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Global differences in lung function by region (PURE): an international, community-based prospective study

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Summary:

Background: Despite the rising burden of chronic respiratory diseases, global data for lung function are not available. L We investigated global variation in lung function in healthy populations by region to establish whether regional1 factors contribute to lung function.

Methods: In an international, community-based prospective study, we enrolled individuals from communities in 17 countries between Jan 1, 2005, and Dec 31, 2009 (except for in Karnataka, India, where enrolment began on Jan 1, S 2003). Trained local staff obtained data from participants with interview-based questionnaires, measured weight and height, and recorded forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC). We analysed data from participants 130–190 cm tall and aged 34–80 years who had a 5 pack-year smoking history or less, who were not affected by specified disorders and were not pregnant, and for whom we had at least two FEV_1 and FVC measurements that did not vary by more than 200 mL. We divided the countries into seven socioeconomic and geographical regions: south Asia (India, Bangladesh, and Pakistan), east Asia (China), southeast Asia (Malaysia), sub-Saharan Africa (South Africa and Zimbabwe), South America (Argentina, Brazil, Colombia, and Chile), the Middle East (Iran, United Arab Emirates, and Turkey), and North America or Europe (Canada, Sweden, and Poland). Data were analysed with non-linear regression to model height, age, sex, and region.

Findings: 153 996 individuals were enrolled from 628 communities. Data from 38 517 asymptomatic, healthy non-smokers (25 614 women; 12 903 men) were analysed. For all regions, lung function increased with height non-linearly, decreased with age, and was proportionately higher in men than women. The quantitative effect of height, age, and sex on lung function differed by region. Compared with North America or Europe, FEV_1 adjusted for height, age, and sex was 31·3% (95% CI 30·8–31·8%) lower in south Asia, 24·2% (23·5–24·9%) lower in southeast Asia, 12·8% (12·4–13·4%) lower in east Asia, 20·9% (19·9–22·0%) lower in sub-Saharan Africa, 5·7% (5·1–6·4%) lower in South America, and 11·2% (10·6–11·8%) lower in the Middle East. We recorded similar but larger differences in FVC. The differences were not accounted for by variation in weight, urban versus rural location, and education level between regions.

Interpretation: Lung function differs substantially between regions of the world. These large differences are not explained by factors investigated in this study; the contribution of socioeconomic, genetic, and environmental investigated in this study; the contribution of socioeconomic, genetic, and environmental factors and their interactions with lung function and lung health need further clarification.

Introduction

The global rise in disease burden from chronic respiratory diseases[1] means that more information is needed about global lung health, particularly factors that adversely affect lung function.[2] Differences in lung function between ethnic groups have previously been investigated, but generally within one country or region.[3] The most widely reported comparisons of lung function (forced expiratory volume in 1 s [FEV_1] and forced vital capacity [FVC]) are between white people and African Americans (decrease of 10–15%[4,5]) and between white people and individuals of Asian origin (decrease of 6–12%[6,7]). Few data are available for other ethnic groups and populations in different geographical regions with vastly different socioeconomic and environmental exposures that could affect lung function.[8]

Our aim was to document the risk factors for chronic respiratory disease burden in adults globally. We deliberately oversampled countries of low to middle income, where the disease burden is high[9] and expected to rise further; little information about lung function and lung health is available for these regions. We postulated that, after adjustment for height, age, and sex, substantial global differences in lung function would be recorded, which would be a result of the complex interactions between genes and environment for each region. These differences could contribute to the baseline population risk for chronic respiratory disease and the global disparity in disease burden.

Methods

Study design and participants

In the international, community-based prospective Population Rural Urban Epidemiology (PURE) study, we enrolled individuals aged 34–80 years from 628 urban and rural communities in 17 countries across five continents. Enrolment occurred between Jan 1, 2005, and Dec 31, 2009, except in Karnataka, India, where it began on Jan 1, 2003.

Details of the enumeration and recruitment methods are provided in the appendix and have been reported elsewhere.[10] We used a multistage, convenience-sampled survey; countries and communities were chosen purposively in the first and second stages, and households or individuals were selected by random sampling in the third stage. We selected countries in different phases of epidemiological transition and where long-term followup was possible. The primary sample unit was the community. We selected a diverse sample of communities in each country purposefully, conveniently, or randomly (appendix), with stratification by urban or rural location.

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In each community, we used a sampling framework to recruit a representative sample of households. In all countries of low to middle income, door-to-door visits were done by trained local staff. In high-income countries, information about the study was initially sent to selected households by post. Study staff subsequently made telephone calls to the selected households, inviting eligible representatives to a central clinic. For both approaches, at least three attempts to contact an individual in each household were made. Households were eligible if at least one member was aged 35–70 years and intended to stay at the address for a further 4 years.

All eligible individuals in the selected households who provided written informed consent were enrolled. When an eligible household or individual refused to participate, demographic information and data about tobacco use, education, and history of cardiovascular disease were recorded in a non-responder form.

The study was coordinated by the Population Health Research Institute (Hamilton, ON, Canada). The protocol was approved by the Hamilton Health Sciences Research Ethics Board and by the local ethics committee at each site.

Procedures

At a second household visit (countries of low and middle income) or during participants' visit to a central clinic (high-income countries), local staff recorded information about demography, medical diagnoses, ethnic origin, tobacco use history, and respiratory symptoms with interview-based questionnaires.[11–14] Questionnaires were translated into the local language with a standardised protocol (appendix). During the second household visit in countries of low and middle income, an appointment was scheduled for physical measurements (including spirometry) and blood and urine tests.

During this appointment, or at the visit to the central clinic in high-income countries, weight was measured on calibrated scales with as little clothing as possible and without shoes. Height was measured with a Frankfort plane against a flat wall, with heels together.

A portable device (MicroGP, MicroMedical, Chatham, IL, USA), chosen for its affordability and ease of use, was used for spirometry measurements, but did not generate flow-volume loops (FVLs). Each participant attempted up to six prebronchodilator forced expiratory manoeuvres while standing and wearing a nose clip. Measurements of maximum effort and forced exhalation for at least 6 s were taken. The three highest measurements of FEV_1, FVC, and peak expiratory flow (PEF) were recorded. Spirometer calibration with a 3 L syringe was done monthly and when thought necessary by local staff (eg, before use in extreme temperatures).

Data quality was maintained in three ways. First, key staff from each centre attended regional training sessions, in which standardised protocols and materials were used. These key staff in turn trained local staff. Local staff were tested on mock participants and certified. Retraining and certification occurred every 18 months. Second, prospective validation was done in 11 countries (Brazil, Canada, China, Colombia, India, Iran, Malaysia, South Africa, Sweden, Turkey, and United Arab Emirates) where study centres had access to pulmonary function

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laboratories. The first 30 participants who attended follow-up visits at the study centre with the highest number of participants in each country were included in prospective validation. Con- current measurements with PURE methods (as used in the field) and in a pulmonary function laboratory (appendix) were obtained for these participants. In South Africa, spirograms were produced at baseline, meaning that FVL measurements were available.

