Kidney function and obstructive lung disease: a bidirectional Mendelian randomisation study

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This Mendelian randomisation study identified that genetically predicted eGFR loss was associated with decrease in FEV_1/FVC and increase in the risk of COPD and late-onset asthma. The causal estimates from FEV_1/FVC to eGFR were nonsignificant. https://bit.ly/3eC99uT

Cite this article as: Park S, Lee S, Kim Y, *et al*. Kidney function and obstructive lung disease: a bidirectional Mendelian randomisation study. *Eur Respir J* 2021; 58: 2100848 [DOI: 10.1183/13993003.00848-2021].

This article has supplementary material available from erj.ersjournals.com

This article has an editorial commentary: https://doi.org/10.1183/13993003.01346-2021

Received: 13 Feb 2021
Accepted: 26 April 2021

Abstract

Background Additional study is warranted to investigate the causal effects between kidney function and obstructive lung disease.

Methods This study was a bidirectional two-sample Mendelian randomisation (MR) analysis. The Chronic Kidney Disease Genetics (CKDGen) genome-wide association study (GWAS) meta-analysis for estimated glomerular filtration rate (eGFR) including individuals of European ancestry (n=567 460) provided the genetic instrument for kidney function and outcome summary statistics. A GWAS for forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) including individuals of European ancestry from the UK Biobank (n=321 047) provided the genetic instrument for FEV_1/FVC and outcome data. A polygenic score (PGS) analysis was performed to test the causal estimates from kidney function to binary obstructive lung disease outcomes, including COPD, asthma and FEV_1/FVC <70%, and to perform nonlinear MR with individual-level UK Biobank data.

Results The causal estimates by summary-level MR indicated that genetically predicted increased kidney function was significantly associated with increased FEV_1/FVC z-scores (10% increase in eGFR; β=0.055, 95% CI 0.024–0.086). The PGS for increased eGFR showed a significant association with a reduced risk of FEV_1/FVC <70% (OR 0.93, 95% CI 0.87–0.99), COPD (OR 0.93, 95% CI 0.87–0.99) and late-onset (age ⩾50 years) asthma (OR 0.93, 95% CI 0.88–0.99). The nonlinear MR demonstrated that the causal effect from eGFR to FEV_1/FVC was apparent in eGFR ranges <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. Conversely, genetically predicted FEV_1/FVC showed nonsignificant causal estimates of eGFR change (β=0.568%, 95% CI −0.458–1.605%).

Conclusion This study supports kidney function impairment as a causative factor for obstructive lung disease.

Introduction

Globally, obstructive lung disease is a major comorbidity with a large socioeconomic burden. In 2017, 3.7% and 3.9% of the global population was estimated to be affected by COPD and asthma, respectively [1]. Furthermore, obstructive lung disease is a major cause of death and loss of overall full health.

Chronic kidney disease (CKD), another major chronic disease worldwide, affected nearly 7 million individuals in 2017, with an increasing prevalence [2]. A previous study reported that both CKD and obstructive lung disease are prevalent in elderly people and that there are common risk factors (*e.g.* smoking) for these two major comorbidities [3]. In addition, observational findings suggest that CKD or obstructive lung disease may increase the risk of the other disease [3–5]. However, whether a causal effect is present for the bidirectional association has yet to be confirmed, because observational results are inevitably affected by unmeasured confounding effects and reverse causation. Evidence for causality would suggest whether appropriate management of kidney function may lead to better lung function, or *vice versa*. Furthermore, the evidence would encourage early screening for or scheduled monitoring of causal factors in individuals with CKD or obstructive lung disease.

Mendelian randomisation (MR) is a widely adopted analytic tool to investigate causal effects in current medicine [6]. MR investigates the association between genetically proxied exposures and an outcome, and the causal estimates from MR are minimally affected by effects from confounders or reverse causation. The method has been shown to identify important causal pathways in the medical literature and utilised to dissect the causal effects in bidirectional associations between diseases that commonly coexist [7, 8].

In this study, we performed a bidirectional MR analysis between a kidney function parameter (estimated glomerular filtration rate (eGFR)) and an objective parameter for obstructive lung function, the forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio. We hypothesised that there would be a directional causal effect between eGFR change and FEV_1/FVC.

Materials and methods

Ethical considerations

The current study was approved by the institutional review boards (IRB) of Seoul National University Hospital (E-2102-001-1191) and the UK Biobank consortium (53799). The requirement for informed consent was waived because the data for this study were anonymous and available in the public domain.

