Effect of long-term exposure to fine particulate matter on lung function decline and risk of chronic obstructive pulmonary disease in Taiwan: a longitudinal, cohort study

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Summary

Background Information on the effects of long-term exposure to fine particulate matter with an aerodynamic diameter of 2·5 μm or less ($PM_{2·5}$) on lung health is scarce. We aimed to investigate the associations between long-term exposure to $PM_{2·5}$, lung function, and chronic obstructive pulmonary disease (COPD) in a large-scale longitudinal cohort.

Methods We included 285 046 participants aged 20 years or older from the Taiwan MJ Health Management Institution cohort, who were recruited between 2001 and 2014 and had spirometric tests during the medical examination visit. We used a satellite-based spatiotemporal model to estimate the 2-year average ground concentration of $PM_{2·5}$ (for the calendar year of each participant's medical examination and for the previous year) at each participant's address. We used the generalised linear mixed model to examine the associations between $PM_{2·5}$ concentrations and lung function and the Cox proportional hazard regression model with time-dependent covariates to investigate the $PM_{2·5}$ effects on COPD development.

Findings Every 5 μg/m³ increment in $PM_{2·5}$ was associated with a decrease of 1·18% for forced vital capacity (FVC), 1·46% for forced expiratory volume in 1 s (FEV_1), 1·65% for maximum mid-expiratory flow (MMEF), and 0·21% for FEV_1:FVC ratio. The decrease accelerated over time. Additional annual declines were observed for FVC (0·14%), FEV_1 (0·24%), MMEF (0·44%), and FEV_1:FVC ratio (0·09%). Compared with the participants exposed to the first quartile of $PM_{2·5}$, participants exposed to the fourth, third, and second quartiles of $PM_{2·5}$ had a hazard ratio of 1·23 (95% CI 1·09–1·39), 1·30 (1·16–1·46), and 1·39 (1·24–1·56) for COPD development, respectively.

Interpretation Long-term exposure to ambient $PM_{2·5}$ is associated with reduced, and faster declines in, lung function. Long-term exposure to ambient $PM_{2·5}$ is also associated with an increased risk of the incidence of COPD. This study reinforces the urgency of global strategies to mitigate air pollution for improvement of pulmonary health and prevention of COPD.

Funding Environmental Health Research Fund of the Chinese University of Hong Kong and PhD Studentship of the Chinese University of Hong Kong.

Lancet Planet Health 2018; 2: e114–25

See **Comment** page e105

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Introduction

Globally, an estimated 4 million deaths (accounting for 7·5% of all deaths) were attributed to ambient particulate matter (PM) pollution in 2016.[1] PM with an aerodynamic diameter of 2·5 μm or less ($PM_{2·5}$) is considered the most important pollutant; it contains various toxic chemicals and penetrates deep into the lungs and cardiovascular system, posing great risks to human health.

Many epidemiological studies[2] have shown that short-term (daily to weekly) exposure to $PM_{2·5}$ might reduce lung function. However, short-term effects might be reversible, and long-term exposure has considerably greater effects.[3]

Studies[4,5] in children have shown that long-term exposure to air pollution is associated with slower growth in lung function; reduction of air pollution might improve lung function growth.[6] Lung function is known to peak aged mid-twenties and then starts to decline.[7] The air pollution-related decline in lung function in adults might result in the development of chronic obstructive pulmonary disease (COPD), the eighth leading cause of disability-adjusted life-years (DALY) lost worldwide in 2016.[8]

Several studies[9–13] have investigated the long-term effects of air pollution on lung function in adults, but only two[9,13] have examined $PM_{2·5}$; the results were inconsistent. Information from large-scale longitudinal cohorts, which can provide more stable and more precise estimates, is scarce. Additionally, to our knowledge, all previous studies were done in white populations and in regions with relatively low concentrations of air pollution. Similarly, information on $PM_{2·5}$ and COPD development from large-scale studies is insufficient. Therefore, we investigated the effects of long-term exposure to $PM_{2·5}$ on lung function and COPD development in a longitudinal cohort in Taiwan.

Research in context

Evidence before this study

We searched PubMed and Google Scholar for related studies published in English before April 1, 2017. We used the search terms "lung function", "pulmonary function", "FVC", "FEV_1", "MMEF", "COPD", or "chronic obstructive pulmonary disease" and "PM", and "particulate matter", and "air pollution". We mainly focused on the studies of long-term exposure to fine particulate matter with an aerodynamic diameter of 2·5 μm or less ($PM_{2·5}$) due to the higher and more stable effects of chronic exposure than those of short-term exposure. Ten studies analysed the associations of long-term exposure to air pollution with lung function in adults, but only two examined $PM_{2·5}$. The effects on maximum mid-expiratory flow (MMEF), an important indicator for small-airway obstruction, remained unclear. Nine studies examined the long-term effects of air pollution on chronic obstructive pulmonary disease (COPD) mortality, hospital admission, and development of COPD. However, three of these nine studies used lung function to define incident COPD, with only one reporting significant effects. Information based on large-scale longitudinal cohorts is scarce. Three studies did systematic reviews and observed the inconsistent associations in the previous studies. One meta-analysis further combined five cohorts in Europe and found that the forced expiratory volume in 1 s (FEV_1) reduced by 44·6 mL and forced vital capacity (FVC) by 59·0 mL for a 10 μg/m³ increment in PM with an aerodynamic diameter of 10 μm or less, but the long-term effects of $PM_{2·5}$ were insignificant.

Added value of this study

Our study provides new evidence for the effects of $PM_{2·5}$ on pulmonary health in Asian adults. For the first time, this study simultaneously confirms that long-term exposure to $PM_{2·5}$ can reduce the lung function (including FVC, FEV_1, MMEF, and the FEV_1:FVC ratio) and result in an increased risk of COPD development in the same population. To the best of our knowledge, this is the largest longitudinal cohort to date. The large sample size and long follow-up period provided strong power to detect the clinically significant adverse effects on pulmonary health. Our study further improves the accuracy and precision of the exposure estimates at individuals' addresses by using a novel spatiotemporal model with a high spatial resolution.

Implications of all the available evidence

This study enhances our understanding that long-term exposure to $PM_{2·5}$ can reduce lung function, and simultaneously increase the risk of COPD development in adults. These findings further advocate the reduction of air pollution to improve pulmonary health.

Methods

Study design and participants

Participants included in this longitudinal cohort study are from the existing Taiwan MJ cohort, with more than 0·5 million participants. All the participants were of Chinese descent and were residing in Taiwan. The cohort profile has been described elsewhere.[14,15] In brief, a private firm, the MJ Health Management Institution, Taipei, Taiwan, has provided residents of Taiwan a standard medical screening programme since 1994. Residents were encouraged to join the programme and visit the firm periodically through a paid membership. The participants received a series of medical examinations including anthropometric measurements, physical examination such as spirometry test and blood and urinary tests, and a standard self-administered questionnaire survey during each visit. Data generated from the medical examinations have been stored on computers since 1996. Written informed consent was given by each participant before participation. This study received ethical approval from the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee.

For the **protocol of the American Thorax Society** see https://www.thoracic.org/statements/resources/pft/PFT2.pdf?

$PM_{2·5}$ exposure assessment

Detailed information on the exposure assessment has been described previously.[14] Briefly, we estimated the ground concentration of $PM_{2·5}$ by using a spatial-temporal model based on the aerosol optical depth. We retrieved the high-resolution (1×1 km) aerosol optical depth from the Moderate Resolution Imaging Spectroradiometer on Terra and Aqua satellites of the US National Aeronautics and Space Administration. This model was validated recently and the correlation coefficients ranged from 0·72 to 0·83.[14]

The address of each participant was geocoded into latitude and longitude to match with the $PM_{2·5}$ concentrations estimated by the model. We estimated the annual average $PM_{2·5}$ concentrations for the calendar year of the medical examination and for the previous year. We used the mean of these two averages (2-year average) as an indicator of long-term exposure to ambient $PM_{2·5}$ air pollution.