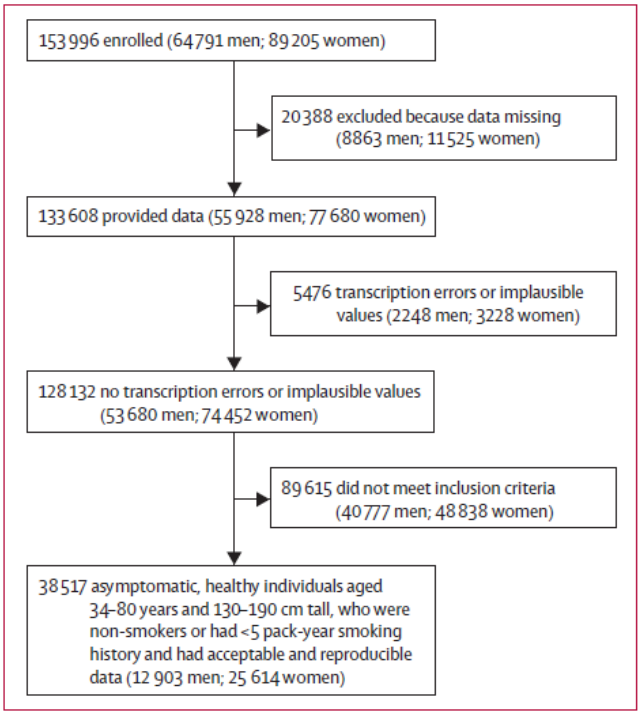

Figure 1: **Study profile**

Third, data were entered electronically into a customised database programmed with range and consistency checks and transmitted to the coordinating centre. Cases with missing values, transcription errors, or implausible data that could not be reconciled were removed.

For analyses, we selected participants with at least two measurements of FEV_1 and FVC with maximum effort, without cough and within 200 mL variability for analysis. Individuals for whom the highest FEV_1 divided by the highest FVC was 0·95 or higher, or less than 0·66, or for whom the highest PEF divided by the highest FEV_1 was less than 1·5 were deemed to have made less than maximum effort and were excluded. We derived these cutoffs from centres with high-quality data for acceptable maximum expiratory effort and forced expiratory time. We removed outliers that had an effect (with Cook's D statistic). Additionally, we excluded participants younger than 34 years and older than 80 years, and those shorter than 130 cm or taller than 190 cm from analyses because of small numbers. Further exclusion criteria were tobacco use of more than 5 pack-years, chronic obstructive pulmonary disease (COPD), asthma, tuberculosis, cancer, pregnancy, regular use of respiratory medications, symptoms of breathlessness with usual activity in the previous 6 months, wheeze, haemoptysis, morning cough, chest tightness, or daily productive cough for 3 months a year for at least 2 years.

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According to the World Bank Classification[15] available when the study began, three of the countries where data were gathered had high income status and 14 low or middle income status. With this information, we divided the 17 countries into seven socioeconomic and geographical regions: south Asia (India, Bangladesh, and Pakistan), east Asia (China), southeast Asia (Malaysia), sub-Saharan Africa (South Africa and Zimbabwe), South America (Argentina, Brazil, Colombia, and Chile), the Middle East (Iran, United Arab Emirates, and Turkey), and North America or Europe (Canada, Sweden, and Poland).

Statistical analysis

Details of model derivation and validation are provided in the appendix. A non-linear multiplicative regression with no intercept (Gauss-Newton method) was the most biologically plausible, best fitting, and parsimonious model.

	Communities			Participants							
	Overall	Urban	Rural	Overall		Women			Men		
				n	Ethnic origin*	n	Age (years)	Height (m)	n	Age (years)	Height (m)
All	628	348 (55·4%)	280 (44·6%)	153 996	..	89 205 (57·9%)	50·0 (9·9)	1·56 (0·07)	64 791 (42·1%)	51·1 (10·0)	1·68 (0·08)
High-income countries											
Canada	82	53 (64·6%)	29 (35·4%)	10 416	8906 (85·5%) European	5590 (53·7%)	53·0 (9·2)	1·62 (0·07)	4826 (46·3%)	53·8 (9·3)	1·75 (0·07)
Sweden	31	28 (90·3%)	3 (9·7%)	4153	3939 (94·8%) European	2194 (52·8%)	52·2 (9·0)	1·66 (0·06)	1959 (47·2%)	53·1 (9·0)	1·79 (0·07)
United Arab Emirates	3	1 (33·3%)	2 (66·7%)	1504	1468 (97·6%) Arab	984 (65·4%)	47·9 (9·9)	1·56 (0·06)	520 (34·6%)	49·1 (10·6)	1·68 (0·08)
Middle-income countries											
Poland	4	1 (25·0%)	3 (75·0%)	2036	2036 (100%) European	1278 (62·8%)	54·3 (9·7)	1·60 (0·06)	758 (37·2%)	53·9 (10·0)	1·73 (0·07)
Argentina	20	6 (30·0%)	14 (70·0%)	7527	7118 (94·6%) Latin American	4629 (61·5%)	51 (10·0)	1·58 (0·07)	2898 (38·5%)	51·0 (10·1)	1·72 (0·07)
Brazil	14	7 (50·0%)	7 (50·0%)	6070	5932 (97·7%) Latin American	3344 (55·1%)	51·8 (9·3)	1·57 (0·07)	2726 (44·9%)	52·4 (9·6)	1·69 (0·07)
Chile	5	2 (40·0%)	3 (60·0%)	3451	3020 (87·5%) Latin American	2286 (66·2%)	51·5 (9·8)	1·53 (0·06)	1165 (33·8%)	52·2 (9·9)	1·66 (0·07)
Colombia	58	35 (60·3%)	23 (39·7%)	7444	7077 (95·1%) Latin American	4773 (64·1%)	50·5 (9·6)	1·54 (0·07)	2671 (35·9%)	51·1 (9·8)	1·66 (0·07)
China	115	45 (39·1%)	70 (60·9%)	46 285	46 166 (99·7%) Chinese	27 193 (58·8%)	50·5 (9·6)	1·56 (0·06)	19 092 (41·2%)	51·1 (9·9)	1·67 (0·06)
Turkey	44	31 (70·5%)	13 (29·5%)	4232	4222 (99·8%) European	2552 (60·3%)	48·8 (9·2)	1·55 (0·06)	1680 (39·7%)	50·4 (9·1)	1·69 (0·07)
Iran	20	11 (55·0%)	9 (45·0%)	6013	6008 (99·9%) Persian	3137 (52·2%)	48·2 (9·2)	1·55 (0·06)	2876 (47·8%)	48·8 (9·1)	1·70 (0·07)
Malaysia	71	53 (74·6%)	18 (25·4%)	15 617	13 331 (85·4%) Malay	8737 (55·9%)	50·4 (9·7)	1·52 (0·06)	6880 (44·1%)	52·0 (10·0)	1·63 (0·07)
South Africa	8	4 (50·0%)	4 (50·0%)	4585	2662 (58·1%) black African; 1872 (40·8%) Bantu	3018 (65·8%)	49·1 (10·5)	1·57 (0·06)	1567 (34·2%)	49·3 (10·0)	1·68 (0·07)
Low-income countries											
Zimbabwe	3	1 (33·3%)	2 (66·7%)	1240	1217 (98·1%) black African	836 (67·4%)	49·8 (10·0)	1·59 (0·06)	404 (32·6%)	52·5 (11·0)	1·68 (0·08)
Bangladesh	56	30 (53·6%)	26 (46·4%)	2934	2919 (99·5%) south Asian	1602 (54·6%)	44·8 (8·9)	1·51 (0·06)	1332 (45·4%)	47·3 (9·7)	1·62 (0·07)
India	90	38 (42·2%)	52 (57·8%)	28 747	28 733 (100·0%) south Asian	16 135 (56·1%)	47·6 (10·2)	1·53 (0·07)	12 612 (43·9%)	49·9 (10·6)	1·65 (0·07)
Pakistan	4	2 (50·0%)	2 (50·0%)	1742	1737 (99·7%) south Asian	917 (52·6%)	46·7 (8·9)	1·56 (0·07)	825 (47·4%)	48·5 (8·8)	1·68 (0·07)

