Association between pulmonary function and rapid kidney function decline: a longitudinal cohort study from CHARLS

Shisheng Han, Yanqiu Xu, Yi Wang

ABSTRACT

Background Pulmonary function has been reported to be associated with chronic kidney disease. However, the relationship between lung function and rapid kidney function decline remains unclear.

Methods Participants aged ≥45 years with complete data from the 2011 and 2015 interviews of the China Health and Retirement Longitudinal Study (CHARLS) were included. Lung function, assessed by peak expiratory flow (PEF), and kidney function, assessed by estimated glomerular filtration rate (eGFR), were tested at the baseline and endpoint surveys. Rapid kidney function decline was defined as a decrease in eGFR ≥3mL/min/1.73 m²/year, and ΔeGFR represented the difference between baseline and endpoint eGFR. Multivariate logistic regression models and linear regression models were employed to evaluate the association between PEF and the risk of rapid eGFR decline, as well as the correlation between PEF and ΔeGFR.

Results A total of 6159 participants were included, with 1157 (18.78%) individuals experiencing a rapid decline in eGFR. After adjusting for potential covariates, higher baseline PEF (Quartile 4 vs Quartile 1, OR=0.95, 95% CI 0.92 to 0.98) and elevated PEF % predicted (OR=0.96, 95% CI 0.94 to 0.99) were found to be associated with a lower risk of rapid eGFR decline. ΔeGFR decreased by 0.217 and 0.124 mL/min/1.73 m² for every 1 L/s increase in baseline PEF (β (95% CI): −0.217 (−0.393 to −0.042)) and 10% increase in PEF % predicted (β (95% CI): −0.124 (−0.237 to −0.011)), respectively. During the follow-up period, ΔeGFR decreased as PEF increased over time among participants in Quartile 1 (β per 1 L/s increase in ΔPEF=−0.581, 95% CI −1.003 to −0.015; β per 10% increase in ΔPEF % predicted=−0.279, 95% CI −0.515 to −0.043).

Conclusions Higher PEF was associated with a slower longitudinal eGFR decline in middle-aged and older adults.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pulmonary function has been previously associated with chronic kidney disease, and there is existing knowledge about the connection between lung and kidney health.

WHAT THIS STUDY ADDS

⇒ This study adds to the existing knowledge by demonstrating that higher peak expiratory flow (PEF) and PEF % predicted are associated with a reduced risk of rapid kidney function decline. It provides new evidence of the beneficial effect of improved lung function on slowing the progression of kidney disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study suggest that targeted improvement in lung function may be beneficial in delaying the progression of renal failure. This could have implications for clinical practice, encouraging interventions to enhance lung function in middle-aged and older adults to potentially mitigate kidney function decline.

INTRODUCTION

Chronic kidney disease (CKD) and chronic lower respiratory diseases pose substantial challenges to global public health, marked by an unfavourable prognosis characterised by elevated mortality rates.1 In recent years, the spotlight has focused on the correlation between lung and kidney health, as lung and kidney function are closely related, both in health and in disease.2 3 Reduced lung function has been linked to an increased long-term risk of developing chronic obstructive pulmonary disease (COPD) and higher prevalences of diabetes, obstructive sleep apnea, hypertension and heart attacks.4 Respiratory complications may directly or indirectly result from circulating uremic toxins, volume overload, electrolyte disorders, acid-base imbalances, cardiovascular alterations and malnutrition, as the estimated glomerular filtration rate (eGFR) declines.5 Additionally, reduced respiratory function, leading to hypoxia and systemic inflammation, has been associated with the occurrence and progression of CKD.6 According to the National Health and Nutrition Examination Survey, the prevalence of respiratory dysfunction increased in patients with CKD to 10% for restrictive and 16% for obstructive lung function.7 Furthermore, albuminuria, a crucial marker of glomerular impairment, has also been linked to the decline in respiratory function and the incidence of COPD.8 Yu et al consistently identified a non-linear dose–response
association between lung capacity measurements and the risk of reduced kidney function in both Chinese and Australian participants through two independent cross-sectional studies. Peak expiratory flow (PEF), representing the instantaneous velocity of expiratory flow during forced spirometry, serves as an easily accessible lung function index for screening impaired pulmonary function in adults aged 40 years or older. According to the interpretive strategies for lung function outlined by the American Thoracic Society and European Respiratory Society, PEF may assist in diagnosing impaired expiratory muscle function, central airflow obstruction and intrapulmonary airway narrowing produced by premature airway collapse, bronchoconstriction or airway inflammation, wall thickening or oedema. PEF is also more sensitive for early identification of central and upper airway obstruction compared with forced expiratory volume in 1 s (FEV1) and/or forced vital capacity (FVC). Recently, PEF was found to be negatively associated with CKD stages. Moreover, reduced pulmonary function has been identified as a risk factor for future incidents of CKD, end-stage renal disease (ESRD) or death during follow-ups of 41 years and 23.6 years in two cohorts. These findings underscore the connection between impaired lung function and adverse long-term outcomes in CKD. However, few studies have focused on the role of lung function in the rapid decline of renal function in CKD populations or in general community-dwelling individuals. In this study, we aimed to investigate the longitudinal association between pulmonary function and the risk of rapid eGFR decline using data from the China Health and Retirement Longitudinal Study (CHARLS).