Study setting

The study was a bidirectional MR analysis (figure 1). The study implemented the CKD Genetics (CKDGen) genome-wide association study (GWAS) meta-analysis data to identify genetic instruments for eGFR and as the outcome data for kidney function. The study implemented the GWAS results for lung function with the UK Biobank data, which is independent from the CKDGen data to construct genetic instruments and as the outcome data for lung function.

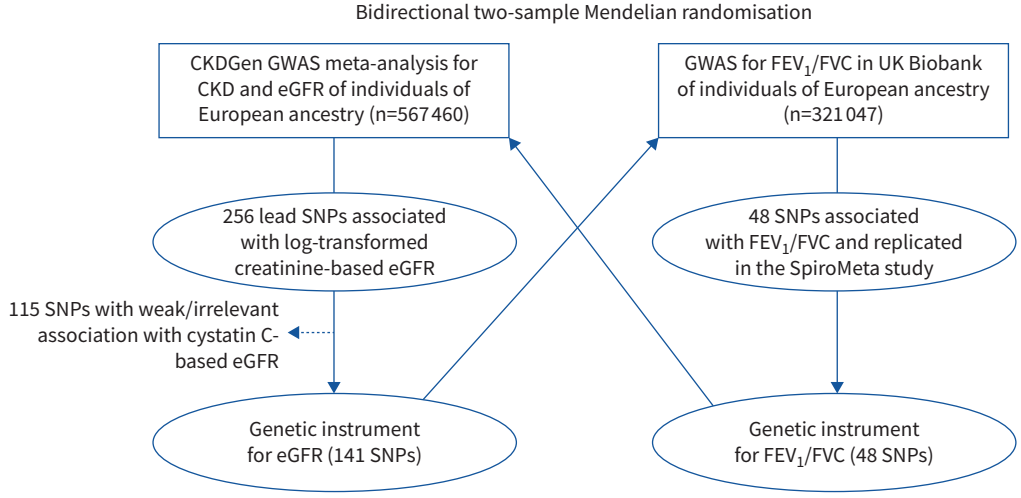

FIGURE 1 Study flow diagram. The study was a bidirectional Mendelian randomisation analysis including data from Chronic Kidney Disease Genetics (CKDGen) and UK Biobank, which were independent. The genetic instruments for kidney function and forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio were developed from each dataset, and applied to the summary statistics of the other. GWAS: genome-wide association study; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SNPs: single nucleotide polymorphisms.

The CKDGen data and genetic instruments for kidney function

The CKDGen consortium performed a meta-analysis of 121 GWAS including 567 460 individuals of European ancestry for log-transformed eGFR and CKD stage ⩾3 (eGFR <60 mL·min^{-1}·1.73 m^{-2}), which was prevalent in 9% of the data [9] (https://ckdgen.imbi.uni-freiburg.de/). In addition, the study reported 256 index single nucleotide polymorphisms (SNPs) with genome-wide significance ($p<5\times10^{-8}$) and the lowest p-value within a 1-Mbp segment for log-transformed eGFR values in individuals of European ancestry. We downloaded the summary statistics for log-transformed eGFR and CKD as the outcome data for kidney function and trimmed the 256 index SNPs to construct the genetic instrument. The unit of the effect sizes for eGFR summary statistics was transformed as percentage change.

For a genetic instrument, as the eGFR values in the CKDGen data are based on creatinine levels, which can be affected by diet or body mass index, we assessed the associations of the SNPs with cystatin C-based eGFR values, which has some superiority over creatinine or blood urea nitrogen [10], in the individual-level UK Biobank data [8, 9]. The GWAS performed within quality-controlled 337 138 UK Biobank participants of white British ancestry was adjusted for age, sex, age×sex, age^2 and the first 10 genetic principal components. We excluded 115 SNPs that did not reach the Bonferroni-adjusted significance level ($p<0.5/256$) with cystatin C-eGFR values or those with regressed β-values in a different direction in the GWAS using the UK Biobank data, leaving 141 SNPs as the genetic instrument for eGFR (supplementary table S1).

GWAS and genetic instruments for FEV_1/FVC

We implemented previous GWAS results for FEV_1/FVC, which included 321 047 individuals of European ancestry with available quality-controlled lung function parameters from the UK Biobank [11]. The study performed a GWAS for the inverse normal transformed z-scores of FEV_1/FVC, adjusted for age, sex, smoking history and height; the summary statistics within the UK Biobank data are available in the public domain (http://ldsc.broadinstitute.org/ldhub/). We downloaded the summary statistics of the UK Biobank data as the outcome summary statistics for FEV_1/FVC.

