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Mortality and cardiovascular and respiratory morbidity in individuals with impaired FEV 1 (PURE): An international, community-based cohort study

MyLinh Duong
McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

Shofiqul Islam
McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

Sumathy Rangarajan
McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

Darryl Leong
McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

Om Kurmi
McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

See next page for additional authors

Authors

MyLinh Duong, Shofiqul Islam, Sumathy Rangarajan, Darryl Leong, Om Kurmi, Koon Teo, Kieran Killian, Gilles Dagenais, Scott Lear, and Romaina Iqbal

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Summary

Background The associations between the extent of forced expiratory volume in 1 s (FEV_1) impairment and mortality, incident cardiovascular disease, and respiratory hospitalisations are unclear, and how these associations might vary across populations is unknown.

Methods In this international, community-based cohort study, we prospectively enrolled adults aged 35–70 years who had no intention of moving residences for 4 years from rural and urban communities across 17 countries. A portable spirometer was used to assess FEV_1. FEV_1 values were standardised within countries for height, age, and sex, and expressed as a percentage of the country-specific predicted FEV_1 value (FEV_1%). FEV_1% was categorised as no impairment (FEV_1% ≥0 SD from country-specific mean), mild impairment (FEV_1% <0 SD to –1 SD), moderate impairment (FEV_1% <–1 SD to –2 SDs), and severe impairment (FEV_1% <–2 SDs [ie, clinically abnormal range]). Follow-up was done every 3 years to collect information on mortality, cardiovascular disease outcomes (including myocardial infarction, stroke, sudden death, or congestive heart failure), and respiratory hospitalisations (from chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis, or other pulmonary conditions). Fully adjusted hazard ratios (HRs) were calculated by multilevel Cox regression.

Findings Among 126 359 adults with acceptable spirometry data available, during a median 7·8 years (IQR 5·6–9·5) of follow-up, 5488 (4·3%) deaths, 5734 (4·5%) cardiovascular disease events, and 1948 (1·5%) respiratory hospitalisation events occurred. Relative to the no impairment group, mild to severe FEV_1% impairments were associated with graded increases in mortality (HR 1·27 [95% CI 1·18–1·36] for mild, 1·74 [1·60–1·90] for moderate, and 2·54 [2·26–2·86] for severe impairment), cardiovascular disease (1·18 [1·10–1·26], 1·39 [1·28–1·51], 2·02 [1·75–2·32]), and respiratory hospitalisation (1·39 [1·24–1·56], 2·02 [1·75–2·32], 2·97 [2·45–3·60]), and this pattern persisted in subgroup analyses considering country income level and various baseline risk factors. Population-attributable risk for mortality (adjusted for age, sex, and country income) from mildly to moderately reduced FEV_1% (24·7% [22·2–27·2]) was larger than that from severely reduced FEV_1% (3·7% [2·1–5·2]) and from tobacco use (19·7% [17·2–22·3]), previous cardiovascular disease (5·5% [4·5–6·5]), and hypertension (17·1% [14·6–19·6]). Population-attributable risk for cardiovascular disease from mildly to moderately reduced FEV_1 was 17·3% (14·8–19·7), second only to the contribution of hypertension (30·1% [27·6–32·5]).

Interpretation FEV_1 is an independent and generalisable predictor of mortality, cardiovascular disease, and respiratory hospitalisation, even across the clinically normal range (mild to moderate impairment).

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Introduction

Many studies have shown the associations of reduced lung function with future risk of mortality, respiratory outcome, and cardiovascular outcomes.[1–4] In current practice, forced expiratory volume in 1 s (FEV_1) is considered to be abnormal when it is lower than –2 standard deviations (SDs) from the population mean for age, height, and sex.[5] However, there is little data on whether mild abnormalities in lung function, within clinically normal range, are associated with similar increases in poor health outcomes.

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Population Health Research Institute, Department of Medicine, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (M Duong MBBS, S Islam PhD, S Rangarajan MSc, D Leong PhD, O Kurmi PhD, Prof K Teo MB, K Killian PhD, Prof P M O'Byrne MB, Prof S Yusuf DPhil); **The Research Institute of St Joe's Hamilton, McMaster University, Hamilton, ON, Canada** (M Duong); **Université Laval, Institut Universitaire de Cardiologie et de Pneumologie de Québec, QC, Canada** (Prof G Dagenais MD); **Faculty of Health Sciences and Department of Biomedical Physiology & Kinesiology, Simon Fraser University, Vancouver, BC, Canada** (Prof S Lear PhD); **Department of Medicine, University of Ottawa, Ottawa, ON, Canada** (Prof A Wielgosz MD); **Department of Pulmonary Medicine, Medical College, Thiruvananthapuram, Kerala, India** (Prof S Nair MD); **Health Action by People, Thiruvananthapuram, Kerala, India** (Prof S Nair); **Madras Diabetes Research Foundation, Chennai, Tamil Nadu, India** (V Mohan MD); **Community Health & Epidemiology, St John's Research Institute, Bangalore, Karnataka, India** (P Mony MD); **Eternal Heart Care Centre and Research Institute, Jaipur, Rajasthan, India** (Prof R Gupta MD); **Post Graduate Institute of Medical Education and Research (PGIMER), School of Public Health, Chandigarh, India** (Prof R Kumar MD); **Department of Community Medicine and**

School of Public Health, Independent University, Dhaka, Bangladesh (Prof O Rahman DSc); Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia (Prof K Yusoff MBBS); University College Sedaya International (UCSI), Cheras, Kuala Lumpur, Malaysia (Prof K Yusoff); Occupational Hygiene and Health Research Initiative, North-West University, Potchefstroom, North West Province, South Africa (Prof J L du Plessis PhD); School of Public Health, University of the Western Cape, Cape Town, South Africa (E U Igumbor PhD); Physiology Department, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe (J Chifamba DPhil); State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Centre for Cardiovascular Disease, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China (Prof W Li PhD, Y Lu PhD, F Zhi BSc, R Yan MSc); Department of Community Health Sciences and Medicine, Aga Khan University, Karachi, Sindh, Pakistan (R Iqbal PhD); Department of Community Health, Faculty of Medicine, University Kebangsaan Malaysia, Kuala Lumpur, Malaysia (Prof N Ismail MD); Department of Social Medicine, Medical University of Wroclaw, Wroclaw, Poland (K Zatonska MD); Division of Endocrinology, Department of Internal Medicine, Medical Faculty of Istanbul University, Istanbul, Turkey (Prof K Karsidag MD); Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, and Sahlgrenska University Hospital, Östra, Göteborg, Sweden (Prof A Rosengren MD); Hypertension Research Centre, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran (A Bahonar MD); Dubai Medical University, Hatta Hospital, Dubai Health Authority, Dubai, United Arab Emirates (A Yusufali MD); Estudios Clinicos Latinoamerica (ECLA), Rosario, Santa Fe, Argentina (P M Lamelas MD); Dante Pazzanese Institute of

Research in context

Evidence before this study

We searched PubMed, Embase, and Cochrane databases and the bibliographies of retrieved papers for relevant publications in English between Jan 1, 1960, and July 1, 2018. We used key search terms "lung function", "lung capacity", "ventilatory capacity", "forced expiratory volume in 1 second (FEV_1)", and "forced vital capacity" to identify reports of lung function and prospectively collected data on mortality and cardiovascular and respiratory events. A large body of evidence shows a strong epidemiological link between reduced lung function and elevated future risk of mortality and cardiorespiratory outcomes. The association extends to reduced lung function levels in early adulthood, indicating that it is independent of ageing. However, few data are available regarding populations outside of high-income countries, where the range of risk exposures, population susceptibility, and aetiological factors for lung function impairment are different. Therefore, the global implications and burden of impaired lung function, and how these aspects might vary across diverse populations, are unknown.

