR or renal function could be affected by different measurement or formulas, and proteinuria, inferred by studies that was associated with VTE, was not included in our study[51].

Conclusion

This study provided compelling evidence from a large population supporting eGFR decline is an independent risk factor for PE, and the risk of PE significantly increased when kidney function declines to the threshold right below the normal level (88/mL/min per 1·73m). These findings indicated that modulation of renal function could be an effective measure for PE prevention, also, given the high global prevalence of CKD and high mortality of PE, there arises the necessity for monitoring the risk of thrombosis and the implementation of preventive strategies concerning PE, in CKD patients.

Authors' contributions

DW, PY, ZZ_1 conceived and designed the study. YL, HL, XZ, YC collected data. YL, HL, GF, HZ, ZH, ZZ_1, HW, HH, XL analyzed and interpreted data. YL and HL replicated the results of this article back-to-back. YL and HL, DW and XL drafted the manuscript. YZ, FX contributed to the design and building of the CURES. XL provided profession of nephrology. XL, ZZ_2, PY, ZZ_1, CW revised the manuscript. ZZ_1 were the lead corresponding authors. All authors participated in the proofreading of the manuscript and provided final approval of the version to be published.

Consent for publication.

All authors participated in the proofreading of the manuscript and provided final approval of the version to be published.

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Conflicts of interest

The authors declare that they have no competing interests.

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Figure 1 Overall Design of The Study

The current study was composed of two components. Firstly, to characterize the observational association between eGFR and PE, we conducted a nested case-control study from two nationwide cohort studies, namely the China pUlmonary thromboembolism REgistry Study (CURES) and the China Health and Retirement Longitudinal Study (CHARLS). Secondly, to estimate the causal-effect relationship between eGFR and PE, bidirectional two-sample MR analyses were conducted. Genome-wide association studies (GWASs) summary-level genetic data for eGFR were derived from a meta-analysis of GWASs involving up to 1.2 million individuals. Summary-level genetic data for PE were derived from the FinnGen consortium R10(10,046 PE cases and 401,128 controls).

Figure 2 Association between eGFR values and PE risk.

Restricted Cubic Spline Model for Risk of Developing Pulmonary Embolism. This figure illustrates the restricted cubic spline model fitted to the relationship between estimated glomerular filtration rate(eGFR) and pulmonary embolism risk. The x-axis represents eGFR in mL/min/1.73m2, while the y-axis depicts the predicted risk of pulmonary embolism. The solid blue line is the estimated odds ratio, and the shaded blue area is the 95% confidence interval, adjusted for covariates including

demographic variables (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases). 88/mL/min per 1.73m^2 was identified as the reference value. When the eGFR was lower than 88/mL/min per 1.73m^2, the result showed a marked increase in PE risk as the eGFR decreased, and then the OR of PE reached plateau as eGFR continued to decrease.

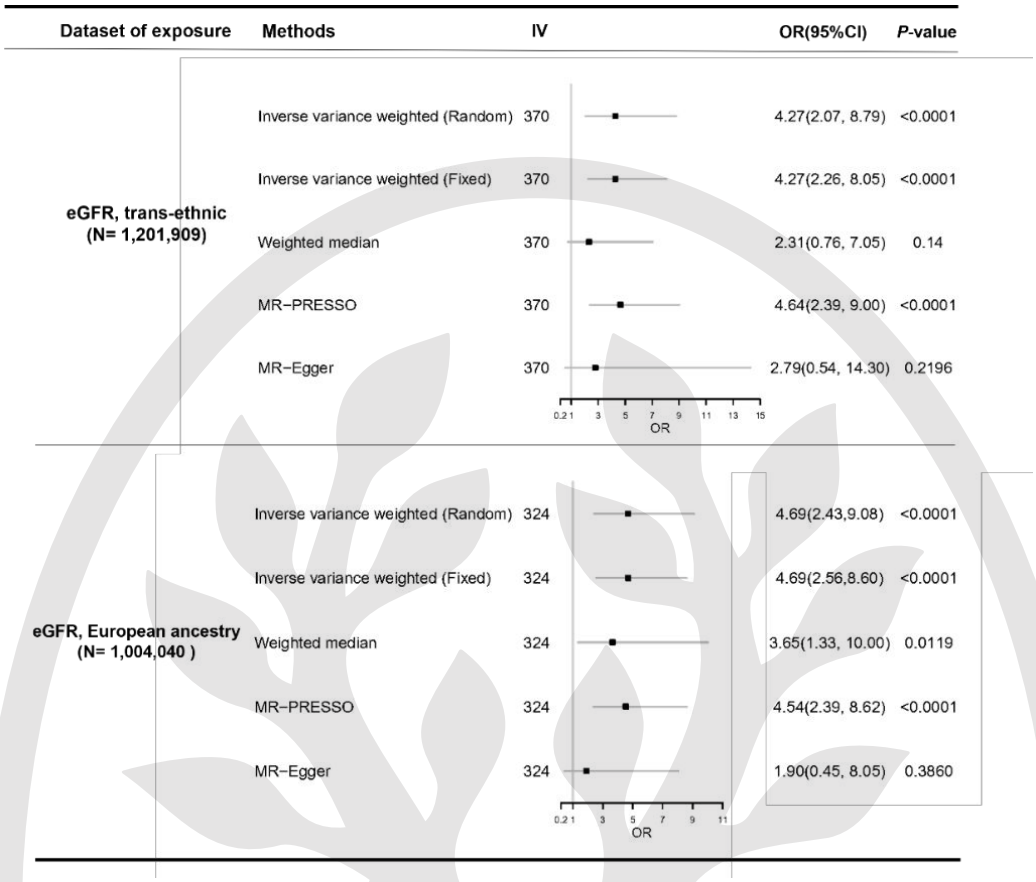
Table 1 Characteristics of Participants in the Nested Case-Control Study Before and After PSM and IPTW

	Unmatched			After PSM[a] and IPTW	
	Controls (CHARLS)	Pulmonary Embolism (CURES)	*p*-value	Controls (CHARLS)	Pulmonary Embolism (CURES)
N	11225	6322		5535·13	5516·77
Male (%)	5204 (46·4)	3320 (52·5)	<0.001	2935·3 (53·0)	2883·4 (52·3)
Age (year±SD)	61·05±9·69	63·22±14·72	<0.001	62·56±9·50	62·95±15·04
BMI (kg/m^2)	23·92±3·92	24·20±3·78	<0.001	24·20±4·05	24·23±3·76
Complications					
Hypertension (%)	3641 (32·4)	2284 (36·1)	<0.001	3552·1 (64·2)	3525·7 (63·9)
DM (%)	1066 (9·5)	760 (12·0)	<0.001	620.3 (11·2)	628·7 (11·4)
Cancer (%)	176 (1·6)	929 (14·7)	<0.001	155·7 (2·8)	148·7 (2·7)
Chronic pulmonary diseases (%)	1507 (13·4)	542 (8·6)	<0.001	485·1 (8·8)	500.4 (9·1)
CVD (%)	1952 (17·4)	1017 (16·1)	<0.001	899·0 (16·2)	927·7 (16·8)
Kidney diseases (%)	1045 (9·3)	132 (2·1)	<0.001	129·8 (2·3)	125·3 (2·3)
eGFR category (%)			<0.001		
eGFR<30	49 (0.4)	95 (1·5)		23·2 (0.4)	88·0 (1·6)
30≤eGFR<60	460 (4·1)	1084 (17·1)		248·5 (4·5)	959·6 (17·4)
60≤eGFR<90	2957 (26·3)	2230 (35·3)		1566·8 (28·3)	1930.7 (35·0)
eGFR>90	7759 (69·1)	2913 (46·1)		3696·7 (66·8)	2538·5 (46·0)

a. the individual propensity to the presence of PE was estimated using a logistic regression model using confounding variables as covariates, including demographic information (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases, kidney diseases)

PSM, propensity score matching; IPTW, inverse probability of treatment weighting; SMD, standardized mean differences; CURES, China Pulmonary Thromboembolism Registry Study; CHARLS, China Health and Retirement longitudinal Survey; BMI, Body Mass index; DM, Diabetes Mellitus; CVD: Cardiovascular Diseases; eGFR, estimated glomerular filtration rate.

Table 2 Two-Sample Mendelian Randomization Revealed That Estimated Glomerular Filtration Rate Decline Was Causally Associated With Pulmonary Embolism.



The forest plot illustrated the Odd ratios and 95% Confidence Interval calculated by inverse variance weighted, maximum likelihood, MR-Egger, and MR-PRESSO methods , using primary and supplementary instrumental variables, when eGFR decline was the exposure and pulmonary embolism was the outcome.

IVs, instrumental variables; eGFR, estimated glomerular filtration rate; PE, pulmonary embolism.

Table 3 Egger regression and MR-PRESSO revealed no evidence of horizontal pleiotropy in the forward MR.

Exposure	Outcome	Egger-intercept	Egger-SE	Egger- *P-value*	MR-PRESSO Distortion Test
eGFR, Trans-ethnic	Pulmonary Embolism	0.001	0.002	0.57	0.9
eGFR European ancestry	Pulmonary Embolism	0.003	0.002	0.17	No significant outliers

Egger regression, and MR-PRESSO test results for horizontal pleiotropy of Mendelian Randomization analyses using primary and supplementary instrumental variables, with estimated glomerular filtration rate (eGFR) as exposure and pulmonary embolism (PE) as outcome.

Table 4 Reverse Mendelian Randomization Indicated No Causal Effect of Pulmonary Embolism On Estimated Glomerular Filtration Rate Decline

Exposure	Outcome	Methods	IVs	OR	95% CI	*P-value*
PE	eGFR, Trans-ethnic	Inverse variance weighted (Random)	15	1.00	0.99,1.00	0.58
		Inverse variance weighted (Fixed)	15	1.00	0.99,1.00	0.15
		Weighted median	15	1.00	0.99,1.00	0.20
		MR-PRESSO	15	1.00	0.99,1.01	0.17
		MR-Egger	15	1.00	0.99,1.00	0.25
PE	eGFR, European ancestry	Inverse variance weighted (Random)	15	1.00	0.99,1.00	0.75
		Inverse variance weighted (Fixed)	15	1.00	0.99,1.00	0.48
		Weighted median	15	1.00	0.99,1.00	0.17
		MR-PRESSO	15	1.00	0.99,1.00	0.71
		MR-Egger	15	1.00	0.99,1.00	0.25

The table illustrated the Odd ratios and 95% Confidence Interval calculated by inverse variance weighted, maximum likelihood, MR-Egger, and MR-PRESSO methods, using primary and supplementary instrumental variables, when pulmonary embolism was the exposure and eGFR decline was the outcome.
IVs, instrumental variables; OR, Odds ratio; CI, Confidence interval

Supplementary Materials:

Supplementary Methods: Cohort profiles on data sources used in the observational study.

Supplementary Table S1 Detailed description on data sources used in the MR analysis and glossary.

Supplementary Table S2 The STROBE-MR checklist

Supplementary Table S3 Instrumental variables for eGFR and their filtering process in Mendelian Randomization.

Supplementary Table S4 Instrumental variables for eGFR in European ancestry and their filtering process in Mendelian Randomization**.**

Supplementary Table S5 Instrumental variables for pulmonary embolism and their filtering process in Mendelian Randomization

Supplementary Table S6 Details of the forward Mendelian randomization

Supplementary Table S7 Heterogeneity test result for the forward MR

Supplementary Table S8 Details of the falsification test

Supplementary Table S9 Heterogeneity test result for the reverse MR

Supplementary Figure S1. Instrumental variables (IVs) used in Mendelian Randomization

Supplementary Figure S2. Funnel plot from single SNP analysis of the two-sample Mendelian Randomization (MR) with (A) eGFR (B) eGFR in European ancestry.

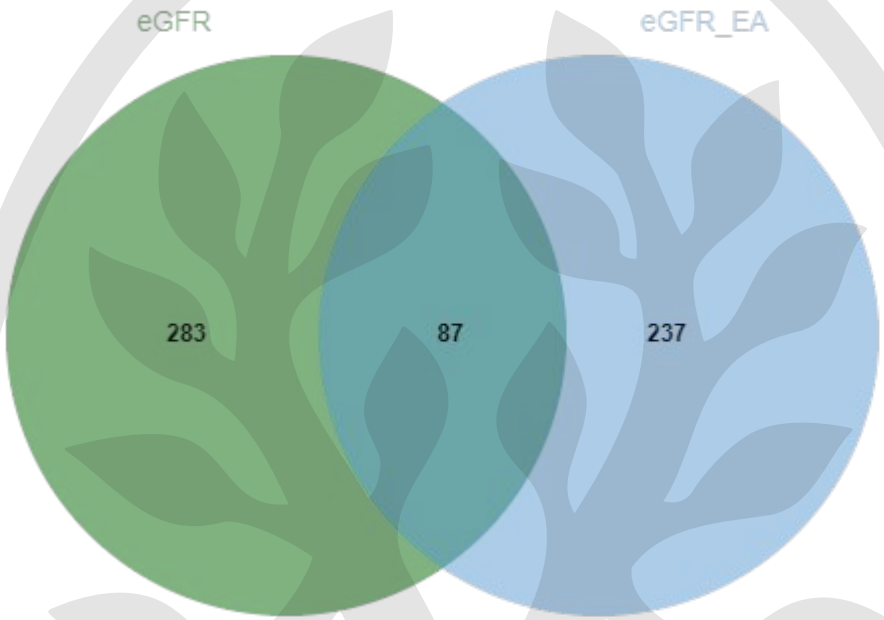
Supplementary Figure S3. Scatter plot of the relationship of the SNP effects on exposure against the SNP effects on outcome.

Supplementary Figure S4. Leave-one-out analysis plot of inverse-variance weighted two-sample Mendelian randomization with eGFR as exposure and PE as outcome.

Supplementary Figure S5. Leave-one-out analysis plot of inverse-variance weighted two-sample Mendelian randomization with eGFR in European ancestry as exposure and PE as outcome.

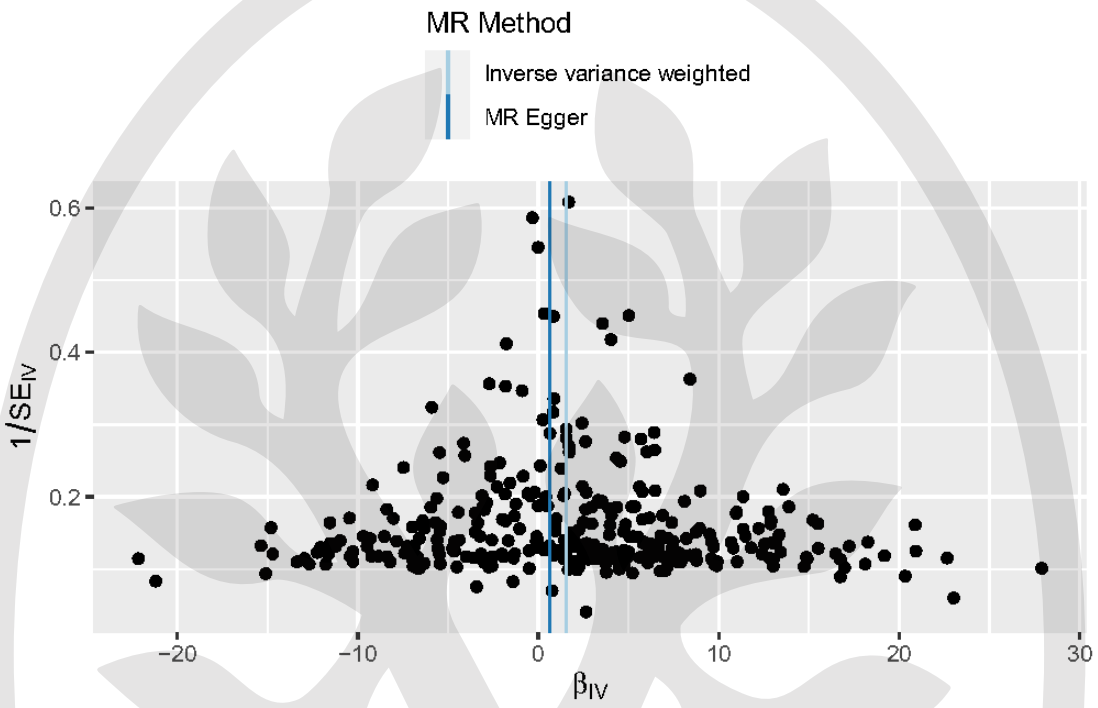
Supplementary Figure S1. Instrumental variables (IVs) used in Mendelian Randomization.

he overlap of identified IVs between two different datasets.

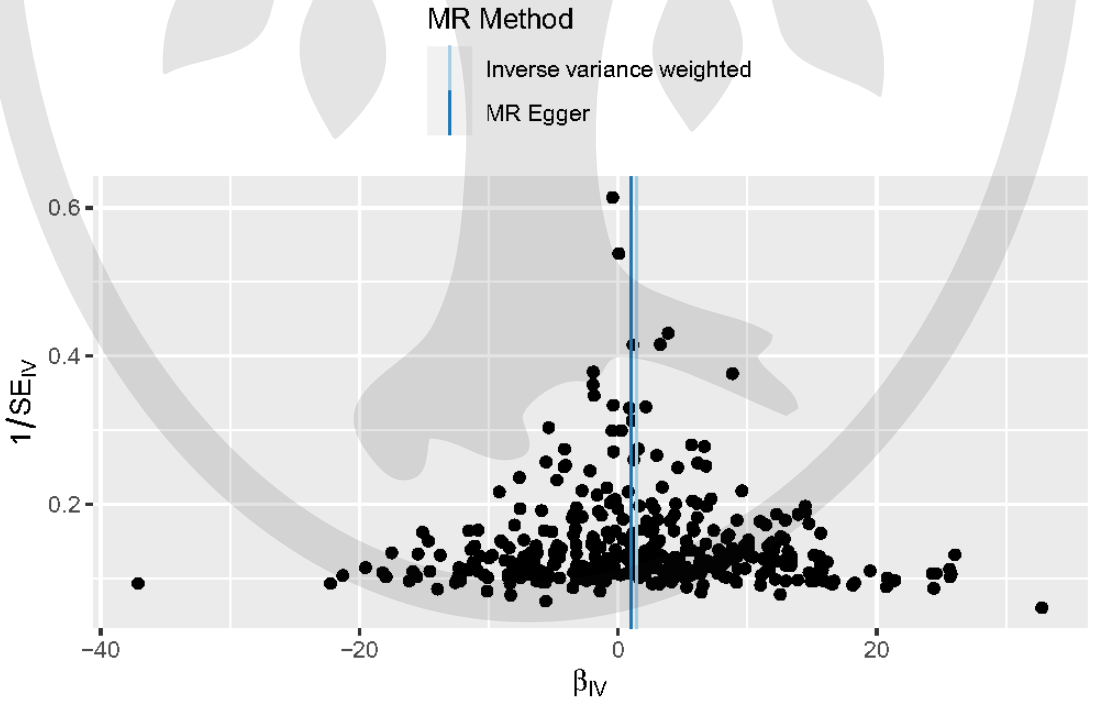


eGFR indicates IV extracted from trans-ethnic GWAS meta-analysis of eGFR; eGFR_EA indicates IV extracted from eGFR GWAS meta-analysis restricted in European ancestry.