Outcomes

Health outcomes were lung function and incident COPD. We used the four parameters of lung function in the present study: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), maximum mid-expiratory flow (MMEF), and FEV_1:FVC ratio.

Spirometric tests were done strictly following the protocol of the American Thorax Society during the medical visit. Spirometry was assessed in a standing position by using Microspiro HI-501 (Chest; Fällanden, Switzerland) or Chestgraph HI-701 (Chest; Tokyo, Japan). All participants were required to blow at least three times, of which at least two were reproducible within 5% for both FVC and FEV_1. The FVC and FEV_1 scores were from

the largest curve and the MMEF score was from the best curve (defined as the largest sum of FEV_1 and FVC) for subsequent reporting and the present data analysis. All tests were done by well trained professionals. The spirometers were calibrated periodically. It was mandatory to document any repairs or alterations of spirometers, in addition to the updates or changes made to the computer software and hardware.

Participants were defined as having COPD if they had a history of physician-diagnosed COPD or a ratio of FEV_1:FVC less than 70% based on the Global Initiative for COPD.[16] The 91709 participants assessed for incident COPD at baseline were followed up and the incident COPD was identified during subsequent visits. The endpoint was the first occurrence of COPD or the last visit if COPD did not occur.

Covariates

Detailed information on the health measurement and quality control has been described previously and in the Technical Reports by MJ Health Research Foundation.[14,15] A standard self-administered questionnaire was used to collect information on the demographic characteristics, medical history, and lifestyle factors. Height and weight were measured with participants wearing light indoor clothing without shoes. Seated blood pressure was measured using an auto-sphygmomanometer (Citizen CH-5000; Tokyo, Japan). An overnight fasting blood sample was taken in the morning and plasma glucose concentrations were measured using an automatic biochemical analyser (7150; Hitachi, Tokyo, Japan).

Covariates were included in the data analysis: age (years), sex (male or female), education (high school or lower [≤12 years], college or university [13–16 years], or postgraduate [>16 years]), body-mass index (BMI; kg/m^2), smoking status (never, former [smoked at least once but quit later], or current [more than once a week]), alcohol consumption (never or seldom [drank less than once a week], former [drank at least once a week but quit later], or current [drinks more than once a week]), physical activity intensity (light [eg, normal walking], moderate [eg, playing basketball but not in a game], high [eg, jogging], or vigorous [eg, running]), vegetable and fruit intake (seldom [<1 serving per day], moderate [1–2 servings per day], or frequent [>2 servings per day]), occupational exposure (information was collected by asking the question "are there any occupational hazards in your workplace?" with a list of occupational hazards and information was retrieved on exposure to dust or solvent in the workplace: yes or no), hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported hypertension), diabetes (defined as fasting blood glucose ≥126 mg/dL or self-reported physician-diagnosed diabetes), self-reported cerebrovascular disease (yes or no), cardiovascular disease (yes or no), hyperlipidaemia (defined as total cholesterol ≥240 mg/dL, triglyceride ≥200 mg/dL, or HDL-C <40 mg/dL), and calendar year and season (spring [March to May], summer [June to August], autumn [September to November], or winter [December to February]) of each medical examination.

Statistical analysis

To investigate the $PM_{2·5}$ effects on pulmonary function, the generalised linear model was used for baseline data analysis and generalised linear mixed model was used for longitudinal data analysis. Lung function was logarithmically transformed to normalise the data for the analysis and then the original scale was transformed back for presentation. Effect estimates were reported as the percentage difference in lung function parameters, with the participants with the first quartile of the $PM_{2·5}$ concentrations as the reference or for each 5 $\mu g/m^3$ increment in the $PM_{2·5}$ concentrations. The percentage difference was calculated using:

$$(e^{\beta}-1)\times 100\%$$

where β is the corresponding coefficient. We gradually added in the potential confounders to observe their effects and a total of four models were developed: model 1, no adjustment; model 2, adjusted for demographical factors (age, sex, and education), BMI, calendar year, and season;

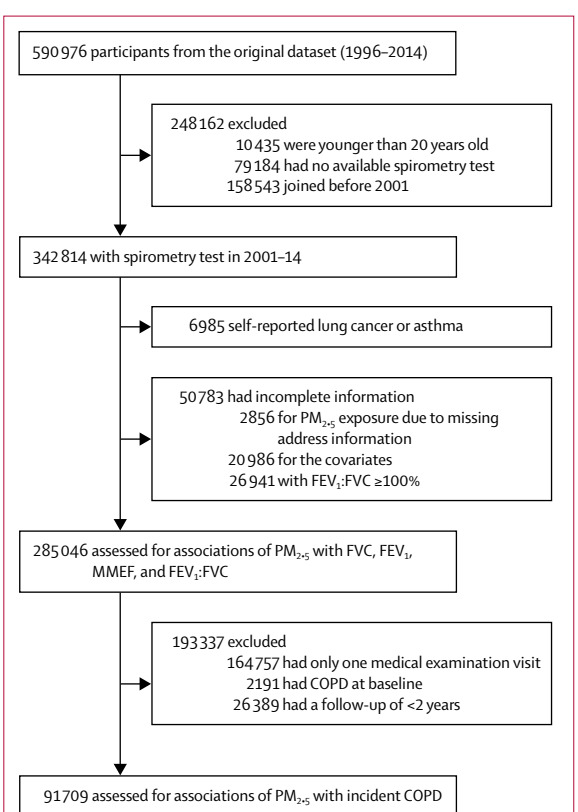

Figure 1: **Flow chart of participant selection**
$PM_{2·5}$=particulate matter with an aerodynamic diameter of 2·5 μm or less. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. MMEF=maximum mid-expiratory flow. COPD=chronic obstructive pulmonary disease.