Added value of this study

In a prospective, international, community-based cohort study involving 126 359 adults from 628 urban and rural communities across 17 high-income, middle-income, and low-income countries, we observed significant and graded increases in rates and risks (standardised for age and sex) of mortality, cardiovascular disease events, and respiratory hospitalisations with decreasing FEV_1 values standardised by country-specific values (FEV_1%). The graded increases in adverse outcomes were significant even for mild reductions in FEV_1% that are commonly accepted as clinically normal (ie, between 0 and –2 SDs below the population mean for age, height, and sex), as well as for abnormal levels (lower than –2 SD). FEV_1% reductions within the normal range showed higher population-attributable risk for mortality than did FEV_1% reductions in the abnormal range, and also contributed more to mortality than did tobacco use, previous cardiovascular disease, and hypertension. The population-attributable risk for incident cardiovascular disease from reduced FEV_1% was second only to the risk from hypertension, and was higher than that of previous cardiovascular disease and tobacco use. The exposure–outcome gradient was consistent across diverse populations from different country income levels and from rural or urban communities, and with different baseline risk levels.

Implications of all the available evidence

Reduced FEV_1 is a strong, independent, and highly generalisable predictor of mortality and cardiovascular disease and respiratory outcomes. The largest population burden is associated with mildly to moderately reduced FEV_1, commonly accepted as being within the normal limits for age, height, and sex. Impaired lung function is a stronger risk factor for mortality and cardiovascular disease events than are most currently accepted conventional risk factors, accounting for one in four deaths and one in six cardiovascular disease events. Reducing the burden of impaired FEV_1, particularly in the mild to moderate range, could have a substantial impact in decreasing mortality and cardiorespiratory morbidity. The highly consistent and continuous graded exposure–outcome relationship observed across populations with diverse risk exposures and susceptibility strongly supports the notion of direct causal relationships between reduced lung function and health outcomes.

Furthermore, most evidence is from western populations in high-income countries, whereas less data and knowledge are available regarding these associations in middle-income and low-income countries,[6–8] where the scope of risk exposures, population susceptibility, and aetiological factors for lung function impairment are different.

The prospective urban rural epidemiology (PURE) study, is an international, community-based cohort study in which adults were enrolled from high-income, middle-income, and low-income countries.[9] As part of the study, we examined the associations between the extent of baseline FEV_1 impairment and future risks of mortality, cardiovascular disease events, and respiratory hospitalisations, and analysed whether these associations vary by socioeconomic, geographical, demographic, and clinical background, with the aim of providing insights into the mechanisms underlying epidemiological links between lung function and cardiorespiratory outcomes.

Methods

Study design and participants

The methods of PURE have been previously published[9] and are summarised in the appendix (pp 5–9). Countries and centres were chosen to provide a wide range of socioeconomic and environmental settings, balanced by the feasibility of achieving high-quality data collection and long-term follow-up. 628 urban and rural communities from 17 countries (high-income, middle-income, and low-income) were included. Standardised approaches were used for the enumeration of households, identification of individuals, recruitment, and data collection. Because collection of data from nationally representative samples in each country was not feasible, the sampling methods were carefully chosen to avoid biases in participant selection based on risk factors and disease prevalence.

Households with members aged 35–70 years who had no intention of moving residences for 4 years were eligible. The demographic and mortality statistics for PURE have been validated against each country's national statistics and have shown good agreement (appendix p 8). The study is coordinated by the Population Health Research Institute, McMaster University (Hamilton, ON, Canada); and approved by the Hamilton Health Sciences research ethics board and by each site's ethics committee.

	Clinically normal range			Clinically abnormal range (severe impairment [n=4093])
	No impairment (n=66 513)	Mild impairment (n=41 508)	Moderate impairment (n=14 245)	
FEV_1%	112·9 (106–122)	91·5 (86–96)	70·7 (64–75·4)	46·9 (35·4–53)
FVC%	111·3 (102–122)	90·1 (82·5–98·5)	71·7 (63·3–83·8)	53·4 (41·7–70·4)
FEV_1/FVC				
Median (IQR)	0·87 (0·8–0·9)	0·86 (0·8–0·9)	0·83 (0·7–0·9)	0·72 (0·6–0·9)
<0·70	1773 (2·7%)	3523 (8·5%)	3272 (23·0%)	1843 (45·0%)
Sex				
Female	38 303 (57·6%)	24 770 (59·7%)	8418 (59·1%)	2028 (49·5%)
Male	28 210 (42·4%)	16 738 (40·3%)	5827 (40·9%)	2065 (50·5%)
Location				
Urban	35 584 (53·5%)	22 799 (54·9%)	7024 (49·3%)	1932 (47·2%)
Rural	30 929 (46·5%)	18 706 (45·1%)	7221 (50·7%)	2161 (52·8%)
Age, years	50 (42–58)	50 (42–58)	52 (43–60)	53 (44–62)
Body-mass index, kg/m^2				
Median (IQR)	25·2 (22·5–28·3)	25·4 (22·4–28·8)	25·3 (22·1–28·9)	24·9 (21·8–28·3)
<18·5	2678 (4·0%)	2078 (5·0%)	902 (6·3%)	294 (7·2%)
Primary or no education	26 414 (39·7%)	16 839 (40·6%)	6890 (48·4%)	2034 (49·7%)
Tobacco use				
Former (last use ≥12 months ago)	8237 (12·4%)	4638 (11·2%)	1547 (10·9%)	588 (14·4%)
Current (last use <12 months ago)	13 188 (19·8%)	8691 (20·9%)	3369 (23·7%)	1064 (26·0%)
Never	44 627 (67·1%)	27 819 (67·0%)	9190 (64·5%)	2398 (58·6%)
Solid fuel for cooking	17 402/65 176 (26·7%)	10 138/40 552 (25·0%)	3701/13 861 (26·7%)	1335/3997 (33·4%)
Handgrip strength, kg	29·3 (22·7–38)	27·7 (21–36)	26·7 (20–34)	28 (20·7–36·7)
Low physical activity*	9648/61 846 (15·6%)	6467/38 958 (16·6%)	2437/13 317 (18·3%)	855/3851 (22·2%)
Alternative healthy eating score†	34·8 (29·5–40·2)	34·8 (29·3–40·3)	34·8 (29·2–40·2)	34·1 (28·3–39·7)
Cardiorespiratory symptoms‡	19 152 (28·8%)	13 495 (32·5%)	5435 (38·2%)	1858 (45·4%)
Inhaler therapy	766 (1·2%)	789 (1·9%)	522 (3·7%)	351 (8·6%)
Hypertension§	14 614 (22·0%)	10 561 (25·4%)	4141 (29·1%)	1229 (30%)
Chronic respiratory disease¶	1973 (3·0%)	2032 (4·9%)	1255 (8·8%)	724 (17·7%)
Diabetes‖	6022 (9·1%)	4629 (11·2%)	1731 (12·2%)	502 (12·3%)
Cardiovascular disease**	2973 (4·5%)	2294 (5·5%)	1011 (7·1%)	371 (9·1%)
Cancers††	1019 (1·5%)	770 (1·9%)	294 (2·1%)	110 (2·7%)