Supplementary Figure S2. Funnel plot from single SNP analysis of the two-sample Mendelian Randomization (MR) with (A) eGFR (B) eGFR in European ancestry



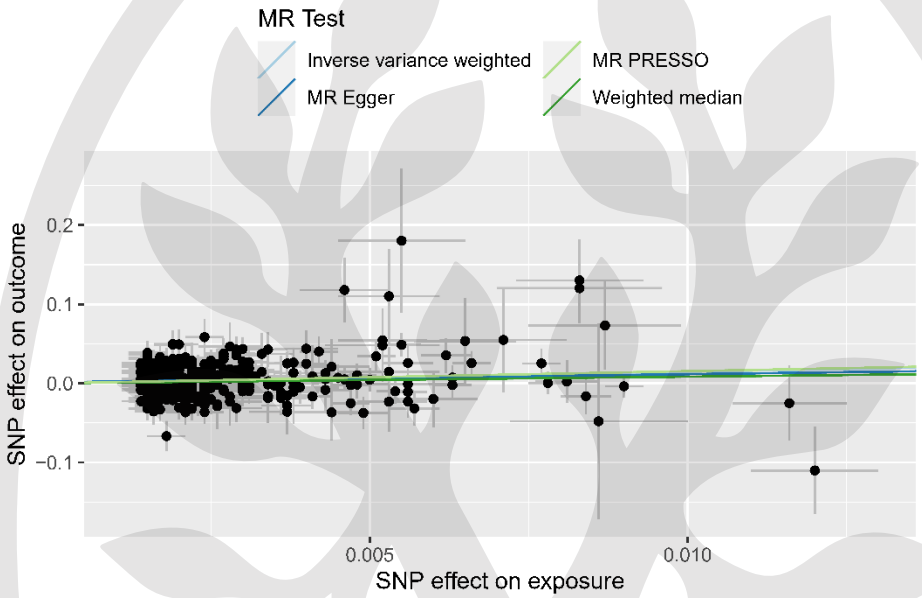
(A) eGFR



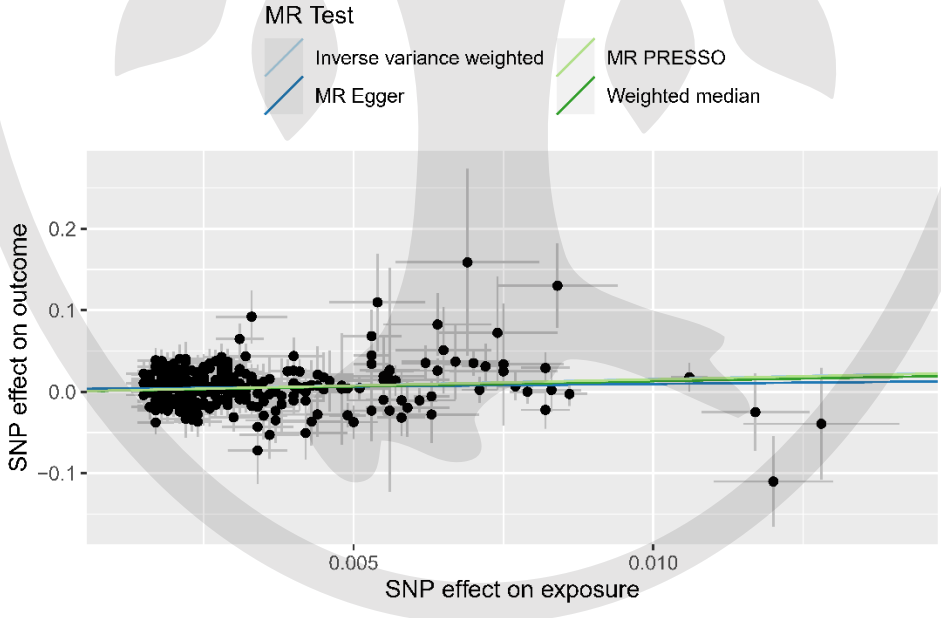
(B) eGFR in European ancestry

Supplementary Figure S3. Scatter plot of the relationship of the SNP effects on exposure against the SNP effects on outcome.

Plot showing the effect sizes of the SNP effects on eGFR or eGFR in European ancestry(x-axes) and the SNP effects on PE(y-axes) with 95% confidence intervals. Each dot represents an SNP used as an IV. The slope of each line corresponds to the estimated causal effect per method. (A) eGFR dataset. (B) dataset of eGFR in European ancestry



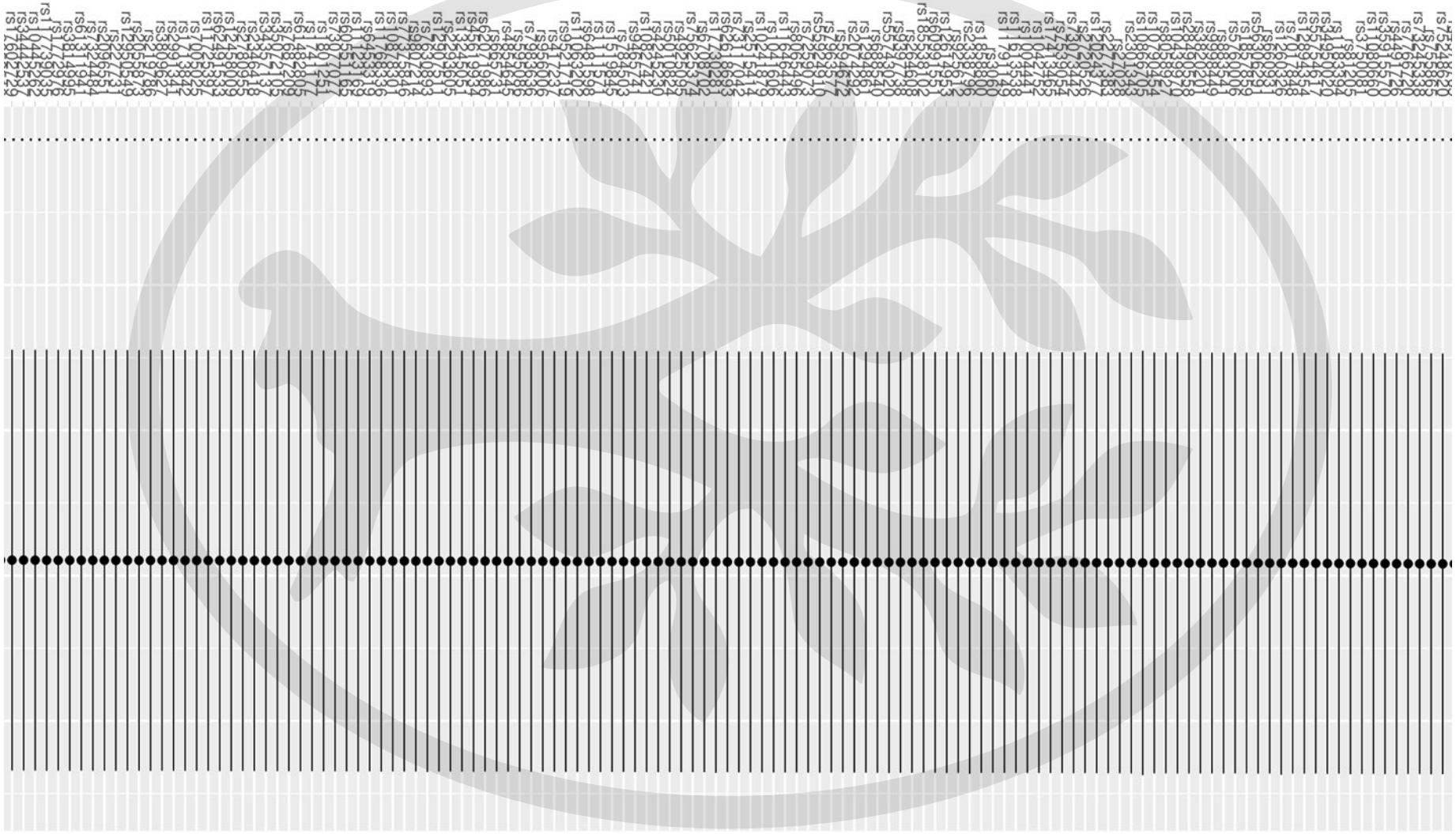
(A) eGFR

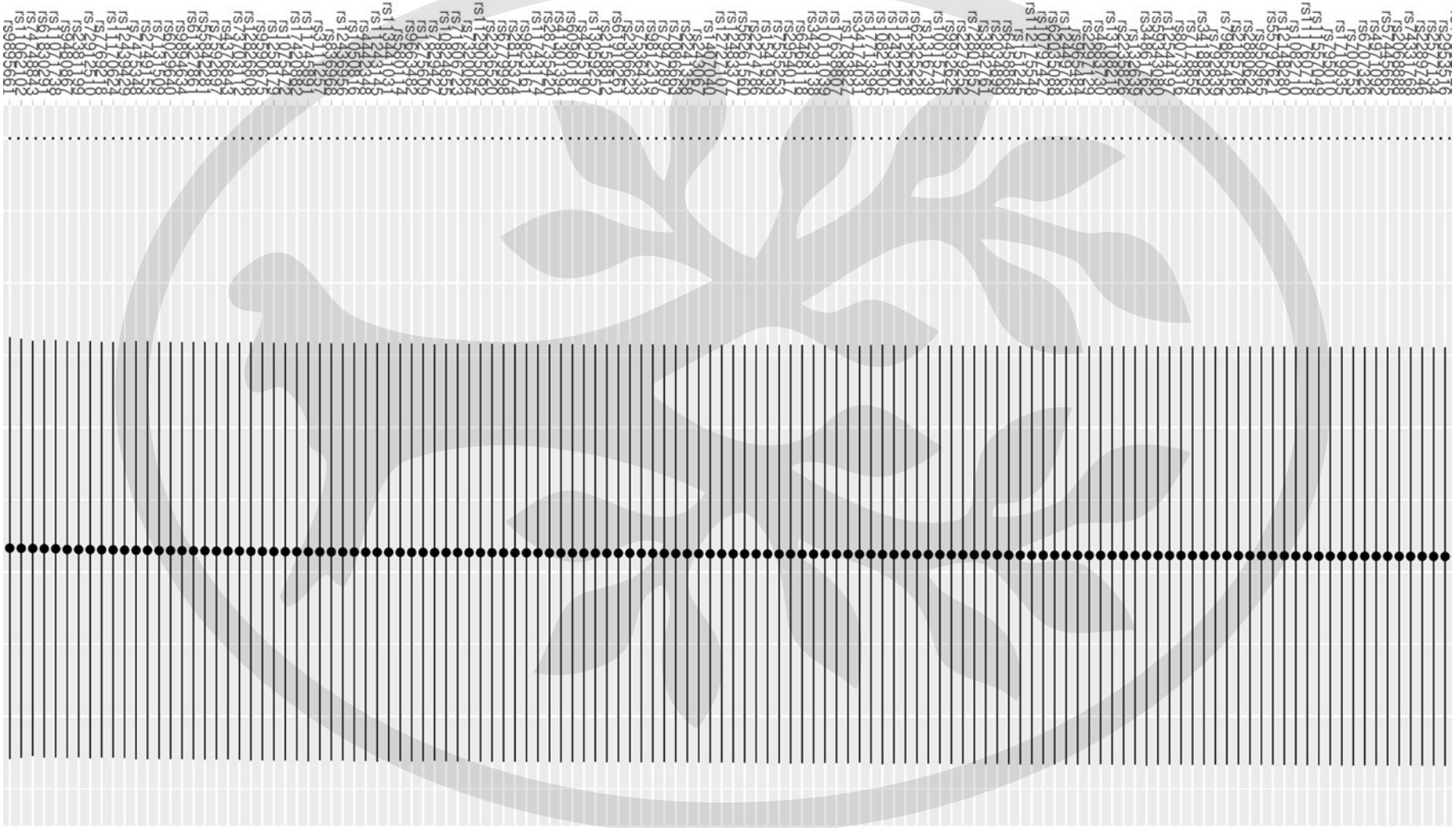


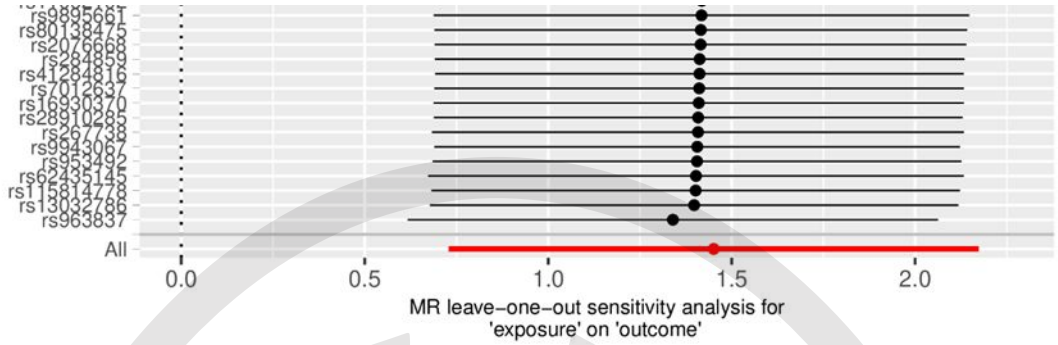
(B) eGFR in European ancestry

Supplementary Figure S4. Leave-one-out analysis plot of inverse-variance weighted two-sample Mendelian randomization with eGFR as exposure and PE as outcome.

The Mendelian Randomization effect size and standard error of the MR-IVW estimates of eGFR on PE are displayed on the X-axis. The Y-axis displays the excluded genetic variant per MR estimate.

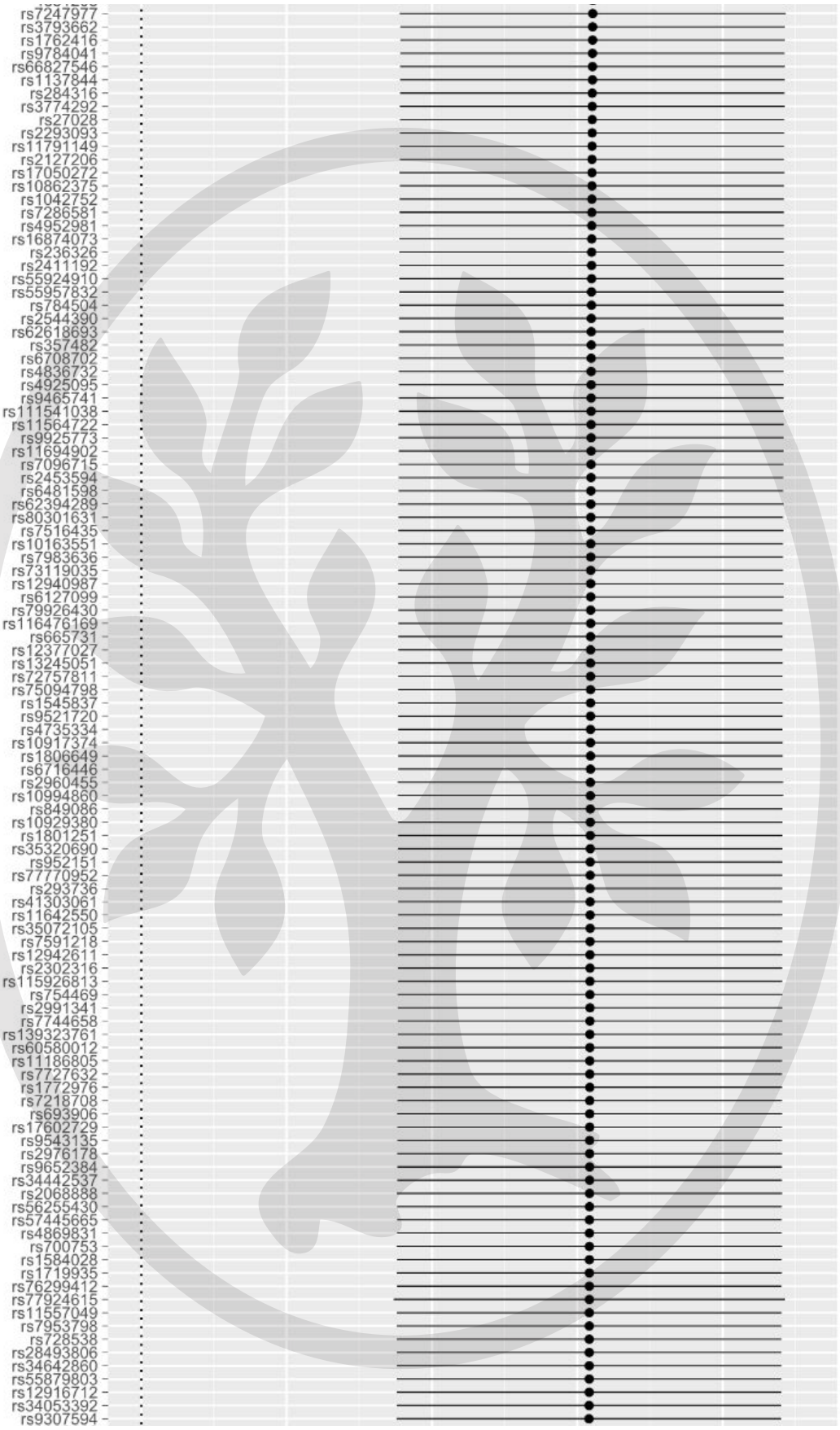


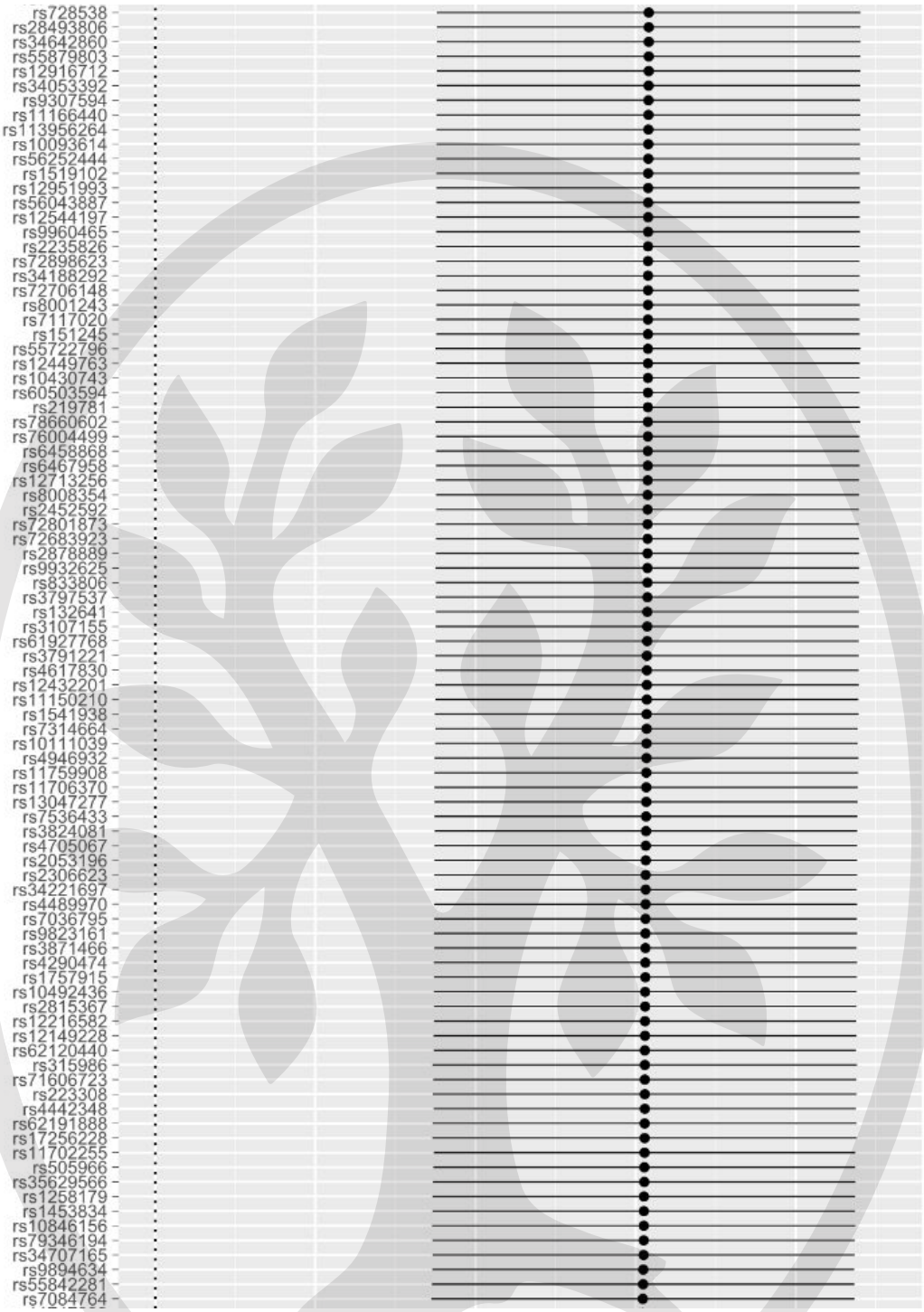


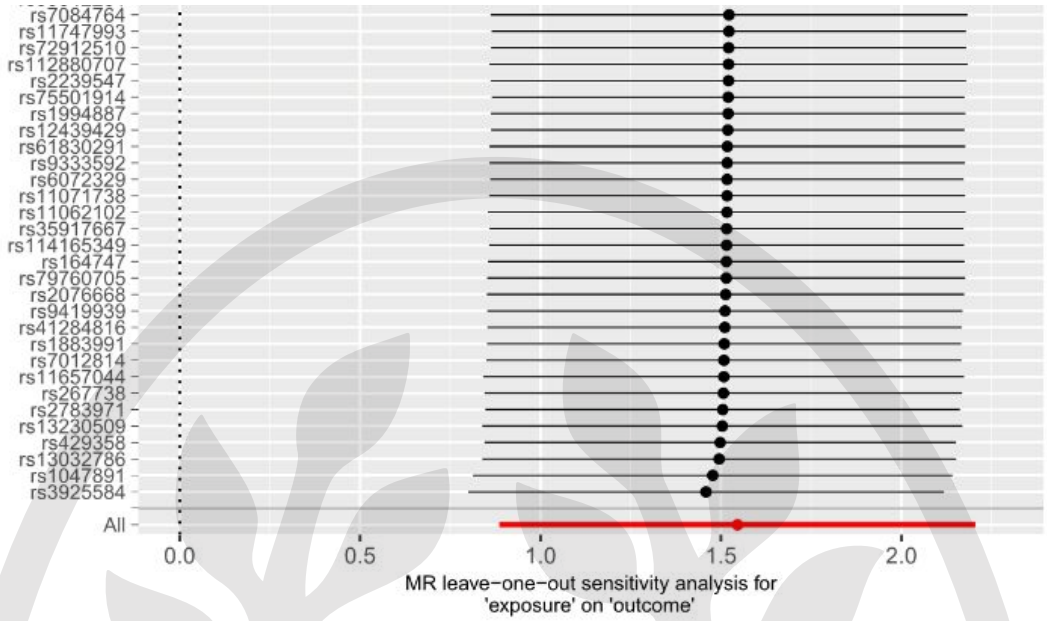


Supplementary Figure S5. Leave-one-out analysis plot of inverse-variance weighted two-sample Mendelian randomization with eGFR in European ancestry as exposure and PE as outcome.

