

Rapid decline in lung function in healthy adults predicts incident excess urinary albumin excretion later in life

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ABSTRACT

Introduction Chronic lung disease, often characterised by rapid decline in lung function, is associated with vascular endothelial dysfunction (characterised by moderate to severe excess urinary albumin excretion (eUAE) but their longitudinal relationship is inadequately studied. In a bidirectional longitudinal examination of healthy adults, we analysed the following two hypotheses: (1) rapid decline (ie, highest tertile of lung function decline) predicts eUAE and (2) eUAE predicts rapid decline.

Methods We performed a secondary data analysis from 3052 eligible participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study. For analysis 1, the predictor was rapid decline in lung function between the peak value (attained at or before CARDIA visit year 10 or Y10 at a mean age of 35 years) and Y20; and the outcome was incident eUAE at Y20 and/or Y25. For analysis 2, the predictor was eUAE at Y10 and the outcome was rapid decline between Y10 and Y20.

Results After adjustment for covariates in analysis 1, rapid decline in FEV₁ or FVC between peak and Y20 predicted incident eUAE at Y20 and/or Y25 (OR 1.51 and 1.44, respectively; $p \leq 0.05$ for both analyses). In analysis 2, eUAE at Y10 did not predict subsequent rapid decline.

Conclusions Healthy adults with rapid decline in lung function are at risk for developing vascular endothelial dysfunction, as assessed by incident eUAE, later in life.

INTRODUCTION

Millions of people worldwide are affected by chronic respiratory diseases, including 64 million people with chronic obstructive pulmonary disease (COPD) which is also the third leading cause of death globally and in the USA.^{1,2} Chronic lung disease, often characterised by rapid decline in lung function and often associated with vascular disorders,³ is cross-sectionally associated with excess urinary albumin excretion (eUAE).⁴ eUAE, a term that encompasses previously used terms of microalbuminuria and macroalbuminuria, is commonly associated with diabetes mellitus, hypertension and ageing. eUAE predicts chronic kidney disease, adverse cardiovascular outcomes and death.⁵ eUAE

Key messages

- Multiple cross-sectional studies have established an association between chronic lung disease and excess urinary albumin excretion, a marker for vascular endothelial dysfunction. This longitudinal study addresses the direction of this association.
- Rapid decline in lung function, but still largely within the normal range of absolute lung function, can be used in healthy adults to predict future risk for vascular endothelial dysfunction, as assessed by incident excess urinary albumin excretion.
- Serial measurement of rapid decline in lung function can be used in healthy individuals to predict future risk for vascular endothelial dysfunction, as assessed by incident excess urinary albumin excretion.

arises from an increased leakage of albumin through the glomerular filtration barrier. This filtration barrier comprises a fenestrated glomerular epithelium consisting of podocytes and glycocalyx, the latter also protects the endothelium against atherosclerosis. This filtration barrier is injured by systemic inflammation and oxidant stress, manifesting as eUAE. In addition to the renovascular bed, eUAE is a marker for endothelial dysfunction that affects the cardiovascular bed.⁶

Our study objective was to examine the association between rapid decline in lung function (a marker for chronic lung disease) and eUAE (a marker for renovascular and cardiovascular endothelial dysfunction) in healthy adults. If eUAE predicts lung function decline in healthy subjects, interventions based on improving vascular endothelial function may help prevent and treat chronic lung disease. On the other hand, if lung function decline predicts eUAE in healthy adults, the former can serve as a novel preclinical marker for future vascular disease. Further, cardiovascular or renovascular disease may



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be preventable and treatable using interventions that either improve lung health or target common mediatory pathways. In a bidirectional longitudinal examination of healthy young adults, we hypothesised in our first analysis that rapid lung function decline predicts eUAE. In our second analysis, we reversed the temporal association and hypothesised that eUAE predicts rapid decline. To help achieve our objective, we analysed the national Coronary Artery Risk Development in Young Adults (CARDIA) dataset. With data collected over 25 years, the CARDIA study provides a unique opportunity to analyse longitudinal changes in both lung function and eUAE.

METHODS

We performed a longitudinal secondary analysis of data from the CARDIA study that is designed to study development of heart disease in healthy adults. Since 1985, the CARDIA study has been collecting data using interviewer-administered and self-administered questionnaires, spirometry and laboratory test results from 5115 randomly selected participants from Birmingham, Alabama, Chicago, Illinois, Oakland, California, and Minneapolis, Minnesota. The participation response rate at the start of the study was approximately 50%. At the time of recruitment, the participants were balanced on race (52% blacks, 48% white) and sex (54% female, 46% male), as well as educational attainment and age distribution (within the age range of 18–30 years). After their initial examination, the participants were asked to follow-up at CARDIA examination visit years 2 (Y2), Y5, Y7, Y10, Y15, Y20 and Y25. The follow-up rates for the survivors at these visits were 91%, 86%, 81%, 79%, 74%, 72% and 72%, respectively. IRB approval was obtained by the CARDIA study and all individual study sites. Written and signed informed consent was obtained from each participant at each examination. Additional details on the CARDIA study have been published previously.⁷

INCLUSION AND EXCLUSION CRITERIA

We excluded all participants with self-reported physician diagnoses of chronic bronchitis (n=106), emphysema (n=8) or kidney disease (n=382) at the CARDIA Y0 visit at a mean age of 25 years in order to focus on healthy young and middle-aged adults. Also excluded were those lost to follow-up after Y0 visit (n=198), those with missing data on spirometry over CARDIA Y0–Y20 such that lung function decline could not be computed (n=1338), those with missing data on urine albumin creatinine ratio at Y20 and/or Y25 (n=28) and two participants who underwent sex change (figure 2).