	Participants at baseline (n=285 046)	All observations (n=590 278)*	Participants assessed for incident COPD at baseline (n=91 709)
Age (years)	41·16 (13·10)	43·46 (12·81)	40·33 (11·97)
Sex			
Male	141 942 (49·80%)	302 958 (51·32%)	46 878 (51·12%)
Female	143 104 (50·20%)	287 320 (48·68%)	44 831 (48·88%)
Education			
High school or lower	111 213 (39·02%)	217 830 (36·90%)	33 421 (36·44%)
College or university	142 100 (49·85%)	299 925 (50·81%)	48 398 (52·77%)
Postgraduate	31 733 (11·13%)	72 523 (12·29%)	9890 (10·78%)
Smoking status			
Never	208 461 (73·13%)	440 094 (74·56%)	68 333 (74·51%)
Former	16 824 (5·90%)	36 859 (6·24%)	5162 (5·63%)
Current	59 761 (20·97%)	113 325 (19·20%)	18 214 (19·86%)
Alcohol consumption			
Never or seldom	234 411 (82·24%)	485 035 (82·17%)	76 229 (83·12%)
Former	8243 (2·89%)	15 232 (2·58%)	2146 (2·34%)
Current	42 392 (14·87%)	90 011 (15·25%)	13 334 (14·54%)
Physical activity intensity			
Light	49 342 (17·31%)	69 600 (11·79%)	19 776 (21·56%)
Moderate	158 925 (55·75%)	361 235 (61·20%)	45 614 (49·74%)
High	51 471 (18·06%)	109 735 (18·59%)	17 309 (18·87%)
Vigorous	25 308 (8·88%)	49 708 (8·42%)	9010 (9·82%)
Vegetable intake			
Seldom	208 247 (73·06%)	415 490 (70·39%)	67 442 (73·54%)
Moderate	72 138 (25·31%)	165 271 (28·00%)	22 861 (24·93%)
Frequent	4661 (1·64%)	9517 (1·61%)	1406 (1·53%)
Fruit intake			
Seldom	93 982 (32·97%)	166 668 (28·24%)	27 390 (29·87%)
Moderate	155 984 (54·72%)	338 644 (57·37%)	52 107 (56·82%)
Frequent	35 080 (12·31%)	84 966 (14·39%)	12 212 (13·32%)
Occupational exposure (solvent or dust)	23 310 (8·18%)	45 552 (7·72%)	7529 (8·21%)
Body-mass index (kg/m²)	23·22 (3·67)	23·35 (3·56)	23·06 (3·48)
Hypertension	47 352 (16·61%)	100 932 (17·10%)	12 988 (14·16%)
Diabetes	14 704 (5·16%)	32 457 (5·50%)	3459 (3·77%)
Cerebrovascular disease	1185 (0·42%)	2555 (0·43%)	261 (0·28%)
Cardiovascular disease	8213 (2·88%)	18 764 (3·18%)	2092 (2·28%)
Hyperlipidaemia	76 401 (26·80%)	154 296 (26·14%)	23 805 (25·96%)
FVC (L)	2·96 (0·86)	2·98 (0·86)	2·96 (0·80)
FEV_1 (L)	2·64 (0·78)	2·66 (0·78)	2·65 (0·72)
MMEF (L/s)	3·41 (1·17)	3·48 (1·19)	3·44 (1·07)
FEV_1:FVC ratio (%)	89·11 (8·35)	89·31 (7·86)	89·73 (6·76)
$PM_{2·5}$ (μg/m³)†	26·74 (7·76)	26·66 (7·56)	26·91 (8·02)
Incident COPD	NA	NA	2297 (2·50%)

Data are mean (SD) for continuous variables and n (%) for categorical variables. COPD=chronic obstructive pulmonary disease. FVC=forced vital capacity. FEV_1=forced expiratory volume in 1 s. MMEF=maximum mid-expiratory flow. $PM_{2·5}$=particulate matter with an aerodynamic diameter of 2·5 μm or less. NA=not applicable. *From all 285 046 participants. †Refers to the average $PM_{2·5}$ concentration for the year of health examination visit and the year before the visit.

Table 1: **Characteristics of the participants**

model 3, further adjusted for lifestyle factors (smoking status, alcohol consumption, physical activity intensity, vegetable intake, and fruit intake), and occupational exposure; and model 4, further adjusted for health factors, including hypertension, diabetes, hyperlipidaemia, self-reported cerebrovascular disease, and self-reported cardiovascular disease. In the longitudinal data analysis, an interaction term ($PM_{2·5}$ [continuous variable of every 5 μg/m³ increase in $PM_{2·5}$]×year [continuous variable of calendar year]) was further added in model 4 to investigate whether the lung function decreases associated with $PM_{2·5}$ accelerated over time. The p value of the interaction term was presented. The coefficient of the interaction term was used to calculate the additional annual percentage decrease of the lung function over time for each 5 μg/m³ increment in the $PM_{2·5}$ concentrations. The concentration-response curves were drawn using the natural cubic spline function.

To investigate the health effects of $PM_{2·5}$ on COPD development, we did a survival analysis by using Cox regression model with time-dependent covariates ($PM_{2·5}$ and age were treated as time-dependent variables because of their breaches of proportional assumption). We used the four adjusted models and calculated hazard ratio (HR) with 95% CI. We used the natural cubic spline function to draw the concentration-response curve.

We also did subgroup analyses stratified by sex (male and female), BMI (<27 kg/m² and ≥27 kg/m²),[17] and smoking status (never, former, and current) to eliminate the potential modifying effects. A series of sensitivity analyses were carried out to test the robustness of the associations by (i) using the annual $PM_{2·5}$ concentration (calendar year of the medical examination); (ii) excluding the participants with a company address to eliminate the potential exposure misclassification by different types of addresses; (iii) excluding participants younger than age 25 years and 30 years old to eliminate the potential effects of lung function growth in their early twenties or twenties, respectively; (iv) testing the risk of COPD development in the participants who were older than age 30 years and 40 years, respectively; (v) testing the risk of COPD development in the 118 098 participants assessed for incident COPD (26 389 participants with a follow-up duration of less than 2 years plus the 91 709 participants); and (vi) excluding the participants with a history of cardiovascular diseases, lung cancer, and COPD to eliminate the potential comorbidity effects (including the analyses for all participants and a subgroup of never smokers).

All the statistical analyses were done using R version 3.3.2. The exposure effects were regarded as statistically significant at the two-tailed 0·05 level.

Results

Of the 342 814 participants aged 20 years or older who joined the programme and had spirometry tests in 2001–14 (when the $PM_{2·5}$ concentration data became

available), we included 285 046 (83·2%) participants with 590 278 observations in the present study to investigate the health effects of $PM_{2·5}$ on lung function (figure 1). Of these participants, 120 289 (42·2%) underwent more than one medical examination and the number of visits ranged from 2 to 21 with a mean of 4·8 visits (SD 2·7). The median visit interval was 18 months (IQR 13–29).