The effect size and standard error of the MR-IVW estimates of on eGFR in European ancestry are displayed on the X-axis. The Y-axis displays the excluded genetic variant per MR estimate.







Supplementary Methods

1.Cohort profiles on data sources used in the observational study.

China pUlmonary thromboembolism REgistry Study (CURES)

The China pUlmonary thromboembolism REgistry Study (CURES) is an ongoing nationwide registry that is recruiting patients with acute symptomatic pulmonary embolism (PE) from 100 medical centers across China. Eligible patients were recruited based on the following inclusion criteria: age ≥18 years and objectively confirmed acute symptomatic PTE or PTE with deep vein thrombosis (DVT). PTE was confirmed by helical computed tomographic pulmonary angiography (CTPA), ventilation-perfusion lung scintigraphy (V/Q scan) or pulmonary angiography. Transthoracic echocardiography was used in patients to assess right ventricular (RV) function. DVT was diagnosed by compression ultrasonography (CUS) or computed tomographic venography. Patients were excluded if any of the following exclusion criteria were met: age <18 years, participating in any other clinical trial with an unknown drug, and suspected venous thromboembolism (VTE) or PTE without confirmed evidence.

China Health and Retirement Longitudinal Study (CHARLS)

The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative longitudinal survey of community-dwelling residents conducted by the National Development Institute of Peking University. This study collected high-quality microscopic data every two years including information on the social, economic, and health circumstances of adults aged 45 years and older via face-to-face interviews. The objectives, study design, methods, and implementation of this database have been described previously. Briefly, 17,708 individuals from 10,287 households in 450 villages/communities were recruited at baseline survey conducted from June 2011 to March 2012, and data of three waves from CHARLS (2011, 2013, and 2015) were used in the present study. The protocols of CHARLS were approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). All participants provided signed informed consent.

2. Measurement methods of main variables used in the nested case-control study.

Biomarker	CHARLS	CURES
Serum Creatinine	Jaffé assay method	Jaffé assay method
Blood pressure	Blood Pressure Monitor	Blood Pressure Monitor
Height	stadiometer	stadiometer
Weight	scale	scale

Diseases	Defination
Cardiovascular diseases	Cardiovascular diseases include coronary heart disease, rheumatic heart disease, cardiomyopathy, cardiac insufficiency, atrial fibrillation or atrial flutter, and hyperlipidemia.
Cancer	Malignant tumors include active tumors and inactive tumors. Types of tumors include lung cancer, esophageal cancer, gastric cancer, pancreatic cancer, colorectal cancer, liver cancer, kidney cancer, prostate cancer, bladder cancer, breast cancer, gynecological tumor, central nervous system tumor, head and neck tumor, and bone tumors, etc..
Chronic pulmonary diseases	Respiratory diseases include chronic obstructive pulmonary disease, pulmonary infection, pulmonary tuberculosis, bronchial asthma, interstitial lung disease, chronic pulmonary heart disease, bronchiectasis, and respiratory failure, etc..
Kidney diseases	chronic nephritis, nephrotic syndrome, and renal insufficiency

3. Disease definition.

Supplementary Table S1 Detailed description on data sources used in the MR analysis.

eGFR indicates estimated glomerular filtration rate**;** PubMed ID, PubMed identifier; PE, Pulmonary Embolism; CKDGen, Chronic Kidney Disease Genetics Consortium; UKB, the UK biobank.

Consortium or cohort study	**Aim of GWAS**	**Sample Size**	**Ethnicity**	**PubMed ID or web source**
The CKDGen Consortium meta-analysis	Trans-ethnic eGFR	1,201,909 (GWAS meta-analysis* for eGFR from CKDGen and UKB)	The CKDGen data encompassing European (n = 567,460), East Asian (n = 165,726), African-American (n = 13,842), South Asian (n = 13,359) and Hispanic ancestry (n = 4,961)(1); the UKB data encompassing European ancestry(n = 436,581)(2)	PubMed ID: 34272381
The CKDGen Consortium meta-analysis	eGFR in European ancestry	1,004,040 (GWAS meta-analysis* from CKDGen and UKB)	100% European ancestry from CKDGen and UKB (2)	PubMed ID: 34272381
FinnGen	Pulmonary Embolism	10,046 pulmonary embolism cases and 401,128	100% European ancestry(Finnish ancestry)	https://www.finngen.fi/fi

*GWASs incorporated in the meta-analyses were adjusted for age, sex, principal components, study site and other study-specific features. All used SNPs used were independent and not in linkage disequilibrium with a distance over 500-kb in the flanking regions and $r2 \leq 0.01$

Supplementary Table S2 STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies[1 2]

Item No.	Section	Checklist item	Page No.	Relevant text from manuscript
1	**TITLE and ABSTRACT**	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study	4	To address this, we employed a nested case-control study from nationwide cohorts, followed by Mendelian randomization (MR) to investigate the potential causal effect of genetically predicted estimated glomerular filtration rate (eGFR) decline on PE.
	INTRODUCTION			
2	**Background**	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question	7	Recently, the relationship between impaired renal function and the pulmonary circulation has been observed. The prevalence of renal insufficiency was reported to be high among PE patients in several large PE registries, ranging between 27% and 49%(9–12). Also, studies have identified that renal impairment was associated with all-cause death, bleeding and PE recurrence among PE patients (13–15). However, whether renal function decline is an independent risk factor for PE is still poorly understood. Thus, large-scale population-based studies to examine the association between renal function are needed. However, conventional observational studies can likely be affected by reverse causality and confounding, leading to potentially biased results.
3	**Objectives**	State specific objectives clearly, including pre-specified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects	8	In this study, we first conducted a nested case-control study from two nationwide cohorts to characterize the observational association between renal function (measured by creatinine-based estimated glomerular filtration rate) and PE, followed by bidirectional MR analyses to estimate the causal relationship between them
	METHODS			
4	**Study design and data sources**	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:		

	a)	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, when available.	10	Trans-ethnic GWAS data for estimated glomerular filtration rate (eGFR) were obtained from the largest meta-analysis on eGFR to date, which pooled data of the Chronic Kidney Disease Genetics Consortium (CKDGen, encompassing European (n = 567,460), East Asian (n = 165,726), African-American (n = 13,842), South Asian (n = 13,359) and Hispanic ancestry (n = 4,961) and the UK Biobank (European)…
	b)	Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Report the sample size, and whether any power or sample size calculations were carried out prior to the main analysis	NA	Used GWAS summary statistics
	c)	Describe measurement, quality control and selection of genetic variants	NA	Used GWAS summary statistics
	d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	NA	Used GWAS summary statistics
	e)	Provide details of ethics committee approval and participant informed consent, if relevant	NA	Irrelevant to the current study
5	**Assumptions**	Explicitly state the three core IV assumptions for the main analysis (relevance, independence and exclusion restriction) as well assumptions for any additional or sensitivity analysis	11	3-step filtering process was employed to select IVs (Supplementary Tables S3-4)(27). First, the IV were clumped with 1000 genomes of European ancestry sample data as a reference to ensure independence between SNP markers (linkage disequilibrium - LD - R2 < 0.001, window size = 1000 kb). Second, IVs associated with confounders (ie. risk factors of exposure including cancer, obesity, hypertension, diabetes, inflammatory bowel diseases) were identified by PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) and excluded. Thirdly, the outcome GWAS summary results of the retained IVs were obtained, except if 1) the IV and were not included in the outcome GWAS 2) the IVs were palindromic and their minimum allele frequency was >0.40, in which case they were defined as directionally ambiguous
6	**Statistical methods: main analysis**	Describe statistical methods and statistics used		
	a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	11	Odds ratios (OR) and corresponding confidence intervals (CI) of PE were scaled to one-unit decrease in log-transformed eGFR.

	b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	11	3-step filtering process was employed to select IVs (Supplementary Tables S3-4)(27). First, the IV were clumped with 1000 genomes of European ancestry sample data as a reference to ensure independence between SNP markers (linkage disequilibrium - LD - R2 < 0.001, window size = 1000 kb). Second, IVs associated with confounders (ie. risk factors of exposure including cancer, obesity, hypertension, diabetes, inflammatory bowel diseases) were identified by PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) and excluded. Thirdly, the outcome GWAS summary results of the retained IVs were obtained, except if 1) the IV and were not included in the outcome GWAS 2) the IVs were palindromic and their minimum allele frequency was >0.40, in which case they were defined as directionally ambiguous
	c)	Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	13	Additional MR estimators, including the weighted median, MR-PRESSO, MR-Egger approaches, were used as complementary analyses to ensure that the causal estimates were robust to heterogeneity and the “no pleiotropy” assumption was not violated
	d)	Explain how missing data were addressed	NA	Used GWAS summary statistics
	e)	If applicable, indicate how multiple testing was addressed	NA	Irrelevant to the current study
7	**Assessment of assumptions**	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	11	First, the IV were clumped with 1000 genomes of European ancestry sample data as a reference to ensure independence between SNP markers (linkage disequilibrium - LD - R2 < 0.001, window size = 1000 kb). Second, IVs associated with confounders (ie. risk factors of exposure including cancer, obesity, hypertension, diabetes, inflammatory bowel diseases) were identified by PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) and excluded. Thirdly, the outcome GWAS summary results of the retained IVs were obtained, except if 1) the IV and were not included in the outcome GWAS 2) the IVs were palindromic and their minimum allele frequency was >0.40, in which case they were defined as directionally ambiguous. Pleiotropy was then examined by MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO), MR-

				Egger. “Weak instrument” was tested by calculating individual the F statistics for IVs as previously described(18). An F-statistics exceeding a threshold of 10 was considered as a non-weak instrument.
8	**Sensitivity analyses and additional analyses**	Describe any sensitivity analyses or additional analyses performed (e.g. comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations)	11-13	Additional MR estimators, including the weighted median, MR-PRESSO, MR-Egger approaches, were used as complementary analyses to ensure that the causal estimates were robust to heterogeneity and the “no pleiotropy” assumption was not violated(30,31) (Supplementary Table 5). Leave-one-out analyses were performed to assess the reliance of the MR analyses. The I2 (%) statistic and P-value were generated to examine the heterogeneity among estimates across individual SNPs. Reverse MR analyses was also conducted to examine the reverse causal effect of PE on eGFR.
9	**Software and pre-registration**			
	a)	Name statistical software and package(s), including version and settings used	13	The R packages “TwosampleMR”, “MRPRESSO” were used to conduct MR analyses with R software (version 4.3.0) and a two-sided P-value <0.05 was considered statistically significant.
	b)	State whether the study protocol and details were pre-registered (as well as when and where)	NA	
	RESULTS			
10	**Descriptive data**			
	a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	NA	Used publicly available GWAS summary statistics
	b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	10	Trans-ethnic GWAS data for estimated glomerular filtration rate (eGFR) were obtained from the largest meta-analysis on eGFR to date, which pooled data of the Chronic Kidney Disease Genetics Consortium (CKDGen, encompassing European (n = 567,460), East Asian (n = 165,726), African-American (n = 13,842), South Asian (n = 13,359) and Hispanic ancestry (n = 4,961) and the UK Biobank (European)…

	c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies		Used publicly available GWAS summary statistics
	d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples ii. Provide information on the number of individuals who overlap between the exposure and outcome studies	10	Population of GWAS of PE exhibits no overlap with the participants of the eGFR GWAS.
11	**Main results**			
	a)	Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale		Supplementary table 2-4
	b)	Report MR estimates of the relationship between exposure and outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference		Table 2
	c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		irrelevant
	d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)		Table 2, Supplementary Table S6, Supplementary Table S9
12	**Assessment of assumptions**			
	a)	Report the assessment of the validity of the assumptions		Supplementary Table S3-S5, Supplementary Table S7-S10, Supplementary Figure S2-S5,
	b)	Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)		Supplementary Table S7-S10
13	**Sensitivity analyses and additional analyses**			
	a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	15	Various methods for MR estimates were employed to assess the causal effect of renal function on PE. The IVW method showed that genetically predicted decline of eGFR was associated with the risk of PE (Figure 2), suggesting poorer renal function was causally associated with PE (OR=4.26, 95%CI 2.07-8.79). Significant heterogeneity was detected across the estimates (Cochrane's Q = 478; P= 0.0001, Supplementary Table S7). The MR-Egger

				intercept indicated the absence of significant pleiotropy (P = 0.6, Supplementary Table S8). Several outliers were identified by MR-PRESSO, but the distortion test showed that the results were not significantly different before and after removal of the outliers (P=0.9).
	b)	Report results from other sensitivity analyses or additional analyses	16	IVW method showed that genetically predicted decline of eGFR was associated with the risk of PE (Figure 2), suggesting poorer renal function was causally associated with PE (OR=4.26, 95%CI 2.07-8.79).
	c)	Report any assessment of direction of causal relationship (e.g., bidirectional MR)	15	In the reverse MR, PE was the exposure to examine its causal effect on renal function. Here, none of the methods (IVW, MR-Egger, MR-PRESSO, Weighted median) showed significant results, suggesting no evidence that PE could affect creatinine-based eGFR (OR=1.00, 95%CI 0.99-1.00, Supplementary Table S9).
	d)	When relevant, report and compare with estimates from non-MR analyses	16	After PSM and IPTW, the demographic variables and comorbidities of the two groups were well-balanced, (Table 1). The distribution of eGFR was shown to be significantly different between PE and controls (P<0.001), with significantly more PE patients present in the <30, 30~60,60~90 quantiles, suggesting that PE was associated with poorer renal function. Then, 11,052 PE and propensity-matched controls were included in the logistic regression and 88/mL/min per 1.73m2 was identified as the reference value.
	e)	Consider additional plots to visualize results (e.g., leave-one-out analyses)	16	Leave-one-out analyses indicated that the results were robust and not driven by any single SNP (Supplementary Figure S4-5).
	DISCUSSION			
14	**Key results**	Summarize key results with reference to study objectives	17	Our nested case-control study based on two large-scale cohorts suggested that low eGFR was associated with PE prevalence, followed by MR analyses using the largest eGFR GWAS to date, indicating that genetically predicted eGFR decline was likely to cause PE. The results of MR were consistent in two different eGFR datasets and in repeated MR analyses employing different

				methods. In conclusion, this is the first study combining large-scale observational analyses and MR analyses to indicate that poor renal function could be one of the causes of PE.
15	**Limitations**	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	20	However, several limitations of the current study are necessary to be discussed. Firstly, a major limitation of the MR design is horizontal pleiotropy, However, in this study, biases induced by pleiotropic effects are likely minimal. There were no indications of horizontal pleiotropy in the MR-Egger test and consistent results were drawn from several sensitivity analyses. Secondly, the results of the nested case-control study could be potentially biased since cases and controls came from two cohorts employing different technical specifications.
16	**Interpretation**			
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	21	In conclusion, this study provided compelling evidence from a large population supporting a causal role of eGFR decline on PE, and the risk of PE significantly increased when kidney function declines to the threshold right below the normal level (88/mL/min per 1.73m).
	b)	Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions	19	To sum up, several mechanisms have been identified that could explain the causal relationship between renal function decline and PE.
	c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	19	The understanding of the relationship between renal function decline and PE risk could be of great significance in clinical practice.
17	**Generalizability**	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	15	370 independent SNPs reaching genome-wide significance ($p < 5 \times 10-8$) were identified as primary instruments for the dataset of trans-ethnic GWAS of eGFR (Supplementary Table S3). At the same time, 324 independent SNPs derived from the eGFR dataset restricted to the European ancestry were identified as supplementary instruments, t
	OTHER INFORMATION			

18	**Funding**	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	21	This study is supported by The National Key Research and Development Program of
19	**Data and data sharing**	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article, or report whether the code is publicly accessible and if so, where	NA	
20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	21	Disclosures The authors have no relevant conflicts of interest to declare.

1. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) Statement. JAMA. 2021;under review.

2. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomisation (STROBE-MR): Explanation and Elaboration. BMJ. 2021;375:n2233.

Supplementary Table 4: Instrumental variables for eGFR in European ancestry and their filtering process in Mendelian Randomization.

				summary statistics in exposure GWAS				filtering process of IVs .					
No	SNP	effect allele	other allele	beta	se	P-value	effect allele frequency	Step 1: LD-independent SNPs were discarded	Step 2: confounders associated SNPs were discarded	Step 3: The SNPs that are		incorporated in the MR analysis	F-statistics
								LD-independent SNPs	associated confounders	palindromic	ambiguous		
1	rs10093614	A	G	0.0018	3.00E-04	2.20E-10	0.3896	Yes		No	No	YES	43
2	rs10111039	A	G	-0.0016	3.00E-04	4.12E-09	0.5952	Yes		No	No	YES	34
3	rs10142359	A	G	-0.0021	3.00E-04	7.94E-15	0.514	Yes		No	No	YES	59
4	rs10151563	A	G	0.0019	3.00E-04	1.16E-11	0.6048	Yes		No	No	YES	48
5	rs10163551	T	C	0.0023	3.00E-04	1.46E-14	0.3017	Yes		No	No	YES	70
6	rs10224002	A	G	-0.0077	3.00E-04	3.55E-142	0.7152	Yes		No	No	YES	789
7	rs10283362	T	C	-0.0021	4.00E-04	2.24E-08	0.1581	Yes		No	No	YES	33
8	rs1042752	A	G	-0.0018	3.00E-04	7.08E-11	0.538	Yes		No	No	YES	43
9	rs10430743	T	G	-0.0027	3.00E-04	1.68E-22	0.4278	Yes		No	No	YES	97
10	rs1047891	A	C	0.007	3.00E-04	2.29E-121	0.313	Yes		No	No	YES	652
11	rs10492436	T	C	-0.002	3.00E-04	6.43E-13	0.3924	Yes		No	No	YES	53
12	rs10498755	T	C	0.0043	5.00E-04	5.80E-18	0.0826	Yes		No	No	YES	89
13	rs10846156	T	G	0.004	3.00E-04	4.13E-31	0.8037	Yes		No	No	YES	213
14	rs10849077	A	G	0.0025	4.00E-04	1.70E-08	0.1433	Yes		No	No	YES	47
15	rs10851885	A	G	-0.0056	3.00E-04	9.74E-69	0.7514	Yes		No	No	YES	417
16	rs10862375	C	G	0.0019	3.00E-04	9.82E-10	0.2762	Yes		YES	No	YES	48
17	rs1087289	T	G	-0.0019	3.00E-04	3.23E-10	0.6103	Yes		No	No	YES	48
18	rs10913015	T	C	0.0016	3.00E-04	3.85E-09	0.422	Yes		No	No	YES	34
19	rs10917374	C	G	-0.0043	5.00E-04	1.50E-16	0.0719	Yes		YES	No	YES	89
20	rs10929380	A	G	0.0019	3.00E-04	8.42E-12	0.3909	Yes		No	No	YES	48
21	rs10994860	T	C	-0.0044	4.00E-04	3.50E-36	0.1844	Yes		No	No	YES	145
22	rs11062102	T	C	-0.0041	3.00E-04	2.32E-47	0.3397	Yes		No	No	YES	224
23	rs11071738	T	C	0.0026	3.00E-04	5.97E-21	0.5276	Yes		No	No	YES	90
24	rs11109717	T	C	0.0017	3.00E-04	8.40E-09	0.6973	Yes		No	No	YES	38
25	rs11150210	A	G	0.0018	3.00E-04	3.15E-08	0.7505	Yes		No	No	YES	43
26	rs111541038	T	C	-0.0032	4.00E-04	2.60E-14	0.8591	Yes		No	No	YES	77
27	rs11166440	A	G	-0.0024	3.00E-04	3.85E-17	0.6284	Yes		No	No	YES	77
28	rs11186805	A	G	-0.002	3.00E-04	2.45E-12	0.3731	Yes		No	No	YES	53
29	rs11261022	A	C	0.0021	3.00E-04	3.11E-14	0.3578	Yes		No	No	YES	59
30	rs112880707	T	C	-0.0056	5.00E-04	3.29E-34	0.1006	Yes		No	No	YES	150
31	rs113572081	C	G	0.0028	4.00E-04	9.22E-13	0.1369	Yes		YES	No	YES	59
32	rs1137844	C	G	0.0021	3.00E-04	7.86E-12	0.6841	Yes		YES	No	YES	59
33	rs113956264	T	C	-0.0075	9.00E-04	1.91E-18	0.033	Yes		No	No	YES	83
34	rs114165349	C	G	-0.0064	9.00E-04	8.63E-13	0.0261	Yes		YES	No	YES	61
35	rs11557049	T	C	0.0044	6.00E-04	8.73E-14	0.0645	Yes		No	No	YES	64
36	rs11564722	T	C	-0.0041	3.00E-04	4.11E-35	0.2406	Yes		No	No	YES	224
37	rs11581292	T	C	0.0017	3.00E-04	6.67E-09	0.4765	Yes		No	No	YES	38
38	rs115926813	A	G	0.0055	7.00E-04	1.00E-14	0.0391	Yes		No	No	YES	74
39	rs11616030	A	C	0.004	5.00E-04	2.31E-16	0.9119	Yes		No	No	YES	77
40	rs11642550	A	G	-0.0018	3.00E-04	2.82E-09	0.303	Yes		No	No	YES	43
41	rs116476169	C	G	0.0056	0.001	2.20E-08	0.0219	Yes		YES	No	YES	38
42	rs1165227	T	C	-0.0023	4.00E-04	6.32E-10	0.1612	Yes		No	No	YES	40
43	rs11657044	T	C	0.0082	4.00E-04	6.70E-111	0.1682	Yes		No	No	YES	503
44	rs11670056	T	C	0.0034	5.00E-04	1.42E-10	0.0754	Yes		No	No	YES	55
45	rs11694902	A	G	-0.0041	4.00E-04	1.46E-25	0.1397	Yes		No	No	YES	126
46	rs11702255	A	G	0.0017	3.00E-04	9.66E-09	0.3692	Yes		No	No	YES	38
47	rs11706370	A	G	-0.0025	3.00E-04	4.47E-17	0.3128	Yes		No	No	YES	83
48	rs11747993	A	G	0.0021	3.00E-04	4.79E-10	0.2516	Yes		No	No	YES	59
49	rs11759908	T	C	0.0027	3.00E-04	2.57E-21	0.4519	Yes		No	No	YES	97
50	rs11786896	T	C	0.0059	7.00E-04	1.21E-19	0.0493	Yes		No	No	YES	85
51	rs11791149	T	C	-0.0023	4.00E-04	1.24E-10	0.8197	Yes		No	No	YES	40
52	rs12145677	A	G	0.0031	3.00E-04	1.34E-25	0.3037	Yes		No	No	YES	128
53	rs12149228	T	C	0.0029	4.00E-04	3.37E-15	0.1635	Yes		No	No	YES	63
54	rs12190287	C	G	-0.002	3.00E-04	1.44E-12	0.6231	Yes	Hypertension	YES	YES	No	53
55	rs12216582	C	G	0.0018	3.00E-04	1.06E-08	0.7081	Yes		YES	No	YES	43
56	rs12377027	A	G	0.002	4.00E-04	1.41E-08	0.817	Yes		No	No	YES	30
57	rs12432201	T	C	-0.0022	3.00E-04	1.98E-13	0.6926	Yes		No	No	YES	64
58	rs12439429	T	C	-0.0017	3.00E-04	1.63E-10	0.5423	Yes		No	No	YES	38
59	rs12449763	A	T	0.0022	3.00E-04	1.20E-10	0.7822	Yes		YES	No	YES	64
60	rs12520984	C	G	-0.0023	3.00E-04	6.48E-16	0.3214	Yes		YES	No	YES	70
61	rs12544197	A	G	0.0016	3.00E-04	7.67E-09	0.491	Yes		No	No	YES	34
62	rs1258179	A	G	0.0021	3.00E-04	5.05E-15	0.4901	Yes		No	No	YES	59
63	rs1260326	T	C	-0.0051	3.00E-04	1.84E-74	0.3929	Yes		No	No	YES	346
64	rs12713256	A	G	-0.0021	3.00E-04	3.47E-11	0.7564	Yes		No	No	YES	59
65	rs12736457	C	G	-0.0058	4.00E-04	1.74E-45	0.8706	Yes		YES	No	YES	252
66	rs12781024	A	T	-0.0017	3.00E-04	4.87E-10	0.5078	Yes		YES	YES	No	38
67	rs12916712	T	C	0.0019	3.00E-04	7.60E-10	0.7261	Yes		No	No	YES	48
68	rs12940987	A	G	0.0048	3.00E-04	2.77E-49	0.7764	Yes		No	No	YES	306
69	rs12942611	A	C	0.0017	3.00E-04	3.42E-09	0.3542	Yes		No	No	YES	38
70	rs12951993	A	G	0.0022	3.00E-04	4.03E-15	0.42	Yes		No	No	YES	64
71	rs13032786	C	G	-0.0032	3.00E-04	3.24E-27	0.6961	Yes		YES	No	YES	136
72	rs13047277	T	C	-0.0024	3.00E-04	7.42E-16	0.71	Yes		No	No	YES	77