Data are n, n (%), or mean (SD). Income level according to 2003 World Bank classification. *As listed in the questionnaire.

Table 1: **Countries, communities, and participants**

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	Overall (n=153 996)	Women (n=89 205)	Men (n=64 791)	South Asia (n=33 423)	East Asia (n=46 285)	Southeast Asia (n=15 617)	Sub-Saharan Africa (n=5825)	South America (n=24 492)	Middle East (n=11 749)	North America or Europe (n=16 605)
Missing data*	20 388 (13·2%)	11 525 (12·9%)	8863 (13·7%)	9009 (27·0%)	900 (1·9%)	6286 (40·3%)	1911 (32·8%)	970 (4·0%)	784 (6·7%)	528 (3·2%)
Errors or implausible values	5476 (3·6%)	3228 (3·6%)	2248 (3·5%)	3522 (10·5%)	530 (1·1%)	298 (1·9%)	62 (1·1%)	370 (1·5%)	234 (2·0%)	460 (2·8%)
Unacceptable data	43 334 (28·1%)	25 445 (28·5%)	17 889 (27·6%)	8495 (25·4%)	14 345 (31·0%)	3779 (24·2%)	1721 (29·5%)	10 460 (42·7%)	2330 (19·8%)	2204 (13·3%)
$FEV_1/FVC < 0·66$	7996 (5·2%)	4522 (5·1%)	3474 (5·4%)	879 (2·6%)	2660 (5·7%)	378 (2·4%)	601 (10·3%)	2178 (8·9%)	552 (4·7%)	748 (4·5%)
$FEV_1/FVC > 0·95$	28 198 (18·3%)	16 340 (18·3%)	11 858 (18·3%)	7262 (21·7%)	9086 (19·6%)	2933 (18·8%)	872 (15·0%)	6018 (24·6%)	871 (7·4%)	1156 (7·0%)
$PEF/FEV_1 < 1·5$	9541 (6·2%)	5972 (6·7%)	3569 (5·5%)	930 (2·8%)	3218 (7·0%)	508 (3·3%)	531 (9·1%)	2836 (11·6%)	1040 (8·9%)	478 (2·9%)
>200 mL variability in at least two FEV_1 or FVC measurements	11 658 (7·6%)	5932 (6·6%)	5726 (8·8%)	3297 (9·9%)	1598 (3·5%)	1014 (6·5%)	498 (8·5%)	3451 (14·1%)	920 (7·8%)	880 (5·3%)
Outside age or height range	1105 (0·7%)	673 (0·8%)	432 (0·7%)	228 (0·7%)	302 (0·7%)	163 (1·0%)	65 (1·1%)	219 (0·9%)	51 (0·4%)	77 (0·5%)
>5 pack-year smoking history	28 134 (18·3%)	6537 (7·3%)	21 597 (33·3%)	1803 (5·4%)	10 241 (22·1%)	1423 (9·1%)	498 (8·5%)	5889 (24·0%)	2564 (21·8%)	5716 (34·4%)
Regular use of respiratory drugs†	3049 (2·0%)	1975 (2·2%)	1074 (1·7%)	577 (1·7%)	713 (1·5%)	379 (2·4%)	132 (2·3%)	334 (1·4%)	292 (2·5%)	622 (3·7%)
Symptoms‡ within previous 6 months	43 578 (28·3%)	26 405 (29·6%)	17 173 (26·5%)	10 834 (32·4%)	6214 (13·4%)	2807 (18·0%)	2525 (43·3%)	11 531 (47·1%)	4067 (34·6%)	5600 (33·7%)
Participants with specific disorders or characteristics§	33 174 (21·5%)	19 378 (21·7%)	13 796 (21·3%)	6268 (18·8%)	7542 (16·3%)	3595 (23·0%)	1326 (22·8%)	6509 (26·6%)	3157 (26·9%)	4777 (28·8%)
Asymptomatic, healthy non-smokers	38 517 (25·0%)	25 614 (28·7%)	12 903 (19·9%)	5945 (17·8%)	17 349 (37·5%)	2694 (17·3%)	799 (13·7%)	3595 (14·7%)	3336 (28·4%)	4799 (28·9%)

Some participants are in more than one exclusion category. Only participants who responded were included. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. PEF=peak expiratory flow. *Any demographic, anthropometric, FEV_1, or FVC data missing. †On at least 4 days every week. ‡Breathlessness with usual activity, cough, sputum, haemoptysis, wheezing or whistling in the chest, early morning cough with chest tightness, or history of cough and sputum production for 3 months a year for at least 2 years. §Chronic obstructive pulmonary disease, asthma, tuberculosis, HIV, cancer, pregnancy, cardiac diseases, diabetes mellitus, malaria, Chagas disease, cerebrovascular disease, and hepatitis.

Table 2: **Participants who met each exclusion criterion by region**

In the base model, FEV_1 (or FVC) was expressed as a function of height, which is the most important explanatory variable. We estimated the effect of age, sex, and region proportionally to height (or calculated the percentage change by multiplying by 100). This proportional scaling to height avoided the large change in absolute lung function recorded in tall individuals compared with short individuals even though the proportional change is the same. We coded age (34 years coded 0; subsequent ages coded consecutively), sex (male coded 0; female 1), and region (North America or Europe coded 0; Middle East 1; South America 2; sub-Saharan Africa 3; east Asia 4; southeast Asia 5; south Asia 6).

We examined model fit by two methods (appendix). First, we used internal validation, deriving the model from a randomly selected subpopulation (80%) and examining model fit on the remaining 20%. This method showed no significant difference between the observed and predicted values. Second, we used face validity by showing that the standardised lung function values (ie, percentage of predicted) in participants with COPD, asthma, tuberculosis, and heart disease showed the expected pattern of impairment in these disorders.