PREDICTOR AND OUTCOME VARIABLES

For the first analysis, the primary outcome was incident eUAE, defined as the new occurrence of moderate to severe eUAE at CARDIA Y20 and/or Y25 examination visits at a mean age of 45 and/or 50 years (without

antecedent excretion). Moderate eUAE or A2 category of albuminuria,⁸ previously termed microalbuminuria, was defined by 25–300 mg of albumin/g of urine creatinine. Severe eUAE or A3 category of albuminuria,⁸ previously termed macroalbuminuria, was defined by >300 mg of albumin/g of urine creatinine (Table E-V in the online supplementary material. This variable was measured by the laboratory analysis of albumin and creatinine in ‘spot’ urine specimens and by calculating the ratio of their values at Y10, Y20 and Y25. Albumin was assessed using a nephelometric procedure with a specific anti-albumin monoclonal antibody, and creatinine was assessed using the Jaffe method. Albumin excretion rate was corrected using the formula $\text{albumin}/(\kappa \times \text{creatinine})$, where κ adjusts for published race and sex differences in typical daily creatinine excretion, as discussed in the online supplementary material.⁹

Alternative outcomes included prevalent eUAE and persistent eUAE. Prevalent eUAE was defined as the occurrence of moderate to severe eUAE at Y20 and/or Y25, irrespective of antecedent excretion. Persistent eUAE was defined by the presence of moderate to severe excess excretion at Y25 plus antecedent excretion on at least one more measurement at Y10, Y15 or Y20 visits.

For the first analysis, the predictor was rapid decline in lung function, as assessed between the peak value (determined from the highest FVC or FEV₁ value at CARDIA Y0, Y2, Y5 and Y10) and Y20 (figure 1). Peak lung function was used rather than Y5 lung function because some participants reached peak lung function before and after Y5. The percentage of participants whose FEV₁ peaked before Y5 was 36.1%, after Y5 was 41.4% and at Y5 was 22.5%. Prebronchodilator spirometry was obtained at these visits using a Collins Survey 8-L water sealed spirometer and an Eagle II Microprocessor (Warren E. Collins, Braintree, Massachusetts, USA). CARDIA Y20 lung function was measured using a dry rolling-seal volume OMI spirometer (Viasys, Loma Linda, California, USA). Standard procedures of the American Thoracic Society were followed at all visits.¹⁰ A detailed description of the testing procedures used during different times was published previously.¹¹

Rapid decline in FEV₁ and FVC was defined by an annualised decline of ≥ 52 mL/year and of ≥ 45.8 mL/year, respectively, between CARDIA peak value and Y20. This definition of rapid decline used the cut point between the highest tertile and the two lower tertiles of decline, established after visually examining the non-linear relationship between decline in lung function and incident eUAE. In additional sensitivity analyses, rapid decline was also examined as a continuous variable.

For the second analysis, our predictor was prevalent eUAE at Y10 and outcome was rapid decline in FVC or FEV₁ between CARDIA Y10 and Y20, as defined above (figure 1).

COVARIATES

Several covariates were considered, most associated with vascular endothelial function.^{12 13} Standard covariates measured at CARDIA Y5 visit included sex, age, race, height, enlarged waist circumference, diabetes mellitus, current smoking status, pack-years of smoking and physical activity. Additional covariates included hypertension which was measured at either Y0, Y2, Y5, Y7 or Y10 visits; change in body mass index (BMI) which was measured between Y0 and Y5 visits; and peak FEV₁ or FVC determined from the highest FVC or FEV₁ value at or before CARDIA Y10 visit. Standard covariates at Y5 visit were selected since Y5 was the median time to attaining peak lung function value in the CARDIA study; the peak lung function value marked the beginning of the measured decline in lung function for studying Hypothesis 1.

Sociodemographic data (age, sex and race) were collected by questionnaire. Self-reported physical activity in the past one year was defined on a five-point Likert scale. High level of activity was defined as more than moderately active, that is, 4 and 5 on the five-point Likert scale. Smoking status was classified as current, former or never-smoker. Height (in cm) without shoes was measured using a vertical ruler; weight (in kg) in light clothing was measured using a calibrated balance beam scale; BMI (in kg/m²) was calculated and change in BMI was defined as $\geq 10\%$ increase or decrease in value between Y0 and Y5.¹⁴ Systemic hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or taking antihypertensive medication at that examination visit. Diabetes mellitus was assessed in response to the question, 'Has a doctor or nurse ever said you had diabetes (high sugar in the blood

or urine)?' Enlarged waist circumference was defined as >102 cm in men and >88 cm in women.

STATISTICAL ANALYSIS

The statistical analysis involved χ^2 and Student's t-test for univariate analysis for categorical and continuous outcomes, respectively. Logistic regression was used for binary outcomes in unadjusted and multivariable models using SAS software V.9.4 and p values <0.05 were considered statistically significant.

RESULTS

Demographic characteristics

Among the 5115 original participants at Y0 visit in the CARDIA cohort, 3052 and 2614 eligible subjects were included for the first and second analyses, respectively (figure 2). Subjects with incident eUAE at Y20 or Y25 had greater prior values of adiposity (ie, greater levels of BMI, change in BMI and waist circumference); greater likelihood of having systemic hypertension, being black and being less physically active; and had lower mean absolute FVC and FEV₁ values, than those without eUAE (table 1). Subjects with rapid decline between CARDIA peak and Y20 visit also had greater prior values of adiposity (ie, greater levels of BMI, change in BMI and waist circumference); greater likelihood of having systemic hypertension, being older, male and current smokers; and had greater urinary albumin creatinine ratio at Y10 than those without rapid decline (table 2).