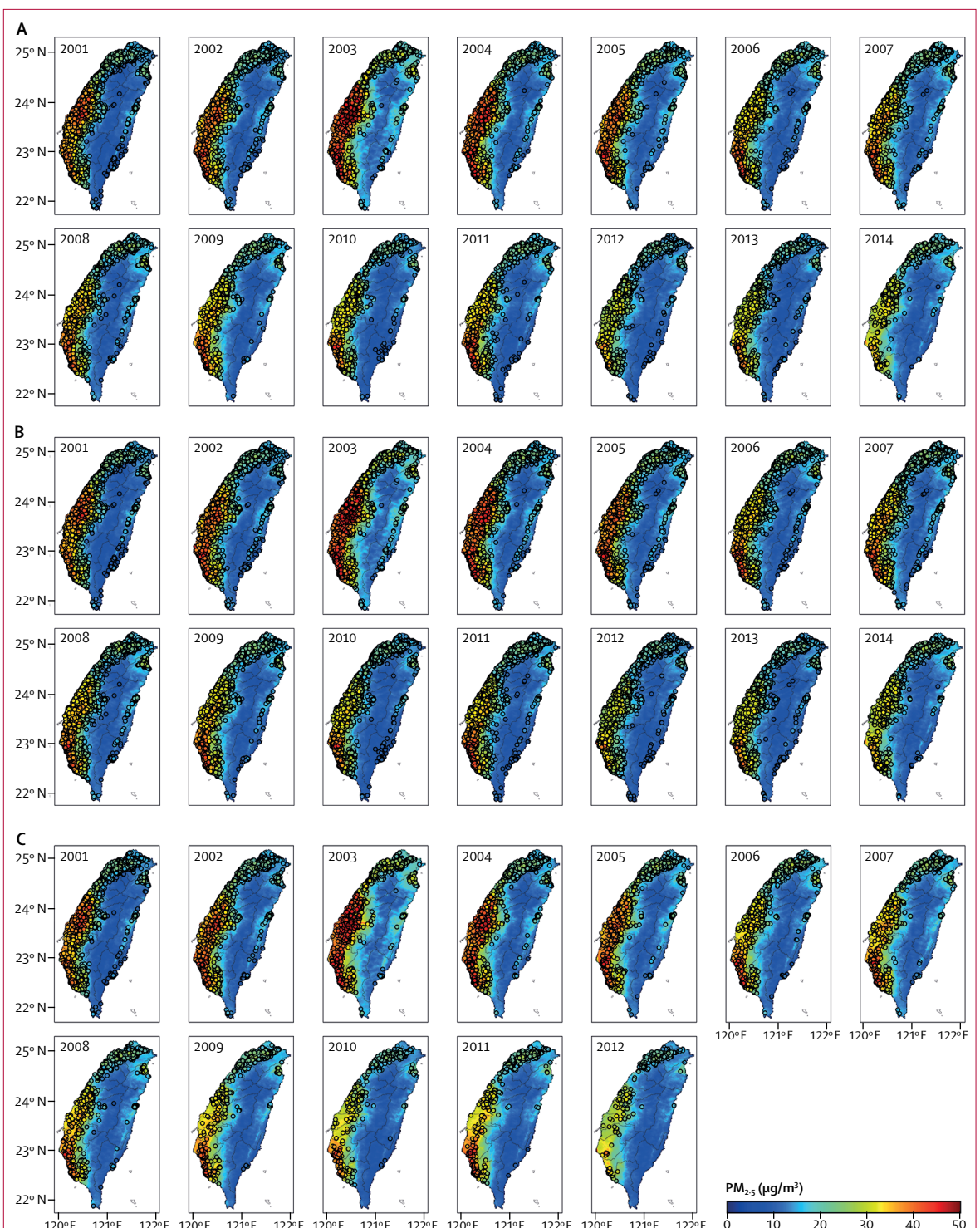

Figure 2 continues on next page

To investigate the health effects of $PM_{2·5}$ on the incidence of COPD, we further excluded 2191 participants who already had COPD (diagnosed by spirometry test or self-reported physician-diagnosed COPD) at their first visit. The 26 389 participants with a follow-up duration of less than 2 years were also excluded because COPD is unlikely to be caused by $PM_{2·5}$ within a short period. A total of 91709 participants were finally included in the analysis. The follow-up duration ranged from 2·0 years to 13·9 years, with a mean of 5·9 years (SD 3·1).

The participants were generally well educated and most were non-smoking (8·1% of female participants were smokers and 45·8% of male participants were smokers) and did not consume alcohol (table 1). The prevalence of COPD was 1·3%. Among the 91 709 participants assessed for incident COPD at baseline, 2297 (2·50%) developed COPD during follow-up (2245 were diagnosed by the spirometric tests and 52 were self-reported physician-diagnosed; table 1).

The locations of the participants and the distribution of $PM_{2·5}$ concentrations are presented by year in figure 2. Most participants lived in the western area (figure 2). The south-western areas were generally the most heavily polluted and the middle-eastern areas were the least heavily polluted (figure 2). The spatial distribution of $PM_{2·5}$ was generally stable over the study period (figure 2). Large spatial contrasts occurred in exposure among the participants for each year (figure 2). The mean $PM_{2·5}$ was 26·74 μg/m³ (SD 7·76) for the 285 046 participants, 26·66 μg/m³ (7·56) for the 590 278 observations, and 26·91 μg/m³ (8·02) for the 91709 participants assessed for incident COPD (table 1).

Regarding the health effects of $PM_{2·5}$ on the lung function parameters, baseline and longitudinal data analyses yielded similar results (tables 2, 3). Results from the adjusted models show that all four parameters decreased with higher exposure to $PM_{2·5}$ (tables 2, 3). Results of the longitudinal analysis using model 4 showed that every 5 μg/m³ increment in $PM_{2·5}$ was associated with a decrease of 1·18% for FVC, 1·46% for FEV_1, 1·65% for MMEF, and 0·21% for FEV_1:FVC (table 3). The interaction term of $PM_{2·5}$×year shows that the decline in all four parameters accelerated over time with additional annual declines of 0·14% for FVC, 0·24% for FEV_1, 0·44% for MMEF, and 0·09% for FEV_1:FVC (table 3). The concentration-response curves also show the decline in FVC, FEV_1, MMEF, and FEV_1:FVC with increments of $PM_{2·5}$ (figure 3).

With regards to $PM_{2·5}$ and COPD development, compared with the participants exposed to first quartile $PM_{2·5}$, participants exposed to second, third, and fourth quartiles had an associated HR of 1·39 (95% CI