Data are n (%) or median (IQR). FEV_1% and FVC% are FEV_1 and FVC values standardised as a percentage of country-specific predicted values. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Defined as <600 metabolic equivalents per min per week from the International Physical Activity Questionnaire. †Scores range from 6–70, with higher scores indicating a more healthy diet. ‡Self-reported symptoms of wheeze, cough, sputum, chest-pain, or breathlessness with usual activity occurring at least weekly within 6 months of baseline questionnaire. §Blood pressure >140/90 mm Hg at baseline visit or a history of hypertension with regular antihypertensive medications. ¶Self-reported history of physician-diagnosed chronic respiratory disease (chronic obstructive pulmonary disorder, tuberculosis, or asthma). ‖Self-reported history of physician-diagnosed diabetes. **Self-reported history of physician-diagnosed cardiovascular disease (include any heart conditions, cerebrovascular disease, or peripheral vascular disease). ††Self-reported history of physician-diagnosed cancer, including all cancer types except for non-melanoma skin cancers.

Table 1: **Baseline characteristics by country-standardised FEV_1% category**

Cardiology, São Paulo, São Paulo, Brazil (Prof A Avezum MD); **Fundacion Oftalmologica de Santander (FOSCAL), Floridablanca, Santander, Colombia** (Prof P Lopez-Jaramillo MD); **and University of La Frontera, Temuco, Chile** (Prof F Lanas MD)

Correspondence to:
Dr MyLinh Duong, Population Health Research Institute, Department of Medicine, McMaster University, Hamilton, ON L8V 1C3, Canada
duongmy@mcmaster.ca

See **Online** for appendix

Procedures

Standardised, interview-based questionnaires were administered to household members aged 35–70 years to elicit information on demographics and household, medical, and risk factors (appendix p 10). Standardised measurements of anthropometrics, blood pressure, handgrip strength, and spirometry were taken. Lung function was measured with a portable spirometer (MicroGP; MicroMedical, Chatham, IL, USA), without spirographs, with use of a standardised protocol. Participants were coached before attempting pre-bronchodilator forced expiratory manoeuvres (maximum six attempts) while standing and wearing a nose-clip. Manoeuvres were observed to ensure maximal effort, forced exhalation time of at least 6 s, and exhalation without coughing. Participants with two or more FEV_1 and forced vital capacity (FVC) measurements within 200 mL variability were selected. The highest FEV_1 values per patient were analysed. The quality of spirometry data has previously been validated and shown strong agreement with FEV_1 values acquired at hospital-based pulmonary

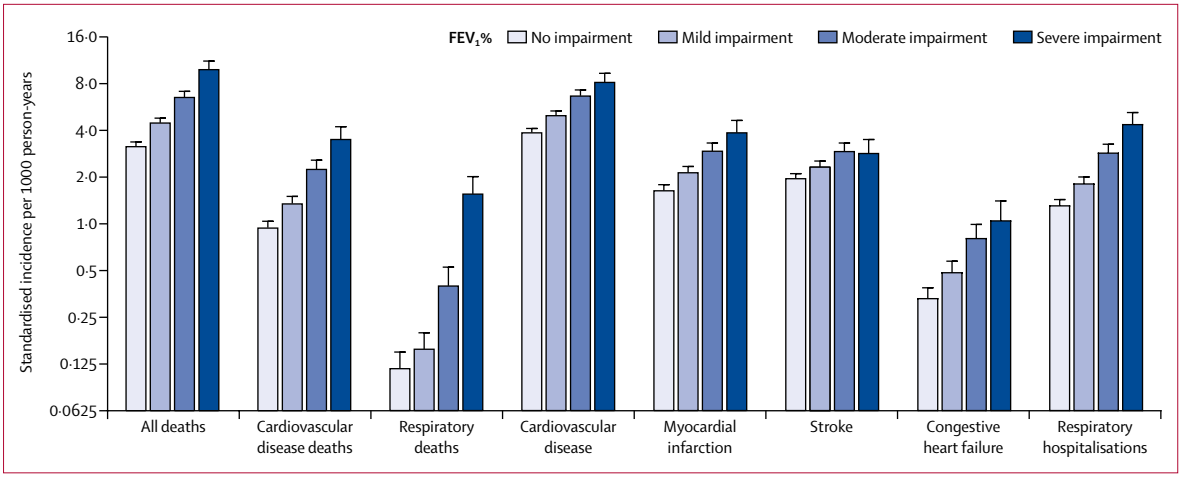

Figure 1: **Incidence of death and cardiovascular and respiratory outcomes by baseline country-standardised FEV_1% impairment category**
Incidence was standardised for age and sex. All deaths includes deaths from any cause except injury. Cardiovascular disease includes myocardial infarction, congestive heart failure, stroke, sudden death, and deaths due to cardiovascular disease. Respiratory hospitalisations include those due to chronic obstructive pulmonary disease, asthma, tuberculosis, pneumonia, or other ICD-10 respiratory conditions, but exclude deaths due to respiratory conditions. Full data are provided in table 2. FEV_1%=forced expiratory volume in 1 s standardised as a percentage of country-specific predicted FEV_1.

laboratories from 531 participants (mean differences 6–161 mL) across sites.[10]

To ensure standardisation and collection of high-quality data, comprehensive operation manuals, regular training workshops, DVDs, and feedback were made available. Data were entered locally into customised databases with ranges and consistency checks, and transmitted centrally for further quality control.

Follow-up for new events related to the outcomes of interest was done every 3 years, with information collected from participants or (if the patient had died) from close relatives (verbal autopsies).[11] All supporting documentation was retrieved and locally adjudicated by trained physicians with use of standardised definitions (appendix pp 11–14). All fatal events and a random subset of non-fatal events were regularly selected for central adjudication to check for consistency across sites.