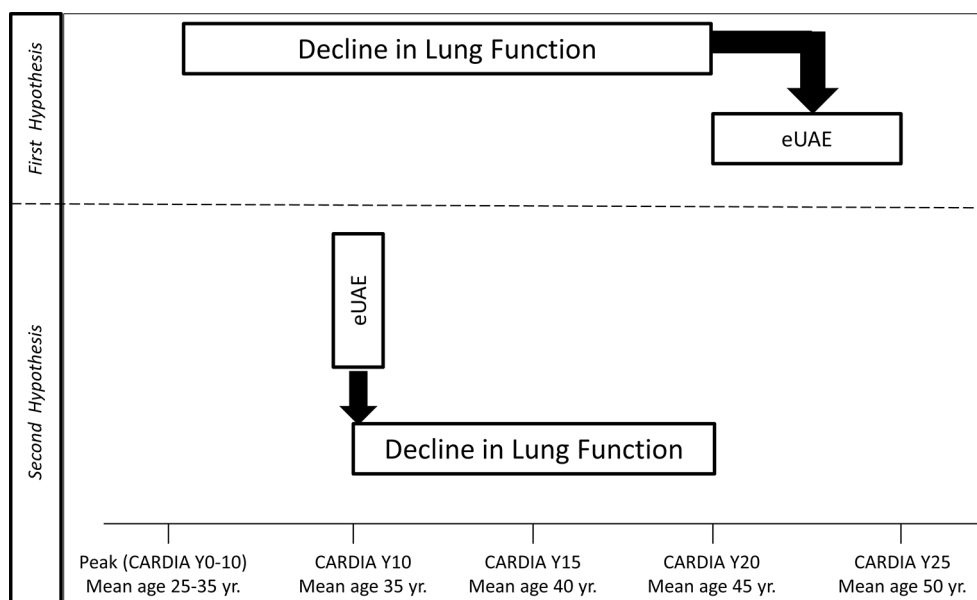


Figure 1 Overview of the bidirectional study plan (X depicts time of measurement for the variable). Age refers to the mean age of the study population at the time of the Coronary Artery Risk Development in Young Adults (CARDIA) examination visit year. eUAE, excess urinary albumin excretion.

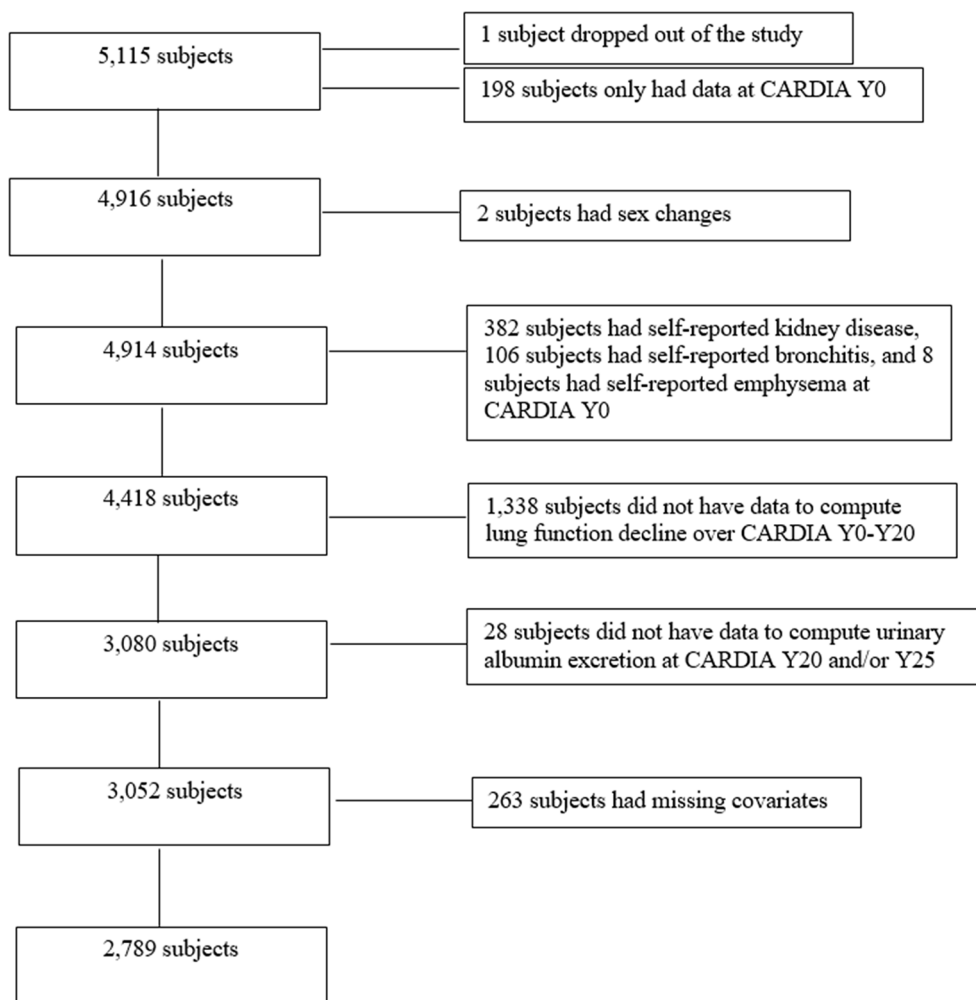


Figure 2 Strengthening the Reporting of Observational Studies in Epidemiology chart for the temporal sequence of analyses. In the first analysis, the predictor was rapid decline in lung function between the peak value (attained at or before Coronary Artery Risk Development in Young Adults (CARDIA) visit year 10 or Y10) and Y20; and the outcome was incident excess urinary albumin excretion (eUAE) at Y20 and/or Y25. For the second analysis, the predictor was eUAE at Y10 and the outcome was rapid decline between Y10 and Y20.