The study reported 48 independent "tier 1" signals that had $p<5\times10^{-9}$ in the UK Biobank and were replicated in the same direction and had $p<10^{-3}$ in the SpiroMeta study, which is a multiethnic GWAS for lung function traits [12], and we implemented the SNPs as the genetic instrument for FEV_1/FVC (supplementary table S2).

Summary-level MR methods

Two-sample MR was performed because the CKDGen and UK Biobank data were independent. The two-sample method has advantages, as it is less biased by observational confounding effects than an MR analysis including overlapping samples.

The multiplicative random-effect inverse-variance weighted method was the main MR method used [13]. This method has strength over the fixed-effect model, as it allows balanced pleiotropic effects and can address the issue of heterogeneity among the variant-specific effects.

In addition, we performed multivariable MR analysis, adjusted for the genetic effects of potential confounders, which were hypertension, dyslipidaemia, diabetes, obesity, current smoking and height (supplementary methods). The genetic effect sizes of the associations were estimated by GWAS in the UK Biobank data, which included 337 138 unrelated white British individuals who passed the quality control filter and was adjusted for age, sex, age×sex, age^2 and the first 10 genetic principal components with PLINK 2.0 [14].

Additionally, we performed MR-Egger regression with bootstrapped standard error, which allows pleiotropic effects for implemented genetic instruments [15]. This method has strength in that it can assess the presence of directional pleiotropy through MR-Egger intercepts. However, this method has weaker statistical power than other MR methods and can still be biased towards false positive findings when a group of SNPs acts through a pleiotropic pathway, which is a violation of the Instrument Strength Independent of Direct Effect assumption [16]. Thus, we performed the weighted-median method, as recommended in the literature [16], which can yield valid causal estimates even when up to half of the instrumented genetic weights are invalid [17]. In addition, we performed MR-PRESSO analysis, which can detect and correct outlier effects [18].

Finally, to robustly attain the independence assumption of MR, we re-performed the analysis after disregarding the SNPs with a strong association ($p<1\times10^{-8}$) with the potential confounders identified in the GWAS in the UK Biobank data described earlier.

The MR analysis was performed using the two-sample MR and multivariable MR package, and a two-sided p-value <0.05 was considered significant [19, 20].

GWAS and polygenic score analysis with the individual-level UK Biobank data

We investigated individual-level UK Biobank data including 337 138 unrelated individuals of white British ancestry to assess binary obstructive lung disease outcomes, including FEV_1/FVC <70%, COPD and asthma [11], by polygenic score (PGS) analysis. The median (interquartile range (IQR)) FEV_1 and FEV_1/FVC values in the study population by best measure were 2.78 (2.31–3.37 L) and 76% (72–80%), respectively. COPD and asthma were algorithmically defined by the UK Biobank consortium identified through self-reports, International Classification of Diseases diagnostic codes and the death registry. There were 12 780 (3.8%) COPD and 44 585 (13.2%) asthma cases out of 337 138, including prevalent/incident cases, in the individual-level dataset. We additionally classified asthma events into child-onset (first diagnosis age <20 years, 13 987 cases), adult-onset (age ⩾20 years, 30 598 cases) and late-onset (age ⩾50 years, 13 377 cases) events. In the analysis, the kidney function PGS was calculated by multiplying the gene dosage matrix with the effect sizes of the genetic instruments with PLINK 2.0. The continuous allele score was included in the logistic regression model adjusted for age, sex, the first 10 genetic principal components, smoking status (none, ex-smoker, current smoker) and height [21].

Nonlinear MR analysis

Nonlinear MR analysis is possible with the availability of individual-level data within the UK Biobank [22]. We used a fractional polynomial method to investigate the shape of the association between eGFR and FEV_1/FVC (supplementary methods). The presence of nonlinearity and a significant nonlinear association between eGFR and FEV_1/FVC were evaluated with the "nlmr" package in R.

Additional exposures and outcomes assessed by summary-level MR

In addition to the main studied phenotypes, we additionally assessed the urine albumin/creatinine ratio, another important marker for defining kidney function impairment that was also assessed by the CKDGen consortium [23] as an additional exposure/outcome trait reflecting kidney function. Other spirometry phenotypes, including FEV_1 and FVC, with available summary statistics in the GWAS meta-analysis utilised were assessed in the bidirectional MR. We also assessed the association between genetically proxied COPD or asthma, predicted by the SNPs reported in previous GWASs that also investigated the UK Biobank data [24, 25], and kidney function outcomes. Detailed information on the materials and methods is described in the supplementary methods.