**METHODS**

**Study population**

The data for this study were sourced from CHARLS, a nationwide longitudinal survey targeting Chinese community-dwelling adults aged 45 years or older from 28 provinces in China. The baseline survey was conducted in 2011, encompassing 150 county-level units and 450 village-level units. The CHARLS protocol was approved by the Biomedical Ethics Review Committee of Peking University (approval number for the household survey: IRB00001052-11015; for biomarker collection: IRB00001052-11014), and informed consents were signed by all the participants.

A total of 17,705 participants were included in the baseline survey in 2011, of which 7448 participants underwent blood tests in both 2011 and 2015. Among them, 6219 participants had available lung function data at both baseline and endpoint. After excluding 60 participants with malignant tumours, 6159 participants were ultimately included for analysis in this study. The participant selection process is visually outlined in figure 1, detailing the sequential steps used to identify the study cohort.

**Measurement of standard biochemistry**

Blood specimens were collected by staff from the Chinese Centre for Disease Control and Prevention (China CDC), subsequently centrifuged and stored at −20°C in local CDC laboratories. These samples were then transported to the CDC in Beijing within 2 weeks and stored at −80°C. The sample assays were conducted at the Youanmen Centre for Clinical Laboratory of Capital Medical University. To detect serum creatinine levels, the rate-blanked and compensated Jaffe creatinine method was employed. During the testing of CHARLS study samples, the laboratory conducted daily checks using quality control samples. Importantly, all test results from these quality control samples fell within the desired target range.

**Exposure**

Lung function, assessed via PEF, was measured using a peak flow metre equipped with a disposable mouthpiece (Everpure Medical Plastic Co, Shanghai, China). Participants were instructed to stand, take a deep breath, position their lips around the outer edge of the mouthpiece and exhale with maximal effort. Three measurements of PEF were taken at 30-s intervals. The highest value among the three PEF results was used for analysis in this study. PEF was assessed at both baseline and endpoint surveys, and APEF was calculated by subtracting the baseline value from the endpoint value. To further enhance the accuracy of lung function evaluation, the ratio of the PEF value to the predicted PEF was also used as an additional exposure. The predicted PEF was calculated using previously validated Zhong Nanshan equations for Chinese adults: $\text{APEF} = \frac{68\times\text{height} − 68\times\text{age}^3 + 0.002\times\text{age}^2 + 1.19}{\text{age} + 0.68}\times\text{height for females}.$

![Figure 1 Flowchart of participant selection. CHARLS, China Health and Retirement Longitudinal Study.](image-url)
Outcome

Kidney function was assessed through eGFR, which was calculated using the CKD-EPI creatinine equation. The eGFR of participants in 2011 and 2015 served as indicators of kidney function at the baseline and endpoint, respectively. Rapid kidney function decline was defined as an eGFR decrease of ≥3 mL/min/1.73 m²/year. Additionally, ΔeGFR, representing the disparity between a participant’s baseline eGFR and the endpoint eGFR, was calculated as an alternative outcome measure.

Covariates

Numerous confounding factors that have previously shown associations with lung function and kidney function decline were identified as covariates, including demographic factors, body mass index (BMI) and obesity, exposure to vapours, gases, dust and fumes (VGDF), living close to traffic, drinking habits, smoking status, hyperuricemia, dyslipidaemia and various comorbidities, such as diabetes, stroke, cardiovascular diseases, hypertension, CKD, chronic lung diseases, allergy and asthma.