Rapid decline in lung function in young to mid adulthood predicts incident eUAE later in life

Rapid decline in FEV₁ between CARDIA peak and Y20 visit predicted incident, prevalent and persistent eUAE at Y20 and/or Y25 (table 2; unadjusted $p \leq 0.006$ for all analyses). Similar results were obtained with rapid decline in FVC as the predictor variable (table 2 and online supplementary tables E-I, E-II and E-VI). On the other hand, rapid decline in FEV₁/FVC ratio (ie, $\geq 0.89\%$ per year, similarly defined by the cut point between the highest tertile and the two lower tertiles) did not predict incident eUAE (OR 1.13, 95% CI 0.87 to 1.48, $p=0.36$).

The associations of incident eUAE with rapid FEV₁ decline remained significant when studying lung function decline as a continuous predictor variable (online supplementary table E-I). The association of incident, prevalent or persistent eUAE with rapid FEV₁ or FVC decline remained significant after adjustment for covariates (table 3).

eUAE in young adulthood does not predict rapid decline in lung function later in life

In the second analysis, categorically defined prevalent eUAE at CARDIA Y10 did not predict rapid decline in either FVC or FEV₁ over the subsequent 10-year time period (table 4). When urinary albumin creatinine ratio was instead studied as a continuous independent variable, it did predict subsequent rapid decline in FEV₁ in univariate analysis ($p=0.04$) (table 4, footnote 1) but not in multivariable analyses.

DISCUSSION

This longitudinal study demonstrates that rapid decline in lung function, although largely within the normal range of lung function, in young to middle-aged healthy adults, predicts incident eUAE excretion later in life. Prevalent eUAE in young adulthood however does not predict rapid decline in lung function later in life in this

Table 1 Characteristics of study participants at Coronary Artery Risk Development in Young Adults (CARDIA) Y5 examination visit (at a mean age of 30 years), stratified by the presence of incident excess urinary albumin excretion (eUAE) at Y20 or Y25 examination visits (at a mean age of 45 or 50 years)

| Characteristics | Incident eUAE present at Y20 or Y25 (n=261) | Incident eUAE absent at Y20 or Y25 (n=2583) | p Value |
|---|---|---|---------|
| | % or mean \pm SD | % or mean \pm SD | |
| Age (years) | 30.1 \pm 3.6 | 30.1 \pm 3.6 | 0.89 |
| Black race | 62.5% | 43.3% | <0.001 |
| Height (cm) | 169.6 \pm 9.5 | 170.6 \pm 9.6 | 0.13 |
| BMI (kg/m ²) | 27.3 \pm 6.0 | 25.4 \pm 5.3 | <0.001 |
| Change in BMI (kg/m ²) | 1.76 \pm 3.06 | 1.46 \pm 2.44 | 0.08 |
| Female sex | 61.7% | 55.5% | 0.06 |
| Increased waist circumference (>102 cm in men, >88 cm in women) | 20.9% | 10.7% | <0.001 |
| Self-reported diabetes mellitus | 0.9% | 1.5% | 0.77 |
| Systemic hypertension | 13.8% | 8.4% | 0.006 |
| Smoking status | | | 0.16 |
| Never-smoker | 58.3% | 62.1% | |
| Former smoker | 12.8% | 14.6% | |
| Current smoker | 28.9% | 23.3% | |
| Smoking pack-years | 2.8 \pm 5.1 | 2.8 \pm 5.6 | 0.92 |
| High level of self-reported physical activity in the past year [†] | 27.9% | 35.4% | 0.03 |
| FVC (L) | 4.1 \pm 1.0 | 4.4 \pm 1.0 | <0.001 |
| FEV ₁ (L) | 3.3 \pm 0.8 | 3.6 \pm 0.8 | <0.001 |
| FEV ₁ /FVC ratio | 0.82 \pm 0.06 | 0.82 \pm 0.07 | 0.99 |
| Urinary albumin creatinine ratio (mg/g) at Y10 | 8.7 \pm 5.7 | 5.3 \pm 3.5 | <0.001 |
| Logarithm of urinary albumin creatinine ratio (mg/g) at Y10 | 0.85 \pm 0.29 | 0.65 \pm 0.25 | <0.001 |

All data were obtained at CARDIA Y5 except change in BMI, incident eUAE and systemic hypertension. Systemic hypertension, defined as systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg or taking antihypertensive medication at or before Y10. Urinary albumin creatinine ratio was measured at Y10, after race and sex correction. Change in BMI was defined between Y0 to Y5.

[†]Self-reported physical activity in the past year at Y5 was defined on a five-point Likert scale. High level of activity is defined as more than moderately active (4 and 5 on five-point Likert scale). BMI, body mass index.

study. Thus, rapid decline in lung function precedes the development of eUAE, a marker for renovascular and/or cardiovascular endothelial dysfunction.¹⁵

This study used subclinical markers of lung and vascular disease as exposure and outcome variables in healthy adults. Rapid decline in lung function in healthy adults is a subclinical marker for subsequent chronic lung disease.¹⁶ The possible mechanisms by which rapid decline may lead to chronic lung disease include activation of inflammation, elastolytic proteases and oxidative stress, and acceleration of ageing within the lung.¹⁷ Lung inflammatory markers may spill over into the systemic circulation¹⁸ and lung oxidative stress may increase advanced glycation end-products (AGEs), activating the

ubiquitously expressed transmembrane receptor for AGEs (RAGE), in turn triggering additional inflammation and end organ injury (figure 3).^{19–21}