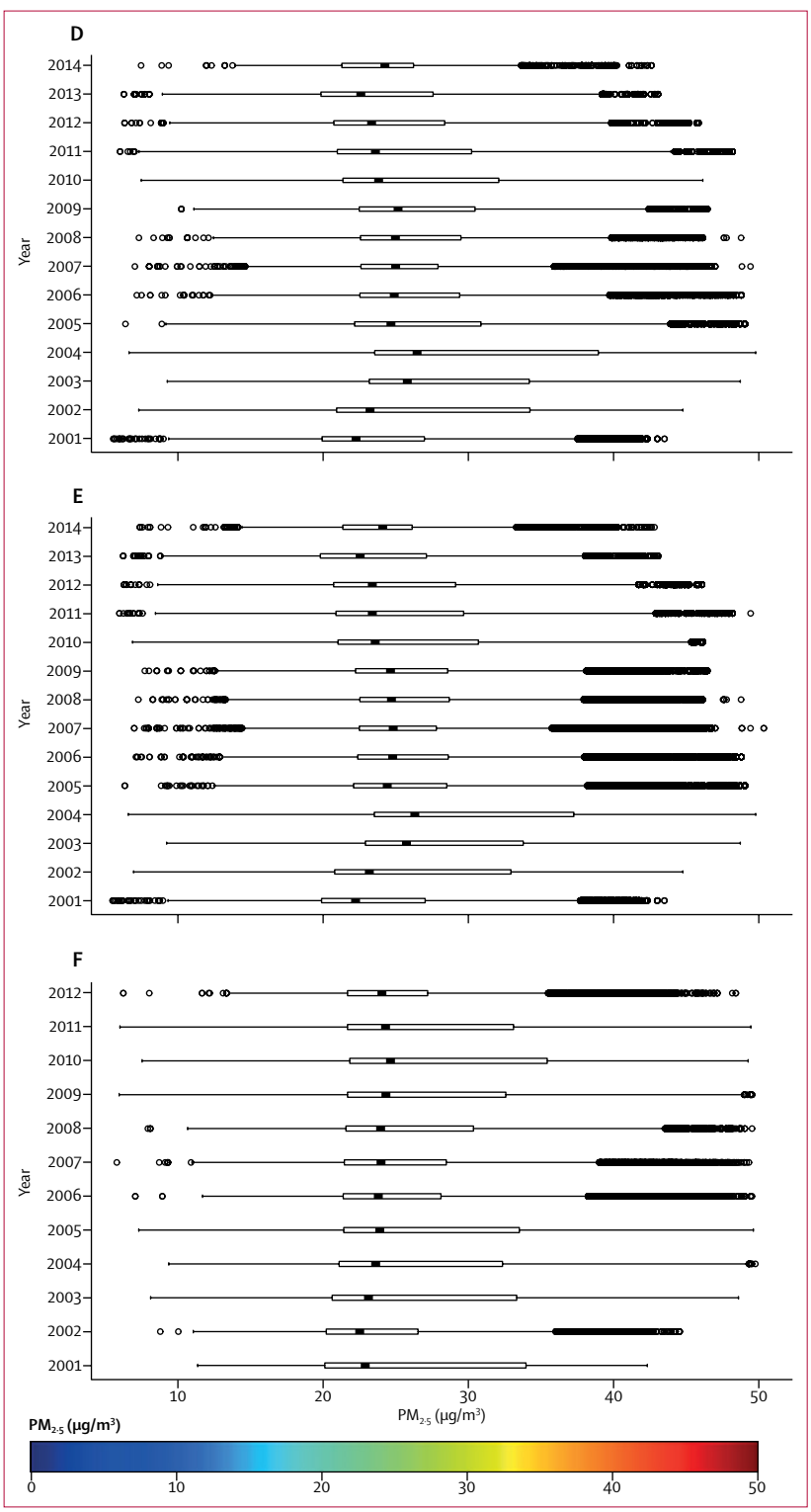

Figure 2: **Spatial distribution of the participants and box plots of $PM_{2·5}$ concentration by year in Taiwan**
(A–C) Spatial distributions of the participants by year. Circles are the address locations of the participants (A, C) or observations (B). (D–F) Distributions of the 2-year average $PM_{2·5}$ concentrations by year. Boxes cover the IQR with a centre line for the median concentration. Whiskers extend to the highest observation within three IQR of the box, with more extreme observations shown as circles. (A, D) Distributions of 285 046 participants at baseline. (B, E) Distributions of the 590 278 observations from the 285 046 participants. (C, F) Distributions of the 91 709 participants assessed for incident COPD at baseline. $PM_{2·5}$=particulate matter with an aerodynamic diameter of 2·5 μm or less. N=North. E=East.

	Model 1		Model 2		Model 3		Model 4	
	Difference (95% CI)	p value	Difference (95% CI)	p value	Difference (95% CI)	p value	Difference (95% CI)	p value
FVC								
Second quartile (21·57–24·03 μg/m³)	0·84% (0·54 to 1·15)	<0·0001	−0·84% (−1·01 to −0·66)	<0·0001	−0·85% (−1·02 to −0·67)	<0·0001	−0·84% (−1·01 to −0·66)	<0·0001
Third quartile (24·03–30·11 μg/m³)	1·59% (1·29 to 1·89)	<0·0001	−1·02% (−1·20 to −0·85)	<0·0001	−1·01% (−1·18 to −0·84)	<0·0001	−0·98% (−1·15 to −0·81)	<0·0001
Fourth quartile (>30·11 μg/m³)	−4·71% (−5·00 to −4·41)	<0·0001	−4·77% (−4·95 to −4·60)	<0·0001	−4·81% (−4·98 to −4·63)	<0·0001	−4·78% (−4·96 to −4·61)	<0·0001
Every 5 μg/m³	−1·33% (−1·40 to −1·26)	<0·0001	−1·17% (−1·21 to −1·13)	<0·0001	−1·18% (−1·22 to −1·14)	<0·0001	−1·17% (−1·21 to −1·13)	<0·0001
FEV_1								
Second quartile (21·57–24·03 μg/m³)	0·73% (0·43 to 1·04)	<0·0001	−1·05% (−1·23 to −0·88)	<0·0001	−1·06% (−1·23 to −0·88)	<0·0001	−1·05% (−1·22 to −0·87)	<0·0001
Third quartile (24·03–30·11 μg/m³)	1·76% (1·45 to 2·07)	<0·0001	−1·04% (−1·21 to −0·87)	<0·0001	−1·03% (−1·20 to −0·85)	<0·0001	−1·00% (−1·18 to −0·83)	<0·0001
Fourth quartile (>30·11 μg/m³)	−4·99% (−5·29 to −4·69)	<0·0001	−5·14% (−5·31 to −4·96)	<0·0001	−5·19% (−5·36 to −5·01)	<0·0001	−5·18% (−5·35 to −5·01)	<0·0001
Every 5 μg/m³	−1·41% (−1·48 to −1·34)	<0·0001	−1·26% (−1·30 to −1·22)	<0·0001	−1·28% (−1·32 to −1·23)	<0·0001	−1·28% (−1·32 to −1·23)	<0·0001
MMEF								
Second quartile (21·57–24·03 μg/m³)	−0·42% (−0·77 to −0·07)	0·0197	−1·95% (−2·21 to −1·68)	<0·0001	−1·94% (−2·21 to −1·68)	<0·0001	−1·95% (−2·22 to −1·69)	<0·0001
Third quartile (24·03–30·11 μg/m³)	0·34% (−0·01 to 0·69)	0·0581	−1·97% (−2·24 to −1·71)	<0·0001	−1·96% (−2·23 to −1·70)	<0·0001	−1·97% (−2·23 to −1·71)	<0·0001
Fourth quartile (>30·11 μg/m³)	−4·71% (−5·05 to −4·37)	<0·0001	−4·91% (−5·17 to −4·64)	<0·0001	−5·01% (−5·27 to −4·75)	<0·0001	−5·02% (−5·28 to −4·76)	<0·0001
Every 5 μg/m³	−1·22% (−1·30 to −1·14)	<0·0001	−1·11% (−1·18 to −1·05)	<0·0001	−1·14% (−1·21 to −1·08)	<0·0001	−1·15% (−1·21 to −1·08)	<0·0001
FEV_1:FVC								
Second quartile (21·57–24·03 μg/m³)	−0·03% (−0·12 to 0·07)	0·6019	−0·17% (−0·26 to −0·07)	0·0004	−0·17% (−0·26 to −0·08)	0·0004	−0·17% (−0·27 to −0·08)	0·0003
Third quartile (24·03–30·11 μg/m³)	0·29% (0·19 to 0·39)	<0·0001	0·03% (−0·07 to 0·12)	0·5993	0·02% (−0·07 to 0·12)	0·6324	0·02% (−0·08 to 0·11)	0·7437
Fourth quartile (>30·11 μg/m³)	−0·19% (−0·29 to −0·10)	<0·0001	−0·24% (−0·34 to −0·15)	<0·0001	−0·28% (−0·37 to −0·18)	<0·0001	−0·28% (−0·38 to −0·19)	<0·0001
Every 5 μg/m³	−0·06% (−0·08 to −0·04)	<0·0001	−0·06% (−0·08 to −0·04)	<0·0001	−0·07% (−0·09 to −0·05)	<0·0001	−0·07% (−0·09 to −0·05)	<0·0001

Lung function was logarithmically transformed to normalise the data for analysis and then the original scale was transformed back to present the effects as percentage difference in lung function parameters with 95% CI. Model 1, no adjustment; model 2, adjusted for demographical factors (age, sex, and education), body-mass index, calendar year, and season; model 3, further adjusted for lifestyle factors (smoking status, alcohol consumption, physical activity intensity, vegetable intake, and fruit intake), and occupational exposure; and model 4, further adjusted for health factors, including hypertension (yes or no), diabetes (yes or no), hyperlipidaemia (yes or no), self-reported cerebrovascular disease (yes or no), and self-reported cardiovascular disease (yes or no). Reference level is the first quartile of $PM_{2·5}$ (<21·57 μg/m³). $PM_{2·5}$=particulate matter with an aerodynamic diameter of 2·5 μm or less. FVC=forced vital capacity. FEV_1=forced expiratory volume in 1 s. MMEF=maximum mid-expiratory flow.

Table 2: **Baseline data analysis for the associations of $PM_{2·5}$ with lung function**

1·24–1·56), 1·30 (1·16–1·46), and 1·23 (1·09–1·39) for COPD development using model 4 (table 4). Every 5 μg/m³ increment in $PM_{2·5}$ was associated with an HR of 1·08 (1·04–1·11) for COPD development. The concentration-response curve is shown in figure 4. Exposure to higher concentrations of $PM_{2·5}$ increased the risk of COPD development.

When we stratified the analyses, larger decreases in lung function were generally observed in female participants and obese participants (appendix). Former smokers also had a slightly larger reduction in FVC and MMEF compared with current and never smokers (appendix). No modifying effects were observed for COPD development (appendix). Results of the sensitivity analyses (appendix) generally yielded similar results.