The baseline demographic and clinical characteristics were recorded through questionnaires, interviews, blood tests and physical examinations. Smoking status was divided into three categories: never smokers, current smokers and former smokers. Participants who had smoked fewer than 100 cigarettes during their lifetime were classified as never smokers. Those who had smoked more than 100 cigarettes and were currently smoking were considered current smokers. Participants who had smoked more than 100 cigarettes but had quit smoking were classified as former smokers. Drinking behaviour was also classified into three categories: never drinkers, frequent drinkers who drank more than once a month and occasional drinkers who drank less than once a month. Hypertension was identified based on self-reported medical diagnoses or systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg during the physical examination. Diabetes was defined as a medical diagnosis of diabetes or having a glycated haemoglobin A1c level of ≥7.0%. CKD was defined as a medical diagnosis of nephropathy by a doctor or an eGFR <60 mL/min/1.73 m². Chronic lung diseases include chronic bronchitis, emphysema or pulmonary heart disease, as diagnosed by a doctor. Other comorbidities, including stroke, cardiovascular disease and asthma, were diagnosed by doctors based on questionnaires. Living close to traffic was defined as residing within a distance of <200 m from a major road, bus stop or train station. Exposure to VGDF was defined as community coal heating or industrial pollution sites within the community.

Statistical analysis

Descriptive statistics were reported as numbers (percentages) for categorical variables and as medians with IQR for continuous variables. Baseline characteristics were compared among participants in different baseline PEF quartiles (Q1–Q4) using appropriate statistical tests, including one-way analysis of variance, Kruskal-Wallis or the χ² test.

A multivariate logistic regression model was used to evaluate the association between PEF quartiles and the risk of rapid decline of eGFR, and a multivariate linear regression model was employed to examine the associations between PEF and ΔeGFR. Three regression models were applied. Model 1 was not adjusted for any covariates. Model 2 was adjusted for age (continuous) and sex (male or female). Model 3 was further adjusted for obesity (yes or no), smoking status (former, current or never), drinking behaviour (frequent, occasional or never), baseline kidney function represented by eGFR (continuous), total cholesterol (continuous), low-density lipoprotein (continuous), serum uric acid (continuous), CKD (yes or no), hypertension (yes or no), diabetes (yes or no), stroke (yes or no), cardiovascular diseases (yes or no), asthma (yes or no), chronic lung diseases (yes or no), living close to traffic (yes or no) and exposure to VGDF (yes or no).

To assess the association between PEF changes from baseline to endpoint and ΔeGFR, baseline PEF was further adjusted in Model 3. A restricted cubic spline analysis was employed to explore the dose–response relationship between PEF and the specified outcomes, and non-linear associations were assessed using the likelihood ratio test.

Subgroup analyses were conducted to investigate the associations in various subgroups, considering factors such as sex (male or female), age (≥60 or <60 years), CKD (yes or no), chronic lung diseases (yes or no), smoking status (current, former or never) and asthma (yes or no).

Several sensitivity analyses were performed to test the robustness of the results. These included the exclusion of the extreme 5% of baseline PEF outliers to mitigate their potential influence, the exclusion of participants with neurodegenerative diseases to reduce potential bias related to comorbidities in PEF testing and an analysis of the correlation between PEF and a more rapid decline in kidney function defined as an eGFR decline of ≥4 mL/min/1.73 m²/year.

All statistical analyses were conducted using R Studio (V.2022.07.2 Build 576, open-source edition). A two-sided p value less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the included participants