Sensitivity analysis with alternative summary statistics for lung function

As the original GWAS (which provided the summary statistics for lung function) was adjusted for genetically heritable traits (smoking or height), this may cause collider bias [26]. In addition, the GWAS was performed towards normal-transformed absolute FEV_1 or FVC value, but a value relative to predicted is a more valid parameter representing an individual's lung function [27]. Therefore, we generated the summary statistics for FEV_1 (z-score relative to predicted value [28]), FVC (z-score relative to predicted value) and FEV_1/FVC, not adjusted for height or smoking, and dealt the confounding effects by multivariable MR analysis with the aforementioned methods.

Results

MR analysis to assess causal estimates from kidney function to FEV_1/FVC

In summary-level MR, a genetic predisposition for higher eGFR was significantly associated with higher FEV_1/FVC levels (figure 2 and table 1). The MR-Egger intercept p-value indicated the absence of significant pleiotropy (p=0.818), and the causal estimates were significant by the multivariable MR analysis and pleiotropy-robust MR sensitivity analysis. The results were consistent even when we disregarded the SNPs with a strong association with the potential confounders (supplementary table S3).

In the PGS analysis, a genetic predisposition for higher eGFR was significantly associated with reduced odds of FEV_1/FVC <70%, COPD and late-onset (age ⩾50 years) asthma (table 2). For child-onset (age <20 years) or adult-onset (age ⩾20 years) asthma, the causal estimates were nonsignificant.

The nonlinear MR analysis again reported a significant association between genetically predicted eGFR and FEV_1/FVC with suspected nonlinearity (association p<0.001, nonlinearity p=0.062) (figure 3). The results demonstrated that the causal effects of eGFR loss on FEV_1/FVC decrease was particularly apparent in eGFR ranges <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$.

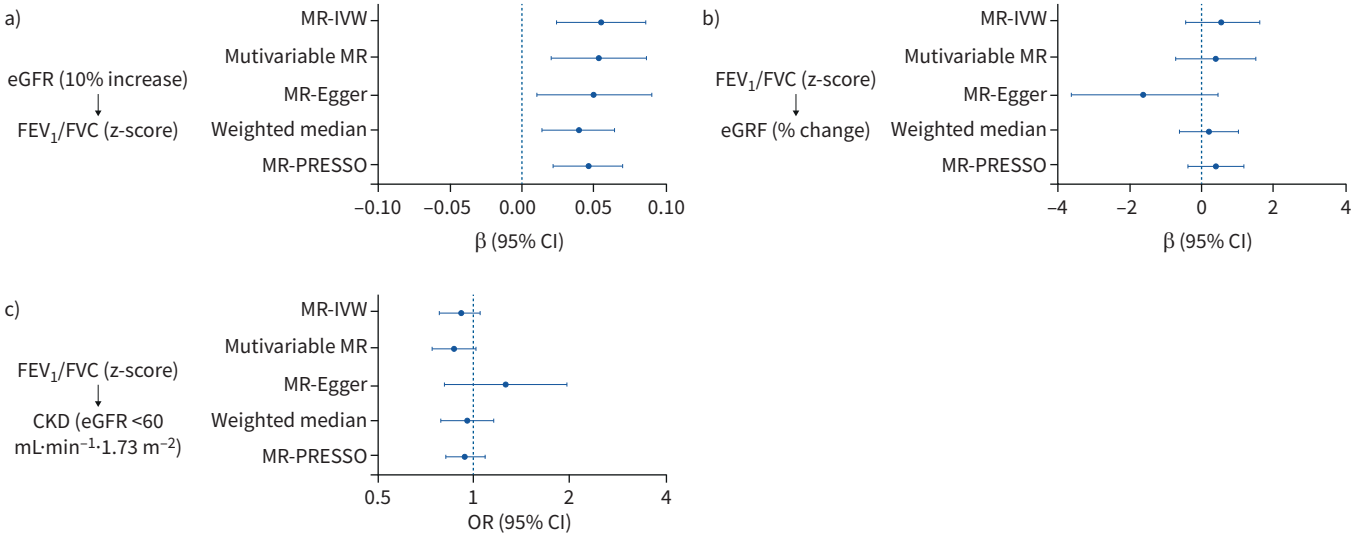

FIGURE 2 Graphical description of the summary-level Mendelian randomisation (MR) analysis results. a) Summary-level MR analysis results showing the causal estimates from a 10% increase in estimated glomerular filtration rate (eGFR) on forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio (z-score); b) summary-level MR results demonstrating the causal estimates from FEV_1/FVC (z-score) to eGFR % change; c) summary-level MR results showing the causal estimates from FEV_1/FVC (z-score) to CKD stage ⩾3, which was defined by eGFR <60 mL·min^{-1}·1.73 m^{-2}. MR-IVW: multiplicative random-effect inverse variance-weighted.