Mirroring rapid decline as a subclinical marker for lung disease, eUAE is a subclinical marker for cardiovascular and renovascular diseases, as well as for clinical renal disease.²² The MONITORING Trends and Determinants of Cardiovascular Diseases study established that eUAE predicted development of ischaemic heart disease in healthy adults, independently of other traditional risk factors.²³ Similar findings were noted with respect to cardiovascular mortality in a large study of patients with chronic renal disease.²⁴ Miettinen *et al* found that the extent of eUAE was cross-sectionally associated with

Table 2 Characteristics of study participants at Coronary Artery Risk Development in Young Adults (CARDIA) Y5 examination visit (at a mean age of 30 years), stratified by rapid lung function decline (between CARDIA Y20 and peak determined from the highest value at Y0, Y2, Y5 and Y10 visits)

| Characteristics | Rapid FEV ₁ decline (n=953) | Non-rapid FEV ₁ decline (n=1889) | p Value | Rapid FVC decline (n=935) | Non-rapid FVC decline (n=1907) | p Value |
|---|---|--|---------|------------------------------|-----------------------------------|---------|
| | % or mean ± SD | % or mean ± SD | | % or mean ± SD | % or mean ± SD | |
| Age (years) | 30.9±3.5 | 29.7±3.6 | <0.001 | 31.2±3.3 | 29.6±3.6 | <0.001 |
| Black race | 45.8% | 46.2% | 0.88 | 49.3% | 56.2% | <0.001 |
| Height (cm) | 172.5±9.4 | 169.6±9.6 | <0.001 | 172.4±9.5 | 169.7±9.5 | <0.001 |
| BMI (kg/m ²) | 26.8±5.6 | 25.3±5.4 | <0.001 | 28.1±5.9 | 24.7±4.9 | <0.001 |
| Change in BMI (kg/m ²) | 1.82±2.57 | 1.33±2.48 | <0.001 | 1.26±2.37 | 1.91±2.75 | <0.001 |
| Female sex | 44.1% | 60.8% | <0.001 | 43.5% | 60.9% | <0.001 |
| Increased waist circumference (>102 cm in men, >88 cm in women) | 15.4% | 11.2% | 0.002 | 21.2% | 8.4% | <0.001 |
| Self-reported diabetes mellitus | 1.5% | 1.9% | 0.54 | 2.0% | 1.6% | 0.36 |
| Systemic hypertension | 10.4% | 6.8% | <0.001 | 12.6% | 5.8% | <0.001 |
| Smoking status | | | | | | |
| Never-smoker | 57.1% | 63.6% | <0.001 | 57.7% | 63.3% | <0.001 |
| Former smoker | 13.8% | 14.5% | | 13.0% | 14.9% | |
| Current smoker | 29.8% | 21.8% | | 29.4% | 21.8% | |
| Smoking pack-years | 3.6±6.4 | 2.4±5.1 | <0.001 | 3.5±6.2 | 2.5±5.2 | <0.001 |
| High level of self-reported physical activity in the past year [†] | 33.4% | 34.9% | 0.45 | 33.2% | 35.0% | 0.35 |
| FVC (L) | 4.57±1.06 | 4.27±1.02 | <0.001 | 4.50±1.07 | 4.30±1.02 | <0.001 |
| FEV ₁ (L) | 3.71±0.84 | 3.49±0.78 | <0.001 | 3.62±0.84 | 3.53±0.78 | 0.007 |
| FEV ₁ /FVC ratio | 0.82±0.08 | 0.82±0.06 | 0.03 | 0.81±0.06 | 0.83±0.07 | <0.001 |
| Urinary albumin creatinine ratio (mg/g) at Y10 | 10.67±31.97 | 7.13±30.39 | 0.25 | 11.0±32.2 | 9.0±30.3 | 0.14 |
| Logarithm of urinary albumin creatinine ratio (mg/g) at Y10 | 0.75±0.72 | 0.72±0.7 | 0.04 | 0.76±0.74 | 0.71±0.70 | 0.001 |

All data were obtained at CARDIA Y5 except change in BMI, rapid FEV₁ or FVC decline, urinary albumin creatinine ratio and systemic hypertension. Systemic hypertension, defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or taking antihypertensive medication at or before Y10. Urinary albumin creatinine ratio was measured at Y10, after race and sex correction. Change in BMI was defined between Y0 to Y5. Rapid decline was defined by the highest tertile of decline and compared with the lower two tertiles. Rapid FEV₁ decline was defined by ≥52 mL/year. Rapid FVC decline was defined by ≥45.8 mL/year.

[†]Self-reported physical activity in the past year at Y5 was defined on a five-point Likert scale. High level of activity is defined as more than moderately active (4 and 5 on five-point Likert scale).

BMI, body mass index.

risk for stroke and lower extremity amputation, independently of traditional risk factors.²⁵ Not only is eUAE the result of injury to the glomerular filtration barrier by systemic inflammation and oxidant stress but its presence may further promote systemic inflammation and oxidative stress, in turn linking it with adverse vascular outcomes.²⁶

It is possible that vascular endothelial dysfunction results from a systemic ‘spillover’ of the local inflammatory and reparative events occurring in the lungs (figure 3).²⁷ Alternatively, vascular endothelial dysfunction and rapid decline may be two forms of expression of the same systemic inflammatory state, although with differing latency periods. Both views have merit but imply