73	rs13064938	T	C	-0.0032	3.00E-04	2.03E-30	0.3902	Yes		No	No	YES	136
74	rs13065446	T	C	0.0045	3.00E-04	7.43E-54	0.6728	Yes		No	No	YES	269
75	rs13099700	A	G	-0.0021	3.00E-04	4.97E-12	0.7216	Yes		No	No	YES	59
76	rs13157326	A	G	0.0024	3.00E-04	1.60E-16	0.4722	Yes		No	No	YES	77
77	rs13227214	C	G	0.0027	3.00E-04	1.71E-23	0.4561	Yes		YES	YES	No	97
78	rs13230509	C	G	0.0064	3.00E-04	1.03E-88	0.6906	Yes		YES	No	YES	545
79	rs13245051	A	G	0.0019	3.00E-04	2.80E-12	0.4457	Yes		No	No	YES	48
80	rs132641	A	G	0.0024	4.00E-04	2.24E-11	0.1658	Yes		No	No	YES	43
81	rs139323761	C	G	-0.0075	0.001	2.08E-14	0.0269	Yes		YES	No	YES	67
82	rs1453834	T	C	0.0021	3.00E-04	9.93E-14	0.4001	Yes		No	No	YES	59
83	rs1458038	T	C	-0.0031	3.00E-04	6.88E-26	0.2957	Yes		No	No	YES	128
84	rs148185902	A	G	0.0128	0.0013	4.92E-22	0.0135	Yes		No	No	YES	116
85	rs151245	T	G	0.002	3.00E-04	4.80E-13	0.6016	Yes		No	No	YES	53
86	rs1519102	C	G	-0.0018	3.00E-04	1.74E-09	0.6884	Yes		YES	No	YES	43
87	rs1541938	T	C	-0.0029	3.00E-04	1.25E-20	0.2637	Yes		No	No	YES	112
88	rs1545837	T	C	0.0021	3.00E-04	1.44E-13	0.6388	Yes		No	No	YES	59
89	rs1548945	T	C	-0.0038	3.00E-04	1.96E-41	0.4145	Yes		No	No	YES	192
90	rs1584028	T	C	-0.0017	3.00E-04	1.68E-10	0.5643	Yes		No	No	YES	38
91	rs1585499	T	C	0.0037	3.00E-04	5.66E-42	0.4569	Yes		No	No	YES	182
92	rs1617634	A	G	-0.0086	3.00E-04	1.00E-200	0.6334	Yes		No	No	YES	984
93	rs164747	T	G	-0.0031	3.00E-04	2.33E-30	0.5684	Yes		No	No	YES	128
94	rs16823029	A	C	0.0053	5.00E-04	3.35E-26	0.0814	Yes		No	No	YES	135
95	rs16874073	T	C	0.0042	6.00E-04	4.28E-11	0.9513	Yes		No	No	YES	59
96	rs17050272	A	G	0.0029	3.00E-04	2.01E-25	0.4193	Yes		No	No	YES	112
97	rs1719935	A	G	-0.0027	3.00E-04	6.86E-23	0.5317	Yes		No	No	YES	97
98	rs17256228	T	C	0.0056	4.00E-04	9.45E-39	0.1084	Yes		No	No	YES	235
99	rs17563	A	G	-0.0018	3.00E-04	5.61E-11	0.4292	Yes		No	No	YES	43
100	rs1757915	A	G	-0.0024	3.00E-04	7.84E-17	0.3532	Yes		No	No	YES	77
101	rs17602729	A	G	-0.0027	4.00E-04	1.70E-10	0.1288	Yes		No	No	YES	55
102	rs1762416	A	G	-0.0018	3.00E-04	1.93E-09	0.3447	Yes		No	No	YES	43
103	rs1772976	T	C	-0.0017	3.00E-04	1.14E-09	0.5183	Yes		No	No	YES	38
104	rs1800574	T	C	0.0063	8.00E-04	4.76E-15	0.03	Yes		No	No	YES	74
105	rs1801251	A	G	-0.0019	3.00E-04	7.64E-12	0.3571	Yes		No	No	YES	48
106	rs1806649	T	C	-0.0027	3.00E-04	1.17E-17	0.255	Yes		No	No	YES	97
107	rs187355703	C	G	-0.0117	9.00E-04	6.67E-40	0.9724	Yes		YES	No	YES	202
108	rs1883991	A	C	0.0028	3.00E-04	2.48E-22	0.6805	Yes		No	No	YES	104
109	rs1887251	T	C	-0.0029	3.00E-04	1.69E-25	0.3626	Yes		No	No	YES	112
110	rs1913641	T	G	0.0021	3.00E-04	2.83E-14	0.4798	Yes		No	No	YES	59
111	rs1994887	A	C	0.002	3.00E-04	6.77E-11	0.2741	Yes		No	No	YES	53
112	rs2053196	T	C	-0.0018	3.00E-04	3.63E-08	0.7876	Yes		No	No	YES	43
113	rs2068888	A	G	0.0031	3.00E-04	7.61E-30	0.4504	Yes		No	No	YES	128
114	rs2076668	A	G	0.0039	3.00E-04	6.91E-43	0.3847	Yes		No	No	YES	202
115	rs2127206	T	C	-0.0015	3.00E-04	4.73E-08	0.5672	Yes		No	No	YES	30
116	rs2145166	A	G	0.0035	4.00E-04	3.68E-17	0.1481	Yes		No	No	YES	92
117	rs2184896	A	C	-0.0019	3.00E-04	9.63E-13	0.4461	Yes		No	No	YES	48
118	rs219781	T	G	-0.0024	3.00E-04	3.28E-15	0.2567	Yes		No	No	YES	77
119	rs223308	A	G	0.003	3.00E-04	4.24E-28	0.5179	Yes		No	No	YES	120
120	rs2235826	A	T	0.0033	4.00E-04	2.05E-20	0.812	Yes		YES	No	YES	81
121	rs2239547	T	C	0.0025	3.00E-04	6.36E-16	0.7345	Yes		No	No	YES	83
122	rs2252281	T	C	-0.0042	3.00E-04	2.02E-50	0.6107	Yes		No	No	YES	235
123	rs2279463	A	G	-0.0082	4.00E-04	2.46E-94	0.8637	Yes		No	No	YES	503
124	rs2293093	C	G	-0.0027	4.00E-04	2.20E-10	0.8883	Yes		YES	No	YES	55
125	rs2302316	A	G	-0.0018	3.00E-04	3.30E-08	0.2353	Yes		No	No	YES	43
126	rs2306623	T	C	0.0021	3.00E-04	1.13E-12	0.3319	Yes		No	No	YES	59
127	rs236326	A	T	-0.0021	3.00E-04	5.90E-11	0.242	Yes		YES	No	YES	59
128	rs2411192	A	T	0.0021	3.00E-04	1.88E-14	0.5909	Yes		YES	No	YES	59
129	rs2412608	T	C	-0.0033	3.00E-04	8.42E-34	0.4941	Yes		No	No	YES	145
130	rs2452592	A	G	0.0016	3.00E-04	7.57E-09	0.3619	Yes		No	No	YES	34
131	rs2453594	T	C	0.0024	4.00E-04	4.41E-12	0.8134	Yes		No	No	YES	43
132	rs2544390	T	C	-0.0016	3.00E-04	1.08E-08	0.374	Yes		No	No	YES	34
133	rs2634675	A	G	-0.0024	3.00E-04	1.77E-17	0.4522	Yes		No	No	YES	77
134	rs2666831	A	T	-0.0015	3.00E-04	2.70E-08	0.3858	Yes		YES	YES	No	30
135	rs267738	T	G	0.0053	3.00E-04	2.38E-57	0.7849	Yes		No	No	YES	374
136	rs27028	A	G	0.0017	3.00E-04	7.97E-10	0.3657	Yes		No	No	YES	38
137	rs2783971	A	C	0.0027	3.00E-04	5.90E-24	0.4729	Yes		No	No	YES	97
138	rs278941	A	G	0.0019	3.00E-04	3.74E-10	0.7179	Yes		No	No	YES	48
139	rs2803959	T	C	-0.0017	3.00E-04	6.72E-10	0.4453	Yes		No	No	YES	38
140	rs2815367	A	G	0.0019	3.00E-04	5.21E-11	0.6502	Yes		No	No	YES	48
141	rs2823139	A	G	0.0032	3.00E-04	3.03E-29	0.3387	Yes		No	No	YES	136
142	rs2834317	A	G	0.0037	4.00E-04	2.80E-22	0.1521	Yes		No	No	YES	102
143	rs284316	T	C	0.0018	3.00E-04	2.22E-09	0.6619	Yes		No	No	YES	43
144	rs28493806	A	G	0.0015	3.00E-04	4.50E-08	0.6243	Yes		No	No	YES	30
145	rs28601761	C	G	-0.0031	3.00E-04	1.70E-28	0.5757	Yes	metabolic syndrome	YES	YES	No	128
146	rs2878889	A	G	0.0018	3.00E-04	3.65E-11	0.5522	Yes		No	No	YES	43
147	rs2899333	A	G	0.0019	3.00E-04	1.12E-10	0.281	Yes		No	No	YES	48
148	rs2900660	A	C	0.0017	3.00E-04	3.06E-10	0.5881	Yes		No	No	YES	38

149	rs293736	A	C	-0.0018	3.00E-04	1.78E-09	0.2741	Yes			No	No	YES	43
150	rs2960455	A	G	-0.0043	3.00E-04	2.05E-46	0.7148	Yes			No	No	YES	246
151	rs2976178	C	G	0.0028	3.00E-04	2.69E-18	0.756	Yes			YES	No	YES	104
152	rs2991341	T	C	0.002	3.00E-04	1.84E-12	0.4134	Yes			No	No	YES	53
153	rs303938	T	G	0.0027	3.00E-04	8.65E-22	0.5975	Yes			No	No	YES	97
154	rs3107155	T	C	0.0018	3.00E-04	3.65E-10	0.395	Yes			No	No	YES	43
155	rs315986	T	C	0.0072	4.00E-04	1.38E-59	0.8911	Yes			No	No	YES	388
156	rs327508	A	G	-0.0023	3.00E-04	4.86E-11	0.205	Yes			No	No	YES	70
157	rs34053392	A	G	-0.0015	3.00E-04	4.41E-08	0.4196	Yes			No	No	YES	30
158	rs34188292	C	G	0.0019	3.00E-04	9.37E-09	0.2651	Yes			YES	No	YES	48
159	rs34221697	A	G	0.0054	8.00E-04	1.13E-10	0.029	Yes			No	No	YES	55
160	rs34442537	C	G	-0.0021	3.00E-04	1.31E-12	0.6788	Yes			YES	No	YES	59
161	rs34642860	T	C	-0.0021	3.00E-04	1.44E-12	0.3054	Yes			No	No	YES	59
162	rs34707165	A	T	0.0019	3.00E-04	1.18E-11	0.6654	Yes			YES	No	YES	48
163	rs35072105	A	G	0.002	3.00E-04	7.74E-13	0.5391	Yes			No	No	YES	53
164	rs35320690	T	C	0.0026	3.00E-04	1.79E-17	0.7225	Yes			No	No	YES	90
165	rs354211	T	C	0.0025	3.00E-04	1.30E-18	0.35	Yes			No	No	YES	83
166	rs35629566	C	G	-0.0028	4.00E-04	5.40E-14	0.8244	Yes			YES	No	YES	59
167	rs357482	T	C	-0.0024	4.00E-04	3.79E-10	0.1425	Yes			No	No	YES	43
168	rs35917667	A	C	-0.0022	3.00E-04	8.98E-12	0.2395	Yes			No	No	YES	64
169	rs35969577	T	G	0.0061	3.00E-04	4.43E-105	0.4162	Yes			No	No	YES	495
170	rs3750082	A	T	-0.0022	3.00E-04	4.20E-14	0.341	Yes			YES	No	YES	64
171	rs3774292	A	T	-0.0029	3.00E-04	5.37E-23	0.6827	Yes			YES	No	YES	112
172	rs3775932	A	C	0.002	3.00E-04	7.00E-14	0.4965	Yes			No	No	YES	53
173	rs3791221	A	G	-0.0022	3.00E-04	1.39E-14	0.6508	Yes			No	No	YES	64
174	rs3793662	T	C	-0.0021	4.00E-04	1.19E-09	0.8075	Yes			No	No	YES	33
175	rs3795503	T	C	-0.0024	3.00E-04	1.57E-16	0.3218	Yes			No	No	YES	77
176	rs3797537	A	G	-0.0021	3.00E-04	1.88E-12	0.7134	Yes			No	No	YES	59
177	rs3812036	T	C	0.0071	3.00E-04	3.89E-109	0.252	Yes			No	No	YES	670
178	rs3814828	A	G	-0.0021	3.00E-04	4.69E-13	0.3841	Yes			No	No	YES	59
179	rs3824081	T	C	0.0015	3.00E-04	1.91E-08	0.4783	Yes			No	No	YES	30
180	rs3850625	A	G	-0.005	4.00E-04	1.52E-31	0.119	Yes			No	No	YES	187
181	rs3871466	T	C	0.0022	4.00E-04	4.12E-08	0.8652	Yes			No	No	YES	36
182	rs3904600	C	G	-0.003	3.00E-04	3.96E-26	0.3706	Yes			YES	YES	No	120
183	rs3925584	T	C	0.0053	3.00E-04	9.31E-86	0.5476	Yes			No	No	YES	374
184	rs41159	A	G	0.0022	3.00E-04	3.06E-15	0.5983	Yes			No	No	YES	64
185	rs41284816	T	G	0.0084	0.001	3.19E-17	0.0225	Yes			No	No	YES	84
186	rs41303061	A	T	0.003	5.00E-04	8.67E-09	0.9289	Yes			YES	No	YES	43
187	rs4233651	A	C	0.0019	3.00E-04	9.76E-12	0.341	Yes			No	No	YES	48
188	rs4290474	C	G	-0.0032	4.00E-04	6.80E-13	0.1116	Yes			YES	No	YES	77
189	rs429358	T	C	0.0031	4.00E-04	5.13E-16	0.8429	Yes			No	No	YES	72
190	rs4434960	A	T	-0.0022	3.00E-04	2.46E-15	0.6153	Yes			YES	No	YES	64
191	rs4442348	A	G	-0.0018	3.00E-04	3.14E-11	0.5065	Yes			No	No	YES	43
192	rs4489970	A	G	-0.0028	4.00E-04	6.38E-11	0.108	Yes			No	No	YES	59
193	rs4567937	A	G	0.0034	3.00E-04	8.91E-31	0.3182	Yes			No	No	YES	154
194	rs4617830	A	C	-0.0024	3.00E-04	2.58E-13	0.7816	Yes			No	No	YES	77
195	rs4656220	T	C	-0.0019	3.00E-04	4.40E-12	0.3708	Yes			No	No	YES	48
196	rs4705067	C	G	0.0019	3.00E-04	1.09E-08	0.2087	Yes			YES	No	YES	48
197	rs4735334	A	G	0.0017	3.00E-04	6.28E-09	0.6982	Yes			No	No	YES	38
198	rs4744712	A	C	0.0049	3.00E-04	1.26E-67	0.399	Yes			No	No	YES	319
199	rs4786429	T	C	0.0022	3.00E-04	2.09E-13	0.7059	Yes			No	No	YES	64
200	rs4820324	C	G	0.0023	3.00E-04	3.82E-17	0.5803	Yes			YES	No	YES	70
201	rs4836732	T	C	-0.0024	3.00E-04	2.33E-18	0.5286	Yes			No	No	YES	77
202	rs4859682	A	C	0.0079	3.00E-04	4.10E-187	0.4477	Yes			No	No	YES	830
203	rs4869831	C	G	0.0021	3.00E-04	4.66E-10	0.2091	Yes			YES	No	YES	59
204	rs4871905	C	G	0.0049	3.00E-04	7.41E-72	0.4165	Yes	serum creatinine		YES	YES	No	319
205	rs4925095	A	G	0.0019	3.00E-04	2.38E-12	0.494	Yes			No	No	YES	48
206	rs4930319	C	G	0.0034	3.00E-04	5.04E-33	0.3516	Yes	Hypertension		YES	YES	No	154
207	rs4945268	T	C	0.0024	4.00E-04	4.21E-11	0.84	Yes			No	No	YES	43
208	rs4946932	A	C	-0.0028	3.00E-04	4.22E-21	0.3022	Yes			No	No	YES	104
209	rs4952981	T	C	0.0027	3.00E-04	9.05E-23	0.5041	Yes			No	No	YES	97
210	rs505966	A	G	-0.0019	3.00E-04	1.20E-09	0.7302	Yes			No	No	YES	48
211	rs514595	T	C	0.0035	4.00E-04	3.09E-21	0.1546	Yes			No	No	YES	92
212	rs55722796	T	C	0.0057	3.00E-04	9.47E-74	0.7487	Yes			No	No	YES	432
213	rs55842281	A	G	0.0023	3.00E-04	6.85E-16	0.3576	Yes			No	No	YES	70
214	rs55879803	T	G	0.0016	3.00E-04	2.86E-08	0.6803	Yes			No	No	YES	34
215	rs55924910	C	G	-0.0026	4.00E-04	2.92E-12	0.8452	Yes			YES	No	YES	51
216	rs55957832	C	G	-0.0035	6.00E-04	3.25E-08	0.9488	Yes			YES	No	YES	41
217	rs56043887	T	C	0.0021	3.00E-04	6.92E-15	0.5111	Yes			No	No	YES	59
218	rs56065557	C	G	0.0032	3.00E-04	2.92E-27	0.3109	Yes			YES	No	YES	136
219	rs56252444	T	G	0.0031	3.00E-04	9.08E-29	0.6208	Yes			No	No	YES	128
220	rs56255430	A	C	-0.0036	5.00E-04	6.93E-13	0.9181	Yes			No	No	YES	62
221	rs57445665	A	G	-0.0021	3.00E-04	3.35E-10	0.2055	Yes			No	No	YES	59
222	rs58650092	A	C	-0.0018	3.00E-04	9.96E-11	0.3923	Yes			No	No	YES	43
223	rs59646751	T	G	0.0023	3.00E-04	1.02E-14	0.3102	Yes			No	No	YES	70
224	rs59860440	T	C	-0.0022	3.00E-04	1.66E-13	0.33	Yes			No	No	YES	64