MR analysis to assess causal estimates of FEV_1/FVC on kidney function

A genetically predicted z-score increase in FEV_1/FVC was nonsignificantly associated with eGFR change or risk of CKD, as well as in the performed sensitivity analyses (figure 2, table 1 and supplementary table S3). The nonlinear MR analysis (figure 3) also reported a nonsignificant association between genetically predicted FEV_1/FVC and eGFR within the UK Biobank dataset (association p=0.765, nonlinearity p=0.791).

MR analysis with urine albumin-to-creatinine ratio, FVC, FEV_1 and genetically predicted obstructive lung disease traits

A summary of the instrumented SNPs for the additional phenotypes is presented in supplementary table S4. We found nonsignificant estimates from the urine albumin/creatinine ratio on FEV_1/FVC, and the

TABLE 1 Bidirectional summary-level Mendelian randomisation (MR) analysis results between kidney function and forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio

Genetically predicted exposure	Outcome	MR-Egger intercept p-value	Cochran's Q statistics p-value	MR method	OR# or β (95% CI)	p-value
eGFR (10% increase)	FEV_1/FVC (z-score)	0.818	<0.001	MR-IVW	0.055 (0.024–0.086)	<0.001
				Multivariable MR	0.053 (0.020–0.086)	0.002
				MR-Egger	0.050 (0.010–0.09)	0.003
				Weighted median	0.039 (0.014–0.064)	0.003
				MR-PRESSO	0.046 (0.021–0.070)	<0.001
FEV_1/FVC (z-score)	eGFR (% change)	0.514	<0.001	MR-IVW	0.568 (−0.458–1.605)	0.279
				Multivariable MR	0.376 (−0.750–1.514)	0.518
				MR-Egger	−1.634 (−3.654–0.429)	0.062
				Weighted median	0.188 (−0.632–1.015)	0.655
				MR-PRESSO	0.378 (−0.39–1.151)	0.341
FEV_1/FVC (z-score)	CKD (OR)	0.874	0.04	MR-IVW	0.91 (0.78–1.05)	0.206
				Multivariable MR	0.87 (0.74–1.02)	0.098
				MR-Egger	1.26 (0.81–1.95)	0.172
				Weighted median	0.95 (0.79–1.15)	0.609
				MR-PRESSO	0.94 (0.82–1.08)	0.396

eGFR: estimated glomerular filtration rate; MR-IVW: multiplicative random-effect inverse-variance weighted method; CKD: chronic kidney disease. #: odds ratio was calculated for CKD outcomes.

TABLE 2 Polygenic score analysis testing the causal estimates from kidney function to binary obstructive lung disease outcomes

	OR (95% CI)[#]	p-value
FEV_1/FVC <70%	0.93 (0.87–0.99)	<0.001
COPD	0.93 (0.87–0.99)	0.028
Asthma	0.98 (0.95–1.02)	0.284
Child-onset asthma (age <20 years)	0.99 (0.93–1.05)	0.729
Adult-onset asthma (age ⩾20 years)	0.98 (0.94–1.02)	0.309
Late-onset asthma (age ⩾50 years)	0.93 (0.88–0.99)	0.029

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: multivariable logistic regression model was constructed adjusted for age, sex, the first 10 genetic principal components, smoking status (none, ex-smoker or current smoker) and height.

reverse direction estimate was also null (supplementary table S5). Additionally, the bidirectional MR analysis with kidney function traits and FVC or FEV_1 did not report a significant finding. When we reassessed the causal estimates from obstructive lung disease on kidney function by genetically predicted COPD or asthma, the causal estimates remained nonsignificant.

Sensitivity analysis with alternative summary statistics for lung function

The causal estimates by multivariable MR analysis, using reweighted summary statistics unadjusted for height or smoking, remained similar as the main findings (supplementary table S6), and higher genetically predicted eGFR was significantly associated with higher FEV_1/FVC. For FEV_1 or FVC relative to predicted value, although the causal estimates were nonsignificant, the estimate from higher eGFR to FEV_1 (β=0.034, 95% CI −0.001–0.070; p=0.063) was larger than that to FVC (β=0.006, 95% CI −0.027–0.038; p=0.731).