Table 3 Unadjusted analyses of the association between rapid decline in lung function as the predictor variable (between Coronary Artery Risk Development in Young Adults (CARDIA) Y20 and peak determined from the highest value at Y0, Y2, Y5 and Y10 visits) and incident, prevalent and persistent excess urinary albumin excretion (eUAE) as outcome variables (latter measured at Y20 and/or Y25 examination visits at a mean age of 45 and/or 50 years)

| Categories of lung function decline | Incident eUAE | | Prevalent eUAE | | Persistent eUAE | |
|---|---------------------|---------|-----------------------|---------|---------------------|---------|
| | Frequency (%) | p Value | Frequency (%) | p Value | Frequency (%) | p Value |
| <i>FEV₁ decline</i> | | | | | | |
| Rapid FEV ₁ decline ≥52 mL/year | 4.0% (n=34/844) | 0.006 | 10.5% (n=107/1019) | 0.006 | 6.6% (n=68/878) | <0.001 |
| Non-rapid FEV ₁ decline <52 mL/year | 2.0% (n=35/1714) | | 7.5% (n=152/2033) | | 3.4% (n=61/1773) | |
| <i>FVC decline</i> | | | | | | |
| Rapid FVC decline ≥45.8 mL/year | 4.3% (n=36/835) | <0.001 | 11.5% (n=116/1006) | <0.001 | 7.1% (n=61/863) | <0.001 |
| Non-rapid FVC decline <45.8 mL/year | 1.9% (n=33/1723) | | 7.0% (n=143/2046) | | 3.3% (n=58/1786) | |

Rapid decline, defined by the highest tertile of decline, was compared with the lower two tertiles. Rapid FEV₁ decline was defined by ≥52 mL/year. Rapid FVC decline was defined by ≥45.8 mL/year.

Incident eUAE was defined as the new occurrence of excretion at Y20 or Y25 examination visits (at a mean age of 45 or 50 years) without antecedent excretion. Prevalent eUAE was defined as excretion at CARDIA Y20 and/or Y25, irrespective of antecedent excretion. Persistent eUAE was defined as excretion at Y25 plus at one or more measurements at Y10, Y15 or Y20.

Similar significant associations were found when studying lung function decline as a continuous predictor variable (online supplementary table E-I). Association of urinary albumin creatinine ratio on lung function decline, both studied as continuous variables, showed significant association with FVC, as shown in online supplementary table E-II.

different conceptual and therapeutic consequences. In the former, the aim of therapy may be centred in improving lung health and local inflammation, whereas in the latter, the centre of therapy may be shifted to ameliorating the systemic inflammatory state.

Our longitudinal finding that rapid decline in lung function in healthy adults predicts vascular endothelial function is supported by several cross-sectional studies. The third US-based National Health and Nutrition Examination Survey (NHANES III) suggests that low lung function is cross-sectionally associated with eUAE, findings that were also demonstrated by the 5th Korea National Health and Nutrition Examination Survey.²⁸ A cross-sectional study of Chinese type 2 diabetics found that gas exchange efficiency during exercise in those with eUAE was lower than those without eUAE.²⁹ Additional support for our findings is provided by cross-sectional studies of patients with chronic lung diseases. Casanova's cross-sectional study confirmed that eUAE was more frequent among patients with COPD than healthysmokers (24% vs 6%) and that eUAE was inversely correlated with arterial oxygenation.⁴ Low arterial oxygenation in patients with COPD has in turn been shown by others to be associated with increased risk for death.³⁰ Ford *et al* have recently demonstrated that the level of UAE is higher in patients with moderate to severe obstructive lung disease compared with those with normal lung function or mild obstructive lung disease. eUAE was also

shown to be associated with all-cause mortality among US adults with obstructive lung disease.³¹ A recent study of a smaller cohort of patients with COPD confirmed that eUAE was related to the Body mass index, airflow Obstruction, Dyspnea and Exercise capacity (BODE) index. Higher BODE scores have been shown to predict mortality in COPD.³² Similarly, there is a limited body of cross-sectional literature that demonstrates that chronic lung disease is associated with atherosclerotic cardiovascular disease, diastolic dysfunction and right and left heart failure.³³ Also published is the cross-sectional association between chronic lung disease (such as COPD) and kidney disease.³⁴ Since we were unable to demonstrate an association between decline in FEV₁/FVC ratio and eUAE, our findings may not be COPD specific but may be relevant to chronic lung diseases in general.

Our longitudinal study fills a critical gap in the existing literature by demonstrating the direction of association between lung and vascular outcomes, a key feature that may help establish causality in future studies. Thus, our study clarifies that the low lung function–eUAE relationship is primarily unidirectional—rapid decline in lung function predicts eUAE but not vice versa in healthy adults. Duprez *et al*³⁵ reported in the MESA study that low lung function, although within the normal absolute range, was correlated with small arterial stiffness, a finding confirmed by another NHANES III study as well.³⁶ Decline in FVC in the CARDIA cohort has been

Table 4 Association between rapid decline in lung function† as the predictor variable (between Coronary Artery Risk Development in Young Adults (CARDIA) Y20 and peak determined from the highest value at Y0, Y2, Y5 and Y10 visits) and incident, prevalent and persistent excess urinary albumin excretion (eUAE) as outcome variables (latter measured at Y20 and/or Y25 examination visits at a mean age of 45 or 50 years)

| eUAE as outcome | Incident (n=2844 for unadjusted model; n=2622 for adjusted model) | Prevalent (n=3052 for unadjusted model; n=2815 for adjusted model) | Persistent (n=2649 for unadjusted model; n=2459 for adjusted model) | Incident (n=2844 for unadjusted model; n=2622 for adjusted model) | Prevalent (n=3052 for unadjusted model; n=2815 for adjusted model) | Persistent (n=2649 for unadjusted model; n=2459 for adjusted model) |
|---|---|--|---|---|--|---|
| Rapid lung function decline as predictor† | FEV ₁ decline as predictor OR (95% CI) | | | FVC decline as predictor OR (95% CI) | | |
| Unadjusted model | 1.34* (1.03 to 1.74) | 1.45** (1.12 to 1.88) | 1.99** (1.38 to 2.88) | 1.46* (1.13 to 1.90) | 1.73** (1.34 to 2.24) | 2.27** (1.57 to 3.28) |
| Adjusted model‡ | 1.51** (1.17 to 1.95) | 1.51** (1.17 to 1.95) | 1.75* (1.14 to 2.68) | 1.44* (1.07 to 1.96) | 1.41* (1.09 to 1.83) | 1.56* (1.01 to 2.41) |