We deemed a p value of less than 0·001 to be significant. All analyses were done with Statistica (version 10).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MD and SY had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Results

153 996 individuals were enrolled from the 628 communities (figure 1). The countries with the highest numbers of participants were China and India (table 1). The proportion of unacceptable data was highest for South America and lowest for North America or Europe (table 2). The large amount of unacceptable data was not associated with low unadjusted lung function measurements (table 2). Healthy individuals excluded because of unacceptable data had similar baseline characteristics to individuals included in the study, confirming that the analysed population was a representative sample (appendix). Other common reasons for exclusion were respiratory symptoms, specified disorders (eg, asthma, HIV, or malaria) or pregnancy, and tobacco smoking (table 2).

	South Asia (n=5945)	East Asia (n=17 349)	Southeast Asia (n=2694)	Sub-Saharan Africa (n=799)	South America (n=3595)	Middle East (n=3336)	North America or Europe (n=4799)
Overall							
Women	3371 (56·7%)	12 906 (74·4%)	1715 (63·7%)	568 (71·1%)	2336 (65·0%)	1990 (59·7%)	2728 (56·8%)
Men	2574 (43·3%)	4443 (25·6%)	979 (36·3%)	231 (29·9%)	1259 (35·0%)	1346 (40·3%)	2071 (43·2%)
From urban communities	2461 (41·4%)	8662 (49·9%)	1210 (44·9%)	439 (54·9%)	2248 (62·5%)	1836 (55·0%)	3689 (76·9%)
Ethnic origin*	5942 (99·9%) south Asian	17 091 (98·5%) Chinese	2303 (85·5%) Malay	796 (99·6%) black African	3496 (97·2%) Latin American	2479 (74·3%) Persian; 178 (5·3%) Arab; 672 (20·1%) European	3911 (81·5%) European
Women							
From urban communities†	1405 (41·7%)	6395 (49·6%)	770 (44·9%)	310 (54·6%)	1508 (64·6%)	1052 (52·9%)	2067 (75·8%)
Age (years)	46·3 (9·5)	49·7 (9·4)	50·3 (9·0)	49·1 (10·4)	51·0 (9·5)	46·9 (8·5)	51·6 (9·1)
Height (cm)	153·0 (6·1)	156·2 (5·8)	152·4 (6·0)	156·5 (6·2)	156·1 (6·9)	155·7 (6·0)	163·1 (6·8)
Weight (kg)	54·5 (13·1)	60·2 (10·5)	62·3 (12·8)	73·8 (20·5)	67·9 (13·3)	71·0 (14·4)	68·9 (13·7)
Body-mass index (kg/m²)	23·2 (5·4)	24·7 (4·0)	26·8 (5·2)	30·1 (7·9)	27·9 (5·2)	29·3 (5·7)	25·9 (5·1)
FEV_1 (L)	1·65 (0·39)	2·18 (0·48)	1·78 (0·44)	1·98 (0·50)	2·24 (0·57)	2·17 (0·46)	2·64 (0·51)
FVC (L)	1·92 (0·46)	2·59 (0·68)	2·05 (0·52)	2·33 (0·58)	2·68 (0·73)	2·59 (0·56)	3·27 (0·66)
FEV_1/FVC	86·6 (5·8)	84·6 (6·6)	87·3 (6·3)	85·4 (6·9)	84·2 (7·4)	84·1 (5·9)	81·3 (6·3)
Education							
None	1220 (36·2%)	1303 (10·1%)	196 (11·4%)	106 (18·7%)	239 (10·2%)	446 (22·4%)	5 (0·2%)
Primary education	516 (15·3%)	3278 (25·4%)	471 (27·5%)	245 (43·1%)	963 (41·2%)	935 (47·0%)	114 (4·2%)
Secondary education	1224 (36·3%)	6628 (51·4%)	761 (44·4%)	194 (34·2%)	635 (27·2%)	459 (23·1%)	764 (28·0%)
Higher education‡	386 (11·5%)	1657 (12·8%)	277 (16·2%)	16 (2·8%)	494 (21·1%)	150 (7·5%)	1827 (70·0%)
Data missing	25 (0·7%)	40 (0·3%)	10 (0·6%)	7 (1·2%)	5 (0·2%)	0	18 (0·7%)
Men							
From urban communities†	1056 (41·0%)	2267 (51·0%)	440 (44·9%)	129 (55·8%)	740 (58·8%)	784 (58·2%)	1622 (78·3%)
Age (years)	47·9 (10·0)	50·2 (10·4)	52·8 (9·2)	50·2 (10·2)	49·8 (9·3)	47·4 (8·9)	50·8 (8·8)
Height (cm)	165·4 (6·7)	167·2 (6·8)	163·0 (7·0)	168·1 (7·3)	168·3 (7·5)	169·7 (6·9)	176·8 (7·4)
Weight (kg)	60·5 (12·9)	69·4 (11·7)	69·2 (13·9)	64·7 (16·7)	78·1 (15·6)	77·5 (13·1)	84·4 (14·3)
Body-mass index (kg/m²)	22·1 (4·3)	24·8 (3·5)	26·0 (4·7)	22·9 (5·9)	27·5 (4·9)	26·9 (4·2)	27·0 (4·2)
FEV_1 (L)	2·34 (0·58)	2·84 (0·66)	2·41 (0·60)	2·65 (0·72)	3·17 (0·79)	3·23 (0·62)	3·71 (0·67)
FVC (L)	2·76 (0·68)	3·40 (0·79)	2·80 (0·70)	3·16 (0·84)	3·86 (0·99)	3·89 (0·75)	4·62 (0·89)
FEV_1/FVC	85·0 (6·3)	84·0 (7·0)	86·4 (6·2)	84·1 (7·1)	82·8 (7·0)	83·0 (5·4)	80·7 (6·1)
Education							
None	453 (17·6%)	246 (5·5%)	67 (6·8%)	52 (22·5%)	124 (9·9%)	92 (6·8%)	1 (0·1%)
Primary education	582 (22·6%)	877 (19·7%)	301 (30·7%)	100 (43·3%)	493 (39·2%)	411 (30·5%)	97 (4·7%)
Secondary education	1036 (40·2%)	2364 (53·2%)	417 (42·6%)	66 (28·6%)	316 (25·1%)	520 (38·6%)	535 (25·8%)
Higher education	488 (19·0%)	929 (20·9%)	186 (19·0%)	10 (4·3%)	323 (25·7%)	323 (24·0%)	1421 (68·6%)
Data missing	15 (0·6%)	27 (0·6%)	8 (0·8%)	3 (1·3%)	3 (0·2%)	0	17 (0·8%)

Data are n (%) or mean (SD). FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Only groups reported by >80% of participants in each region listed; as listed in the questionnaire. †Percentages calculated with total number of women or men. ‡Trade school, college, and university.

Table 3: **Baseline characteristics of healthy asymptomatic participants by region**

38 517 asymptomatic, healthy non-smokers made up the final population (figure 1). More women than men were included overall and in each region (tables 2, 3). More than 80% of participants in each region were from the ethnic group in the majority, except in the Middle East (table 3). Included men were taller than women, and had higher unadjusted FEV_1 and FVC across all regions (table 3). Participants from North America or Europe were the tallest, and had the highest unadjusted lung function (table 3).