Discussion

In this study, a higher genetically predicted eGFR was significantly associated with a higher FEV_1/FVC and a lower risk of both COPD and late-onset asthma. In contrast, the causal estimates from FEV_1/FVC on

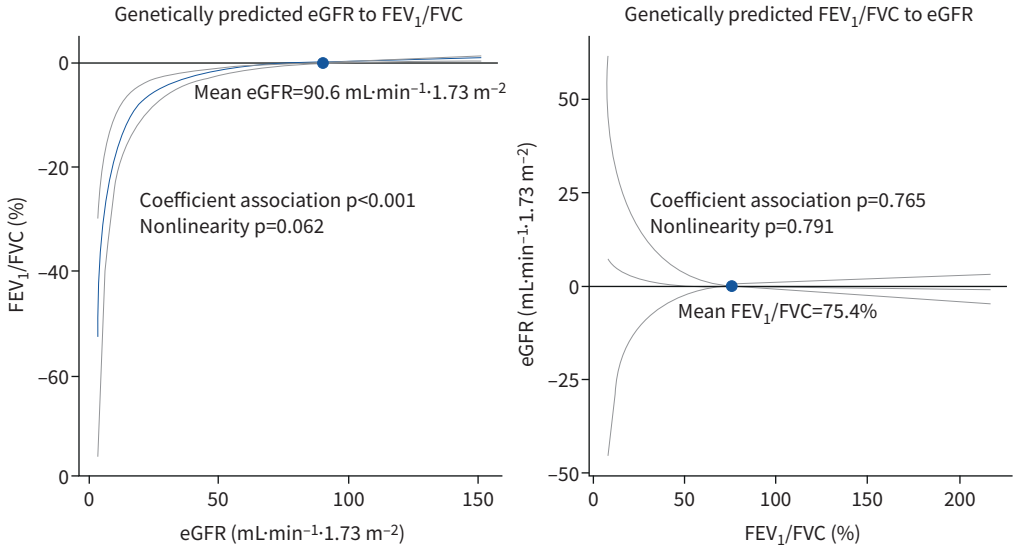

FIGURE 3 Nonlinear Mendelian randomisation analysis demonstrating the association between genetically predicted exposure and outcome. The strength of a nonlinear association and the nonlinear p-values are presented within the figure. The reference points were the mean value of the exposures (90.6 mL·min^{-1}·1.73 m^{-2} for estimated glomerular filtration rate (eGFR) and 75.4% for forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) values). The analysis was performed within the UK Biobank dataset, and white individuals of British ancestry passing the quality control filter and those with complete information for phenotypical eGFR and FEV_1/FVC best measurement value were included in the analysis.

eGFR and the risk of CKD were nonsignificant. Our study supports that eGFR loss would be a causal factor for obstructive lung disease.

A close association between kidney function and obstructive lung disease has been reported. In the National Health and Nutrition Examination Survey in the United States, decreased kidney function was associated with increased odds of obstructive lung disease [3]. Similar associations were identified in Chinese and Australian populations [29]. In the Atherosclerosis Risk in Communities study, reduced lung function was an independent predictor for an increased risk of CKD progression [5]. Conversely, in COPD patients, CKD was prevalent [30, 31], and the presence of asthma or COPD has been suggested as a risk factor for CKD [4, 32]. However, as delayed diagnosis is possible for both kidney function impairment and obstructive lung function, and as the two functional impairments share risk factors, a causal effect could not be confirmed through previous observational studies. In this MR investigation, the causal estimates from eGFR to FEV_1/FVC were significant, which was considered to be from a stronger effect from eGFR to FEV_1 than to FVC. The results supported the presence of causal effects from high eGFR to high FEV_1/FVC and the reduced risk of obstructive lung disease, including COPD and late-onset asthma.

MR requires three assumptions to be met to demonstrate causal effects [6]. The relevance assumption stating that the genetic instrument should be strongly associated with the exposure of interest was attained, as we implemented relevant SNPs reported from previous large GWASs. We made efforts to minimise the possibility of horizontal pleiotropy to attain the independence and restriction-exclusion assumptions by performing multivariable MR analysis or MR sensitivity analysis. As the results were consistent throughout the implemented methods, we successfully assessed the causal estimates between eGFR and FEV_1/FVC.

The current study results suggest that clinicians should monitor eGFR in obstructive lung disease patients. The nonlinear MR results emphasise that the causal effects would be mostly apparent in the eGFR ranges where overt CKD is usually defined. A future study may investigate whether appropriate management for preventing eGFR loss or delaying CKD progression, including interventions for metabolic disorders or appropriate volume control, is beneficial for lung function. Conversely, clinicians may screen lung function in individuals at high risk of CKD, particularly those with a common risk factor such as smoking behaviour, as the risk of COPD or late-onset asthma may be further increased due to low eGFR.