225	rs60068692	A	G	-0.0044	7.00E-04	2.21E-10	0.0492	Yes		No	No	YES	47
226	rs6011067	C	G	-0.0036	5.00E-04	7.76E-13	0.9193	Yes		YES	No	YES	62
227	rs60503594	T	C	0.0022	3.00E-04	6.21E-15	0.6616	Yes		No	No	YES	64
228	rs6055748	A	G	0.0018	3.00E-04	6.31E-10	0.6914	Yes		No	No	YES	43
229	rs60580012	T	C	0.0019	3.00E-04	4.43E-11	0.334	Yes	High grade serous ovarian cancer	No	No	YES	48
230	rs6072329	A	G	-0.0018	3.00E-04	8.72E-11	0.3959	Yes		No	No	YES	43
231	rs6127099	A	T	0.0048	3.00E-04	3.83E-52	0.7204	Yes		YES	No	YES	306
232	rs61830291	A	C	0.004	5.00E-04	1.40E-17	0.9021	Yes		No	No	YES	77
233	rs61927768	A	G	0.0019	3.00E-04	1.08E-10	0.3004	Yes		No	No	YES	48
234	rs62120440	A	G	0.0017	3.00E-04	1.97E-10	0.5219	Yes		No	No	YES	38
235	rs62187541	A	G	0.0037	5.00E-04	1.23E-11	0.9318	Yes		No	No	YES	66
236	rs62191888	T	G	-0.0033	3.00E-04	1.51E-30	0.3266	Yes		No	No	YES	145
237	rs62394289	A	G	-0.0042	4.00E-04	1.06E-23	0.1184	Yes		No	No	YES	132
238	rs62618693	T	C	-0.0038	7.00E-04	1.40E-08	0.0441	Yes		No	No	YES	35
239	rs6458868	T	C	0.002	3.00E-04	5.18E-13	0.6471	Yes		No	No	YES	53
240	rs6467958	T	C	-0.0024	3.00E-04	2.19E-15	0.273	Yes		No	No	YES	77
241	rs6481598	C	G	-0.0021	3.00E-04	1.87E-10	0.7847	Yes		YES	No	YES	59
242	rs6546861	T	C	-0.0063	3.00E-04	3.74E-85	0.229	Yes		No	No	YES	528
243	rs665731	T	C	0.0022	4.00E-04	6.20E-10	0.1851	Yes		No	No	YES	36
244	rs66827546	A	G	0.0025	3.00E-04	2.60E-15	0.2626	Yes		No	No	YES	83
245	rs6708702	A	G	0.0019	3.00E-04	4.61E-10	0.3019	Yes		No	No	YES	48
246	rs6716446	A	G	-0.0018	3.00E-04	1.58E-08	0.7546	Yes		No	No	YES	43
247	rs693906	C	G	0.004	4.00E-04	2.02E-25	0.1491	Yes	diabetes	YES	No	YES	120
248	rs6968865	A	T	0.0026	3.00E-04	2.87E-20	0.3711	Yes		YES	No	YES	90
249	rs700753	C	G	-0.0034	3.00E-04	2.30E-32	0.3435	Yes		YES	No	YES	154
250	rs7012814	A	G	-0.0029	3.00E-04	2.65E-26	0.4722	Yes		No	No	YES	112
251	rs7019647	A	G	-0.0021	3.00E-04	1.85E-12	0.7347	Yes		No	No	YES	59
252	rs7036795	T	C	0.0022	3.00E-04	2.22E-10	0.8008	Yes		No	No	YES	64
253	rs7084764	A	G	-0.0028	3.00E-04	2.79E-24	0.4975	Yes		No	No	YES	104
254	rs7096715	T	C	0.0019	3.00E-04	8.99E-12	0.4217	Yes		No	No	YES	48
255	rs7117020	T	G	0.0019	3.00E-04	4.10E-12	0.5545	Yes		No	No	YES	48
256	rs71606723	A	T	-0.0024	3.00E-04	6.57E-14	0.7697	Yes		YES	No	YES	77
257	rs7210770	A	G	0.0017	3.00E-04	2.96E-09	0.5949	Yes		No	No	YES	38
258	rs7218708	A	G	0.0016	3.00E-04	6.50E-09	0.4843	Yes		No	No	YES	34
259	rs7247977	T	C	0.0049	3.00E-04	2.40E-71	0.6056	Yes		No	No	YES	319
260	rs72683923	T	C	0.0074	0.001	2.73E-13	0.9801	Yes	Hypertension	No	No	YES	66
261	rs72706148	T	C	0.0069	0.0012	2.03E-09	0.0182	Yes		No	No	YES	40
262	rs72757811	T	C	0.0016	3.00E-04	2.17E-08	0.645	Yes		No	No	YES	34
263	rs72801873	A	G	-0.0065	8.00E-04	1.17E-16	0.9688	Yes		No	No	YES	79
264	rs728538	T	G	-0.0023	4.00E-04	1.10E-10	0.8259	Yes		No	No	YES	40
265	rs7286581	A	T	-0.0022	4.00E-04	6.35E-09	0.2004	Yes		YES	No	YES	36
266	rs72868882	T	G	0.0034	6.00E-04	2.27E-09	0.0653	Yes		No	No	YES	38
267	rs72898623	A	G	0.0031	4.00E-04	5.31E-13	0.1117	Yes		No	No	YES	72
268	rs72912510	A	G	0.0026	3.00E-04	1.16E-13	0.204	Yes		No	No	YES	90
269	rs73116888	T	C	0.004	5.00E-04	1.02E-17	0.0995	Yes		No	No	YES	77
270	rs73119035	A	G	-0.0034	4.00E-04	4.04E-17	0.8668	Yes		No	No	YES	86
271	rs73119306	A	G	0.0031	3.00E-04	7.04E-23	0.7547	Yes		No	No	YES	128
272	rs7314664	T	C	0.0022	4.00E-04	4.21E-08	0.8685	Yes		No	No	YES	36
273	rs73245338	T	G	-0.0034	6.00E-04	1.07E-09	0.0645	Yes		No	No	YES	38
274	rs7326821	A	G	-0.0023	4.00E-04	2.12E-10	0.8264	Yes		No	No	YES	40
275	rs736820	A	G	0.0018	3.00E-04	1.03E-10	0.3742	Yes		No	No	YES	43
276	rs74424138	A	C	0.0026	4.00E-04	1.50E-09	0.1239	Yes		No	No	YES	51
277	rs7492724	A	G	-0.002	3.00E-04	7.29E-12	0.7082	Yes		No	No	YES	53
278	rs750714	A	G	0.0019	3.00E-04	6.76E-12	0.4238	Yes		No	No	YES	48
279	rs75094798	A	T	-0.004	5.00E-04	7.21E-16	0.0935	Yes		YES	No	YES	77
280	rs7516435	A	G	-0.0031	3.00E-04	5.06E-26	0.6884	Yes		No	No	YES	128
281	rs7536433	T	C	-0.0025	3.00E-04	1.88E-13	0.2111	Yes		No	No	YES	83
282	rs754469	A	G	0.0024	3.00E-04	2.25E-17	0.5205	Yes		No	No	YES	77
283	rs75501914	A	G	-0.0033	6.00E-04	1.12E-08	0.0656	Yes		No	No	YES	36
284	rs7565830	A	G	0.0018	3.00E-04	2.81E-09	0.7246	Yes		No	No	YES	43
285	rs7591218	A	G	-0.0018	3.00E-04	1.54E-09	0.3042	Yes		No	No	YES	43
286	rs76004499	C	G	0.0067	9.00E-04	3.72E-13	0.9736	Yes		YES	No	YES	66
287	rs760418	C	G	0.002	3.00E-04	7.95E-14	0.5249	Yes		YES	YES	No	53
288	rs76273615	A	G	-0.003	4.00E-04	1.81E-13	0.8691	Yes		No	No	YES	67
289	rs76299412	A	G	-0.0022	4.00E-04	1.25E-08	0.1511	Yes		No	No	YES	36
290	rs7667050	T	C	-0.0019	3.00E-04	4.09E-12	0.4692	Yes		No	No	YES	48
291	rs7727632	T	C	0.0025	4.00E-04	3.21E-08	0.1044	Yes		No	No	YES	47
292	rs7740107	A	T	-0.0029	3.00E-04	7.19E-22	0.738	Yes		YES	No	YES	112
293	rs7744658	A	G	0.0024	4.00E-04	2.68E-09	0.8687	Yes		No	No	YES	43
294	rs77770952	C	G	0.0046	7.00E-04	2.44E-10	0.0378	Yes		YES	No	YES	52
295	rs77924615	A	G	-0.0106	3.00E-04	2.15E-200	0.1984	Yes	Hypertension	No	No	YES	1494
296	rs78054198	T	G	-0.0022	4.00E-04	4.82E-08	0.1399	Yes		No	No	YES	36
297	rs78099806	C	G	0.0042	7.00E-04	3.92E-09	0.961	Yes		YES	No	YES	43
298	rs78444298	A	G	0.012	0.001	4.44E-31	0.0193	Yes		No	No	YES	172
299	rs784504	C	G	-0.0022	4.00E-04	1.71E-09	0.807	Yes		YES	No	YES	36
300	rs78660602	A	G	0.0055	5.00E-04	2.57E-31	0.9066	Yes		No	No	YES	145

301	rs79270185	T	C	-0.0058	9.00E-04	1.49E-11	0.0261	Yes	No	No	YES	50
302	rs79346194	A	G	0.0021	3.00E-04	7.07E-13	0.6921	Yes	No	No	YES	59
303	rs7953798	T	G	0.0045	5.00E-04	6.43E-21	0.09	Yes	No	No	YES	97
304	rs79760705	T	G	-0.0062	4.00E-04	1.08E-46	0.1115	Yes	No	No	YES	288
305	rs7983636	A	G	-0.0032	5.00E-04	6.55E-10	0.0758	Yes	No	No	YES	49
306	rs79926430	T	C	-0.0029	5.00E-04	2.91E-08	0.074	Yes	No	No	YES	40
307	rs8001243	A	G	-0.0023	3.00E-04	7.59E-14	0.7108	Yes	No	No	YES	70
308	rs8008354	T	C	0.0018	3.00E-04	1.96E-08	0.2577	Yes	No	No	YES	43
309	rs80282103	A	T	-0.0083	5.00E-04	2.61E-62	0.9181	Yes	YES	No	YES	330
310	rs80301631	C	G	0.0048	8.00E-04	1.76E-08	0.03	Yes	YES	No	YES	43
311	rs8046545	A	G	0.0017	3.00E-04	2.43E-09	0.6435	Yes	No	No	YES	38
312	rs8062982	C	G	0.0022	3.00E-04	6.06E-15	0.424	Yes	YES	YES	No	64
313	rs807624	T	G	-0.0036	3.00E-04	3.09E-37	0.3489	Yes	No	No	YES	172
314	rs8096658	C	G	-0.0052	3.00E-04	6.40E-71	0.5114	Yes	YES	YES	No	360
315	rs81205	A	C	-0.003	3.00E-04	3.32E-26	0.5375	Yes	No	No	YES	120
316	rs833806	T	G	-0.0028	5.00E-04	3.75E-09	0.1143	Yes	No	No	YES	38
317	rs849086	A	G	-0.0019	3.00E-04	2.04E-10	0.2802	Yes	No	No	YES	48
318	rs881858	A	G	0.0055	3.00E-04	4.04E-77	0.6967	Yes	No	No	YES	402
319	rs9307594	A	G	-0.0018	3.00E-04	1.74E-11	0.528	Yes	No	No	YES	43
320	rs9333592	T	C	-0.0053	5.00E-04	9.51E-22	0.0779	Yes	No	No	YES	135
321	rs9373056	T	C	-0.0029	3.00E-04	2.10E-23	0.32	Yes	No	No	YES	112
322	rs9419939	A	G	-0.0029	4.00E-04	2.77E-16	0.188	Yes	No	No	YES	63
323	rs9465741	A	C	-0.0023	3.00E-04	1.92E-16	0.5438	Yes	No	No	YES	70
324	rs952151	A	G	0.0023	3.00E-04	3.86E-13	0.2341	Yes	No	No	YES	70
325	rs9521720	C	G	0.0021	3.00E-04	1.17E-13	0.4005	Yes	YES	No	YES	59
326	rs9543135	A	G	-0.0022	4.00E-04	1.74E-09	0.8314	Yes	No	No	YES	36
327	rs9652384	A	G	-0.0016	3.00E-04	2.48E-09	0.4236	Yes	No	No	YES	34
328	rs9784041	T	C	-0.0022	4.00E-04	8.13E-09	0.1604	Yes	No	No	YES	36
329	rs9823161	A	G	-0.0025	3.00E-04	4.35E-15	0.6871	Yes	No	No	YES	83
330	rs9868185	A	G	-0.0029	3.00E-04	3.86E-26	0.5316	Yes	No	No	YES	112
331	rs9894634	T	C	0.0019	3.00E-04	2.84E-12	0.6003	Yes	No	No	YES	48
332	rs9925773	A	G	0.0028	3.00E-04	1.04E-18	0.2721	Yes	No	No	YES	104
333	rs9932625	A	G	0.0033	3.00E-04	4.66E-25	0.2295	Yes	No	No	YES	145
334	rs9934475	A	G	-0.0018	3.00E-04	5.41E-11	0.4155	Yes	No	No	YES	43
335	rs9960465	T	C	-0.0035	3.00E-04	2.36E-26	0.2085	Yes	No	No	YES	163

Supplementary Table 3: Instrumental variables for eGFR and their filtering process in Mendelian Randomization.

	summary statistics in exposure GWAS							filtering process of IVs .					
No	SNP	effect allele	other allele	beta	se	P-value	effect allele frequency	Step 1: LD-independent SNPs were discarded	Step 2: confounders associated SNPs were discarded	Step 3: The SNPs that are palindromic were removed		incorporated in the MR analysis	F-statistics
								LD-independent SNPs were discarded	associated confounders	palindromic	ambiguous		
1	rs10015716	G	A	0.0015	3.00E-04	7.01E-09	0.3578	Yes		No	No	Yes	25
2	rs10035662	C	A	0.0015	3.00E-04	3.05E-09	0.3196	Yes		No	No	Yes	25
3	rs10040082	C	T	0.0018	3.00E-04	8.87E-12	0.6104	Yes		No	No	Yes	36
4	rs1004441	G	A	0.0018	3.00E-04	3.07E-11	0.2509	Yes		No	No	Yes	36
5	rs10111039	G	A	0.0015	3.00E-04	1.33E-08	0.4263	Yes		No	No	Yes	25
6	rs10142359	G	A	0.0021	3.00E-04	1.85E-16	0.5083	Yes		No	No	Yes	49
7	rs10151563	A	G	0.0018	3.00E-04	1.09E-12	0.6208	Yes		No	No	Yes	36
8	rs10182296	G	A	0.002	3.00E-04	9.22E-15	0.3599	Yes		No	No	Yes	44
9	rs10206899	T	C	0.0063	3.00E-04	3.32E-84	0.7745	Yes		No	No	Yes	441
10	rs10224210	C	T	0.0078	3.00E-04	1.57E-139	0.2773	Yes	Hypertension	No	No	No	676
11	rs10241879	T	A	0.0017	3.00E-04	2.61E-11	0.3829	Yes		Yes	No	Yes	32
12	rs10283362	C	T	0.0021	3.00E-04	4.94E-10	0.8416	Yes		No	No	Yes	49
13	rs1041606	T	C	0.0018	3.00E-04	8.70E-09	0.2407	Yes		No	No	Yes	36
14	rs10419627	A	G	0.0017	3.00E-04	3.20E-11	0.6049	Yes	Diabetes	No	No	No	32
15	rs1042752	G	A	0.0018	3.00E-04	4.49E-12	0.4399	Yes		No	No	Yes	36
16	rs10439970	G	T	0.003	3.00E-04	2.42E-29	0.3178	Yes		No	No	Yes	100
17	rs10445262	A	G	0.0015	3.00E-04	1.89E-08	0.6975	Yes		No	No	Yes	25
18	rs10447437	A	G	0.0015	3.00E-04	1.68E-09	0.5325	Yes	Hypertension	No	No	No	25
19	rs1047891	A	C	0.007	3.00E-04	4.91E-116	0.3044	Yes	Hypertension	No	No	No	544
20	rs1050816	C	T	0.0031	3.00E-04	7.74E-32	0.6703	Yes		No	No	Yes	107
21	rs10746942	G	A	0.0047	3.00E-04	1.64E-72	0.3679	Yes		No	No	Yes	245
22	rs1075472	G	A	0.0027	3.00E-04	6.63E-16	0.1847	Yes		No	No	Yes	81
23	rs10769264	T	C	0.0023	3.00E-04	1.05E-19	0.3726	Yes	Hypertension	No	No	No	59
24	rs10790454	C	A	0.0021	3.00E-04	5.00E-15	0.2608	Yes		No	No	Yes	49
25	rs10797427	C	T	0.0017	3.00E-04	2.57E-11	0.3956	Yes		No	No	Yes	32
26	rs10821905	G	A	0.0043	3.00E-04	3.85E-37	0.8201	Yes		No	No	Yes	205
27	rs10821944	G	T	0.002	3.00E-04	1.95E-13	0.2882	Yes		No	No	Yes	44
28	rs10824855	G	A	0.0018	3.00E-04	1.76E-09	0.5525	Yes		No	No	Yes	36
29	rs1082710	T	G	0.0016	3.00E-04	2.21E-09	0.3931	Yes		No	No	Yes	28
30	rs10827421	T	C	0.0018	3.00E-04	6.16E-12	0.4439	Yes		No	No	Yes	36
31	rs10850001	A	T	0.0017	3.00E-04	1.11E-10	0.4535	Yes	Hypertension	Yes	Yes	No	32
32	rs10851885	G	A	0.0056	3.00E-04	4.00E-69	0.2485	Yes		No	No	Yes	348
33	rs10857147	A	T	0.0033	3.00E-04	3.64E-36	0.7039	Yes	Hypertension	Yes	No	No	121
34	rs10866705	C	A	0.0063	3.00E-04	2.24E-120	0.2606	Yes		No	No	Yes	441
35	rs1087289	G	T	0.0018	3.00E-04	2.90E-12	0.4121	Yes		No	No	Yes	36
36	rs10878301	A	T	0.0016	3.00E-04	4.59E-09	0.6879	Yes		Yes	No	Yes	28
37	rs10892358	G	A	0.0016	3.00E-04	2.13E-10	0.426	Yes		No	No	Yes	28
38	rs10934753	A	G	0.002	3.00E-04	4.92E-15	0.4081	Yes		No	No	Yes	44
39	rs11057413	A	G	0.0018	3.00E-04	1.93E-09	0.6759	Yes		No	No	No	36
40	rs11062102	C	T	0.004	3.00E-04	9.39E-53	0.6202	Yes		No	No	Yes	178
41	rs11063202	G	A	0.0026	4.00E-04	3.19E-10	0.1214	Yes		No	No	Yes	42
42	rs11071738	T	C	0.0025	3.00E-04	1.59E-23	0.5497	Yes		No	No	Yes	69
43	rs11080660	A	G	0.0014	3.00E-04	3.63E-08	0.553	Yes		No	No	Yes	22
44	rs11109717	T	C	0.0017	3.00E-04	2.71E-08	0.706	Yes		No	No	Yes	32
45	rs1111571	G	A	0.0026	3.00E-04	6.71E-22	0.2762	Yes		No	No	Yes	75
46	rs11123169	C	T	0.0025	3.00E-04	2.73E-21	0.3253	Yes		No	No	Yes	69
47	rs11160318	A	G	0.0017	3.00E-04	2.39E-10	0.3649	Yes		No	No	Yes	32
48	rs11170624	G	T	0.0024	3.00E-04	2.32E-12	0.8149	Yes		No	No	Yes	64
49	rs111760718	A	G	0.0023	4.00E-04	5.35E-09	0.1322	Yes		No	No	Yes	33
50	rs11202328	C	T	0.0022	4.00E-04	5.89E-10	0.786	Yes		No	No	Yes	30
51	rs112175548	T	C	0.0019	3.00E-04	7.32E-14	0.6386	Yes		No	No	Yes	40
52	rs11237450	C	A	0.0026	3.00E-04	1.18E-14	0.789	Yes		No	No	Yes	75
53	rs11243145	A	G	0.003	3.00E-04	1.28E-23	0.6261	Yes		No	No	Yes	100
54	rs112905092	T	C	0.0087	0.0012	2.85E-13	0.0168	Yes		No	No	Yes	53
55	rs11441031	T	C	0.0031	3.00E-04	9.73E-20	0.1644	Yes		No	No	Yes	107
56	rs11557049	T	C	0.0044	6.00E-04	8.97E-14	0.0645	Yes		No	No	Yes	54
57	rs115814778	A	G	0.0083	0.0013	4.22E-11	0.0131	Yes		No	No	Yes	41
58	rs11613538	T	G	0.0019	3.00E-04	2.96E-09	0.7679	Yes		No	No	Yes	40
59	rs11616030	A	C	0.0039	5.00E-04	2.90E-16	0.9119	Yes		No	No	Yes	61
60	rs11646443	G	A	0.0017	3.00E-04	1.68E-08	0.6653	Yes		No	No	Yes	32
61	rs11673381	G	A	0.0014	3.00E-04	4.97E-08	0.5081	Yes		No	No	Yes	22
62	rs11676298	C	G	0.0023	3.00E-04	3.53E-12	0.8144	Yes		Yes	No	Yes	59
63	rs11725397	C	G	0.0016	3.00E-04	1.28E-09	0.3385	Yes		Yes	No	Yes	28
64	rs11743174	C	T	0.0018	3.00E-04	7.45E-11	0.3046	Yes		No	No	Yes	36
65	rs11745891	C	T	0.0056	4.00E-04	8.63E-41	0.1085	Yes		No	No	Yes	196
66	rs11768336	T	C	0.0022	3.00E-04	1.13E-16	0.3245	Yes		No	No	Yes	54
67	rs117739035	T	G	0.0053	8.00E-04	2.77E-11	0.0375	Yes		No	No	Yes	44
68	rs11786896	T	C	0.006	7.00E-04	2.88E-19	0.0494	Yes		No	No	Yes	73
69	rs11791149	C	T	0.002	3.00E-04	1.96E-09	0.207	Yes		No	No	Yes	44
70	rs1183394	G	A	0.0024	4.00E-04	4.14E-09	0.8715	Yes		No	No	Yes	36
71	rs11856921	C	A	0.0027	3.00E-04	3.19E-25	0.5867	Yes		No	No	Yes	81
72	rs12024377	G	A	0.0017	3.00E-04	1.85E-11	0.5964	Yes		No	No	Yes	32
73	rs12037201	T	G	0.0024	3.00E-04	4.49E-19	0.2548	Yes		No	No	Yes	64
74	rs12061708	A	G	0.0022	3.00E-04	2.74E-16	0.2999	Yes		No	No	Yes	54
75	rs12148121	C	T	0.0018	3.00E-04	2.60E-11	0.2748	Yes		No	No	Yes	36
76	rs12148280	G	A	0.0028	4.00E-04	1.13E-10	0.8947	Yes		No	No	Yes	49
77	rs12152266	T	C	0.0019	3.00E-04	3.96E-12	0.308	Yes		No	No	Yes	40
78	rs12212034	T	C	0.0022	3.00E-04	4.08E-17	0.3606	Yes		No	No	Yes	54
79	rs12432201	C	T	0.002	3.00E-04	9.74E-15	0.3374	Yes		No	No	Yes	44
80	rs12436956	T	G	0.0015	3.00E-04	1.53E-08	0.323	Yes		No	No	Yes	25
81	rs12439429	C	T	0.0015	3.00E-04	2.59E-09	0.4513	Yes		No	No	Yes	25
82	rs12449763	A	T	0.0022	3.00E-04	2.92E-11	0.7876	Yes		Yes	No	Yes	54
83	rs12450700	T	G	0.0017	3.00E-04	2.83E-11	0.6105	Yes		No	No	Yes	32
84	rs12458009	T	G	0.0029	3.00E-04	1.51E-25	0.7533	Yes		No	No	Yes	93
85	rs12483377	A	G	0.0028	5.00E-04	4.57E-09	0.0852	Yes		No	No	Yes	31
86	rs12544197	A	G	0.0016	3.00E-04	3.69E-10	0.4909	Yes		No	No	Yes	28
87	rs12575164	T	C	0.0021	3.00E-04	1.91E-10	0.7849	Yes		No	No	Yes	49
88	rs1258179	A	G	0.002	3.00E-04	9.76E-16	0.5065	Yes		No	No	Yes	44