Discussion

To the best of our knowledge, this is the largest longitudinal cohort study to date to investigate the associations between long-term exposure to ambient $PM_{2·5}$ and the four parameters of lung function. We found that $PM_{2·5}$ was consistently associated with reduced lung function, as indicated by all four parameters. Inverse linear concentration-response

See Online for appendix

	Model 1		Model 2		Model 3		Model 4	
	Difference (95% CI)	p value	Difference (95% CI)	p value	Difference (95% CI)	p value	Difference (95% CI)	p value
FVC								
Second quartile (21·68–24·16 μg/m³)	−1·76% (−1·86 to −1·67)	<0·0001	−1·31% (−1·41 to −1·21)	<0·0001	−1·52% (−1·62 to −1·43)	<0·0001	−1·39% (−1·48 to −1·30)	<0·0001
Third quartile (24·16–29·03 μg/m³)	−2·81% (−2·93 to −2·69)	<0·0001	−2·09% (−2·20 to −1·97)	<0·0001	−2·20% (−2·31 to −2·10)	<0·0001	−2·16% (−2·27 to −2·05)	<0·0001
Fourth quartile (>29·03 μg/m³)	−4·94% (−5·12 to −4·76)	<0·0001	−4·05% (−4·18 to −3·91)	<0·0001	−4·31% (−4·45 to −4·16)	<0·0001	−4·39% (−4·53 to −4·24)	<0·0001
Every 5 μg/m³	−1·54% (−1·59 to −1·50)	<0·0001	−1·16% (−1·19 to −1·12)	<0·0001	−1·12% (−1·16 to −1·08)	<0·0001	−1·18% (−1·21 to −1·14)	<0·0001
$PM_{2·5}$ × year*	NA	NA	NA	NA	NA	NA	−0·14% (−0·14 to −0·14)	<0·0001
FEV_1								
Second quartile (21·68–24·16 μg/m³)	−2·56% (−2·65 to −2·46)	<0·0001	−1·89% (−1·98 to −1·80)	<0·0001	−1·99% (−2·08 to −1·90)	<0·0001	−2·24% (−2·25 to −2·23)	<0·0001
Third quartile (24·16–29·03 μg/m³)	−3·94% (−4·05 to −3·82)	<0·0001	−2·72% (−2·82 to −2·61)	<0·0001	−3·00% (−3·11 to −2·89)	<0·0001	−3·37% (−3·38 to −3·36)	<0·0001
Fourth quartile (>29·03 μg/m³)	−6·24% (−6·42 to −6·06)	<0·0001	−4·77% (−4·92 to −4·62)	<0·0001	−5·26% (−5·41 to −5·11)	<0·0001	−5·37% (−5·38 to −5·36)	<0·0001
Every 5 μg/m³	−1·54% (−1·59 to −1·50)	<0·0001	−1·28% (−1·32 to −1·25)	<0·0001	−1·35% (−1·36 to −1·35)	<0·0001	−1·46% (−1·47 to −1·60)	<0·0001
$PM_{2·5}$ × year*	NA	NA	NA	NA	NA	NA	−0·24% (−0·24 to −0·24)	<0·0001
MMEF								
Second quartile (21·68–24·16 μg/m³)	−4·31% (−4·46 to −4·16)	<0·0001	−3·10% (−3·25 to −2·96)	<0·0001	−3·46% (−3·61 to −3·32)	<0·0001	−3·66% (−3·81 to −3·52)	<0·0001
Third quartile (24·16–29·03 μg/m³)	−6·64% (−6·82 to −6·47)	<0·0001	−5·04% (−5·21 to −4·87)	<0·0001	−5·03% (−5·20 to −4·86)	<0·0001	−5·33% (−5·49 to −5·16)	<0·0001
Fourth quartile (>29·03 μg/m³)	−9·08% (−9·32 to −8·84)	<0·0001	−6·29% (−6·51 to −6·07)	<0·0001	−6·57% (−6·79 to −6·35)	<0·0001	−6·61% (−6·83 to −6·40)	<0·0001
Every 5 μg/m³	−2·62% (−2·69 to −2·56)	<0·0001	−1·53% (−1·59 to −1·48)	<0·0001	−1·51% (−1·57 to −1·46)	<0·0001	−1·65% (−1·71 to −1·60)	<0·0001
$PM_{2·5}$ × year*	NA	NA	NA	NA	NA	NA	−0·44% (−0·44 to −0·44)	<0·0001
FEV_1:FVC								
Second quartile (21·68–24·16 μg/m³)	−0·21% (−0·28 to −0·15)	<0·0001	−0·27% (−0·33 to −0·21)	<0·0001	−0·27% (−0·33 to −0·21)	<0·0001	−0·27% (−0·33 to −0·21)	<0·0001
Third quartile (24·16–29·03 μg/m³)	−0·01% (−0·08 to 0·05)	0·6934	−0·15% (−0·21 to −0·09)	<0·0001	−0·15% (−0·21 to −0·09)	<0·0001	−0·15% (−0·22 to −0·09)	<0·0001
Fourth quartile (>29·03 μg/m³)	−0·81% (−0·88 to −0·75)	<0·0001	−0·82% (−0·88 to −0·76)	<0·0001	−0·86% (−0·92 to −0·80)	<0·0001	−0·87% (−0·93 to −0·81)	<0·0001
Every 5 μg/m³	−0·21% (−0·22 to −0·19)	<0·0001	−0·19% (−0·21 to −0·18)	<0·0001	−0·20% (−0·22 to −0·19)	<0·0001	−0·21% (−0·22 to −0·19)	<0·0001
$PM_{2·5}$ × year*	NA	NA	NA	NA	NA	NA	−0·09% (−0·09 to −0·09)	<0·0001

Lung function was logarithmically transformed to normalise the data for analysis and then the original scale was transformed back to present the effects as percentage difference in lung function parameters with 95% CI. Model 1, no adjustment; model 2, adjusted for demographical factors (age, sex, and education), body-mass index, calendar year, and season; model 3, further adjusted for lifestyle factors (smoking status, alcohol consumption, physical activity intensity, vegetable intake, and fruit intake), and occupational exposure; and model 4, further adjusted for health factors, including hypertension (yes or no), diabetes (yes or no), hyperlipidaemia (yes or no), self-reported cerebrovascular disease (yes or no), and self-reported cardiovascular disease (yes or no). Reference level is the first quartile of $PM_{2·5}$ (<21·68 μg/m³). $PM_{2·5}$=particulate matter with an aerodynamic diameter of 2·5 μm or less. FVC=forced vital capacity. NA=not applicable. FEV_1=forced expiratory volume in 1 s. MMEF=maximum mid-expiratory flow. *Additional annual percentage decrease in lung function over time for each 5 μg/m³ increment in the $PM_{2·5}$ concentration.

Table 3: **Longitudinal data analysis for the associations of $PM_{2·5}$ with lung function**

associations were observed. $PM_{2·5}$ was also consistently associated with an accelerated annual decline in lung function. In line with the negative impacts on lung function, $PM_{2·5}$ appeared to increase the risk of COPD development. Our study, for the first time, simultaneously confirmed that long-term exposure to $PM_{2·5}$ has a negative impact on lung function and resulted in an increased risk of COPD development in the same population. 251·6 million patients with COPD were estimated worldwide for 2016.[18] Based on the calculation formula of population attributable fraction[19] and the fact that exposure to air pollution is ubiquitous, we estimated that a universal increment of 5 μg/m³ in $PM_{2·5}$ might contribute to 18·6 million cases of COPD if the effect magnitude of 1·08 is valid globally.