The characteristics stratified by quartiles of baseline PEF levels among the included 6159 participants are presented in table 1. The median age of the participants was 58 years (IQR 52–64), with 54.59% being female. The median baseline PEF was 290 L/min (IQR 200–370), with a median PEF % predicted of 76.62% (IQR 56.68–94.76%). The median endpoint PEF was 300 L/min (IQR 227–380), and the median endpoint PEF % predicted was 85.57% (IQR 66.39%–103.36%). Participants with higher PEF tended to be younger (Q4 vs Q1: median age 55 (IQR 49–61) vs 62 (IQR 56–69) years) and were less likely to be female (Q4 vs Q1: 21.37% vs 68.85%).
Table 1  Characteristics of included participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>Baseline PEF (L/min)</th>
<th>Quartile 1 (≤200)</th>
<th>Quartile 2 (201–290)</th>
<th>Quartile 3 (291–370)</th>
<th>Quartile 4 (&gt;370)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>6159</td>
<td>1605</td>
<td>1567</td>
<td>1499</td>
<td>1488</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline PEF % predicted</td>
<td>76.62 (56.68, 94.76)</td>
<td>45.69 (35.37, 54.57)</td>
<td>70.76 (61.34, 79.19)</td>
<td>88.26 (76.55, 98.03)</td>
<td>103.13 (90.64, 115.82)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Endpoint PEF, L/min</td>
<td>300 (227, 380)</td>
<td>215 (150, 290)</td>
<td>270 (220, 330)</td>
<td>320 (270, 372)</td>
<td>420 (350, 480)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Baseline eGFR, mL/min/1.73 m²</td>
<td>95.30 (85.01, 102.71)</td>
<td>93.06 (82.64, 100.56)</td>
<td>95.71 (86.02, 102.28)</td>
<td>96.15 (86.12, 103.89)</td>
<td>96.69 (86.13, 103.93)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Endpoint eGFR, mL/min/1.73 m²</td>
<td>91.80 (80.81, 99.14)</td>
<td>89.35 (77.35, 96.68)</td>
<td>92.42 (81.45, 99.41)</td>
<td>92.59 (81.46, 100.11)</td>
<td>93.28 (82.28, 99.83)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Rapid kidney decline, no. %</td>
<td>1157 (18.78%)</td>
<td>330 (20.56%)</td>
<td>299 (19.08%)</td>
<td>282 (18.81%)</td>
<td>246 (16.53%)</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>Age, year</td>
<td>58 (52, 64)</td>
<td>62 (56, 69)</td>
<td>59 (52, 65)</td>
<td>57 (50, 63)</td>
<td>55 (49, 61)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sex, no. female %</td>
<td>3362 (54.59%)</td>
<td>1105 (68.85%)</td>
<td>1078 (68.79%)</td>
<td>861 (57.44%)</td>
<td>318 (21.37%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.29 (21.05, 25.94)</td>
<td>22.75 (20.45, 25.39)</td>
<td>23.20 (20.87, 26.04)</td>
<td>23.75 (21.49, 26.10)</td>
<td>23.60 (21.44, 26.07)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>190.59 (167.01, 214.95)</td>
<td>190.98 (167.78, 216.50)</td>
<td>190.98 (168.94, 214.76)</td>
<td>191.37 (165.85, 216.50)</td>
<td>187.89 (165.08, 212.63)</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>113.66 (92.78, 136.47)</td>
<td>112.89 (92.40, 135.31)</td>
<td>114.05 (94.33, 135.70)</td>
<td>115.01 (92.01, 139.18)</td>
<td>112.31 (92.01, 134.83)</td>
<td>0.244</td>
<td></td>
</tr>
<tr>
<td>C reactive protein, mg/L</td>
<td>0.99 (0.54, 2.08)</td>
<td>1.02 (0.56, 2.24)</td>
<td>0.97 (0.53, 2.10)</td>
<td>1.02 (0.55, 1.99)</td>
<td>0.97 (0.53, 1.94)</td>
<td>0.584</td>
<td></td>
</tr>
<tr>
<td>Uric acid, mg/L</td>
<td>4.23 (3.53, 5.08)</td>
<td>4.10 (3.48, 4.94)</td>
<td>4.08 (3.42, 4.86)</td>
<td>4.18 (3.49, 5.07)</td>
<td>4.59 (3.83, 5.45)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Smoking status, no. %</td>
<td>1838 (29.95%)</td>
<td>364 (22.82%)</td>
<td>344 (22.02%)</td>
<td>442 (29.55%)</td>
<td>688 (46.36%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Drinking behaviour, no. %</td>
<td>498 (8.11%)</td>
<td>125 (7.84%)</td>
<td>85 (5.44%)</td>
<td>96 (6.42%)</td>
<td>192 (12.94%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease, no. %</td>
<td>4132 (61.94%)</td>
<td>1106 (69.34%)</td>
<td>1133 (72.54%)</td>
<td>958 (64.04%)</td>
<td>604 (40.70%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Chronic lower respiratory disease, no. %</td>
<td>1538 (24.99%)</td>
<td>314 (19.59%)</td>
<td>286 (18.26%)</td>
<td>350 (23.35%)</td>
<td>588 (39.57%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease, no. %</td>
<td>484 (7.86%)</td>
<td>97 (6.05%)</td>
<td>97 (6.19%)</td>
<td>122 (8.14%)</td>
<td>168 (11.31%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hypertension, no. %</td>
<td>4132 (67.14%)</td>
<td>1192 (74.36%)</td>
<td>1183 (75.54%)</td>
<td>1027 (68.51%)</td>
<td>730 (49.13%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Asthma, no. %</td>
<td>524 (8.51%)</td>
<td>176 (10.97%)</td>
<td>114 (7.28%)</td>
<td>126 (8.41%)</td>
<td>108 (7.26%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease, no. %</td>
<td>723 (11.82%)</td>
<td>257 (16.14%)</td>
<td>194 (12.48%)</td>
<td>152 (10.17%)</td>
<td>120 (8.12%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Living close to traffic, no. %</td>
<td>619 (10.10%)</td>
<td>294 (18.44%)</td>
<td>134 (8.60%)</td>
<td>106 (7.09%)</td>
<td>85 (5.74%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Exposure to vapours, gases, dust and fumes, no.</td>
<td>980 (15.91%)</td>
<td>224 (13.96%)</td>
<td>254 (16.21%)</td>
<td>242 (16.14%)</td>
<td>260 (17.47%)</td>
<td>0.059</td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables are shown as medians (25th and 75th percentiles), and categorical variables are described as numbers (percentages). eGFR, estimated glomerular filtration rate; PEF, peak expiratory flow.
Individuals with higher PEF had higher levels of eGFR, both at baseline (Q4 vs Q1: 96.69 (IQR 86.13–103.93) vs 93.06 (IQR 82.64–100.56) mL/min/1.73 m²) and at the endpoint (Q4 vs Q1: 93.28 (IQR 82.28–99.83) vs 89.35 (IQR 77.35–96.68) mL/min/1.73 m²). Participants with increased PEF also had higher levels of serum uric acid (Q4 vs Q1: 4.59 (IQR 3.83–5.45) vs 4.10 (IQR 3.48–4.94) mg/dL) and a higher BMI (Q4 vs Q1: 23.60 (IQR 21.44–26.07) vs 22.75 (IQR 20.45–25.39) kg/m²). Furthermore, individuals with higher PEF showed a lower prevalence of CKD (Q4 vs Q1: 7.26% vs 10.97%), hypertension (Q4 vs Q1: 22.61% vs 27.75%), chronic lung diseases (Q4 vs Q1: 5.74% vs 18.44%), cardiovascular diseases (Q4 vs Q1: 8.12% vs 16.14%) and asthma (Q4 vs Q1: 1.22% vs 7.58%). No significant difference in the prevalence of diabetes was found among participants with different quartiles of PEF, and there were no notable differences in serum levels of cholesterol, low-density lipoprotein or C reactive protein.