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501 individuals participated in prospective validation. The difference between FEV_1 measurements in the field and the laboratory was small (≤200 mL) for all regions (appendix), suggesting that field measurements of FEV_1 were valid. Differences in FVC measurements of greater than 200 mL were recorded in South America, the Middle East, and east Asia (appendix). The variability of the differences in FEV_1 and FVC was greatest for the Middle East, east Asia, and south Asia, suggesting decreased agreement. Retrospective analysis of FVL measurements for 30 participants in South Africa showed than 20 (67%) of 30 had acceptable FVL measurements as defined by American Thoracic Society standards.

The fitted base model was FEV_1 or $FVC=(a \times height^b) \times (1+c \times age) \times (1+d \times male\ sex) \times (1 + e \times region)$. For all regions, FEV_1 increased with height and decreased with age for both men and women (figure 2). FEV_1 and FVC related to height in a non-linear fashion (tables 4, 5). The mean cross-sectional reduction in FEV_1 per year after age 34 years is proportional to height (table 4). The increase in FEV_1 conferred by male sex was almost 19% (table 4). Compared with North America or Europe, all other regions had proportionally lower adjusted FEV_1 and FVC (figure 3; tables 4, 5). The greatest differences were reported for south Asia, southeast Asia, and sub-Saharan Africa (figure 3; tables 4, 5).

The quantitative effect of height, age, and sex on lung function differed by region (table 6). Furthermore, the proportion of explained variance (pseudo-R^2) was highest for North America or Europe and the Middle East (table 6), suggesting that other predictors of lung function are not covered by this model for the other regions.

To assess for potential confounders of this regional difference, we added other covariates, such as education level, urban versus rural location, and weight to the base model (tables 4, 5). Although these variables significantly contributed to lung function, they had little effect on regional lung function differences and therefore were not confounders (tables 4, 5). Furthermore, the fit of the model did not improve (no increase in pseudo-R^2; tables 4, 5).

The ratio between FEV_1 and FVC was inversely correlated to height and age, but had no association with sex (figure 4). The ratio differed by region for any height, age, and sex (figure 4).

Discussion

To our knowledge, we have provided the first large-scale assessment of global variation in lung function in asymptomatic non-smokers in different regions of the world (panel).

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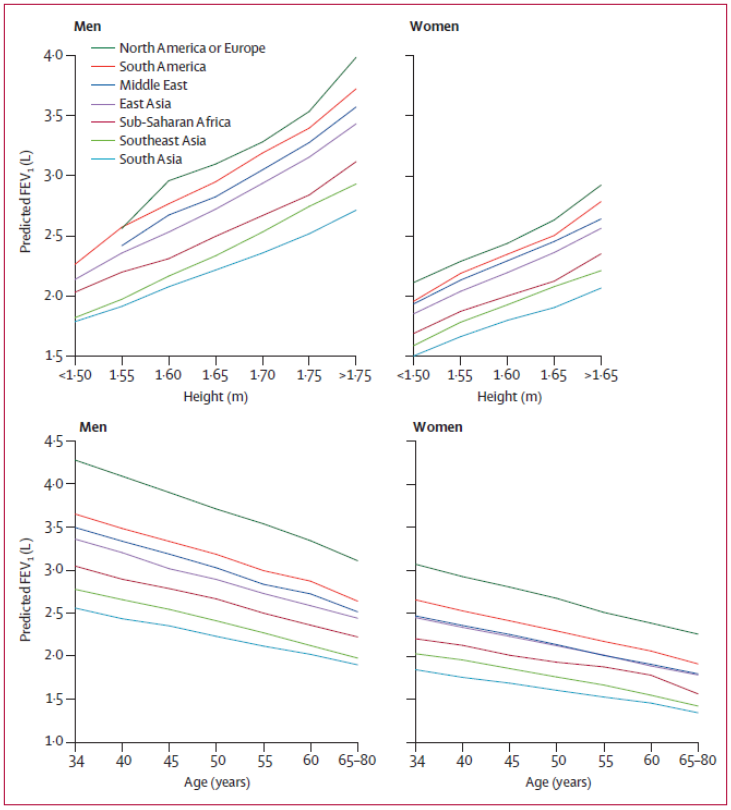

Figure 2: **FEV$_1$ by height and age in men and women by region**
Prediction with the base model. FEV$_1$=forced expiratory volume in 1 s.

	Base model*	Adjusted model†
a‡	1·14 (0·013, 1·12 to 1·17)	1·13 (0·015, 1·11 to 1·16)
b	2·02 (0·022, 1·98 to 2·06)	2·03 (0·026, 1·98 to 2·08)
c§¶	−0·75% (0·007, −0·76 to −0·74)	−0·70% (0·008, −0·71 to −0·68)
d§||	18·7% (0·28, 18·2 to 19·3)	18·2% (0·31, 17·6 to 18·8)
e§**	..	..
South Asia	−31·3% (0·25, −31·8 to −30·8)	−30·2% (0·30, −30·8 to −29·6)
Southeast Asia	−24·2% (0·36, −24·9 to −23·5)	−22·4% (0·41, −23·2 to −21·6)
East Asia	−12·8% (0·23, −13·4 to −12·4)	−12·4% (0·28, −12·9 to −11·8)
Sub-Saharan Africa	−20·9% (0·54, −22·0 to −19·9)	−19·7% (0·63, −21·0 to −18·5)
South America	−5·7% (0·33, −6·4 to −5·1)	−6·5% (0·37, −7·3 to −5·8)
Middle East	−11·2% (0·31, −11·8 to −10·6)	−9·4% (0·38, −10·1 to −8·7)
Primary education	..	1·13 (0·34, 0·46 to 1·80)
Secondary education	..	0·98 (0·31, 0·37 to 1·60)
Higher education	..	3·67 (0·38, 2·93 to 4·41)
Urban community	..	−1·12 (0·21, −1·58 to −0·75)
Weight	..	−0·041 (0·008, −0·06 to −0·03)

Estimates are mean (SE, 95% CI). Base model: FEV$_1$=(a×height^b)×(1+c×age)×(1+d× male sex)×(1+e×region). All estimates are significant at p<0·0001. In the adjusted model, education level (compared with no education), urban (compared with rural) location, and weight (kg) were added to test their role as potential confounders for regional differences in lung function. FEV$_1$=forced expiratory volume in 1 s. *Pseudo-R^2=69%; residual SD 0·41. †Pseudo-R^2=61%; residual SD 0·46. ‡Proportionality constant relating the units for height (m) to lung function (L/sec). §Estimated as proportional change, but have been expressed as percentages by multiplying by 100 for ease of interpretation. ¶Cross-sectional age-related change in lung function per year after age 34 years relative to height. ||Proportional difference in men compared with women, relative to height and age. **Proportional difference compared with North America or Europe relative to height, age, and sex.

