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ENVIRONMENTAL EPIDEMIOLOGY

Air pollution and lung function in the European Community Respiratory Health Survey

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Background The association of long-term air pollution and lung function has not been studied across adult European multi-national populations before. The aim of this study was to determine the association between long-term urban background air pollution and lung function levels, as well as change in lung function among European adults.

Methods Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and the ratio thereof (FEV1/FVC) were assessed at baseline and after 9 years of follow-up in adults from 21 European centres (followed-up sample 5610). Fine particles ($PM_{2.5}$) were measured in 2000/2001 using central monitors.

Results Despite sufficient statistical power no significant associations were found between city-specific annual mean $PM_{2.5}$ and average lung function levels. The findings also do not support an effect on change in lung function, albeit statistical power was insufficient to significantly detect such an association.

Conclusions The inability to refuse the null hypothesis may reflect (i) no effect of urban air pollution on lung function or (ii) inherent biases due to the study design. Examples of the latter are lack of individual-level air quality assignment, not quantified within-city contrasts in traffic-related pollution, or the heterogeneity of the studied populations and their urban environments. Future studies on long-term effects of air pollution on lung function could increase statistical power and reduce potential misclassification and confounding by characterizing exposure on the level of individuals, capturing contrasts due to local sources, in particular traffic.

Keywords $PM_{2.5}$, FEV1, FVC, adults, longitudinal, multilevel

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Introduction

Spirometric measures of lung function, namely maximum forced vital capacity (FVC) and maximum forced expiratory volume in 1 s (FEV1) are early indicators of chronic respiratory and systemic inflammation, as well as premature cardio-respiratory mortality.[1] These same outcomes have been associated with ambient air pollution,[2] therefore lung function is an important link in the investigation of chronic effects of ambient air pollution.

Lung function increases throughout childhood, peaks around age 20–25, and thereafter slowly decreases. There is strong evidence for an adverse effect of air pollution on lung function growth from the Southern California Children's Health Study.[3] In adults, several cross-sectional studies observed lower levels of lung function in more polluted communities.[4,5] The Swiss SAPALDIA study is currently the only notable longitudinal study reporting significant associations between long-term exposure to air pollution and decline in lung function,[6] whereas the earlier longitudinal studies had substantial limitations.[7–10]

The European Community Respiratory Health Survey (ECRHS) is the most comprehensive multi-centre respiratory cohort study in adults in Europe.[11] The standardized air pollution protocol of ECRHS was adopted by 21 participating centres.[12] The aim of this project was to test the hypotheses that long-term urban background air pollution was associated with both *lung function level* (cross-sectional analysis) and *change in lung function* (longitudinal analysis), respectively.

Methods

Details on the study protocol[11] and lung function data[13] have been published. In brief, participants aged 20–44 were randomly selected from 20 cities in 10 countries. Respiratory health assessment was conducted in 1991–93 and repeated in 2000–2002, using spirometry and administered questionnaires.

Of the 21 centres, 18 used the same spirometer at both occasions. Spirometers at baseline were Biomedin (Padova, Italy) in 12 centres, SensorMedics hot wire spirometer (Yorba Linda, USA) in five centres, SensorMedics dry seal spirometer in two centres and Jaeger Pneumotach (Würzburg, Germany) in two centres. Equipment changed in Erfurt (replaced Jaeger Pneumotach by same model) and Antwerp City and South (switched from SensorMedics dry spirometer to Jaeger Masterscope). The spirometry protocol was consistent with American Thoracic Society (ATS) guidelines.[14] Measurements not fulfilling the ATS criteria for repeatability, extreme outliers, and subjects missing data for either FEV1 or FVC were excluded from the analysis. FEV1, FVC and FEV1/FVC ratio were used as outcomes.

Detailed methods and results of the air pollution assessment were published previously.[12,15,16] Fine particles ($PM_{2.5}$) were measured at one central monitor in each centre. Annual means derived between June 2000 and December 2001 were used as surrogates for long-term air pollution levels, as done in other studies.[4,5] Thereafter the elemental composition and light absorbance of the particles were analysed using standard methods.[15]

Questionnaire information included respiratory symptoms, asthma status, medication use, smoking status, occupational history, household characteristics, residential history, socio-demographic characteristics, sensitization to grass and cat allergens,[17] and bronchial hyper-responsiveness.[18]

A three-level hierarchical model (survey, subject, centre) was used, similar to the approach presented by Gauderman and colleagues.[3] A detailed description of the statistical methods is provided in the online supplement.

In brief, the two lung function measurements were regressed against age (centred at mean = 38.4 years). Adjustments were made for time dependent covariates (survey level), time-independent subject-specific covariates (subject level), and centre-specific covariates (centre level). The three levels were integrated into one model using *xtmixed* in STATA version 9.0 (Statacorp LP, College Station, TX, USA), allowing to assess separate effects of $PM_{2.5}$ on lung function level and change in lung function simultaneously.