This study has several important strengths. First, it is a longitudinal cohort study and data were collected from a standard medical screening programme where all the procedures were approved according to ISO 9001.[20] The incidence of COPD was mainly identified by the repeated spirometry tests. Most previous studies used mortality or hospital admission data, or both. However, neither

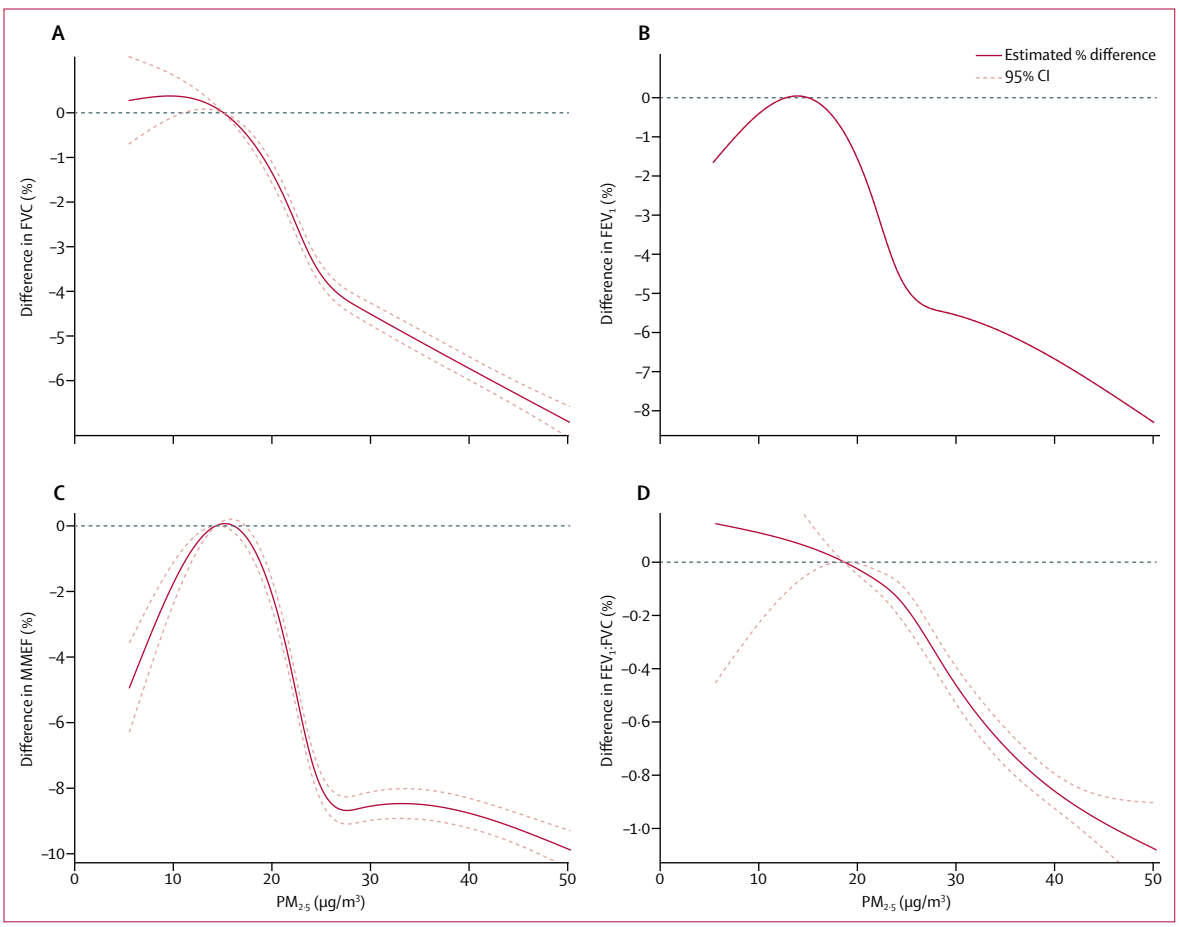

Figure 3: **Concentration-response curves between $PM_{2·5}$ and lung function**
Longitudinal associations of $PM_{2·5}$ with FVC (A), FEV_1 (B), MMEF (C), and FEV_1:FVC (D). $PM_{2·5}$=particulate matter with an aerodynamic diameter of 2·5 μm or less. FVC=forced vital capacity. FEV_1=forced expiratory volume in 1 s. MMEF=maximum mid-expiratory flow.

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Second quartile (21·42–23·94 μg/m³)	1·31 (1·17–1·46)	<0·0001	1·39 (1·24–1·56)	<0·0001	1·39 (1·24–1·56)	<0·0001	1·39 (1·24–1·56)	<0·0001
Third quartile (23·94–31·86 μg/m³)	1·16 (1·04–1·31)	0·0104	1·29 (1·15–1·45)	<0·0001	1·30 (1·16–1·46)	<0·0001	1·30 (1·16–1·46)	<0·0001
Fourth quartile (>31·86 μg/m³)	1·14 (1·01–1·29)	0·0278	1·22 (1·08–1·37)	0·0013	1·24 (1·10–1·39)	0·0005	1·23 (1·09–1·39)	0·0006
Every 5 μg/m³	1·05 (1·02–1·08)	0·0011	1·07 (1·04–1·10)	<0·0001	1·08 (1·05–1·11)	<0·0001	1·08 (1·04–1·11)	<0·0001

Model 1, no adjustment; model 2, adjusted for demographical factors (age, sex, and education), body-mass index, calendar year, and season; model 3, further adjusted for lifestyle factors (smoking status, alcohol consumption, physical activity intensity, vegetable intake, and fruit intake), and occupational exposure; and model 4, further adjusted for health factors, including hypertension (yes or no), diabetes (yes or no), hyperlipidaemia (yes or no), self-reported cerebrovascular disease (yes or no), and self-reported cardiovascular disease (yes or no). Reference level is the first quartile of $PM_{2·5}$ (<21·42 μg/m³). $PM_{2·5}$=particulate matter with an aerodynamic diameter of 2·5 μm or less. HR=hazard ratio.

Table 4: **Associations of $PM_{2·5}$ with chronic obstructive pulmonary disease development**

mortality nor hospital admission studies can unambiguously distinguish acute from long-term effects on the development of the underlying pathophysiological changes.[21] Second, we took into account the potential effects of a wide range of confounders or modifiers and the associations remained robust. Third, the large sample size enabled us to detect the small effects of $PM_{2·5}$ on lung function and COPD development. The large sample size

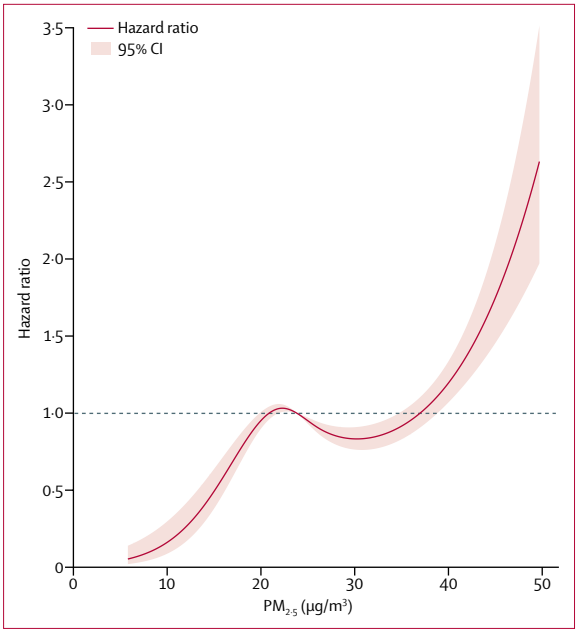

Figure 4: **Concentration-response curve between $PM_{2·5}$ and chronic obstructive pulmonary disease development**
$PM_{2·5}$=particulate matter with an aerodynamic diameter of 2·5 μm or less.

also enabled us to provide stable results and more precise estimates. Finally, we used a novel spatiotemporal model with a high-spatial resolution to estimate the long-term exposure of $PM_{2·5}$ concentration. This technology enables us to have individual-level exposure and overcome the spatial coverage and interpolation problems that occur when using only data from monitoring stations. Furthermore, by using the satellite data, we could trace the change of $PM_{2·5}$ exposure over time and take into account the impact of change on lung function and COPD development.