†Rapid decline was defined by the highest tertile of decline and compared with the lower two tertiles. Rapid FEV₁ decline was defined by ≥ 52 mL/year. Rapid FVC decline was defined by ≥ 45.8 mL/year.

‡Multivariable model above was adjusted for standard covariates (ie, sex, enlarged waist circumference, diabetes mellitus, age, race, height, current smoking status, pack-year smoking history, physical activity) plus hypertension, change in BMI and peak FEV₁ or FVC. Standard covariates were obtained at Y5 visit. Hypertension was measured at or before Y10; change in BMI was measured between Y0 and Y5; and peak FEV₁ or FVC was determined from the highest FVC or FEV₁ value at or before Y10. Additional adjustment for exploratory covariates, that is, change in BMI between Y0 and Y20, the sum of smoking pack-years over Y0 and Y20, fasting blood glucose levels at Y7 and self-reported asthma status at Y5, did not change the relationship between rapid decline in FEV₁ or FVC and incident eUAE (online supplementary table E-VI).

Incident eUAE was defined as the new occurrence of excretion at Y20 or Y25 examination visits (at a mean age of 45 or 50 years) without antecedent excretion. Prevalent eUAE was defined as excretion at CARDIA Y20 and/or Y25, irrespective of antecedent excretion. Persistent eUAE was defined as excretion at Y25 plus at one or more measurements at Y10, Y15, or Y20.

* $p \leq 0.05$, ** $p \leq 0.001$.

BMI, body mass index.

previously reported to predict diastolic dysfunction.³⁷ Jacobs *et al* have previously reported in the same cohort that decline in lung function in healthy adults predicted future incident systemic hypertension but not vice versa.³⁸ Our findings extend this previous understanding

by demonstrating that the association between rapid decline and incident eUAE may be similarly unidirectional in healthy adults.

The strengths of our study relate to its longitudinal cohort design, large sample size with repeated

Table 5 Unadjusted association between prevalent excess urinary albumin excretion (eUAE) at Coronary Artery Risk Development in Young Adults (CARDIA) Y10 visit as the predictor variable and rapid lung function decline as outcome variable (latter measured between CARDIA Y10 and Y20 visits)

| Prevalent eUAE | Frequency of rapid decline | OR (95% CI) | p Value |
|--|----------------------------|---------------------|---------|
| <i>Rapid FEV₁ decline (≥ 52 mL/year) as outcome</i> | | | |
| Prevalent eUAE present (n=117) | 24.8% | 1.07 (0.70 to 1.64) | 0.76 |
| Prevalent eUAE absent (n=2497) | 23.6% | | |
| <i>Rapid FVC decline (≥ 45.8 mL/year) as outcome</i> | | | |
| Prevalent eUAE present (n=117) | 41.0% | 1.17 (0.80 to 1.70) | 0.42 |
| Prevalent eUAE absent (n=2497) | 37.4% | | |

Rapid decline, defined by the highest tertile of decline, was compared with the lower two tertiles. Additional analysis using urinary albumin-creatinine ratio at CARDIA Y10 as a continuous predictor and rapid lung function decline as outcome variable showed similar results for rapid FVC decline as outcome ($p=0.14$) but a significant association with rapid FEV₁ decline as outcome ($p=0.04$). Additional analysis using lung function decline as a continuous variable is presented in online supplementary table E-III and showed similar results as shown in the table above.