The main models were adjusted for height and smoking status. To investigate further potential confounding and effect modification, varying degrees of adjustment and various sub-samples were used, respectively. Specific emphasis was put on the sensitivity of the analysis towards adjustment for height and age. All statistical models were stratified by sex.Comparisons of baseline lung function were used to assess potential bias due to loss to follow-up.

Power calculations for significantly detectable effect sizes were conducted in Quanto (version 1.1.1 http://hydra.usc.edu/gxe) using centre random effects after adjusting for height, age, and smoking status. The size of a significantly ($\alpha = 0.05$, $\beta = 0.8$) detectable effect on FEV1 level (cross-sectional difference) was 39 ml (1.2% of mean FEV1) and 58 ml (1.4%) per $PM_{2.5}$ contrast of 10 $\mu g/m^3$, in women and men, respectively, and slightly larger for FVC (~1.5%). These effect sizes are comparable to those reported by others.[4] Relative power was considerably smaller to detect an effect on change in lung function. Significantly detectable effects for change in FEV1 were 4.2 ml/year (16.6% of mean change in FEV1) and 4.8 ml/year (14.5%) per 10 $\mu g/m^3$ of $PM_{2.5}$, in women and men, respectively (see online supplement for details).

Results

Lung function was measured in 8864 subjects at baseline and 5610 at follow-up (follow-up rate 63%; range across centres: 43–85%). Limiting the data set

to subjects with complete, valid records resulted in a sample of 4290 subjects (ATS criteria not fulfilled: 733 subjects; exclusion of extreme values: 279; incomplete: 308).

Compared with those lost to follow-up, participants were on average 1 year older, slightly more often women (52% vs 49%), less likely to ever have smoked (55% vs 60%), and their lung function was slightly lower (FEV1: 3.78 l vs 3.84 l; FVC: 4.66 l vs 4.57 l) (see online supplement for more details; Table 2). The main characteristics of the participants are listed in Table 1.

Annual mean concentrations of $PM_{2.5}$ ranged from 3.7 to 44.7 $\mu g/m^3$ across all centres; 16 centres had concentrations between 13 and 24 $\mu g/m^3$ (Figure 1) (for a map of the 21 centres, see the online supplement).

Correlations between centre means of subjects' characteristics and $PM_{2.5}$ are listed in Table 1. Centre mean height, mean age at the end of education, and average number of reported respiratory symptoms at follow-up showed the strongest correlations with $PM_{2.5}$ (Pearson $r = -0.5$).

Table 1 Means (SD) and proportions of relevant variables for the complete sample and lowest and highest centre for each variable, by sex

	Women			**Men**			
Sample size	All 2250	Lowest 40	Highest 201	All 2040	Lowest 16	Highest 187	
Continuous variables	Mean (SD)	Lowest	Highest	Mean (SD)	Lowest	Highest	**Pearson *r****
$PM_{2.5}$ [$\mu g/m^3$][a]	16.8 (8.8)	3.7	44.9	17.1 (9.2)	3.7	44.9	1
Length of follow-up	8.9 (0.78)	7.0	10.4	8.9 (0.76)	7.0	10.4	0.03
FEV1[l] BL	3.25 (0.46)	3.04	3.46	4.36 (0.63)	4.05	4.82	−0.22
FEV1[l] FU	3.03 (0.46)	2.87	3.31	4.07 (0.63)	3.78	4.66	−0.13
Change in FEV1(ml/year)	−25.3 (24.1)	−14.70	−40.1	−33.1 (30.3)	−18.2	−53.5	0.25
FVC[l] BL	3.88 (0.53)	3.60	4.15	5.33 (0.74)	4.92	5.61	−0.32
FVC[l] FU	3.72 (0.54)	3.46	3.94	5.09 (0.76)	4.76	5.44	−0.24
Change in FVC(ml/year)	−17.8 (29.7)	0.0	−33.4	−27.1 (39.0)	−8.3	−46.8	0.30
FEV1/FVC BL	0.84 (0.06)	0.81	0.88	0.82 (0.06)	0.78	0.87	0.38
FEV1/FVC FU	0.81 (0.06)	0.80	0.85	0.80 (0.06)	0.77	0.86	0.17
Age BL	33.9 (7.1)	31.6	36.9	34.0 (7.1)	30.0	37.4	0.09
Age FU	42.8 (7.0)	40.6	46.0	42.9 (7.1)	37.8	45.7	0.16
Height (cm)	163.6 (6.5)	158.3	167.4	176.5 (7.1)	170.5	180.9	−0.46
BMI BL (kg/m^2)	23.1 (3.8)	21.6	24.7	24.5 (3.2)	23.3	26.0	−0.08
BMI FU (kg/m^2)	24.7 (4.6)	22.9	27.3	25.9 (3.6)	24.5	27.5	−0.29
Age end education	21.0 (7.8)	17.1	28.4	21.0 (7.4)	17.2	26.4	−0.48
No. of reported symptoms[b] BL	2.2 (2.95)	1.2	3.2	2.0 (2.72)	1.3	3.3	−0.17
No. of reported symptoms[b] FU	2.3 (3.00)	1.4	3.3	2.2 (2.87)	1.3	3.2	−0.46
Indicator variables	Percentage (SD)	Lowest	Highest	Percentage (SD)	Lowest	Highest	Pearson r*
Ever smoked BL	52 (50)	36	65	60 (49)	45	73	0.02
Ever smoked FU	52 (50)	37	60	61 (49)	47	73	0.10
Current smoker BL	31 (46)	13	51	37 (48)	20	62	0.07
Current smoker FU	27 (44)	13	42	30 (46)	15	58	0.14
Ex-smoker BL	40 (49)	17	63	40 (49)	15	59	−0.14
Ex-smoker FU	50 (50)	11	72	52 (50)	21	69	−0.17
ETS BL	53 (50)	24	82	59 (49)	31	85	0.30
ETS FU	38 (48)	16	72	43 (49)	20	81	0.22
SES based on occup. group							
Managers/professionals; non-manual	25 (44)	11	48	32 (47)	10	56	−0.12