Most previous studies did not include the parameter MMEF, an important indicator of small airway function. Our study found that the effects on MMEF appear to be slightly greater than those on FEV_1 and FVC (every 5 μg/m³ increase of $PM_{2·5}$ was associated with 1·65% lower in MMEF *vs* 1·46% for FEV_1 and 1·18% for FVC), suggesting long-term exposure to $PM_{2·5}$ might be more harmful to small airway function.

Most previous studies have focused on PM with an aerodynamic diameter of 10 μm or less (PM_{10}), black carbon, and gaseous pollutants, or simply used a proxy for air pollution such as the distance to a major road.[10–12,22–25] The SAPALDIA study[25] showed that an increase of 10 μg/m³ in PM_{10} was associated with a decrease of 1·03% in FEV_1; decreasing the exposure might attenuate the decline.[26] The Normative Aging Study[12] found that black carbon had adverse effects on FEV_1 and FVC and reported that an increase of 0·5 μg/m³ in black carbon with a 5-year exposure was associated with a decrease of 6–7% in FEV_1 and FVC. Other studies[10,11,25] of cross-sectional design generally reported a negative association with FEV_1. Schikowski and colleagues[10] found that every 7 μg/m³ increase of PM_{10} was associated with a reduction of 3·7% in FVC and 5·1% in FEV_1. For the two studies reporting on $PM_{2·5}$, the ESCAPE study[13] did not find any significant associations whereas the Framingham Heart Study[9] found negative associations with FEV_1 and FVC (each 2 μg/m³ increase in $PM_{2·5}$ was associated with a 13·5 mL lower FEV_1 and 18·7 mL lower FVC), but not for the FEV_1:FVC ratio.

It might be difficult to compare our study with previous studies directly. Our study was targeted to an Asian population and participants were relatively younger and healthier than previous studies. Furthermore, the $PM_{2·5}$ concentrations were much higher than those concentrations in North America and Europe. Information on air pollution and COPD development in Asian populations is rare. By contrast, COPD is an important public health challenge in Asia. The 2015 Global Burden of Disease Study[27] shows that Asia has the largest disease burden of COPD in the world. The age-standardised DALY rate in India is 2001–4500 per 100 000 people, which is the highest in the world.[27] China has a rate of 1001–2000 per 100 000 people.[27] Many Asian countries and regions are experiencing serious air pollution. Our study suggests ambient $PM_{2·5}$ air pollution might serve as one important contributor to such high prevalence of COPD in these Asia countries and regions.

Our results show that female participants generally had larger decreases in lung function, which is in line with the ESCAPE study.[13] The potential mechanism is unclear, but this discrepancy might be attributed to the smaller proportion of smokers in female participants than in male participants. Smoking and air pollutants might share the same pathways, which leads to airway inflammation and changes in pulmonary function. Smoking might play a dominant role in smokers. Therefore, the additional exposure to air pollutants might not result in similar effect magnitudes as for non-smokers. In our study, obese participants were more sensitive to the effect of $PM_{2·5}$ on lung function compared with those with normal BMI, consistent with the findings of the ESCAPE and SAPALDIA studies.[13,28] Obesity can reduce the expiratory reserve volume and residual capacity through airway calibre and[29] was also found to be associated with oxidative stress and inflammation.[28,30]

In line with the negative impacts on lung function, we found that long-term exposure to $PM_{2·5}$ was associated with an increased risk of COPD development. When $PM_{2·5}$ was treated as a continuous variable, an approximate linear concentration-response association was observed. However, the linear concentration-response association disappeared when $PM_{2·5}$ was categorised into quartiles. We do not know the exact reasons for this effect, but speculate that the use of category variable led to a loss of information and an increase in uncertainty. Several previous studies[10,31–34] also show that air pollution was associated with an increased

risk of COPD mortality or hospital admission, which are consistent with our study. These studies reported odds ratios or HRs ranging from 1·01 to 1·11. However, other studies,[9,35–37] including the Framingham Study, Harvard Six Cities Study, ESCAPE Study, and American Cancer Society Study, did not show significant associations. This inconsistency has been well discussed in the review by Schikowski and colleagues.[21]

The biological mechanism of chronic $PM_{2·5}$ effects on lung function in human beings remains unclear. Churg and colleagues[38] reported that PM particles are fibrogenic and can result in airway wall remodelling, and subsequently cause chronic airflow obstruction. Repetitive ozone exposure can elevate inflammation and damage small airway function.[39] Evidence from experiments on mice also shows that exposure to ambient air particles could lead to pulmonary inflammation, resulting in anthracosis and emphysema.[40] Further studies are warranted to illustrate the mechanism.

This study has certain limitations. First, we only included ambient air pollution because information on indoor air pollution was unavailable. Although some studies have shown that indoor and outdoor PM concentrations are highly correlated, we could not exclude the possible influence of some factors that affect indoor PM concentrations, such as the type of cooking fuel and home ventilation characteristics. However, we accounted for smoking, one of the most important sources of household air pollution in a developed economy. Second, we did not take into account the effects of other gaseous pollutants, such as NO_x and ozone. We used the single pollutant model in this study. Therefore, we could not distinguish whether the observed effects were because of $PM_{2·5}$ alone or joint effects of the pollutants. Third, the $PM_{2·5}$ exposure concentrations were calculated at the fixed addresses and participants' activity patterns were not taken into account. More advanced technologies are needed for more accurate exposure assessment in future studies. Fourth, in a clinical setting, post-bronchodilator FEV_1:FVC should be used to diagnose COPD because without a validated bronchial dilation test, the risk for misdiagnosis of COPD increases. However, we speculated that the misdiagnosis in this study was probably not systemically related to $PM_{2·5}$ exposure (ie, the participants with higher $PM_{2·5}$ exposure were more likely to be misdiagnosed as having COPD). Thus, the misdiagnosis was most probably random and should not have affected the direction of the association. Finally, the participants in this study were relatively well educated and healthy. Therefore, we should be cautious when adapting the results to the general population.

In summary, long-term exposure to ambient $PM_{2·5}$ is associated with a reduced lung function with respect to all four parameters: FEV_1, FVC, MMEF, and FEV_1:FVC ratio. Long-term exposure to ambient $PM_{2·5}$ is also associated with an accelerated decline in lung function and an increased risk of COPD development. We advocate urgent strategies for global air pollution reduction to improve pulmonary health.

Contributors

XQL conceived and designed the study. L-YC, AKHL, and XQL acquired the data. CG and ZZ searched the literature. CG and XQL analysed and interpreted the data. CG and XQL drafted the manuscript. All authors critically revised the manuscript. XQL obtained the funding. L-YC, AKHL, and XQL supervised this study.

Declaration of interests

We declare no competing interests. We affirm that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies are disclosed.

Acknowledgments

We would like to thank MJ Health Research Foundation for the authorisation of using MJ health data (authorisation code MJHR2015002A). Any interpretation or conclusion related to this manuscript does not represent the views of MJ Health Research Foundation. We are also grateful to the anonymous reviewers and the editor for their valuable comments.

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