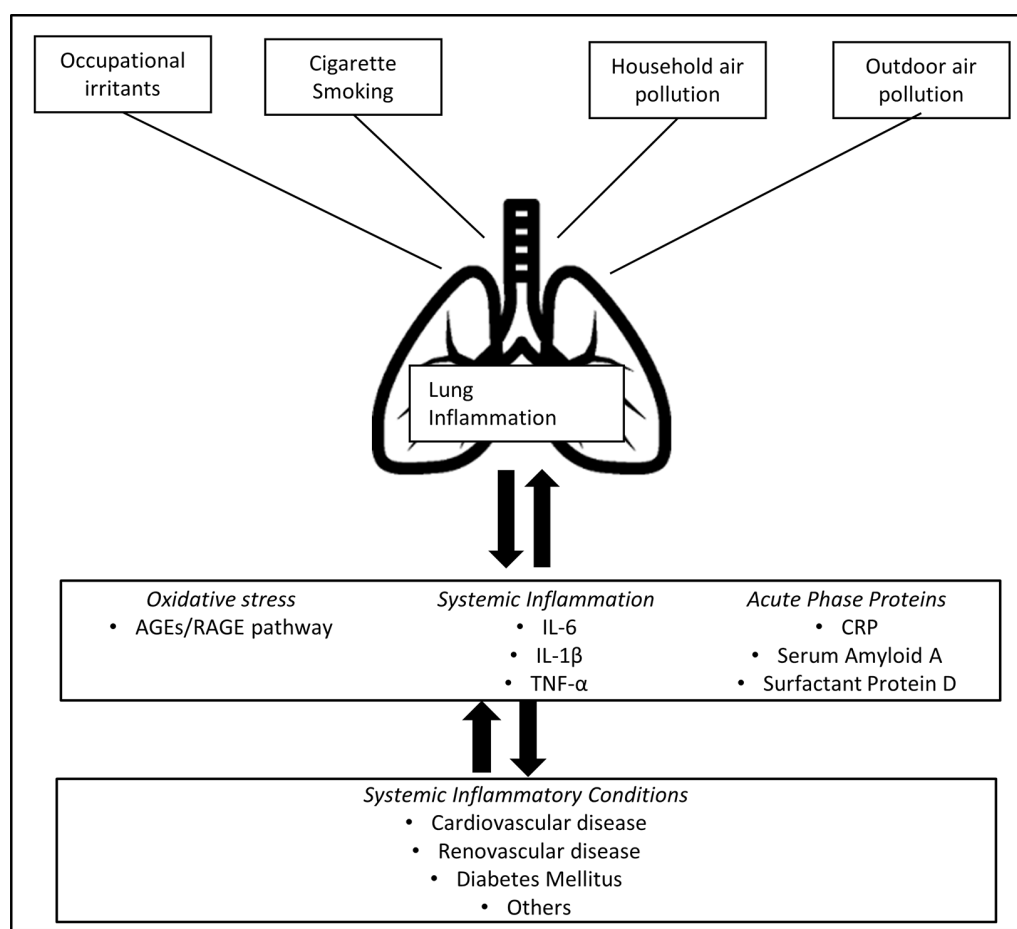


Figure 3 Hypothesised conceptual framework of the association between lung and vascular events. Although speculative, the study findings that rapid decline in lung function predicts incident excess urinary albumin excretion later in life may be explained by lung inflammation, which causes a ‘spillover’ of local cytokines, acute-phase proteins and oxidative stress into the systemic circulation. Systemic inflammation in turn may affect endothelial function in renovascular and cerebrovascular beds, leading to renovascular and cardiovascular diseases. Alternatively, vascular endothelial dysfunction and lung inflammation may be two forms of expression of the same systemic inflammatory state, although with differing latency periods. AGEs, advanced glycation end-products; CRP, C reactive protein; IL, interleukin; RAGE, transmembrane receptor for AGEs; TNF- α , tumour necrosis factor-alpha.

measurements, national multicentre patient recruitment, inclusion of a large minority population and women, focus on subclinical outcomes rather than established disease states and a novel hypothesis that could possibly link chronic lung disease to vascular endothelial function. In addition, by excluding the presence of lung and renal disease at the start of the study, our finding of the association between rapid decline and incident eUAE in a healthy population broadens the scope of this association as it has been previously described to be present only in diseased populations. Further, using a relatively young and healthy study population with relatively few comorbidities helps decrease the bias related to the association.

Our study has several limitations. One limitation is that only 117 subjects had eUAE at CARDIA Y10. We may be therefore underpowered to study our second analysis that eUAE predicts rapid decline. Since a small number of subjects with eUAE in our study had severe eUAE (ie, >300mg/g; consistent with the previously used term macroalbuminuria; online supplementary table E-V), our

findings primarily examine moderate eUAE, consistent with the previously used term microalbuminuria. This is acceptable since moderate eUAE or microalbuminuria is an established marker for vascular endothelial function.⁶ While eUAE is a marker for renovascular and/or cardiovascular endothelial dysfunction, there is limited data on its use in predicting outcomes in other vascular beds. Several characteristics of those subjects who were excluded from our study were significantly different from those included, as seen in online supplementary table E-IV, but the clinical differences in those characteristics that do not form the basis for exclusion criteria are quite small. This is therefore an unlikely source for selection bias. In addition, subject-reported physician diagnosis of chronic bronchitis, emphysema or kidney disease at the Y0 visit was used as exclusion criteria instead of standard clinical definitions for these diseases as this information was not available in the CARDIA data set at Y0 visit, which may have resulted in underexclusion or overexclusion of subjects at study start. The study did not exclude subjects with asthma. This

approach is reasonable since subjects with asthma do not demonstrate a different rate of FEV₁ decline than those without asthma.³⁹ Additional adjustment for self-reported asthma however did not change the results of the study (see online supplementary table E-VI). Exclusion of subjects with missing data may bias results in any cohort study but our high cohort retention rates and non-differential loss to follow-up between those with and without rapid decline indicate that this is an unlikely explanation for our findings. Post-bronchodilator spirometric values were not available. The slope of decline calculated from the post-bronchodilator measurement has however been shown in the literature to have a similar variance as the pre-bronchodilator measurement.⁴⁰ Based on the questionnaire, there were six pregnant women during the Y20 exam and three during the Y25 exam. Additionally, a total of 93 patients in the CARDIA study died of cardiovascular/renovascular causes by the Y25 visit. Patients who died before follow-up were classified as missing data. Since there were very few pregnant women (0.3%) and relatively few deaths (0.5%), they are an unlikely source of misclassification bias. We did not exclude the small number of study participants whose lung function fell outside the normal range; 5.3% of participants at Y5 visit had FEV₁ below the Hankinson-defined lower limit of normal.⁴¹ However, lung function below the lower limit of normal at Y5 was not related to rapid decline (p=0.09).

CONCLUSION

Serial measurement of rapid decline in lung function, but still largely within the normal range of absolute lung function, in young to mid adulthood, can be used in healthy individuals to predict future risk for renovascular and cardiovascular endothelial dysfunction, as assessed by incident eUAE. The implication of our study findings is that improvement in lung health and in lung and/or systemic inflammation may help improve vascular endothelial function, thereby decreasing the morbidity and mortality related to renovascular and cardiovascular diseases.

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