Because current reference values do not sufficiently cover the scope of ethnic and geographical regions represented in PURE, measured FEV_1 values were internally standardised within each country. An allometric[10] equation previously derived and validated in PURE was used to regress FEV_1 to height, age, and sex on all acceptable spirometry data stratified by country. The resultant regression models generated country-specific predicted FEV_1 values. Measured FEV_1 values were standardised as a percentage of country-specific predicted FEV_1 (ie, $FEV_1\% = FEV_1 \div \text{predicted } FEV_1 \times 100$), which compared participants' FEV_1 values to their respective country mean FEV_1 for individuals of that height, age, and sex. The resultant country-standardised FEV_1%s were normally distributed, centring (mean) on 100% with SDs, which varied by country (appendix p 15). Country-specific SDs were used to standardise FEV_1% impairment across countries into four categories: no impairment ($FEV_1\% \geq 0$ SD from population mean), mild impairment ($FEV_1\%$ <0 SD to –1 SD from population mean), moderate impairment ($FEV_1\%$ <–1 SD to –2 SD from population mean), and severe impairment ($FEV_1\%$ <–2 SD from population mean [ie, clinically abnormal range]). We also did further analyses of the effects of FVC%, standardised by country and categorised into four groups (no impairment, mild impairment, moderate impairment, and severe impairment) on the basis of country-specific SDs, as was done for FEV_1%. In addition, we compared our findings to results from similar analyses using the Global Lung Initiative (GLI) predictive values[12] to express measured FEV_1.

Outcomes

The outcomes examined were death (excluding deaths due to injuries), cardiovascular disease (myocardial infarction, stroke, sudden death, or congestive heart failure), and admission to hospital for respiratory reasons (from chronic obstructive pulmonary disease, asthma, pneumonia, tuberculosis, or other pulmonary conditions) in relation to FEV_1% category.

Statistical analysis

The associations between FEV_1% and the specified outcomes were examined with use of multilevel Cox models, treating centres as random effects. Hazard ratios (HRs), with the no impairment group used as the reference, were adjusted for age (continuous); sex; country income (high, middle, or low); urban or rural community; body-mass index (<20 kg/m², 20 to <30 kg/m², or ≥30 kg/m²); education (up to primary level, secondary level, or trade, college, or university level); cooking fuel use (electricity or gas, or solid fuel); tobacco use (ever or never); alcohol use (ever or never); inhaled medication use; hypertension (defined as self-reported hypertension with anti-hypertensive medications or measured blood

	Clinically normal range			Clinically abnormal range (severe impairment [n=4093])
	No impairment (n=66 513)	Mild impairment (n=41 508)	Moderate impairment (n=14 245)	
All deaths				
Number of events	2187 (3·3%)	1838 (4·4%)	1005 (7·1%)	458 (11·2%)
HR (95% CI) versus no impairment group	1 (ref)	1·27 (1·18–1·36)	1·74 (1·60–1·90)	2·54 (2·26–2·86)
HR (95% CI) versus adjacent group	..	..	1·38 (1·26–1·50)*	1·46 (1·28–1·65)†
Cardiovascular disease deaths				
Number of events	654 (1·0%)	556 (1·3%)	341 (2·4%)	156 (3·8%)
HR (95% CI) versus no impairment group	1 (ref)	1·32 (1·16–1·50)	1·92 (1·65–22·3)	2·77 (2·26–3·40)
HR (95% CI) versus adjacent group	..	..	1·46 (1·25–1·70)*	1·44 (1·16–1·79)†
Respiratory deaths				
Number of events	89 (0·1%)	65 (0·2%)	64 (0·4%)	74 (1·8%)
HR (95% CI) versus no impairment group	1 (ref)	1·22 (0·85–1·76)	2·53 (1·72–3·74)	8·06 (5·43–12·0)
HR (95% CI) versus adjacent group	..	..	2·08 (1·39–3·11)*	3·18 (2·12–4·77)†
Cardiovascular disease				
Number of events	2522 (3·8%)	1937 (4·7%)	926 (6·5%)	349 (8·5%)
HR (95% CI) versus no impairment group	1 (ref)	1·18 (1·10–1·26)	1·39 (1·28–1·51)	2·02 (1·75–2·32)
HR (95% CI) versus adjacent group	..	..	1·18 (1·08–1·29)*	1·27 (1·11–1·46)†
Myocardial infarction				
Number of events	1038 (1·6%)	813 (2·0%)	402 (2·8%)	164 (4·0%)
HR (95% CI) versus no impairment group	1 (ref)	1·16 (1·05–1·28)	1·43 (1·26–1·63)	1·95 (1·61–2·36)
HR (95% CI) versus adjacent group	..	..	1·23 (1·08–1·40)*	1·37 (1·11–1·68)†
Stroke				
Number of events	1318 (2%)	927 (2·2%)	412 (2·9%)	123 (3·0%)
HR (95% CI) versus no impairment group	1 (ref)	1·09 (0·99–1·19)	1·22 (1·08–1·37)	1·20 (0·97–1·48)
HR (95% CI) versus adjacent group	..	..	1·12 (0·99–1·27)*	0·99 (0·79–1·24)†
Congestive heart failure				
Number of events	229 (0·3%)	202 (0·5%)	122 (0·9%)	47 (1·1%)
HR (95% CI) versus no impairment group	1 (ref)	1·45 (1·18–1·78)	2·09 (1·64–2·66)	2·56 (1·80–3·64)
HR (95% CI) versus adjacent group	..	..	1·44 (1·13–1·84)*	1·23 (0·85–1·77)†
Respiratory hospitalisation				
Number of events	751 (1·1%)	663 (1·6%)	365 (2·6%)	169 (4·1%)
HR (95% CI) versus no impairment group	1 (ref)	1·39 (1·24–1·56)	2·02 (1·75–2·32)	2·97 (2·45–3·60)
HR (95% CI) versus adjacent group	..	..	1·45 (1·26–1·67)*	1·47 (1·20–1·80)†

Frequency data are n (% from total participants within impairment category). HRs referenced to the no impairment group were estimated with a multilevel Cox proportional hazards model adjusted for age, sex, urban or rural community, body-mass index, handgrip strength, educational level, cooking fuel, country income level, tobacco use status, alcohol use status, self-reported diabetes or cardiorespiratory disease or HIV infection, hypertension, inhaler therapy, physical activity, dietary pattern, and centres as random effects. HRs referenced to next most severe impairment group (ie, moderate *vs* mild, severe *vs* moderate) were calculated with use of similar fully adjusted mixed effects Cox models. HR=hazard ratio. *Referenced to mild impairment group. †Referenced to moderate impairment group.