Table 4: **Estimates of parameters of base and adjusted models for FEV$_1$**

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	Base model*	Adjusted model†
a‡	1·31 (0·016, 1·28 to 1·34)	1·30 (0·017, 1·27 to 1·34)
b	2·14 (0·023, 2·10 to 2·19)	2·25 (0·027, 2·19 to 2·30)
c§¶	−0·69% (0·008, −0·67 to −0·70)	−0·63% (0·009, −0·64 to −0·61)
d§‖	18·7% (0·30, 18·2 to 19·3)	18·1% (0·33, 17·5 to 18·7)
e§**	..	..
South Asia	−34·9% (0·25, −35·4 to −34·4)	−34·2% (0·29, −34·7 to −33·6)
Southeast Asia	−29·1% (0·36, −29·8 to −28·3)	−27·4% (0·40, −28·2 to −26·7)
East Asia	−15·8% (0·23, −16·2 to −15·3)	−15·8% (0·27, −16·3 to −15·3)
Sub-Saharan Africa	−24·3% (0·55, −25·4 to −23·2)	−23·3% (0·67, −24·5 to −22·0)
South America	−8·0% (0·33, −8·6 to −7·3)	−8·7% (0·37, −9·5 to −8·0)
Middle East	−13·5% (0·31, −14·1 to −12·9)	−11·8% (0·37, −12·5 to −11·1)
Primary education	..	1·54 (0·36, 0·84 to 2·24)
Secondary education	..	0·99 (0·32, 0·35 to 1·63)
Higher education	..	3·76 (0·39, 2·99 to 4·52)
Urban community	..	−2·25 (0·22, −2·68 to −1·83)
Weight	..	−0·09 (0·007, −0·11 to −0·08)

Estimates are mean (SE, 95% CI). Base model: FVC=(a×height^b)×(1+c×age)×(1+d×male sex)×(1+e×region). All estimates are significant at p<0·0001. In the adjusted model, education level (compared with no education), urban (compared with rural) location, and weight (kg) were added to test their role as potential confounders for regional differences in lung function. FVC=forced vital capacity. *Pseudo-R^2=69%; residual SD 0·52. †Pseudo-R^2=62%; residual SD 0·57. ‡Proportionality constant relating the units for height (m) to lung function (L/sec). §Estimated as proportional change, but have been expressed as percentages by multiplying by 100 for ease of interpretation. ¶Cross-sectional age-related change in lung function per year after age 34 years relative to height. ||Proportional difference in men compared with women, relative to height and age. **Proportional difference compared with North America or Europe relative to height, age, and sex.

Table 5: **Estimates of parameters of base and adjusted models for FVC**

We reported a significant and substantial difference in lung function between regions, with North America and Europe having the highest lung function and south Asia the lowest. These differences are not explained by variation in distribution of height, age, sex, weight, urban versus rural settings, or education levels.

Lung function differences between healthy populations across the world are expected and are attributed to fixed anthropometric differences that are believed to be genetic.[3] However, this belief is not supported by studies showing greater genetic variation within than between populations,[19] and that a large proportion of reported differences in lung function between populations is not explained by variation in genetic ancestry markers.[20] Alternatively, some evidence suggests that anthropometric features and lung function can change with time and place, driven by socioeconomic and

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environmental changes.[16–18,21] US- born individuals of Indian and Japanese origin are taller and have larger lung volumes than individuals born in the Indian subcontinent[16] and Japan[17] who subsequently moved to the USA. Moreover, children of Indian origin aged 11–13 years who are born in the UK have longer leg length (a marker of good nutrition early in life) than do those who have recently moved to the UK.[18] Additionally, those born in the UK have body dimensions that resemble those of Europeans.[21] Similarly, trends in increasing somatic growth and lung capacity in successive cohorts within a country that parallel improvements in living standards with time have been documented.[22,23]

However, such changing characteristics have not been shown in European populations.[24,25] We speculated that the higher socioeconomic status and living standards of populations of European descent are similar and stable across time and place, allowing maximum lung function to be attained and leaving little room for further improvement or variation. In support of this hypothesis, we recorded that the usual predictors (height, age, and sex) explained a higher proportion of lung function variability in North America or Europe and the Middle East, where mainly high- income and urban-dominated countries were included, than elsewhere. Regions of low or middle income are more contextually diverse than those of high income, with varying conditions that can adversely affect lung function, leading to a greater unexplained variance in lung function.

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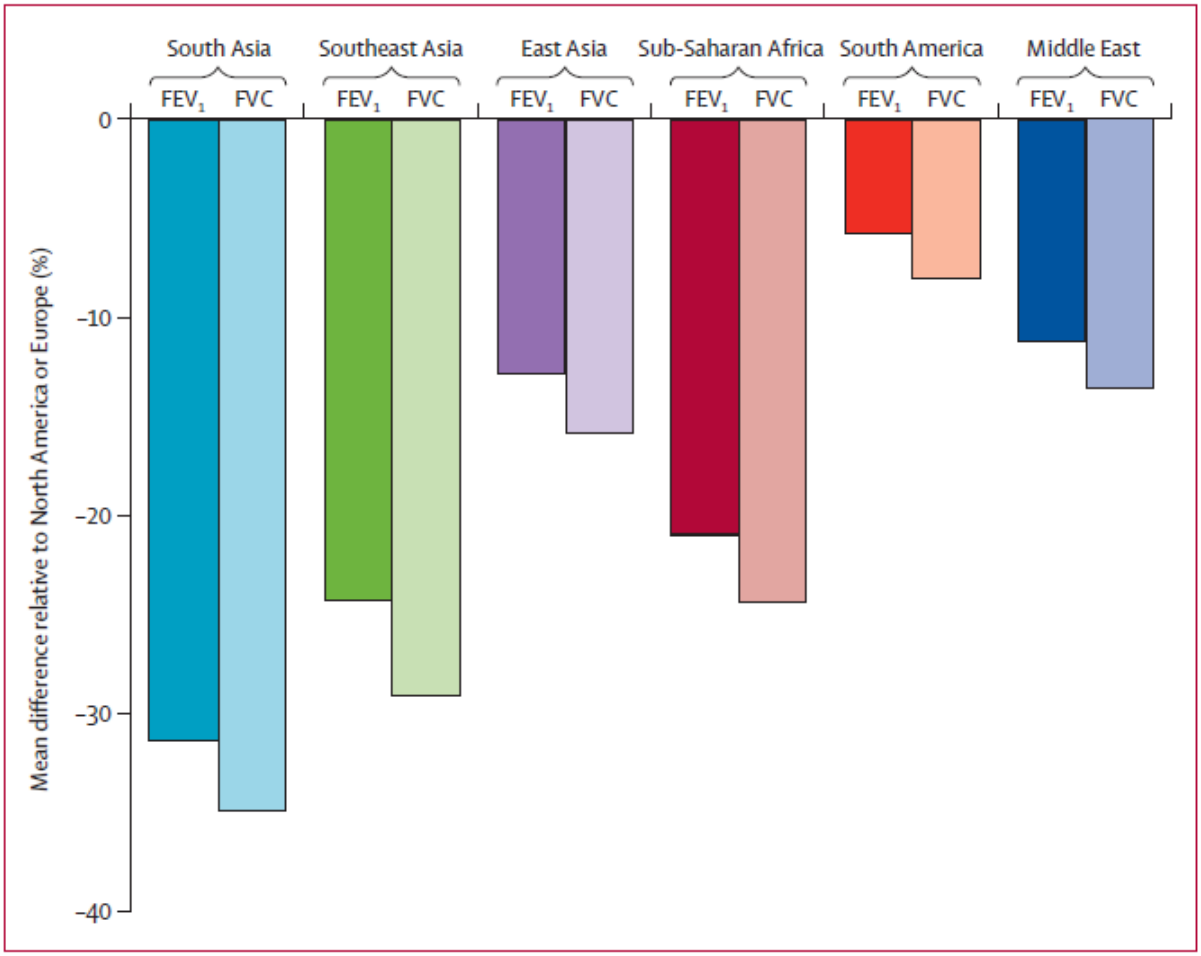