89	rs1260326	C	T	0.005	3.00E-04	3.12E-84	0.5909	Yes		No	No	Yes	278
90	rs12614953	T	C	0.0026	3.00E-04	4.79E-24	0.4957	Yes		No	No	Yes	75
91	rs12713261	C	T	0.0024	3.00E-04	8.03E-20	0.3402	Yes		No	No	Yes	64
92	rs12727107	G	A	0.0014	3.00E-04	2.07E-08	0.4717	Yes		No	No	Yes	22
93	rs12736457	G	C	0.0057	4.00E-04	4.86E-45	0.1295	Yes		Yes	No	Yes	203
94	rs1275609	G	A	0.002	3.00E-04	1.18E-14	0.6385	Yes		No	No	Yes	44
95	rs12826808	A	T	0.0038	3.00E-04	4.54E-31	0.7781	Yes		Yes	No	Yes	160
96	rs12894354	T	C	0.0017	3.00E-04	2.98E-11	0.3468	Yes		No	No	Yes	32
97	rs12907511	G	C	0.0018	3.00E-04	1.35E-10	0.7128	Yes		Yes	No	Yes	36
98	rs1294861	G	T	0.0018	3.00E-04	4.14E-08	0.2549	Yes		No	No	Yes	36
99	rs12950549	G	A	0.0016	3.00E-04	1.39E-09	0.3664	Yes		No	No	Yes	28
100	rs13032786	G	C	0.003	3.00E-04	1.37E-29	0.3229	Yes		Yes	No	Yes	100
101	rs13059257	T	C	0.0053	8.00E-04	1.66E-10	0.0294	Yes		No	No	Yes	44
102	rs13064938	C	T	0.0031	3.00E-04	1.22E-32	0.5875	Yes		No	No	Yes	107
103	rs13108218	G	A	0.0018	3.00E-04	5.08E-12	0.5955	Yes		No	No	Yes	36
104	rs13140982	G	A	0.0016	3.00E-04	4.04E-09	0.6607	Yes		No	No	Yes	28
105	rs13157326	A	G	0.0024	3.00E-04	1.55E-21	0.4573	Yes		No	No	Yes	64
106	rs13159523	A	G	0.0025	3.00E-04	1.11E-22	0.5028	Yes		No	No	Yes	69
107	rs1316739	A	G	0.0016	3.00E-04	4.01E-09	0.2738	Yes		No	No	Yes	28
108	rs1321917	C	G	0.0023	3.00E-04	4.95E-19	0.4259	Yes		Yes	Yes	No	59
109	rs13245051	A	G	0.0019	3.00E-04	2.27E-13	0.4518	Yes		No	No	Yes	40
110	rs132639	A	T	0.0025	3.00E-04	8.83E-14	0.18	Yes		Yes	No	Yes	69
111	rs1407040	C	T	0.002	3.00E-04	1.93E-14	0.3312	Yes		No	No	Yes	44
112	rs148635648	G	A	0.0038	4.00E-04	1.14E-18	0.1008	Yes		No	No	Yes	90
113	rs151245	T	G	0.0022	3.00E-04	9.61E-18	0.6069	Yes		No	No	Yes	54
114	rs1519845	G	A	0.0017	3.00E-04	1.64E-11	0.3755	Yes		No	No	Yes	32
115	rs1541939	T	G	0.0029	3.00E-04	3.25E-20	0.6803	Yes		No	No	Yes	93
116	rs154656	A	T	0.0031	3.00E-04	1.73E-33	0.4273	Yes	Hypertension	Yes	Yes	No	107
117	rs1548945	C	T	0.0037	3.00E-04	3.26E-47	0.5696	Yes		No	No	Yes	152
118	rs166775	T	C	0.0017	3.00E-04	1.65E-10	0.6687	Yes		No	No	Yes	32
119	rs16823029	A	C	0.0053	5.00E-04	1.08E-27	0.0824	Yes		No	No	Yes	112
120	rs16827879	T	C	0.0018	3.00E-04	3.72E-08	0.2387	Yes		No	No	Yes	36
121	rs16874052	A	G	0.0044	6.00E-04	1.34E-13	0.9512	Yes		No	No	Yes	54
122	rs16930370	C	T	0.0042	3.00E-04	1.36E-34	0.1713	Yes		No	No	Yes	196
123	rs17050272	A	G	0.0028	3.00E-04	7.08E-28	0.4264	Yes	Diabetes	No	No	No	87
124	rs1711667	T	G	0.0017	3.00E-04	8.55E-11	0.5974	Yes		No	No	Yes	32
125	rs1713842	T	A	0.0024	3.00E-04	1.68E-11	0.8579	Yes		Yes	No	Yes	64
126	rs1719935	G	A	0.0026	3.00E-04	4.08E-24	0.451	Yes		No	No	Yes	75
127	rs17216707	T	C	0.0048	3.00E-04	6.88E-46	0.81	Yes		No	No	Yes	256
128	rs1741177	A	G	0.0016	3.00E-04	8.82E-10	0.7031	Yes		No	No	Yes	28
129	rs17413465	C	A	0.0025	3.00E-04	1.15E-13	0.8155	Yes		No	No	Yes	69
130	rs17420882	G	T	0.0024	3.00E-04	5.06E-20	0.2855	Yes		No	No	Yes	64
131	rs17563	G	A	0.0017	3.00E-04	4.29E-11	0.5378	Yes		No	No	Yes	32
132	rs1757915	G	A	0.0023	3.00E-04	1.66E-19	0.6587	Yes	Hypertension	No	No	No	59
133	rs17602729	G	A	0.0028	4.00E-04	2.34E-10	0.8712	Yes		No	No	Yes	49
134	rs17638807	C	T	0.0016	3.00E-04	6.49E-10	0.5238	Yes		No	No	Yes	28
135	rs17713396	T	C	0.0022	3.00E-04	1.61E-17	0.338	Yes		No	No	Yes	54
136	rs1772976	C	T	0.0016	3.00E-04	1.42E-10	0.5087	Yes		No	No	Yes	28
137	rs17730281	G	A	0.0043	3.00E-04	2.44E-54	0.747	Yes		No	No	Yes	205
138	rs1783827	A	G	0.0019	3.00E-04	2.03E-13	0.5799	Yes		No	No	Yes	40
139	rs1800574	T	C	0.0065	8.00E-04	8.82E-16	0.031	Yes	Diabetes	No	No	No	66
140	rs1801251	G	A	0.0019	3.00E-04	7.73E-14	0.6497	Yes		No	No	Yes	40
141	rs1844334	C	T	0.002	3.00E-04	2.55E-14	0.6346	Yes		No	No	Yes	44
142	rs1851285	G	C	0.0015	3.00E-04	2.58E-09	0.4933	Yes		Yes	Yes	No	25
143	rs185538102	A	G	0.0086	0.0014	1.34E-09	0.9895	Yes		No	No	Yes	38
144	rs1857859	G	A	0.0018	3.00E-04	6.33E-11	0.7062	Yes		No	No	Yes	36
145	rs1858800	C	T	0.0022	3.00E-04	7.09E-18	0.6694	Yes		No	No	Yes	54
146	rs187355703	G	C	0.0116	9.00E-04	4.16E-40	0.0276	Yes		Yes	No	Yes	166
147	rs1887252	C	G	0.0024	3.00E-04	6.08E-20	0.6263	Yes		No	No	Yes	64
148	rs1913641	T	G	0.0019	3.00E-04	2.78E-14	0.4907	Yes		No	No	Yes	40
149	rs2007458	A	G	0.0021	3.00E-04	8.90E-17	0.5688	Yes		No	No	Yes	49
150	rs2034899	G	T	0.002	3.00E-04	6.94E-14	0.2755	Yes		No	No	Yes	44
151	rs2055873	C	T	0.0015	3.00E-04	1.01E-08	0.7058	Yes		No	No	Yes	25
152	rs2068888	A	G	0.0029	3.00E-04	2.59E-30	0.4722	Yes		No	No	Yes	93
153	rs2072379	T	C	0.0021	3.00E-04	3.14E-16	0.6878	Yes		No	No	Yes	49
154	rs2074292	G	A	0.0015	3.00E-04	9.59E-09	0.455	Yes		No	No	Yes	25
155	rs2076668	A	G	0.0037	3.00E-04	1.32E-46	0.3687	Yes		No	No	Yes	152
156	rs2095567	C	T	0.0018	3.00E-04	1.73E-11	0.2686	Yes		No	No	Yes	36
157	rs2096551	C	G	0.0016	3.00E-04	2.57E-10	0.3962	Yes		Yes	No	Yes	28
158	rs2158812	T	C	0.0052	7.00E-04	1.60E-14	0.0709	Yes		No	No	Yes	55
159	rs216364	C	T	0.0021	3.00E-04	4.03E-15	0.2701	Yes		No	No	Yes	49
160	rs2185786	T	C	0.0015	3.00E-04	2.29E-09	0.6027	Yes		No	No	Yes	25
161	rs2186797	C	T	0.0031	5.00E-04	1.70E-08	0.064	Yes	Hypertension	No	No	No	38
162	rs219786	T	C	0.0026	3.00E-04	2.39E-15	0.7871	Yes		No	No	Yes	75
163	rs223317	T	C	0.003	3.00E-04	8.74E-30	0.6634	Yes	Hypertension	No	No	No	100
164	rs2235826	A	T	0.0031	3.00E-04	1.18E-20	0.8012	Yes		Yes	No	Yes	107
165	rs2236520	T	C	0.0021	3.00E-04	6.86E-15	0.7006	Yes		No	No	Yes	49
166	rs2241358	C	G	0.0016	3.00E-04	6.16E-10	0.6868	Yes		Yes	No	Yes	28
167	rs2250067	T	C	0.0028	3.00E-04	2.07E-28	0.4839	Yes		No	No	Yes	87
168	rs2274786	C	T	0.0015	3.00E-04	2.79E-09	0.3546	Yes		No	No	Yes	25
169	rs2275848	G	T	0.0021	3.00E-04	5.04E-10	0.1886	Yes	Obesity	No	No	No	49
170	rs227731	G	T	0.0021	3.00E-04	3.53E-16	0.4423	Yes		No	No	Yes	49
171	rs2277383	G	T	0.0025	4.00E-04	1.74E-11	0.1552	Yes		No	No	Yes	39
172	rs2279252	G	A	0.0052	9.00E-04	4.82E-09	0.9505	Yes		No	No	Yes	33
173	rs2289746	T	C	0.0019	3.00E-04	1.43E-12	0.377	Yes		No	No	Yes	40
174	rs2293605	C	T	0.0024	4.00E-04	4.59E-09	0.8797	Yes		No	No	Yes	36
175	rs2297129	A	G	0.0022	3.00E-04	3.43E-17	0.6621	Yes		No	No	Yes	54
176	rs2297853	G	T	0.0015	3.00E-04	8.67E-09	0.6314	Yes		No	No	Yes	25
177	rs2301343	T	G	0.0024	3.00E-04	2.11E-14	0.7565	Yes		No	No	Yes	64
178	rs2306623	T	C	0.002	3.00E-04	6.66E-15	0.32	Yes		No	No	Yes	44
179	rs2338796	G	A	0.0046	3.00E-04	4.16E-70	0.3297	Yes		No	No	Yes	235
180	rs2346418	G	A	0.0016	3.00E-04	1.45E-10	0.5015	Yes		No	No	Yes	28