Table 2: **Number of events and adjusted HRs by country-standardised FEV_1% impairment category**

pressure >140/90 mm Hg); known cardiovascular diseases (all cardiac conditions, strokes, peripheral vascular disease), chronic respiratory diseases (chronic obstructive pulmonary disease, asthma, tuberculosis, or other pulmonary diseases), cancers (excluding non-melanoma skin cancers), HIV infection, or diabetes; physical activity (low, moderate, or high) on the International Physical Activity Questionnaire;[13] dietary pattern (healthy eating score[14]); and handgrip strength. The proportional hazards assumption was checked by visual inspection of log–log plots. Population-attributable risk was calculated with use of the SAS Macro[15] based on the Cox model, adjusted for age, sex, and country income level.

Separate stratified analyses were done for country-income (high *vs* middle *vs* low [World Bank 2006 Classification]); urban versus rural community; tobacco use (ever *vs* never [self-reported use of zero tobacco products per day and zero days of use per year]); age (<50 years *vs* 50–65 years *vs* >65 years); cooking fuel use (gas or electricity *vs* solid fuel); healthy (no history of tobacco or alcohol use, cardiorespiratory symptoms, cardiovascular disease, Chagas disease, chronic respiratory disease, cancers, HIV infection, hypertension, diabetes, malaria, tuberculosis, hepatitis, or pregnancy) versus not healthy status; and baseline self-reported cardiorespiratory status (no known cardiovascular

	Population-attributable risk for death	Population-attributable risk for cardiovascular disease
Mild to moderate FEV_1 impairment (0 SDs to –2 SDs below population mean)	24·7% (22·2–27·2)	17·3% (14·8–19·7)
Severe FEV_1 impairment (lower than –2 SD below population mean)	3·7% (2·1–5·2)	7·5% (5·1–10·0)
Tobacco use	19·7% (17·2–22·3)	7·5% (5·2–9·9)
Previous cardiovascular disease	5·5% (4·5–6·5)	12·2% (11·0–13·4)
Hypertension	17·1% (14·6–19·6)	30·1% (27·6–32·5)
Solid fuel for cooking (all countries)	12·8% (10·6–15·0)	7·3% (5·3–9·2)
Solid fuel for cooking (low-income countries only)	19·7% (15·1–24·2)	12·7% (7·0–18·2)
FEV_1 below 50th percentile	25·5% (23·0–28·0)	18·2% (15·7–20·8)
Systolic blood pressure above 50th percentile	12·2% (8·9–15·5)	33·3% (30·2–36·2)
FEV_1 below 20th percentile	15·6% (14·0–17·2)	10·6% (9·0–12·1)
Systolic blood pressure above 80th percentile	12·1% (10·1–14)	22·6% (20·6–24·7)
FEV_1 below 5th percentile	7·1% (6·1–8·1)	3·7% (2·9–4·5)
Systolic blood pressure above 95th percentile	6·2% (5·1–7·2)	9·7% (8·6–10·9)

Population-attributable risks (% [95% CI]) were based on a Cox model, adjusted for age, sex, and country income level. FEV_1 and systolic blood pressure were standardised within each population. FEV_1=forced expiratory volume at 1 s.

Table 3: **Population-attributable risks for death and cardiovascular disease from different major risk factors**

disease, chronic respiratory disease, or current respiratory symptoms [no self-reported wheeze, cough, sputum, or breathlessness with usual activity occurring at least weekly in the past 6 months] *vs* current respiratory symptoms only *vs* known chronic respiratory disease only *vs* known cardiovascular disease).

With the same multilevel Cox regression method, we also compared each category against the previous (less impaired) category to assess the incremental increases in HR between one FEV_1% category and the next. HRs were plotted to examine for potential interactions between strata with FEV_1%. Given the multiple comparisons, nominally significant p values should be interpreted cautiously, unless very small ($p<0·001$) or the results form a coherent pattern. All analyses were done in SAS version 9.4.

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Results

Of the 164 162 participants enrolled in the PURE study between Jan 1, 2005, and March 29, 2017, 126 359 had acceptable spirometry data (appendix p 16). Baseline data were collected from Jan 1, 2005, to Dec 30, 2009, and baseline characteristics of participants in the different FEV_1% categories are shown in table 1. 14 700 (11·6%) of participants were enrolled from high-income countries, 89 926 (71·2%) from middle-income countries, and 21 733 (17·2%) from low-income countries.

Follow-up was done from Jan 1, 2008, to Dec 30, 2013, and was complete for 157 267 (95·8%) participants. During a median follow-up period of 7·8 years (IQR 5·6–9·5), 5488 (4·3%) of participants died, 5734 (4·5%) had cardiovascular disease events, and 1948 (1·5%) had respiratory hospitalisation. Mortality and incidence of cardiovascular disease events (standardised for age and sex) showed graded increases with decreasing FEV_1% (figure 1), and Cox analyses showed significant incremental increases in risk with each level of FEV_1 impairment (table 2), indicating a dose-response relationship that was continuous throughout all levels of impairment (appendix p 17). Although HRs were modest in the groups with mild or moderate impairment in FEV_1% (within the clinically normal range), the absolute numbers of events showed a high burden of disease in these groups. By contrast, the severely reduced FEV_1% group (in the clinically abnormal range) had the highest risk but accounted for a low proportion of events (458 [8·3%] of 5488 deaths, and 156 [6·1%] 5734 cardiovascular disease events).

The population-attributable risk for mortality from mildly to moderately impaired (clinically normal) FEV_1% (24·7% [95% CI 22·2–27·2]) was more than six times higher than that from severely impaired (clinically abnormal) FEV_1% (3·7% [2·1–5·2]; table 3, appendix p 18), and was higher than the population-attributable risks from tobacco use, solid fuel cooking, previous cardiovascular disease, and hypertension. Similarly, the population-attributable risk for incident cardiovascular disease from mildly to moderately impaired FEV_1% (17·3% [14·8–19·7]) was two times higher than that from severely impaired FEV_1% (7·5% [5·1–10·0]), and was higher than that the population-attributable risks from previous cardiovascular disease, tobacco use, and solid fuel cooking, but lower than that of hypertension (table 3). The population-attributable risk for mortality from mildly to moderately impaired FEV_1% was consistently higher than that of hypertension across all FEV_1% levels and systolic blood pressure levels standardised within the population.