***Figure 3*: Proportional difference in FEV_1 and FVC for each region relative to North America or Europe, adjusted for age, height, and sex**

All adjusted proportional differences significant at p<0·0001. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity.

	a (proportionality constant)	b (height exponent)	c (age coefficient)*	d (male coefficient)*	Pseudo-R^2	Residual SD
FEV_1						
North America or Europe	1·10 (0·027, 1·04 to 1·15)	2·09 (0·048, 1·99 to 2·18)	−0·70% (0·016, −0·73 to −0·67)	17·4% (0·64, 16·1 to 18·6)	76%	0·388
South Asia	0·79 (0·021, 0·75 to 0·83)	1·99 (0·060, 1·87 to 2·11)	−0·88% (0·019, −0·92 to −0·85)	23·8% (0·86, 22·1 to 25·5)	56%	0·391
Southeast Asia	0·88 (0·039, 0·81 to 0·96)	2·04 (0·099 (1·84, 2·23)	−0·93% (0·030, −0·98 to −0·87)	20·9% (1·26, 18·5 to 23·4)	56%	0·393
East Asia	1·09 (0·018, 1·05 to 1·12)	1·83 (0·036, 1·76 to 1·90)	−0·70% (0·011, −0·72 to −0·67)	16·8% (0·43, 15·9 to 17·6)	53%	0·417
Sub-Saharan Africa	0·79 (0·063, 0·67 to 0·91)	2·35 (0·170, 2·01 to 2·68)	−0·86% (0·051, −0·96 to −0·76)	16·6% (0·02, 12·3 to 20·9)	53%	0·446
South America	1·05 (0·032, 0·99 to 1·12)	2·07 (0·065, 1·95 to 2·20)	−0·81% (0·022, −0·86 to −0·77)	20·3% (0·90, 18·6 to 22·1)	70%	0·435
Middle East	0·88 (0·027, 0·83 to 0·94)	2·25 (0·066, 2·12 to 2·38)	−0·77% (0·024, −0·82 to −0·72)	23·8% (0·96, 21·9 to 25·7)	71%	0·398
FVC						
North America or Europe	0·99 (0·027, 0·94 to 1·05)	2·64 (0·052, 2·54 to 2·74)	−0·57% (0·020, −0·61 to −0·53)	13·4% (0·68, 12·1 to 14·7)	67%	0·572
South Asia	0·89 (0·026, 0·84 to 0·94)	2·04 (0·066, 1·91 to 2·17)	−0·83% (0·022, −0·87 to −0·79)	25·0% (0·94, 23·2 to 26·8)	54%	0·475
Southeast Asia	0·93 (0·043, 0·85 to 1·01)	2·21 (0·101, 2·01 to 2·40)	−0·83% (0·034, −0·89 to −0·76)	20·3% (1·30, 17·8 to 22·9)	51%	0·486
East Asia	1·39 (0·028, 1·34 to 1·45)	1·61 (0·042, 1·53 to 1·69)	−0·61% (0·014, −0·63 to −0·58)	17·7% (0·51, 16·7 to 18·7)	37%	0·587
Sub-Saharan Africa	0·90 (0·076, 0·75 to 1·05)	2·42 (0·180, 2·06 to 2·77)	−0·84% (0·065, −0·95 to −0·73)	15·7% (2·29, 11·2 to 20·2)	51%	0·541
South America	1·11 (0·046, 1·01 to 1·19)	2·23 (0·087, 2·06 to 2·41)	−0·65% (0·033, −0·71 to −0·58)	21·0% (1·21, 18·6 to 23·4)	49%	0·720
Middle East	1·02 (0·034, 0·94 to 1·09)	2·29 (0·071, 2·16 to 2·43)	−0·71% (0·027, −0·77 to −0·66)	24·2% (1·03, 22·2 to 26·3)	69%	0·505

Data are mean (SE, 95% CI) unless otherwise stated. The prediction model was applied to each region separately to examine for variation in the relation between FEV_1 or FVC and height, age, and sex across regions. The model applied was FEV_1 or FVC=(a×height^b)×(1+c×age)×(1+d×male sex). All estimates were significant at <0·0001. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. *Estimated as proportional change to height and provided as percentage difference for each year greater than age 34 years, and for men compared with women.

***Table 6*: Prediction model by region**

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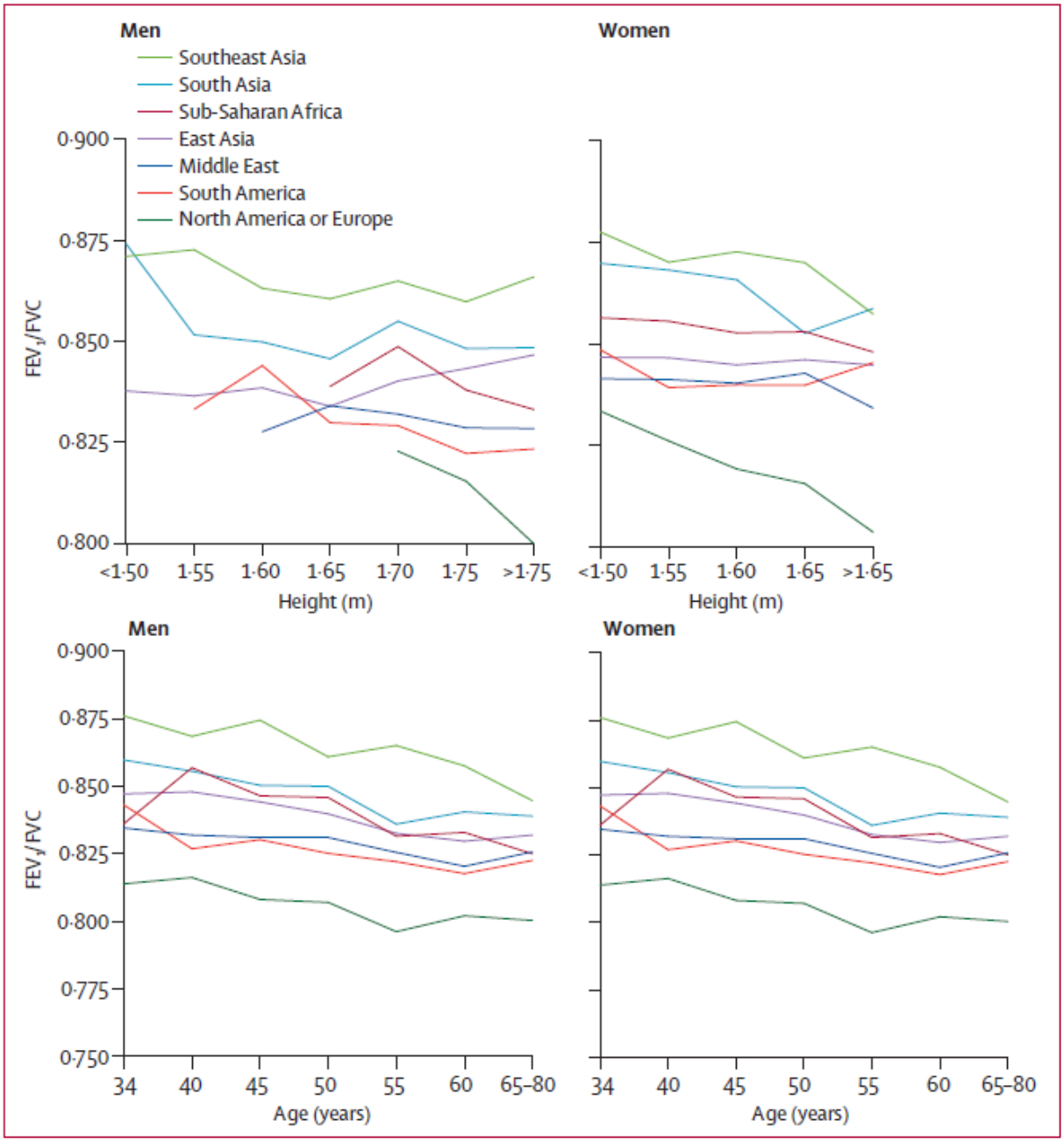