A hypothesis for the suggested causal effect can be found in the literature. In obstructive lung disease patients, an inappropriate volume status may cause poor prognosis or acute exacerbation events [33]. A previous *in vivo* experimental study suggested that alveolar oedema causes impairment in alveolar and lung compliance, leading to over-distension injury in air-filled alveoli [34]. As the kidney is the core organ for volume homeostasis, impaired kidney function may have a causal effect on lung function through inappropriate volume control. This is supported by the fact that fluid overload due to CKD was associated with obstructive lung function in haemodialysis patients and was relieved through ultrafiltration by dialysis [35]. However, as the consequences of reduced eGFR are diverse, various mechanisms, including distant effects from neurohormonal alteration, metabolic impairment and electrolyte disturbance may also be considered potential mechanisms related to the current findings.

The nonsignificant causal estimates from FEV_1/FVC on kidney function should be interpreted with caution. The UK Biobank cohort is a relatively healthy population; thus, the current signals for FEV_1/FVC may not reflect severe pulmonary dysfunction [36]. Therefore, the result may not show the causal effects from acute respiratory distress or severe hypoxaemia, which would certainly affect kidney function by causing ischaemic injury. In addition, as two-sample MR is prone to false-negative findings, it is possible that a modest degree of causal effects from FEV_1/FVC on kidney function may exist. What this study suggests is that the direction from kidney function to lung function may be prioritised rather than the reverse direction of causal effects in the general population.

There are several limitations to this study. First, as lung function is dynamic and subtypes of obstructive lung disease are diverse, the effects of reduced eGFR on various patient statuses (*e.g.* acute exacerbation or resting state) may be different. Second, the magnitude of the effect from relevant clinical intervention could not be determined through an MR study; thus, the clinical effects may differ in estimate sizes from the current genetic results [37]. Third, this study could not investigate the causal effects of kidney function on a subjective breathing symptom, which is also an important parameter of obstructive lung disease. That FEV_1/FVC is not the sole parameter for obstructive lung disease should be reminded. Last, the study was mainly limited to European ethnicity; thus, the generalisability of the current findings should be expanded in a future study.

In conclusion, this study showed that genetically predicted eGFR was significantly associated with obstructive lung disease. Early detection of eGFR decline and obstructive lung disease may be recommended in clinical guidelines for CKD and obstructive lung disease patients, respectively. Further studies may investigate the benefits of appropriate management of kidney function impairment with regard to the risk and prognosis of COPD or late-onset asthma.

Acknowledgements: The study was implemented through data provided by the UK Biobank consortium (application number 53799). We thank the investigators of the prior studies who provided the valuable genetic summary statistics for this study.

Data sharing: The data for this study are available in the public domain. The polygenic score for eGFR in the individual-level UK Biobank data will be made available in the consortium website. CKDGen data: https://ckdgen.imbi.uni-freiburg.de/; GWAS for FEV_1/FVC: https://ckdgen.imbi.uni-freiburg.de/; UK Biobank data: https://biobank.ndph.ox.ac.uk/showcase/

Conflict of interest: None declared.

Support statement: This work was supported by the Industrial Strategic Technology Development Program – Development of Bio-core Technology (10077474, Development of early diagnosis technology for acute/chronic renal failure) funded by the Ministry of Trade, Industry and Energy (MOTIE, Korea) and a grant from SNU R&DB Foundation (800-20190571). The study was performed independently by the authors. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Soriano JB, Kendrick PJ, Paulson KR, *et al.* Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2020; 8: 585–596.
2 Bikbov B, Purcell CA, Levey AS, *et al.* Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; 395: 709–733.
3 Navaneethan SD, Mandayam S, Arrigain S, *et al.* Obstructive and restrictive lung function measures and CKD: National Health and Nutrition Examination Survey (NHANES) 2007–2012. *Am J Kidney Dis* 2016; 68: 414–421.
4 Gaddam S, Gunukula SK, Lohr JW, *et al.* Prevalence of chronic kidney disease in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *BMC Pulm Med* 2016; 16: 158.
5 Sumida K, Kwak L, Grams ME, *et al.* Lung function and incident kidney disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2017; 70: 675–685.
6 Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* 2018; 362: k601.
7 Choi KW, Chen CY, Stein MB, *et al.* Assessment of bidirectional relationships between physical activity and depression among adults: a 2-sample mendelian randomization study. *JAMA Psychiatry* 2019; 76: 399–408.
8 Yu Z, Coresh J, Qi G, *et al.* A bidirectional Mendelian randomization study supports causal effects of kidney function on blood pressure. *Kidney Int* 2020; 98: 708–716.
9 Wuttke M, Li Y, Li M, *et al.* A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet* 2019; 51: 957–972.
10 Lees JS, Welsh CE, Celis-Morales CA, *et al.* Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. *Nat Med* 2019; 25: 1753–1760.
11 Shrine N, Guyatt AL, Erzurumluoglu AM, *et al.* New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. *Nat Genet* 2019; 51: 481–493.
12 Soler Artigas M, Wain LV, Repapi E, *et al.* Effect of five genetic variants associated with lung function on the risk of chronic obstructive lung disease, and their joint effects on lung function. *Am J Respir Crit Care Med* 2011; 184: 786–795.
13 Burgess S, Davey Smith G, Davies NM, *et al.* Guidelines for performing Mendelian randomization investigations. *Wellcome Open Res* 2020; 4: 186.
14 Chang CC, Chow CC, Tellier LC, *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* 2015; 4: 7.
15 Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015; 44: 512–525.
16 Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol* 2017; 32: 377–389.
17 Bowden J, Davey Smith G, Haycock PC, *et al.* Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol* 2016; 40: 304–314.