181	rs2381199	G	T	0.0019	3.00E-04	1.79E-08	0.2547	Yes		No	No	Yes	40
182	rs2412608	C	T	0.0033	3.00E-04	1.51E-38	0.5065	Yes	Hypertension	No	No	No	121
183	rs243067	G	T	0.0014	3.00E-04	1.74E-08	0.6037	Yes		No	No	Yes	22
184	rs2433601	C	T	0.009	3.00E-04	1.00E-200	0.3982	Yes		No	No	Yes	900
185	rs2440164	G	A	0.0041	3.00E-04	3.24E-57	0.3721	Yes		No	No	Yes	187
186	rs246234	G	C	0.0016	3.00E-04	2.19E-09	0.6988	Yes		Yes	No	Yes	28
187	rs2469953	T	C	0.0015	3.00E-04	1.45E-08	0.4383	Yes		No	No	Yes	25
188	rs2515414	C	A	0.0014	3.00E-04	2.55E-08	0.5396	Yes		No	No	Yes	22
189	rs2577134	C	T	0.0015	3.00E-04	2.13E-08	0.2902	Yes		No	No	Yes	25
190	rs2607775	G	C	0.0015	3.00E-04	3.82E-09	0.479	Yes		Yes	Yes	No	25
191	rs2634675	G	A	0.0024	3.00E-04	3.24E-20	0.5133	Yes		No	No	Yes	64
192	rs264608	C	T	0.0018	3.00E-04	3.63E-11	0.6903	Yes		No	No	Yes	36
193	rs267738	T	G	0.0051	3.00E-04	8.31E-57	0.7901	Yes		No	No	Yes	289
194	rs27028	A	G	0.0016	3.00E-04	6.45E-10	0.3592	Yes		No	No	Yes	28
195	rs2720526	G	A	0.0015	3.00E-04	1.98E-08	0.253	Yes		No	No	Yes	25
196	rs2749153	A	G	0.003	3.00E-04	5.67E-28	0.7093	Yes		No	No	Yes	100
197	rs2780955	A	T	0.0014	3.00E-04	3.76E-08	0.3962	Yes		Yes	No	Yes	22
198	rs2781649	G	A	0.003	3.00E-04	6.20E-21	0.241	Yes		No	No	Yes	100
199	rs2808454	T	A	0.0021	3.00E-04	4.13E-16	0.5196	Yes		Yes	Yes	No	49
200	rs281380	T	C	0.0021	3.00E-04	8.72E-16	0.5954	Yes	Hypertension	No	No	No	49
201	rs2815374	A	G	0.0018	3.00E-04	1.41E-11	0.6614	Yes		No	No	Yes	36
202	rs2823139	A	G	0.0031	3.00E-04	7.20E-32	0.3332	Yes	Hypertension	No	No	No	107
203	rs2834320	G	A	0.0036	3.00E-04	3.68E-25	0.1555	Yes		No	No	Yes	144
204	rs284859	G	T	0.0029	3.00E-04	7.34E-18	0.8065	Yes		No	No	Yes	93
205	rs28490558	A	G	0.0021	3.00E-04	2.43E-11	0.2491	Yes		No	No	Yes	49
206	rs28735420	G	T	0.0033	5.00E-04	1.91E-10	0.0711	Yes		No	No	Yes	44
207	rs2880624	C	T	0.0014	3.00E-04	2.88E-08	0.3986	Yes		No	No	Yes	22
208	rs28817415	T	C	0.0078	3.00E-04	1.00E-200	0.425	Yes		No	No	Yes	676
209	rs288753	G	A	0.0027	3.00E-04	2.79E-25	0.6513	Yes		No	No	Yes	81
210	rs28910285	C	T	0.0029	3.00E-04	5.70E-29	0.6939	Yes		No	No	Yes	93
211	rs2906163	C	T	0.0014	3.00E-04	2.81E-08	0.3352	Yes	Hypertension	No	No	No	22
212	rs2953516	C	T	0.0026	3.00E-04	3.59E-22	0.705	Yes		No	No	Yes	75
213	rs2954017	C	T	0.0029	3.00E-04	1.13E-30	0.5308	Yes		No	No	Yes	93
214	rs2991341	T	C	0.0019	3.00E-04	9.90E-14	0.3907	Yes		No	No	Yes	40
215	rs303937	T	A	0.0028	3.00E-04	2.73E-27	0.5636	Yes		Yes	Yes	No	87
216	rs3060	C	T	0.0022	4.00E-04	8.35E-09	0.157	Yes		No	No	Yes	30
217	rs3111257	T	C	0.0015	3.00E-04	1.45E-08	0.5622	Yes		No	No	Yes	25
218	rs3119304	C	T	0.0084	4.00E-04	1.07E-96	0.1206	Yes		No	No	Yes	441
219	rs34174031	A	G	0.0055	0.001	1.95E-08	0.023	Yes		No	No	Yes	30
220	rs34188292	C	G	0.0017	3.00E-04	4.11E-08	0.2832	Yes		Yes	No	Yes	32
221	rs34293138	T	C	0.0024	3.00E-04	2.02E-19	0.6963	Yes		No	No	Yes	64
222	rs34357137	C	G	0.0028	3.00E-04	1.25E-25	0.7315	Yes		Yes	No	Yes	87
223	rs34442537	G	C	0.0019	3.00E-04	4.70E-13	0.3151	Yes		Yes	No	Yes	40
224	rs34460334	T	C	0.0034	5.00E-04	2.10E-12	0.9149	Yes	Hypertension	No	No	No	46
225	rs34861762	T	C	0.0048	3.00E-04	7.42E-79	0.4006	Yes		No	No	Yes	256
226	rs34950020	G	A	0.0024	3.00E-04	1.11E-20	0.6862	Yes		No	No	Yes	64
227	rs35072105	A	G	0.0019	3.00E-04	4.64E-14	0.5569	Yes		No	No	Yes	40
228	rs35915570	C	T	0.0022	3.00E-04	3.67E-17	0.5907	Yes		No	No	Yes	54
229	rs35969577	T	G	0.0056	3.00E-04	1.14E-106	0.3946	Yes		No	No	Yes	348
230	rs3750081	T	G	0.0022	3.00E-04	6.60E-18	0.5917	Yes		No	No	Yes	54
231	rs3755880	A	G	0.0015	3.00E-04	2.19E-08	0.2878	Yes	Hypertension	No	No	No	25
232	rs3757387	C	T	0.0027	3.00E-04	6.54E-27	0.4301	Yes		No	No	Yes	81
233	rs3775932	A	C	0.0019	3.00E-04	3.25E-14	0.5024	Yes		No	No	Yes	40
234	rs3794991	T	C	0.0033	4.00E-04	5.85E-14	0.0879	Yes	Diabetes	No	No	No	68
235	rs3795503	C	T	0.0023	3.00E-04	3.31E-18	0.6591	Yes		No	No	Yes	59
236	rs3809627	C	A	0.0015	3.00E-04	1.27E-08	0.5658	Yes		No	No	Yes	25
237	rs3814995	C	T	0.0023	3.00E-04	3.43E-14	0.6583	Yes		No	No	Yes	59
238	rs3820201	A	G	0.0016	3.00E-04	5.81E-10	0.5826	Yes		No	No	Yes	28
239	rs3842761	G	C	0.0038	3.00E-04	5.64E-33	0.7256	Yes		Yes	No	Yes	160
240	rs3850625	G	A	0.0049	4.00E-04	1.59E-32	0.881	Yes		No	No	Yes	150
241	rs3918226	T	C	0.0033	5.00E-04	2.51E-11	0.0826	Yes	Hypertension	No	No	No	44
242	rs3925003	T	C	0.0016	3.00E-04	1.11E-09	0.575	Yes		No	No	Yes	28
243	rs41284816	T	G	0.0083	0.001	3.50E-17	0.0226	Yes		No	No	Yes	69
244	rs41301394	C	T	0.0027	3.00E-04	1.90E-23	0.6951	Yes		No	No	Yes	81
245	rs417237	G	T	0.0017	3.00E-04	1.29E-10	0.4091	Yes		No	No	Yes	32
246	rs4245230	A	G	0.0022	3.00E-04	3.81E-18	0.4733	Yes		No	No	Yes	54
247	rs4275190	T	C	0.0018	3.00E-04	5.06E-12	0.6936	Yes		No	No	Yes	36
248	rs429358	T	C	0.0029	3.00E-04	3.00E-17	0.848	Yes	Diabetes	No	No	No	93
249	rs4376843	C	G	0.0017	3.00E-04	1.34E-10	0.31	Yes		Yes	No	Yes	32
250	rs4442348	G	A	0.0018	3.00E-04	7.54E-13	0.515	Yes		No	No	Yes	36
251	rs4491726	G	A	0.0034	3.00E-04	1.20E-28	0.3137	Yes		No	No	Yes	128
252	rs4515954	C	A	0.0023	3.00E-04	1.66E-11	0.1919	Yes		No	No	Yes	59
253	rs45619934	T	G	0.003	3.00E-04	1.11E-30	0.3404	Yes		No	No	Yes	100
254	rs4666821	G	T	0.002	3.00E-04	7.10E-15	0.4787	Yes	Thyroid cancer	No	No	No	44
255	rs4683730	A	G	0.0014	3.00E-04	4.18E-08	0.3641	Yes		No	No	Yes	22
256	rs4854645	A	G	0.0016	3.00E-04	1.33E-10	0.4829	Yes		No	No	Yes	28
257	rs4925095	A	G	0.0019	3.00E-04	6.44E-14	0.4869	Yes		No	No	Yes	40
258	rs4970765	C	T	0.0031	3.00E-04	1.88E-24	0.2976	Yes		No	No	Yes	107
259	rs4971092	T	C	0.0028	4.00E-04	6.52E-12	0.8799	Yes		No	No	Yes	49
260	rs5010824	G	A	0.0021	3.00E-04	2.27E-09	0.852	Yes		No	No	Yes	49
261	rs55658481	G	A	0.0019	3.00E-04	5.94E-13	0.6773	Yes		No	No	Yes	40
262	rs55743020	T	G	0.0034	3.00E-04	1.23E-40	0.6293	Yes		No	No	Yes	128
263	rs55754617	C	T	0.0019	3.00E-04	1.07E-08	0.8086	Yes		No	No	Yes	40
264	rs55797621	T	C	0.0015	3.00E-04	2.10E-08	0.7475	Yes		No	No	Yes	25
265	rs55842281	A	G	0.0022	3.00E-04	1.34E-16	0.4037	Yes		No	No	Yes	54
266	rs55924910	G	C	0.0024	3.00E-04	5.72E-12	0.1541	Yes		Yes	No	Yes	64
267	rs56034896	T	C	0.0016	3.00E-04	1.11E-09	0.4533	Yes		No	No	Yes	28
268	rs56065557	C	G	0.0031	3.00E-04	8.19E-32	0.3166	Yes		Yes	No	Yes	107
269	rs56261560	T	C	0.0017	3.00E-04	1.98E-08	0.3508	Yes		No	No	Yes	32
270	rs56283550	G	A	0.0053	4.00E-04	1.34E-44	0.856	Yes	Breast cancer	No	No	No	176
271	rs56306291	A	T	0.0026	3.00E-04	5.31E-16	0.2487	Yes		Yes	No	Yes	75
272	rs57445665	G	A	0.0022	3.00E-04	1.48E-11	0.7994	Yes		No	No	Yes	54

273	rs5750561	T	A	0.0024	3.00E-04	1.46E-20	0.6051	Yes		Yes	No	Yes	64
274	rs5760006	C	T	0.0021	4.00E-04	3.84E-08	0.1784	Yes		No	No	Yes	28
275	rs580114	A	G	0.0018	3.00E-04	3.45E-11	0.285	Yes		No	No	Yes	36
276	rs58117425	A	G	0.0019	3.00E-04	3.44E-09	0.2281	Yes	Hypertension	No	No	No	40
277	rs59343080	A	T	0.0025	3.00E-04	6.49E-13	0.1421	Yes		Yes	No	Yes	69
278	rs594672	T	C	0.0014	3.00E-04	1.77E-08	0.5167	Yes		No	No	Yes	22
279	rs595086	G	A	0.0015	3.00E-04	3.14E-08	0.6857	Yes		No	No	Yes	25
280	rs59646751	T	G	0.0024	3.00E-04	1.68E-19	0.3043	Yes		No	No	Yes	64
281	rs59860440	C	T	0.002	3.00E-04	1.24E-14	0.6874	Yes		No	No	Yes	44
282	rs6029640	A	G	0.0019	3.00E-04	4.99E-13	0.5747	Yes		No	No	Yes	40
283	rs60551165	C	T	0.0017	3.00E-04	1.19E-09	0.2736	Yes		No	No	Yes	32
284	rs6055748	A	G	0.0018	3.00E-04	7.28E-09	0.6915	Yes		No	No	Yes	36
285	rs60580012	T	C	0.0018	3.00E-04	4.24E-12	0.3216	Yes	Serous invasive ovarian cancer	No	No	No	36
286	rs60580012	T	C	0.0018	3.00E-04	4.24E-12	0.3216	Yes	Invasive ovarian cancer	No	No	No	36
287	rs60580012	T	C	0.0018	3.00E-04	4.24E-12	0.3216	Yes	High grade serous ovarian cancer	No	No	No	36
288	rs60691990	T	C	0.0016	3.00E-04	4.61E-08	0.6715	Yes		No	No	Yes	28
289	rs60980181	A	T	0.0027	4.00E-04	2.90E-14	0.157	Yes		Yes	No	Yes	46
290	rs60991551	A	C	0.0019	4.00E-04	4.93E-08	0.166	Yes		No	No	Yes	23
291	rs61311941	A	G	0.0028	4.00E-04	5.61E-10	0.8792	Yes		No	No	Yes	49
292	rs61327861	A	G	0.0029	4.00E-04	1.70E-12	0.1331	Yes		No	No	Yes	53
293	rs61482805	C	G	0.0021	3.00E-04	1.49E-15	0.6824	Yes		Yes	No	Yes	49
294	rs61830291	A	C	0.004	5.00E-04	1.42E-17	0.9022	Yes		No	No	Yes	64
295	rs61910261	G	T	0.0014	3.00E-04	1.60E-08	0.4106	Yes		No	No	Yes	22
296	rs62035088	G	A	0.0027	3.00E-04	6.73E-16	0.8358	Yes		No	No	Yes	81
297	rs62071986	T	C	0.0041	7.00E-04	6.25E-09	0.041	Yes		No	No	Yes	34
298	rs62187537	C	T	0.0037	6.00E-04	2.07E-11	0.9327	Yes		No	No	Yes	38
299	rs622076	A	G	0.004	4.00E-04	1.16E-25	0.1501	Yes	Diabetes	No	No	No	100
300	rs62325228	G	T	0.0022	3.00E-04	3.33E-10	0.856	Yes		No	No	Yes	54
301	rs62330280	A	G	0.002	3.00E-04	1.97E-15	0.4959	Yes	Hypertension	No	No	No	44
302	rs6243145	T	G	0.0066	3.00E-04	8.01E-99	0.6447	Yes		No	No	Yes	484
303	rs62491533	T	C	0.0027	3.00E-04	3.87E-15	0.8201	Yes		No	No	Yes	81
304	rs62618693	C	T	0.0038	7.00E-04	2.51E-08	0.9559	Yes		No	No	Yes	29
305	rs6445924	G	A	0.0019	3.00E-04	1.05E-08	0.8275	Yes		No	No	Yes	40
306	rs6453319	C	A	0.0014	3.00E-04	3.85E-08	0.5741	Yes		No	No	Yes	22
307	rs6458868	T	C	0.002	3.00E-04	2.08E-14	0.6589	Yes		No	No	Yes	44
308	rs6468118	C	G	0.002	3.00E-04	2.92E-15	0.3713	Yes		Yes	No	Yes	44
309	rs6481598	G	C	0.0022	3.00E-04	3.42E-11	0.2104	Yes		Yes	No	Yes	54
310	rs6540119	T	A	0.0015	3.00E-04	3.20E-08	0.643	Yes		Yes	No	Yes	25
311	rs6541410	C	G	0.0015	3.00E-04	6.68E-09	0.6258	Yes		Yes	No	Yes	25
312	rs660931	C	T	0.0016	3.00E-04	5.67E-09	0.6837	Yes		No	No	Yes	28
313	rs665731	T	C	0.0021	3.00E-04	1.36E-10	0.1844	Yes		No	No	Yes	49
314	rs6700683	T	A	0.0022	3.00E-04	1.61E-17	0.551	Yes		Yes	Yes	No	54
315	rs6707326	G	A	0.0016	3.00E-04	2.42E-10	0.4469	Yes		No	No	Yes	28
316	rs6708702	A	G	0.0019	3.00E-04	8.87E-13	0.3531	Yes		No	No	Yes	40
317	rs6779998	A	G	0.0017	3.00E-04	6.20E-11	0.5272	Yes		No	No	Yes	32
318	rs67861508	G	A	0.0016	3.00E-04	2.30E-09	0.3233	Yes	Diabetes	No	No	No	28
319	rs688540	A	G	0.0025	4.00E-04	1.95E-10	0.8667	Yes		No	No	Yes	39
320	rs6968865	A	T	0.0023	3.00E-04	1.13E-19	0.4043	Yes		Yes	No	Yes	59
321	rs7005025	C	A	0.002	3.00E-04	5.01E-15	0.6423	Yes		No	No	Yes	44
322	rs700753	G	C	0.0032	3.00E-04	1.09E-35	0.6684	Yes		Yes	No	Yes	114
323	rs7012637	G	A	0.0027	3.00E-04	4.33E-26	0.5118	Yes		No	No	Yes	81
324	rs7017848	A	G	0.0014	3.00E-04	4.14E-08	0.3932	Yes		No	No	Yes	22
325	rs7027509	T	C	0.0016	3.00E-04	3.66E-10	0.3243	Yes		No	No	Yes	28
326	rs7086663	A	T	0.0014	3.00E-04	2.91E-08	0.3821	Yes		Yes	No	Yes	22
327	rs7087356	T	A	0.0018	3.00E-04	2.92E-12	0.4901	Yes		Yes	Yes	No	36
328	rs7088058	C	T	0.0015	3.00E-04	3.17E-09	0.6159	Yes	Diabetes	No	No	No	25
329	rs7131509	C	T	0.0021	3.00E-04	1.91E-16	0.3751	Yes		No	No	Yes	49
330	rs71606723	T	A	0.0022	3.00E-04	6.48E-12	0.2253	Yes		Yes	No	Yes	54
331	rs7161243	T	C	0.0016	3.00E-04	3.83E-09	0.7177	Yes		No	No	Yes	28
332	rs7169629	G	C	0.0019	3.00E-04	2.92E-14	0.5015	Yes		Yes	Yes	No	40
333	rs7178859	T	C	0.0024	3.00E-04	2.36E-13	0.2118	Yes		No	No	Yes	64
334	rs7199123	T	A	0.0015	3.00E-04	2.31E-08	0.3058	Yes		Yes	No	Yes	25
335	rs7248248	A	T	0.0018	3.00E-04	1.30E-12	0.4379	Yes		Yes	Yes	No	36
336	rs7259073	C	T	0.0038	6.00E-04	1.59E-10	0.0859	Yes		No	No	Yes	40
337	rs72629024	G	C	0.0037	4.00E-04	2.93E-20	0.2361	Yes		Yes	No	Yes	86
338	rs72683923	T	C	0.0073	0.001	3.02E-13	0.9801	Yes	Hypertension	No	No	No	53
339	rs72801857	T	C	0.0065	8.00E-04	1.05E-16	0.0326	Yes		No	No	Yes	66
340	rs72830437	A	G	0.0028	5.00E-04	2.99E-08	0.0695	Yes		No	No	Yes	31
341	rs72912510	A	G	0.0027	3.00E-04	3.36E-16	0.1993	Yes		No	No	Yes	81
342	rs73073442	C	T	0.0056	9.00E-04	5.24E-10	0.9747	Yes		No	No	Yes	39
343	rs73077077	G	A	0.0021	3.00E-04	2.65E-10	0.8076	Yes		No	No	Yes	49
344	rs73117042	C	T	0.003	4.00E-04	5.68E-18	0.1332	Yes		No	No	Yes	56
345	rs7320064	G	A	0.002	3.00E-04	2.18E-09	0.1844	Yes		No	No	Yes	44
346	rs7324484	G	A	0.002	3.00E-04	4.41E-15	0.3517	Yes		No	No	Yes	44
347	rs73245338	G	T	0.0034	6.00E-04	1.09E-09	0.9361	Yes		No	No	Yes	32
348	rs7326821	G	A	0.0021	3.00E-04	2.55E-10	0.1731	Yes		No	No	Yes	49
349	rs736820	A	G	0.0016	3.00E-04	2.18E-10	0.3735	Yes		No	No	Yes	28
350	rs73703112	T	G	0.0021	3.00E-04	1.97E-15	0.6917	Yes		No	No	Yes	49
351	rs7397189	T	G	0.0031	3.00E-04	9.44E-22	0.7654	Yes		No	No	Yes	107
352	rs7405696	C	G	0.0015	3.00E-04	1.42E-08	0.434	Yes	Diabetes	Yes	Yes	No	25
353	rs7405696	C	G	0.0015	3.00E-04	1.42E-08	0.434	Yes	Prostate cancer	Yes	Yes	No	25
354	rs74331768	A	G	0.003	5.00E-04	2.55E-09	0.097	Yes		No	No	Yes	36
355	rs74748843	T	C	0.0046	7.00E-04	1.14E-09	0.0545	Yes		No	No	Yes	43
356	rs7475348	C	T	0.003	3.00E-04	5.44E-32	0.5241	Yes		No	No	Yes	100
357	rs7492724	G	A	0.0022	3.00E-04	4.25E-16	0.2796	Yes		No	No	Yes	54
358	rs7514579	A	C	0.0025	3.00E-04	7.12E-15	0.7737	Yes		No	No	Yes	69
359	rs75248620	G	A	0.0036	5.00E-04	2.25E-13	0.9188	Yes		No	No	Yes	52
360	rs7535253	C	T	0.0024	3.00E-04	2.16E-13	0.7596	Yes		No	No	Yes	64
361	rs7536433	C	T	0.0026	3.00E-04	2.11E-15	0.7638	Yes		No	No	Yes	75
362	rs7539054	A	C	0.0021	3.00E-04	2.79E-14	0.7097	Yes		No	No	Yes	49
363	rs755865	G	A	0.0043	4.00E-04	1.41E-26	0.8706	Yes		No	No	Yes	116
364	rs75625374	G	C	0.0036	6.00E-04	2.03E-10	0.9403	Yes		Yes	No	Yes	36

365	rs7592697	T	C	0.0019	3.00E-04	9.75E-13	0.6639	Yes		No	No	Yes	40
366	rs76273615	G	A	0.0029	4.00E-04	4.07E-16	0.1391	Yes		No	No	Yes	53
367	rs7630893	T	C	0.0045	3.00E-04	4.78E-63	0.722	Yes		No	No	Yes	225
368	rs7687209	C	T	0.0021	3.00E-04	5.44E-16	0.5984	Yes		No	No	Yes	49
369	rs77375846	C	T	0.003	4.00E-04	5.55E-14	0.1314	Yes		No	No	Yes	56
370	rs7740107	T	A	0.003	3.00E-04	1.99E-21	0.2621	Yes		Yes	No	Yes	100
371	rs7766720	C	T	0.0026	4.00E-04	5.24E-09	0.1035	Yes		No	No	Yes	42
372	rs7769218	G	A	0.002	3.00E-04	9.47E-10	0.202	Yes		No	No	Yes	44
373	rs77897671	C	T	0.0022	3.00E-04	8.91E-11	0.1864	Yes		No	No	Yes	54
374	rs77924615	G	A	0.0106	3.00E-04	1.00E-200	0.8014	Yes	Hypertension	No	No	No	1248
375	rs7829427	A	G	0.0015	3.00E-04	2.72E-08	0.2734	Yes		No	No	Yes	25
376	rs78444298	A	G	0.012	0.001	2.19E-30	0.0189	Yes		No	No	Yes	144
377	rs784503	A	G	0.002	3.00E-04	6.73E-10	0.2376	Yes		No	No	Yes	44
378	rs792839	G	A	0.0016	3.00E-04	1.25E-09	0.677	Yes		No	No	Yes	28
379	rs7947897	T	C	0.0014	3.00E-04	2.85E-08	0.6173	Yes		No	No	Yes	22
380	rs795010	T	A	0.0019	3.00E-04	1.33E-12	0.2624	Yes		Yes	No	Yes	40
381	rs7963577	C	T	0.0022	3.00E-04	2.02E-11	0.2153	Yes		No	No	Yes	54
382	rs7983636	G	A	0.0031	5.00E-04	3.55E-10	0.9221	Yes		No	No	Yes	38
383	rs79865452	A	G	0.0071	0.001	3.11E-12	0.9785	Yes		No	No	Yes	50
384	rs80138475	C	T	0.0062	4.00E-04	8.64E-50	0.8886	Yes		No	No	Yes	240
385	rs80282103	T	A	0.0081	5.00E-04	2.91E-62	0.0868	Yes		Yes	No	Yes	262
386	rs8058927	G	A	0.0025	4.00E-04	1.12E-12	0.841	Yes		No	No	Yes	39
387	rs8065496	T	C	0.0014	3.00E-04	4.29E-08	0.3985	Yes		No	No	Yes	22
388	rs8073316	T	A	0.0015	3.00E-04	5.21E-09	0.6823	Yes		Yes	No	Yes	25
389	rs807624	G	T	0.0035	3.00E-04	4.69E-41	0.6073	Yes		No	No	Yes	136
390	rs8096658	G	C	0.0054	3.00E-04	1.88E-75	0.4723	Yes		Yes	Yes	No	324
391	rs8101667	C	T	0.0047	3.00E-04	2.63E-73	0.6316	Yes		No	No	Yes	245
392	rs81205	C	A	0.003	3.00E-04	7.12E-32	0.4787	Yes		No	No	Yes	100
393	rs836968	C	T	0.0018	3.00E-04	9.80E-12	0.6813	Yes		No	No	Yes	36
394	rs848446	A	G	0.0041	3.00E-04	5.91E-54	0.2713	Yes	Hypertension	No	No	No	187
395	rs881858	A	G	0.0054	3.00E-04	5.10E-93	0.7032	Yes		No	No	Yes	324
396	rs883541	A	G	0.0024	3.00E-04	6.17E-19	0.7386	Yes		No	No	Yes	64
397	rs925612	T	C	0.0014	3.00E-04	2.68E-08	0.4953	Yes		No	No	Yes	22
398	rs9318186	G	A	0.0019	3.00E-04	4.72E-14	0.5193	Yes		No	No	Yes	40
399	rs9376148	C	A	0.0015	3.00E-04	3.36E-09	0.3633	Yes		No	No	Yes	25
400	rs9397738	G	A	0.003	4.00E-04	3.15E-17	0.1526	Yes		No	No	Yes	56
401	rs9465741	C	A	0.0021	3.00E-04	1.91E-16	0.4843	Yes		No	No	Yes	49
402	rs9480867	G	A	0.0034	3.00E-04	9.81E-23	0.847	Yes		No	No	Yes	128
403	rs948494	A	G	0.0034	3.00E-04	7.89E-40	0.3357	Yes		No	No	Yes	128
404	rs950965	A	G	0.0018	3.00E-04	4.70E-12	0.3808	Yes		No	No	Yes	36
405	rs9521719	A	G	0.0019	3.00E-04	4.79E-14	0.3945	Yes		No	No	Yes	40
406	rs953492	A	G	0.0027	3.00E-04	1.09E-25	0.4518	Yes		No	No	Yes	81
407	rs956006	C	T	0.0017	3.00E-04	1.10E-10	0.6712	Yes		No	No	Yes	32
408	rs9590675	G	T	0.0021	3.00E-04	1.72E-16	0.5858	Yes		No	No	Yes	49
409	rs963837	T	C	0.0055	3.00E-04	9.85E-102	0.5595	Yes		No	No	Yes	336
410	rs965484	C	T	0.0026	3.00E-04	7.41E-25	0.5716	Yes		No	No	Yes	75
411	rs9663482	C	G	0.0024	3.00E-04	2.77E-12	0.1963	Yes		Yes	No	Yes	64
412	rs9807214	A	G	0.0022	3.00E-04	2.73E-13	0.2923	Yes		No	No	Yes	54
413	rs9812319	C	T	0.0022	3.00E-04	1.12E-17	0.6652	Yes		No	No	Yes	54
414	rs9823161	G	A	0.0025	3.00E-04	3.52E-16	0.3578	Yes		No	No	Yes	69
415	rs9894634	T	C	0.0019	3.00E-04	3.66E-14	0.5724	Yes		No	No	Yes	40
416	rs9895661	C	T	0.0077	3.00E-04	2.51E-114	0.2302	Yes		No	No	Yes	659
417	rs9932625	A	G	0.0033	3.00E-04	1.15E-32	0.2485	Yes		No	No	Yes	121
418	rs9943067	T	C	0.0019	3.00E-04	3.76E-13	0.4264	Yes		No	No	Yes	40
419	rs9998449	G	A	0.0017	3.00E-04	1.87E-10	0.3274	Yes		No	No	Yes	32