**Association between baseline PEF and the risk of rapid kidney function decline**

After a 4-year follow-up period, 1157 (18.78%) participants experienced a rapid decline in eGFR. Individuals with the highest quartile of baseline PEF exhibited a reduced risk of rapid eGFR decline compared with those with the lowest quartile of baseline PEF across all three regression models (Q4 vs Q1: Model 1, OR=0.96, 95% CI 0.93 to 0.99, p=0.004; Model 2, OR=0.95, 95% CI 0.92 to 0.98, p=0.002; Model 3, OR=0.95, 95% CI 0.92 to 0.98, p=0.002). Similarly, a higher quartile of baseline PEF % predicted was also associated with a reduced risk of rapid renal function decline during follow-up (Q4 vs Q1: Model 1, OR=0.97, 95% CI 0.94 to 0.99, p=0.008; Model 2, OR=0.96, 95% CI 0.94 to 0.99, p=0.009; Model 3, OR=0.96, 95% CI 0.94 to 0.99, p=0.013) (table 2).

**Association between baseline PEF and ΔeGFR**

Using multivariate linear regression models, we observed a negative association between baseline PEF and ΔeGFR (Model 1: β=−0.203, 95% CI −0.358 to −0.049, p=0.009; Model 2: β=−0.298, 95% CI −0.473 to −0.123, p=0.008; Model 3: β=−0.217, 95% CI −0.393 to −0.042, p=0.015). Similarly, we found a negative correlation between baseline PEF % predicted and ΔeGFR (Model 1: β=−0.203, 95% CI −0.358 to −0.049, p=0.009; Model 2: β=−0.298, 95% CI −0.473 to −0.123, p=0.008; Model 3: β=−0.217, 95% CI −0.393 to −0.042, p=0.015). In the restricted cubic spline analysis performed to investigate the dose–response relationships between baseline PEF and the rapid decline of eGFR (figure 2A–D), we identified a linear negative association between PEF and ΔeGFR, as well as between PEF and the risk of rapid eGFR decline. Similar correlations were also observed between baseline PEF % predicted and rapid kidney function decline.