18 Verbanck M, Chen CY, Neale B, *et al.* Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* 2018; 50: 693–698.
19 Hemani G, Zheng J, Elsworth B, *et al.* The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018; 7: e34408.
20 Sanderson E, Davey Smith G, Windmeijer F, *et al.* An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings. *Int J Epidemiol* 2019; 48: 713–727.
21 Choi SW, Mak TS, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. *Nat Protoc* 2020; 15: 2759–2772.
22 Staley JR, Burgess S. Semiparametric methods for estimation of a nonlinear exposure-outcome relationship using instrumental variables with application to Mendelian randomization. *Genet Epidemiol* 2017; 41: 341–352.
23 Teumer A, Li Y, Ghasemi S, *et al.* Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria. *Nat Commun* 2019; 10: 4130.
24 Sakornsakolpat P, Prokopenko D, Lamontagne M, *et al.* Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. *Nat Genet* 2019; 51: 494–505.
25 Johansson Å, Rask-Andersen M, Karlsson T, *et al.* Genome-wide association analysis of 350 000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema. *Hum Mol Genet* 2019; 28: 4022–4041.
26 Aschard H, Vilhjálmsson BJ, Joshi AD, *et al.* Adjusting for heritable covariates can bias effect estimates in genome-wide association studies. *Am J Hum Genet* 2015; 96: 329–339.
27 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-year age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
28 Gupta RP, Strachan DP. Ventilatory function as a predictor of mortality in lifelong non-smokers: evidence from large British cohort studies. *BMJ Open* 2017; 7: e015381.
29 Yu D, Chen T, Cai Y, *et al.* Association between pulmonary function and renal function: findings from China and Australia. *BMC Nephrol* 2017; 18: 143.
30 Incalzi RA, Corsonello A, Pedone C, *et al.* Chronic renal failure: a neglected comorbidity of COPD. *Chest* 2010; 137: 831–837.
31 van Gestel YR, Chonchol M, Hoeks SE, *et al.* Association between chronic obstructive pulmonary disease and chronic kidney disease in vascular surgery patients. *Nephrol Dial Transplant* 2009; 24: 2763–2767.
32 Huang HL, Ho SY, Li CH, *et al.* Bronchial asthma is associated with increased risk of chronic kidney disease. *BMC Pulm Med* 2014; 14: 80.
33 Kantor DB, Hirshberg EL, McDonald MC, *et al.* Fluid balance is associated with clinical outcomes and extravascular lung water in children with acute asthma exacerbation. *Am J Respir Crit Care Med* 2018; 197: 1128–1135.
34 Perlman CE, Lederer DJ, Bhattacharya J. Micromechanics of alveolar edema. *Am J Respir Cell Mol Biol* 2011; 44: 34–39.
35 Yılmaz S, Yildirim Y, Yilmaz Z, *et al.* Pulmonary function in patients with end-stage renal disease: effects of hemodialysis and fluid overload. *Med Sci Monit* 2016; 22: 2779–2784.
36 Fry A, Littlejohns TJ, Sudlow C, *et al.* Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 2017; 186: 1026–1034.
37 Burgess S, Butterworth A, Malarstig A, *et al.* Use of Mendelian randomisation to assess potential benefit of clinical intervention. *BMJ* 2012; 345: e7325.