Supplementary Table 5 : Instrumental variables for pulmonary embolism and their filtering process in Mendelian Randomization.

		summary statistics in exposure GWAS					filtering process of IVs .				
No	SNP	effect allele	other allele	beta	se	P-value	effect allele f	Step 1: LD-independent SNPs were discarded	Step 2: confounders associated SNPs were discarded	Step 3: The SNPs that are palindromic were removed		incorporated in the MR analysis	F-statistics
								LD-independent SNPs were discarded	associated confounders	palindromic	ambiguous		
1	rs114767153	T	A	-0.26431	0.0483773	4.67E-08	0.0276682	Yes		Yes	No	Yes	30
2	rs149244513	A	G	0.239484	0.0397589	1.71E-09	0.0304327	Yes		No	No	Yes	36
3	rs1560711	T	C	0.147893	0.0194283	2.69E-14	0.824074	Yes		No	No	Yes	58
4	rs2066865	A	G	0.22968	0.0152117	1.65E-51	0.301218	Yes		No	No	Yes	228
5	rs2905083	G	A	0.0866968	0.0150216	7.86E-09	0.622206	Yes		No	No	Yes	33
6	rs3756011	A	C	0.229943	0.0143556	9.62E-58	0.428808	Yes		No	No	Yes	257
7	rs6025	T	C	0.53838	0.0440911	2.73E-34	0.0200849	Yes		No	No	Yes	149
8	rs6087685	C	G	0.0832972	0.0152629	4.83E-08	0.323524	Yes		Yes	No	Yes	30
9	rs62350309	G	A	-0.189155	0.0248726	2.85E-14	0.102341	Yes		No	No	Yes	58
10	rs665082	C	G	-0.166139	0.0294015	1.60E-08	0.941445	Yes		Yes	No	Yes	32
11	rs6816960	A	T	-0.160707	0.0269726	2.55E-09	0.0847583	Yes		Yes	No	Yes	35
12	rs77165492	C	T	0.20312	0.0266095	2.29E-14	0.0718385	Yes		No	No	Yes	58
13	rs78807356	T	G	0.5019	0.0763756	4.98E-11	0.00656601	Yes		No	No	Yes	43
14	rs79583052	G	A	0.210159	0.0349834	1.89E-09	0.0395208	Yes		No	No	Yes	36
15	rs80137017	T	C	-0.233246	0.0244481	1.42E-21	0.107741	Yes		No	No	Yes	91

Supplementary Table S6 Details of the forward Mendelian randomization

Fixed-effect and random-effect Inverse variance weighted , weighted median, MR-Egger, and MR-PRESSO with estimated glomerular filtration rate (eGFR) as exposure and pulmonary embolism (PE) as outcome.

Exposure	Outcome	Methods	IVs	OR	95% CI	*P-value*
eGFR	PE	Inverse variance weighted (Random)	370	4.27	2.07, 8.79	<0.0001
		Inverse variance weighted (Fixed)	370	4.27	2.26, 8.05	<0.0001
		Weighted median	370	2.31	0.76, 7.05	0.14
		MR-PRESSO	370	4.64	2.39, 9.00	<0.0001
		MR-Egger	370	2.79	0.54, 14.30	0.2196
eGFR in European ancestry	PE	Inverse variance weighted (Random)	324	4.69	2.43,9.08	<0.0001
		Inverse variance weighted (Fixed)	324	4.69	2.56,8.60	<0.0001
		Weighted median	324	3.65	1.33, 10.00	0.0119
		MR-PRESSO	324	4.54	2.39, 8.62	<0.0001
		MR-Egger	324	1.90	0.45, 8.05	0.3860

IVs, instrumental variables; OR, Odds ratio; CI, Confidence interval

Supplementary Table S7 Heterogeneity test result for the forward MR

Heterogeneity test for MR with estimated glomerular filtration rate (eGFR) as exposure and pulmonary embolism (PE) as outcome.

Exposure	Outcome	Cochran's Q IVW	Cochran's Q MR-Egger	Q_*P-value* IVW	Q_*P-value* MR-Egger
eGFR	Pulmonary Embolism	479	478	<0.001	<0.001
eGFR in European ancestry	Pulmonary Embolism	384	381	0.012	0.011

Supplementary Table S8 Details of the reverse falsification result.

Exposure	Outcome	Method	Number of SNPs	Beta	SE	P value	OR	Lower 95%CI	Upper 95% CI
eGFR multi-ethnicity	Dementia	MR Egger	355	1.268769	1.994608	0.525124	3.556471	0.071314	177.3634
		Weighted median	355	0.415023	0.447796	0.354024	1.514405	0.629608	3.642619
		Inverse variance weighted	355	1.267349	0.932989	0.174345	3.551424	0.570462	22.10948
		Simple mode	355	0.944965	1.067353	0.376577	2.572722	0.317573	20.84212
		Weighted mode	355	0.276918	0.607196	0.648626	1.319058	0.401244	4.336307
eGFR multi-ethnicity	Actinic keratosis	MR Egger	355	0.170957	0.755665	0.82115	1.18644	0.26978	5.217725
		Weighted median	355	-0.30968	0.513715	0.546632	0.733685	0.268057	2.008136
		Inverse variance weighted	355	-0.10826	0.353606	0.759475	0.897391	0.448731	1.79464
		Simple mode	355	-1.55165	1.313296	0.238199	0.211897	0.016152	2.779874
		Weighted mode	355	0.020623	0.629751	0.973894	1.020837	0.297099	3.507612

Supplementary Table S8 Heterogeneity test result for the reverse MR.

Heterogeneity test for MR with as pulmonary embolism (PE) exposure and estimated glomerular filtration rate (eGFR) as outcome.

Exposure	Outcome	Cochran's Q IVW	Cochran's Q MR-Egger	Q_*P-value* IVW	Q_*P-value* MR-Egger
Pulmonary Embolism	eGFR	94	87	<0.001	<0.001
Pulmonary Embolism	eGFR in European ancestry	67	57	<0.001	<0.001

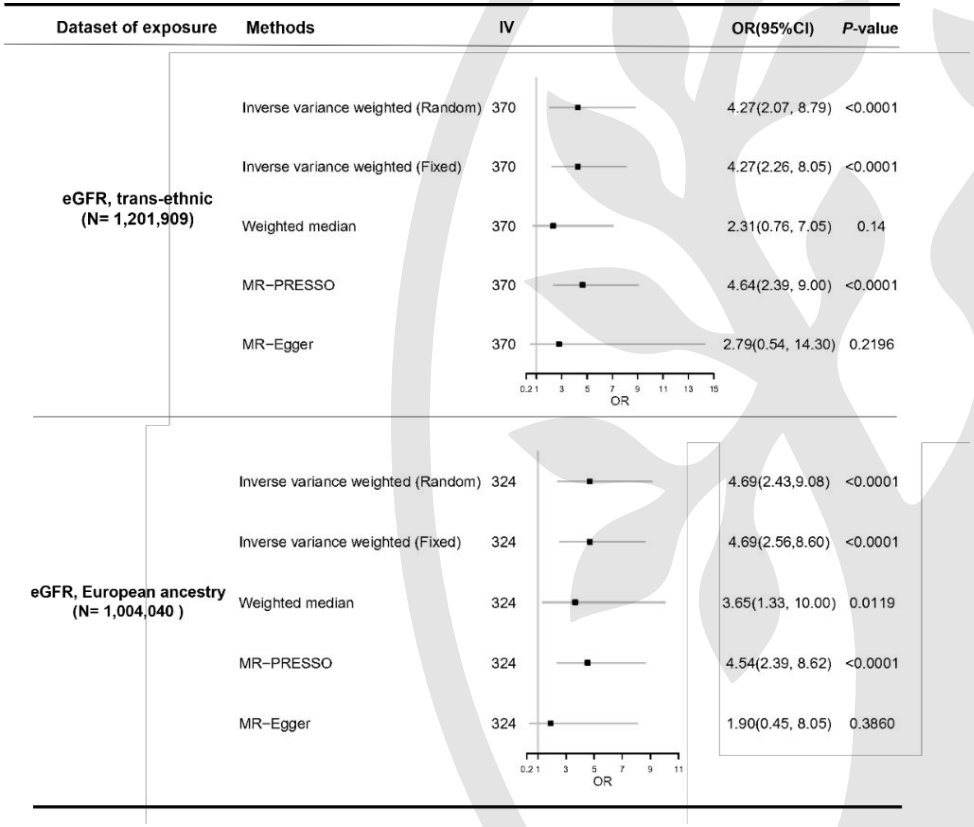
Table 1 Characteristics of Participants in the Nested Case-Control Study Before and After Propensity Score Matching and inverse probability of treatment weighting

	Unmatched			After PSM[a] and IPTW			
	Controls (CHARLS)	Pulmonary Embolism (CURES)	*p*-value	Controls (CHARLS)	Pulmonary Embolism (CURES)	*p*-value	SMD
N	11225	6322		5535.13	5516.77		
Male (%)	5204 (46.4)	3320 (52.5)	<0.001	2935.3 (53.0)	2883.4 (52.3)	0.370	0.015
Age (year±SD)	61.05±9.69	63.22±14.72	<0.001	62.56±9.50	62.95±15.04	0.086	0.031
BMI (kg/m^2)	23.92±3.92	24.20±3.78	<0.001	24.20±4.05	24.23±3.76	0.659	0.008
Complications							
Hypertension (%)	3641 (32.4)	2284 (36.1)	<0.001	3552.1 (64.2)	3525.7 (63.9)	0.749	0.006
DM (%)	1066 (9.5)	760 (12.0)	<0.001	620.3 (11.2)	628.7 (11.4)	0.730	0.006
Cancer (%)	176 (1.6)	929 (14.7)	<0.001	155.7 (2.8)	148.7 (2.7)	0.621	0.007
Chronic pulmonary diseases (%)	1507 (13.4)	542 (8.6)	<0.001	485.1 (8.8)	500.4 (9.1)	0.501	0.011
CVD (%)	1952 (17.4)	1017 (16.1)	<0.001	899.0 (16.2)	927.7 (16.8)	0.363	0.015
Kidney diseases (%)	1045 (9.3)	132 (2.1)	<0.001	129.8 (2.3)	125.3 (2.3)	0.748	0.005
eGFR category (%)			<0.001			<0.001	0.524
eGFR<30	49 (0.4)	95 (1.5)		23.2 (0.4)	88.0 (1.6)		
30≤eGFR<60	460 (4.1)	1084 (17.1)		248.5 (4.5)	959.6 (17.4)		
60≤eGFR<90	2957 (26.3)	2230 (35.3)		1566.8 (28.3)	1930.7 (35.0)		
eGFR>90	7759 (69.1)	2913 (46.1)		3696.7 (66.8)	2538.5 (46.0)		

a. the individual propensity to the presence of PE was estimated using a logistic regression model using confounding variables as covariates, including demographic information (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases, kidney diseases)

PSM, propensity score matching; IPTW, inverse probability of treatment weighting; SMD, standardized mean differences; CURES, China Pulmonary Thromboembolism Registry Study; CHARLS, China Health and Retirement longitudinal Survey; BMI, Body Mass index; DM, Diabetes Mellitus; CVD: Cardiovascular Diseases; eGFR, estimated glomerular filtration rate.

Table 2 Two-Sample Mendelian Randomization Revealed That Estimated Glomerular Filtration Rate Decline Was Causally Associated with Pulmonary Embolism.



The forest plot illustrated the Odd ratios and 95% Confidence Interval calculated by inverse variance weighted, maximum likelihood, MR-Egger, and MR-PRESSO methods , using primary and supplementary instrumental variables, when eGFR decline was the exposure and pulmonary embolism was the outcome.
IVs, instrumental variables; eGFR, estimated glomerular filtration rate; PE, pulmonary embolism.

Table 3 Egger regression and MR-PRESSO revealed no evidence of horizontal pleiotropy in the forward MR.

Exposure	Outcome	Egger-intercept	Egger-SE	Egger- *P-value*	MR-PRESSO Distortion Test
eGFR, Trans-ethnic	Pulmonary Embolism	0.001	0.002	0.57	0.9
eGFR European ancestry	Pulmonary Embolism	0.003	0.002	0.17	No significant outliers

Egger regression, and MR-PRESSO test results for horizontal pleiotropy of Mendelian Randomization analyses using primary and supplementary instrumental variables, with estimated glomerular filtration rate (eGFR) as exposure and pulmonary embolism (PE) as outcome.

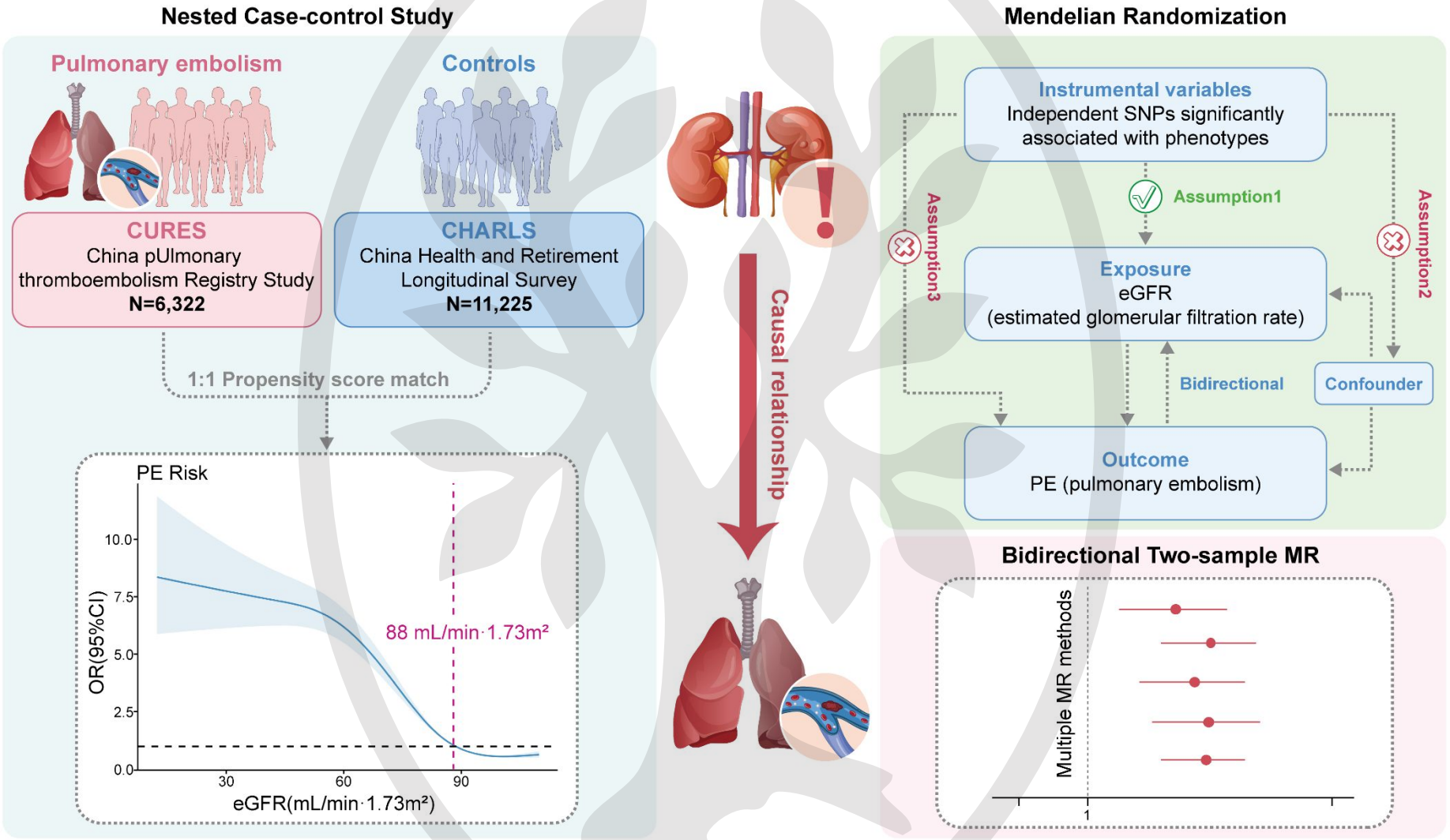
Table 4 Reverse Mendelian Randomization Indicated No Causal Effect of Pulmonary Embolism On Estimated Glomerular Filtration Rate Decline

Exposure	Outcome	Methods	IVs	OR	95% CI	*P-value*
PE	eGFR, Trans-ethnic	Inverse variance weighted (Random)	15	1.00	0.99,1.00	0.58
		Inverse variance weighted (Fixed)	15	1.00	0.99,1.00	0.15
		Weighted median	15	1.00	0.99,1.00	0.20
		MR-PRESSO	15	1.00	0.99,1.01	0.17
		MR-Egger	15	1.00	0.99,1.00	0.25
PE	eGFR, European ancestry	Inverse variance weighted (Random)	15	1.00	0.99,1.00	0.75
		Inverse variance weighted (Fixed)	15	1.00	0.99,1.00	0.48
		Weighted median	15	1.00	0.99,1.00	0.17
		MR-PRESSO	15	1.00	0.99,1.00	0.71
		MR-Egger	15	1.00	0.99,1.00	0.25

The table illustrated the Odd ratios and 95% Confidence Interval calculated by inverse variance weighted, maximum likelihood, MR-Egger, and MR-PRESSO methods, using primary and supplementary instrumental variables, when pulmonary embolism was the exposure and eGFR decline was the outcome.

IVs, instrumental variables; OR, Odds ratio; CI, Confidence interval

Figure 1 Overall Design of The Study



The current study was composed of two components. Firstly, to characterize the observational association between eGFR and PE, we conducted a nested case-control study from two nationwide cohort studies, namely the China pUlmonary thromboembolism REgistry Study (CURES) and the China Health and Retirement Longitudinal Study (CHARLS). Secondly, to estimate the causal-effect relationship between eGFR and PE, bidirectional two-sample MR analyses were conducted. Genome-wide association studies (GWASs) summary-level genetic data for eGFR were derived from a meta-analysis of GWASs involving up to 1.2 million individuals. Summary-level genetic data for PE were derived from the FinnGen consortium R10(10,046 PE cases and 401,128 controls).