**Association between PEF changes and ΔeGFR**

Although no associations were found between changes in PEF/PEF % predicted and ΔeGFR during follow-up, a negative association between ΔPEF and ΔeGFR was observed in individuals in Q4 of baseline PEF, after adjusting for potential confounding factors (Model 3: β per 1 L/s increase in ΔPEF=−0.581, 95% CI −1.003 to −0.158, p=0.007; β per 10% increase in ΔPEF % predicted=−0.329, 95% CI −0.515 to −0.043, p=0.020) (table 4). Similarly, the risk of rapid eGFR decline decreased by 2% and 1% for every 1 L/s increase in PEF and 10% increase in PEF % predicted, respectively (Model 3: ΔeGFR, OR=0.98, 95% CI 0.97 to 0.99, p=0.002; ΔPEF % predicted, OR=0.99, 95% CI 0.98 to 1.00, p=0.010) (table 4).

### Table 2: Associations between PEF and rapid estimated glomerular filtration rate decline

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2 OR (95% CI)</th>
<th>P value</th>
<th>Quartile 3 OR (95% CI)</th>
<th>P value</th>
<th>Quartile 4 OR (95% CI)</th>
<th>P value</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Reference</td>
<td>0.99</td>
<td>(0.96 to 1.01)</td>
<td>0.286</td>
<td>0.98</td>
<td>(0.96 to 1.01)</td>
<td>0.212</td>
</tr>
<tr>
<td>Model 2</td>
<td>Reference</td>
<td>0.99</td>
<td>(0.96 to 1.02)</td>
<td>0.418</td>
<td>0.98</td>
<td>(0.96 to 1.01)</td>
<td>0.292</td>
</tr>
<tr>
<td>Model 3</td>
<td>Reference</td>
<td>0.98</td>
<td>(0.96 to 1.01)</td>
<td>0.233</td>
<td>0.98</td>
<td>(0.96 to 1.01)</td>
<td>0.254</td>
</tr>
<tr>
<td>PEF % predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Reference</td>
<td>0.98</td>
<td>(0.95 to 1.01)</td>
<td>0.149</td>
<td>0.97</td>
<td>(0.95 to 1.00)</td>
<td>0.062</td>
</tr>
<tr>
<td>Model 2</td>
<td>Reference</td>
<td>0.98</td>
<td>(0.96 to 1.01)</td>
<td>0.216</td>
<td>0.98</td>
<td>(0.95 to 1.01)</td>
<td>0.120</td>
</tr>
<tr>
<td>Model 3</td>
<td>Reference</td>
<td>0.98</td>
<td>(0.95 to 1.01)</td>
<td>0.171</td>
<td>0.98</td>
<td>(0.95 to 1.00)</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Model 1 was an unadjusted model, and Model 2 was adjusted for age (continuous) and sex (male or female). Model 3 was further adjusted for obesity (yes or no), smoking status (former, current or never), drinking behaviour (frequent, occasional or never), baseline kidney function, diabetes (yes or no), stroke (yes or no), chronic kidney disease (yes or no), hypertension (yes or no), diabetes (yes or no), stroke (yes or no), cardiovascular disease (yes or no), asthma (yes or no), and chronic lung disease (yes or no), living close to traffic (yes or no) and exposure to vapours, gases, dust, fumes and industrial pollution (yes or no).
Subgroup analysis

Subgroup analyses were conducted based on various characteristics, including age, sex, CKD, chronic lung diseases, smoking status and asthma, as shown in figure 3. We found that higher baseline PEF and elevated PEF % predicted were associated with a reduced risk of rapid eGFR decline in males, participants aged over 60 years and current smokers. However, this association was not significant in females, those under 60 years old and former or never smokers. Regardless of the presence of CKD, PEF exhibited a renoprotective effect by slowing the decline of eGFR. However, this beneficial effect was only evident in individuals without chronic lung disease (Q4 vs Q1: Model 3, OR=0.95, 95% CI 0.92 to 0.98, p=0.004) and participants without asthma (Q4 vs Q1: Model 3, OR=0.95, 95% CI 0.92 to 0.98, p=0.002), while it was not observed in those with chronic lung diseases and asthma.