Figure 4: **Ratio of FEV_1 to FVC by height and age in men and women by region**
Regional coefficient estimating the proportional difference relative to North America or Europe with the same base model (ie, with adjustment for height, age, and sex) was significant at p<0·0001. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity.

Reported adverse conditions include early life exposures to outdoor[26] and indoor air pollution,[27] second-hand cigarette smoke,[28] respiratory infections,[29] nutritional factors,[30] overcrowding,[31] and low birthweight.[32] Failure to adjust for socioeconomic status (and the associated risk factors) has been proposed to confound the relation between ethnic origin or regions and low lung function.[3,8] However, adjustment for weight (for body dimension), urban versus rural location (physical environment), and education level (socioeconomic status) had little effect on the lung function gradient across regions in our study. This finding suggests that the situation is far more complex than previously thought, that the regional lung function difference is a result

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of wide-ranging effects of known and unknown factors, and that the interaction between genes and the environment cannot be fully adjusted for within one model.

Panel: Research in context

Systematic review

We searched PubMed, Embase, and the Cochrane database for reports published in English between Jan 1, 1960, and Jan 1, 2013. We used the terms "lung function or lung capacity or ventilatory capacity" and "ethnicity or race or populations or regions or countries or global" to identify data for lung function differences between populations worldwide. We identified a large amount of evidence that has established the lung function differences between two or more healthy populations of different ethnic or racial groups within the same country or region.[4,6,7,16-18] However, lung function differences worldwide—particularly those of countries of low to middle income—is unknown.

Interpretation

To our knowledge, our study is the first to examine the lung function differences between several asymptomatic non-smoking populations from different regions of the world with a consistent method for collection and comparison of data at one time. Lung function differences across a wide range of ethnic groups living in different geographical locations are a result of the present genetic, socioeconomic, and environmental global landscape. Furthermore, the differences were not accounted for by variation in height, age, sex, weight, urban versus rural settings, and educational levels.

Our findings have important public health implications. The large differences in lung function between regions, if partly driven by the disadvantaged environment in some regions, raise concerns about whether a difference should be expected, particularly when the same conditions that predict low lung function can adversely affect general health and mortality.[33] This overlap could partly explain the well known epidemiological link between low lung function and increased mortality.[34] It also puts into question the use of ethnic-specific values of lung function, because they could lead to an underestimation of the true mortality risk in non-white populations.[35] Our findings draw attention to the need for improved understanding of the social and gene–environment factors that affect lung function and their prognostic implications.

Several aspects and limitations of our study need further discussion. First, we took a sociogeographic approach to the comparison of lung function, because it will set the framework for future analyses of the contextual mechanisms contributing to lung health inequalities across regions. However, this cross-sectional analysis cannot delineate the effects of genes versus contextual factors on lung function. As lung function in regions undergoing socioenvironmental changes driven by economic growth is tracked, the contextual and genetic effect can be better defined.

Second, our statistical approach was based on biologically plausible principles combined with robust regression modelling that can handle data that do not meet linear model assumptions (non-linear associations between predictors and lung function, and non-constant variability). It also allows for the complex interactions between the explanatory variables of lung function. This scaling of differences in lung function relative to North America or Europe is similar to an approach endorsed by the American Thoracic Society and the European Respiratory Society.[25]

Third, the scale of our study, most of which was done in resource-challenged and remote areas, meant that use of advanced, costly spirometers that can provide FVL was

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impractical. Therefore, we were unable to retrospectively verify data from individuals and instead used other criteria to validate our data epidemiologically, such as selection of recordings that meet criteria of the American Thoracic Society or European Respiratory Society for maximum effort (repeatability, without cough, and >6 s), comparisons of reported and predicted values for small differences (internal validity), establishment of the expected changes in spirometry values for individuals with various medical disorders (face validity), and investigation of agreement between field and pulmonary laboratory measurements in 501 participants from 11 countries (external validity). Furthermore, our findings are in keeping with other studies that have shown that individuals from North America and Europe have the highest lung function but lowest ratio of FEV_1 to FVC compared with some other ethnic or geographical groups.[4,25] Similarly, the key questionnaires (demographics and tobacco-use history) were taken from large international epidemiological studies[13,14] that have been translated and applied to regions or countries that are similar to those included in our study. Information about symptoms was internally validated by comparison of lung function differences between participants with and without symptoms. Moreover, all centres and operators were trained in the same way on the same equipment and questionnaires. Together with the large sample size and numbers of included centres in each region, the validation will mean measurement errors (if present) are random and therefore would tend to underestimate the true differences between regions. Collectively, these considerations give us confidence about the validity of the group data generated by our study.

Finally, postbronchodilator measurements were not feasible at baseline data collection, in view of the scale of our study, but are recommended by international guidelines for the diagnosis of airway diseases.[36] However, we used the same inclusion and exclusion criteria and prebronchodilator values as in other studies that examined lung function differences between ethnic groups, meaning that our conclusions can be compared with reported data.[4,6,25] Although differences between the prebronchodilator and postbronchodilator values have since been shown to be small in healthy European populations,[37] no similar information about populations outside of this region is available. These differences will be investigated in a subgroup of PURE in the next phase of data collection to address the issue of subclinical diseases in regions of low and middle income.

Contributors

MD, SI, PMO'B, HJS, KK, and SY interpreted data and wrote the report. MD, SI, and KK analysed data. SR coordinated the study. KT and SY designed the study. EI, JC, LL, WL, TI, KS, MS, KV, RY, KZ, AO, AR, HH, WA, RD, GO, PL-J, and PS collected data.

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Conflicts of interest

We declare that we have no conflicts of interest.

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