Severity of FEV_1% impairment was also associated with graded increases in risk of myocardial infarction, congestive heart failure, stroke, cardiovascular disease deaths, and respiratory deaths (table 2). Dose-response relationship with mortality was consistent across populations from different country income levels, rural and urban communities, tobacco use status, age, cooking fuel, and baseline cardiorespiratory morbidity status (figure 2, table 4). The effect of reduced FEV_1% on mortality was independent and additive to the increased mortality associated with old age (>65 years), low-income country residence, rural setting, tobacco use, solid-fuel cooking, and known cardiovascular disease at baseline. In the absence of FEV_1% impairment, standardised mortality incidence was similar among those with self-reported respiratory symptoms or physician-diagnosed chronic respiratory disease alone and those without any cardiorespiratory morbidity (figure 2). However, moderate

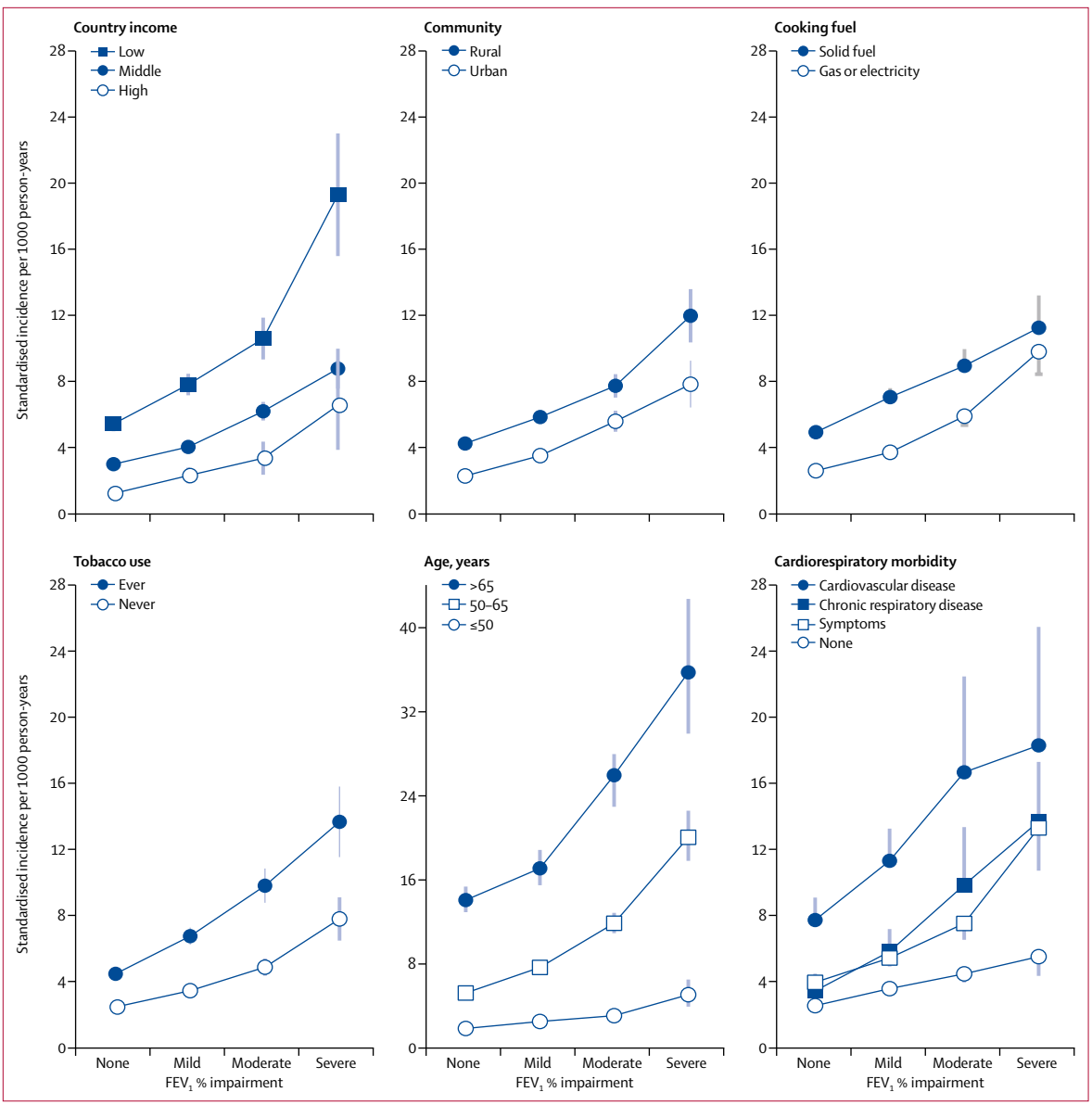

***Figure 2*: Incidence of mortality by country-standardised FEV_1% impairment, stratified by subpopulation**
Incidence was standardised for age and sex. Error bars are 95% CIs. Baseline cardiorespiratory morbidity was defined as none (no symptoms and no known cardiorespiratory disease), symptoms (cardiorespiratory symptoms only, without any known cardiorespiratory disease), chronic respiratory disease only, and cardiovascular disease (including all cardiac conditions and cerebrovascular disease). FEV_1%=forced expiratory volume in 1 s standardised as a percentage of country-specific predicted FEV_1.

or severe FEV_1% impairment had a greater effect on mortality risk in the presence of cardiorespiratory symptoms or chronic respiratory disease than in their absence (table 4, appendix pp 19–20). Severe FEV_1% impairment had the greatest effect on mortality in the youngest subgroup (<50 years). A pattern of increasing mortality risk with decreasing FEV_1% was observed across most geographical regions and also in healthy individuals (appendix pp 22–23).

Impaired FEV_1% was also associated with respiratory deaths and hospitalisations (table 4), and risk of respiratory events was especially high in the group with severe (clinically abnormal) impairments in FEV_1%. Even so, the absolute number of respiratory events (including deaths and hospitalisations) in the groups with mildly to moderately reduced FEV_1 was more than double the number in the group with severely reduced FEV_1%.

In sensitivity analyses, the addition of the 7476 participants who had been removed because of spirometry data of suboptimal quality, adjustment for wealth index and other socioeconomic indicators, and removal of participants with obstructive impairment (FEV_1/FVC ratio