Sensitivity analysis

When the participants with extreme 5% of baseline PEF were excluded (<110 or >900 L/min), the results indicated that elevated PEF could reduce the risk of rapid eGFR decline, but no such effect was observed for PEF % predicted (table 5). Additional sensitivity analysis demonstrated robust findings even after removing subjects with Alzheimer’s disease, brain atrophy and Parkinson’s disease. Furthermore, when using ΔeGFR >4 mL/min/1.73 m²/year as an outcome, the results remained stable.

DISCUSSION

This cohort study provided evidence that lung function, defined as PEF and PEF % predicted, was negatively associated with the risk of rapid kidney function decline. Higher baseline lung function was associated with a slower decline in eGFR, and these associations were found to be linear through dose–response analysis. Subgroup analysis further revealed that the protective effect of high PEF on kidney function is particularly prominent in males, individuals over 60 years old, current smokers and those without chronic lung diseases and asthma. Interestingly, this protective effect holds true whether an individual has CKD or not, as higher PEF is consistently correlated with a reduced risk of renal function decline.

Previous studies have indeed indicated an association between lung dysfunction and the degree of kidney function impairment, even in diabetic kidney disease. In line with these findings, our cohort study confirmed a negative association between PEF and eGFR, both at the baseline and endpoint surveys. Moreover, our study suggested that an increase in baseline PEF was correlated with a reduced rate of eGFR decline, indicating that improved lung function may lower the risk of rapid kidney function deterioration and delay the progression of kidney disease. Our further analysis of the association between PEF changes over time and renal function decline confirmed this, particularly among individuals...
with low baseline PEF. These results aligned with a study by Pelaia et al., who found that patients with COPD with a rapid decline in renal function, defined by an eGFR decrease of >5 mL/min/1.73 m²/year, had significantly lower FEV1, FVC and FEV1/FVC.31 Impaired pulmonary function has been linked to factors such as malnutrition, inflammation, protein-energy wasting and cardiovascular disease, in both early CKD, advanced CKD and ESRD.32 33 These factors have indeed been associated with the severity and progression of CKD, as indicated in previous studies.34–36 PEF monitoring, as an easily accessible lung function index, has been found to be non-inferior to spirometry for screening purposes of lung dysfunction.37 Additionally, PEF has been described as a component of the diagnosis of respiratory sarcopenia, which is associated with worsened renal function and a high risk of ESRD.38–40

Hypoxia has been recognised as a pivotal factor in the pathogenesis of CKD progression, inducing damage to renal tubular epithelial cells and subsequent fibroblast proliferation and inflammatory reactions, collectively leading to tubulointerstitial fibrosis.41 Consequently, both systemic and local hypoxia, arising from diminished lung function, may play a role in advancing CKD through tubulointerstitial injury. Many cytokines have been reported to play a role in the bidirectional crosstalk...
between the lungs and kidneys. Systemic inflammation triggered by hypoxia can contribute to the development of pulmonary and systemic endothelial dysfunction, which, in turn, leads to emphysema, pulmonary arterial hypertension and chronic renal injury. Interleukin-6 (IL-6), a well-known cytokine produced by pulmonary cells, enters the systemic circulation and induces inflammatory damage to renal tubules through the recruitment

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PEF (Q4 vs. Q1)</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>P interaction</th>
<th>PEF% pred(Q4 vs. Q1)</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3 Subgroup analysis between peak expiratory flow and rapid kidney function decline. Regression model was adjusted for age (continuous), sex (male or female), obesity (yes or no), smoking status (former, current, or never), drinking behaviour (frequent, occasional or never), baseline kidney function (continuous), baseline PEF (continuous), total cholesterol (continuous), low-density lipoprotein (continuous), serum uric acid (continuous), chronic kidney disease (yes or no), hypertension (yes or no), diabetes (yes or no), stroke (yes or no), cardiovascular disease (yes or no), asthma (yes or no), chronic lung diseases (yes or no), living close to traffic (yes or no) and exposure to vapours, gases, dust and industrial pollution (yes or no).
of macrophages and monocytes. It also activates various inflammatory mediators, including IL-1β, IL-8, IL-10, tumour necrosis factor-α and monocyte chemoattracting protein. Renal ischemia, on the other hand, can affect angiotensin-converting enzyme (ACE) expression and promote pulmonary vascular permeability, which impairs pulmonary function. Notably, chronic renal endothelial injury to the glomeruli, renal tubules, interstitium and vessels was more severe in patients with COPD than in those without COPD, according to a report by Polverino et al. Mice exposed to cigarette smoke also developed albuminuria and glomerular injury. Additionally, increased oxidative stress and activation of advanced glycation end products (AGE) and the receptor for AGE signalling have been observed in pulmonary and renal endothelial cells in patients with COPD and cigarette smoke-exposed mice. Treating with an ACE inhibitor reduced the activation of oxidative stress and improved the progression of both renal and pulmonary diseases. In addition, acid-base balance may also play a role in the underlying mechanisms of pulmonary-renal crosstalk. When renal failure occurs in patients with COPD, the compensatory role of the kidney in respiratory acidosis may be less effective, leading to reduced ammonia genesis and titratable acidity production with a consequently smaller increase in serum bicarbonate and more severe acidosis, which promotes kidney disease progression.

Impaired lung function also shares several common risk factors with CKD, including old age, smoking, hypertension, cardiovascular disease and obesity, as supported by the baseline characteristics of our cohort. Furthermore, accumulating evidence has suggested that this coexistence triggers bidirectional disease progression. Other possible mechanisms include a higher risk of receiving nephrotoxic antibiotics in patients with lung diseases compared with those without. These findings reveal the pathological basis of renal injury caused by decreased pulmonary function, encompassing factors such as hypoxia, systemic inflammation, endothelial dysfunction, haemodynamic disorders, oxidative stress, acidosis, comorbidities and the administration of potential nephrotoxic agents.

Males, older age and smoking were found to be risk factors for rapid eGFR decline; however, current existing evidence is not consistent. In our study, we found that an increase in baseline PEF might reduce the risk of rapid deterioration of kidney function among these populations. What’s particularly interesting is that this protective effect of elevated PEF holds true regardless of whether an individual has CKD or not, highlighting the potential for targeted improvements in lung function to delay the progression of renal failure. This offers a new perspective on addressing kidney health through lung function enhancement.

This study has several strengths that enhance the validity and reliability of the findings. Notably, it is the first study to investigate the link between PEF and longitudinal kidney function decline based on a large cohort in China. Additionally, we employed a comprehensive assessment of the association between PEF and rapid eGFR decline, using a combination of restricted cubic spline analysis and multiple regression models, with meticulous inclusion of several covariates. These rigorous methodological approaches significantly enhance the credibility of the findings.

However, it is important to acknowledge certain limitations of this study. First, we evaluated respiratory function using only PEF, as other lung function parameters such as FEV1, FVC and FEV1/FVC were not available in CHARLS. Therefore, further studies are needed to validate our findings regarding the association between lung function and rapid kidney function decline using
different parameters. Second, the exclusion of participants with missing data on PEF and serum creatinine levels could introduce potential bias. Third, information on albuminuria was not available in CHARLS, and the association between PEF and albuminuria failed to be assessed.

CONCLUSIONS

PEF was negatively correlated with longitudinal eGFR decline, and an increase in PEF might reduce the risk of rapid deterioration of renal function. Further research is required to validate these findings and explore the potential mechanisms underlying this association.

Acknowledgements

We thank the participants and staff of CHARLS involved in this study, as all the data were derived from CHARLS.

Contributors

YW contributed to the study design, SH performed the data analysis and completed the original manuscript, acting as guarantor. YX participated in the revision of this manuscript. All authors have approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82274391), National Key Research and Development Program of China (Grant number: 2019YFC1709401) and the Project from Science and Technology Commission of Shanghai Municipality (Grant number: 20211902100).

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants. The CHARLS protocol was approved by the Biomedical Ethics Review Committee of Peking University (approval number for the household survey: IRB00001052-11101; for biomarker collection: IRB00001052-11104). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available in a public, open access repository. Data are available upon reasonable request.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Yi Wang http://orcid.org/0000-0001-9335-5334

REFERENCES


44 Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (Ace2) is a key modulator of the renin angiotensin system in health and disease. *Int J Pept* 2012;2012:256294.