	No impairment		Mild impairment		Moderate impairment		Severe impairment	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)	Deaths	HR (95% CI)	Deaths	HR (95% CI)
Country income								
High	112/7679 (1·5%)	1 (ref)	122/4914 (2·5%)	1·48 (1·12–1·95)	67/1653 (4·1%)	2·00 (1·44–2·78)	38/454 (8·4%)	2·85 (1·88–4·32)
Middle	1398/47 827 (2·9%)	1 (ref)	1089/29 054 (3·7%)	1·23 (1·13–1·35)	609/9974 (6·1%)	1·71 (1·53–1·90)	288/3071 (9·4%)	2·38 (2·06–2·75)
Low	677/11 007 (6·2%)	1 (ref)	627/7540 (8·3%)	1·28 (1·12–1·46)	329/2618 (12·6%)	1·73 (1·47–2·03)	132/568 (23·2%)	2·73 (2·14–3·48)
Age, years								
≤50	465/31 476 (1·5%)	1 (ref)	396/19 965 (2·0%)	1·21 (1·03–1·43)	143/6060 (2·4%)	1·32 (1·04–1·67)	62/1621 (3·8%)	2·79 (2·03–3·85)
50–65	1203/30 033 (4·0%)	1 (ref)	1043/18 234 (5·7%)	1·37 (1·25–1·50)	595/6774 (8·8%)	1·90 (1·70–2·13)	275/1950 (14·1%)	2·68 (2·30–3·13)
>65	519/5004 (10·4%)	1 (ref)	399/3309 (12·1%)	1·09 (0·94–1·27)	267/1411 (18·9%)	1·64 (1·39–1·95)	121/522 (23·2%)	2·12 (1·68–2·67)
Community								
Urban	841/35 584 (2·4%)	1 (ref)	736/22 799 (3·2%)	1·21 (1·08–1·35)	389/7024 (5·5%)	1·70 (1·48–1·95)	166/1932 (8·6%)	2·56 (2·11–3·12)
Rural	1345/30 929 (4·3%)	1 (ref)	1102/18 709 (5·9%)	1·30 (1·19–1·43)	616/7221 (8·5%)	1·76 (1·58–1·97)	292/2161 (13·5%)	2·53 (2·17–2·94)
Cooking fuel								
Gas or electricity	1259/48 356 (2·6%)	1 (ref)	1071/30 785 (3·5%)	1·22 (1·12–1·34)	600/10 296 (5·8%)	1·71 (1·53–1·92)	284/2691 (10·6%)	2·56 (2·20–2·97)
Solid fuel	928/17 977 (5·2%)	1 (ref)	767/10 591 (7·2%)	1·33 (1·19–1·48)	405/3915 (10·3%)	1·74 (1·52–1·99)	174/1388 (12·5%)	2·59 (2·14–3·13)
Tobacco use								
Never	1168/44 627 (2·6%)	1 (ref)	920/27 819 (3·3%)	1·23 (1·11–1·35)	492/9190 (5·4%)	1·68 (1·49–1·90)	196/2398 (8·2%)	2·58 (2·16–3·08)
Ever	1002/21 425 (4·7%)	1 (ref)	909/13 329 (6·8%)	1·30 (1·18–1·44)	507/4916 (10·3%)	1·78 (1·58–2·02)	262/1652 (15·9%)	2·49 (2·12–2·93)
Baseline cardiorespiratory symptoms and diseases								
None	1257/45 276 (2·8%)	1 (ref)	951/26 557 (3·6%)	1·26 (1·14–1·39)	418/8194 (5·1%)	1·59 (1·40–1·81)	138/1997 (6·9%)	2·13 (1·74–2·61)
Cardiorespiratory symptoms only	643/16 554 (3·9%)	1 (ref)	581/10 940 (5·3%)	1·25 (1·10–1·42)	328/3955 (8·3%)	1·83 (1·56–2·14)	159/1113 (14·3%)	2·84 (2·31–3·49)
Chronic respiratory disease	63/1710 (3·7%)	1 (ref)	83/1717 (4·8%)	1·11 (0·76–1·63)	112/1085 (10·3%)	2·25 (1·57–3·24)	98/612 (16·0%)	3·38 (2·32–4·93)
Cardiovascular disease	224/2973 (7·5%)	1 (ref)	223/2294 (9·7%)	1·38 (1·12–1·69)	147/1011 (14·5%)	1·75 (1·38–2·21)	63/371 (17·0%)	2·04 (1·49–2·80)

Mortality data are n/N (%) for each group and stratum. HRs were estimated with multilevel Cox proportional hazards models adjusted for demographic, socioeconomic, and clinical covariates, with centres as random effects within strata. See appendix for plots of HRs within strata by FEV_1% category.

Table 4: **Number of deaths and HR for stratified models**

<0·70) or restrictive impairment (country-standardised FVC% <–2 SDs from population mean) did not meaningfully alter the effect of FEV_1% impairment on mortality observed in our primary analyses (appendix p 24).

The analysis of the associations between country-standardised FVC% and death (due to all causes, excluding injury), respiratory deaths, cardiovascular disease events, and respiratory hospitalisations yielded similar findings to those of the FEV_1% analysis, showing increasing risk of these events with worsening FVC% (appendix p 25).

Finally, when FEV_1 values were standardised to GLI predicted values[12] rather than PURE country-specific predicted values, we found similar exposure–outcome gradients for mortality, cardiovascular disease, and respiratory hospitalisations. However, PURE country-standardised FEV_1 values showed stronger associations with risk of these events (ie, steeper gradients when HRs were plotted against impairment category) than those of the GLI-standardised FEV_1 values, suggesting better prediction of outcomes with PURE country-specific standardisation (appendix p 26).

Discussion

This large, international, community-based, prospective study involving 126 359 adults from 628 urban and rural communities in 17 countries yielded three main findings. First, we observed significant and graded relationships between decreasing baseline FEV_1% and increasing risks of mortality, cardiovascular disease, and respiratory events. The exposure–outcome gradients were continuous throughout all levels of FEV_1% impairment, whether or not impairment was defined as clinically normal or abnormal by current standards of practice.[5] Second, the population-attributable risks for mortality and incident cardiovascular disease from impaired FEV_1 were high, contributing to around a quarter of deaths and a sixth of cardiovascular disease events. These contributions were higher than those of other major risk factors such as hypertension, previous cardiovascular disease, tobacco use, and solid fuel cooking. Furthermore, the contribution of mildly to moderately impaired FEV_1% (within the clinically normal range) was several times larger than that of severe FEV_1% impairment (in the abnormal range), suggesting that only a small subset of individuals on the risk continuums for death or cardiovascular disease have severe FEV_1% impairment. Third, the increased risk of mortality in individuals with FEV_1% impairment was consistent across populations from diverse socioeconomic, geographical, demographic, and clinical backgrounds. The effect of reduced FEV_1% was independent and

additive to the elevated risk of mortality from low-income country, rural community, older age, tobacco use, and known cardiovascular disease. However, the effect of reduced FEV_1% was multiplicative when associated with respiratory symptoms, known chronic respiratory disease, and younger age (<50 years), where it has larger prognostic implications. The consistency of the dose–response relationship across populations of diverse risk exposures, susceptibility, and underlying aetiological factors for lung function impairment strongly suggests a direct causal relationship between reduced lung function and cardiorespiratory health outcomes.

The associations between reduced lung function (including FEV_1 and FVC reductions[6,16]) and future risk of mortality or cardiovascular disease have long been recognised, but mainly in high-income countries.[1–4,17,18] Reduced lung function has also been associated with comorbidities including diabetes,[19] renal dysfunction,[20] and neurocognitive disease.[21] Some of these associations have been recognised for minor impairments in lung function during early adulthood,[22,23] which have remained significant for decades during follow-up,[24] suggesting that they are unrelated to ageing or reverse causality. Reduced lung function might share similar trajectories and early developmental pathways with many of the chronic comorbidities associated with increased risk of mortality. Contributing to this field of research, our findings show that the association between lung function and mortality is robust and generalisable across populations from diverse country income levels, geographical regions, and communities, and in individuals with and without tobacco use or known cardiorespiratory disease. Even after adjusting for well known risk factors, reduced FEV_1% remained significant in predicting mortality and cardiovascular disease events, including myocardial infarction, stroke, congestive heart failure, and death due to cardiovascular disease. The reasons for the associations between reduced lung function and the many diverse disease outcomes are unknown. In chronic obstructive pulmonary disease, which has been associated with various extrapulmonary comorbidities and is increasingly being considered to be a multisystem disease,[25] postulated mechanisms for these associations include common or shared risk factors (such as cigarette smoking) between the conditions, or a direct effect from the lungs (such as inflammation in the lungs causing reduced lung function as well as systemic effects on other organs or systems). In our sensitivity analyses, removing participants with obstructive (and restrictive) impairment, these associations remained unchanged. We speculate that reduced FEV_1% might be an important indicator of frailty or inherent susceptibility to developing chronic diseases. Alternatively, reduced FEV_1% might be causally related to systemic (inflammatory) pathways with multiorgan effects. Understanding such pathophysiological links could lead to novel and targeted approaches to prevent and reduce the burden of multiple diseases, including cardiovascular and respiratory diseases, as well as to reduce mortality.

Consistent with the scarce existing data,[2] we found a graded relationship between declining FEV_1% (throughout clinically normal and abnormal ranges) and increasing risk of adverse outcomes. The absolute numbers of events were higher in the groups with mildly or moderately reduced FEV_1% than in with severely reduced FEV_1%. Therefore, the use of fixed thresholds (such as <–2 SD from population mean) to define lung function impairment might substantially underestimate the adverse effects of reduced lung function on health. This relationship is analogous to the continuous associations between blood pressure or LDL cholesterol with cardiovascular disease,[26,27] and suggests that approaches to improving lung function in those with mildly to moderately reduced FEV_1 could have a large impact on the burden of both respiratory and cardiovascular diseases.

The population-attributable risk for mortality from reduced FEV_1% was higher than the risks contributed by several major risk factors, including tobacco use, hypertension, and previous cardiovascular disease. All levels of FEV_1% impairment showed greater contributions to mortality than did hypertension, suggesting that the effect is independent of the thresholds used. Furthermore, reduced FEV_1% was second only to hypertension in terms of its contribution to incident cardiovascular disease events, suggesting that FEV_1% impairment is an important and under-recognised risk factor that contributes substantially to the global burden of cardiovascular disease.

In stratified analyses, for similar levels of FEV_1%, low country income, rural community setting, and solid-fuel cooking were associated with increased mortality due to factors independent of FEV_1%. Added to this was a consistent and graded increase in mortality with lower baseline FEV_1%. The consistency of this relationship across populations from diverse socioeconomic and geographical backgrounds, with different risk exposures and aetiological factors for lung function impairment, strongly suggests a direct causal relationship. This notion is further supported by the dose–response and temporal relationships between reduced FEV_1% at baseline and follow-up health outcomes, which, in keeping with Hill's criteria, are suggestive of underlying causality.[28] The same pattern was observed in low-risk subgroups, such as non-tobacco users, young participants (<50 years of age), and healthy participants, where the effects of confounders such as tobacco, senescence, and subclinical cardiorespiratory disease are minimised. Therefore, a simple measure of reduced FEV_1 across populations might be a feasible and informative marker for the population health burden, even in low-resource settings.

Another notable finding was the independent and additive effect of reduced FEV_1% on the elevated risk associated with pre-existing cardiovascular disease at baseline. A 2016 study showed that the prevalence of

obstructive lung function impairment was increased among people with cardiovascular disease.[29] Patients with both cardiovascular disease and obstructive lung function impairment had increased incidence of cardiorespiratory symptoms, emergency room visits, and poorer health status compared with patients with cardiovascular disease only. Our data complement these findings, showing that reduced FEV_1% is an independent risk factor associated with a two-fold increase in mortality above the elevated mortality risk conferred by cardiovascular disease alone. Thus, reduced FEV_1 concomitant with cardiovascular disease has prognostic implications for mortality and morbidity. We also observed a larger effect of reduced FEV_1% in participants with physician-diagnosed chronic respiratory disease or current respiratory symptoms, suggesting a greater prognostic effect of reduced FEV_1% in these subgroups. However, existing symptoms or chronic respiratory disease alone—without FEV_1% impairment—were not associated with increased future risk of mortality, suggesting that these clinical features per se have no prognostic implications. This finding reaffirms the need for lung function assessments in those suspected of having chronic respiratory disease, as recommended by international guidelines.[5]

Our study had several limitations. First, because FEV_1 was measured by use of a portable spirometer that did not provide spirographs, individual effort could not be verified. However, we had previously validated our method by comparing data obtained from hospital-based pulmonary function laboratories with field data in 531 participants from the 17 participating countries, which showed strong agreement without biases in the FEV_1.[10] The consistency of our findings in different settings also adds to the validation of these measurements and the practical value of spirometry assessments for epidemiological purposes, even in low-resource settings. Second, we used internally validated methodology for the adjustment and standardisation of lung function by height, age, and sex within and across populations.[10] This practice was necessary because there was no single set of commonly used reference values that was able to cover the scope of ethnic and geographical regions in PURE. The GLI multiethnic reference equations provide the most widely endorsed reference values for four major ethnic groups,[12] but are poorly representative for populations from south Asia, South America, sub-Saharan Africa, and Malaysia, which collectively contributed 40% of the PURE study population. GLI offers an "other" category for all other ethnic groups, but requires extrapolation of values that are not well matched by geographical region or ethnic background for these populations. Nevertheless, GLI-standardised FEV_1% values showed a pattern of association with mortality, cardiovascular disease, and respiratory hospitalisations similar to, albeit less strong than, that of PURE country-standardised values, suggesting that our approach is valid, and potentially better, for predicting outcomes because it is customised by country.

The strengths of our study include its large sample size, inclusion of populations from diverse settings, and the prospective and standardised approach to data collection, outcome ascertainment, and adjustments for a large number of confounders.

In summary, we showed a significant and graded relationship between lower baseline country-standardised FEV_1% and future risk of mortality and cardiorespiratory morbidity. Addressing mild reductions in lung function could have a substantial effect on the population burden of cardiorespiratory diseases, particularly in high-risk groups such as tobacco users, people with known cardiovascular disease, and those living in poorly resourced settings. Further studies are also needed to examine how routine lung function measurement can help to better inform on the overall risk for poor general health outcomes.

Contributors

All listed authors contributed to the intellectual conceptualisation of PURE, study design, planning, and collection of PURE data. MLD, SI, SR, and SY contributed to the statistical analysis and write up of the study. All authors contributed to the final approval of the manuscript. MLD, PMO'B, and SY have full responsibility for the overall content of this work.

Declaration of interests

We declare no competing interests.

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