(continued)

Table 1 Continued

Indicator variables	Women			Men			Pearson *r**
	Percentage (SD)	Lowest	Highest	Percentage (SD)	Lowest	Highest	
Technicians and associate professions	18 (39)	4	29	17 (37)	6	27	−0.33
Other non-manual	36 (48)	19	50	16 (37)	3	36	0.32
Skilled manual	2 (16)	0	13	19 (39)	3	30	−0.27
Semi-skilled or unskilled manual	7 (25)	0	21	13 (34)	3	24	−0.03
Unclassifiable or unknown	11 (31)	1	29	3 (17)	0	14	0.38
Trucks pass home constantly[c]	14 (35)	4	27	12 (33)	6	27	0.01
Ever asthma BL	8 (27)	2	17	6 (24)	0	14	0.17
Ever asthma FU	12 (33)	3	21	9 (28)	1	19	−0.15
Ever rhinitis BL	27 (44)	9	38	24 (43)	9	32	−0.24
Sensitization IgE (>0.7 kU/L)BL[d]	22 (41)	5	34	29 (45)	14	41	0.25

Last column lists the Pearson correlation between particulate matter with dynamic diameter upto 2.5 μm ($PM_{2.5}$ or fine particles) and centre means of the variables.
[a]Means are weighted by sample size.
[b]Symptoms asked for were: 'Wheezing in the last 12 months (12 m)', 'Breathless when wheezing', 'Wheezing without cold', 'Woken up with tight chest 12 m', 'Short breath at rest 12 m', 'Short breath active 12 m', 'Woken up with short breath 12 m', 'Woken by cough 12 m', 'Cough morning winter', 'Cough anytime winter', 'Cough 3 m per year', 'Phlegm morning winter', 'Phlegm anytime winter', 'Phlegm 3 m per year', 'Ever asthma', 'Doctor asthma', 'Current asthma (12 m)', 'Current asthma treatment', 'Ever rhinitis'.
[c]At follow-up only.
[d]*D. pteronyssinus*, timothy grass, cat and *C. herbarium* allergens.
*Pearson correlation coefficients >0.43 or <−0.43 are statistically significant ($P < 0.05$).
BMI, Body mass index [weight/height^2 (kg/m^2)]; BL, at baseline, FU, at follow-up; ETS, Environmental tobacco smoke; SES, Socio-economic status.

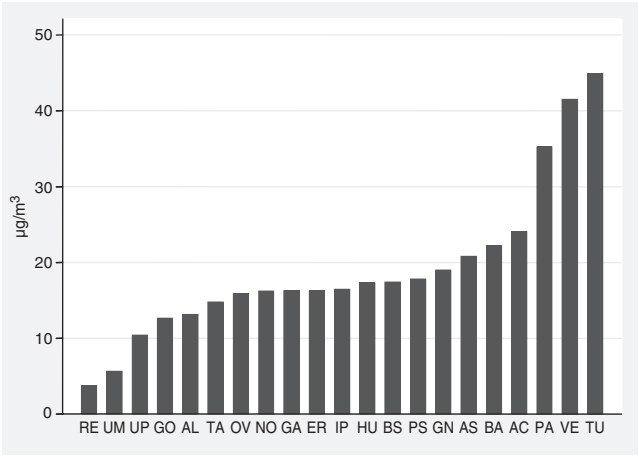

Figure 1 Distribution of $PM_{2.5}$ annual mean concentrations across ECRHS centres. *Note:* Al, Albacete; AC, Antwerp City; AS, Antwerp South; BA, Barcelona; BS, Basel; GA, Galdakao; GN, Grenoble; GO, Gothenburg; HU, Huelva; IP, Ipswich; NO, Norwich; OV, Oviedo; RE, Reykjavik; PA, Pavia; PS, Paris; TA, Tartu; TU, Turin; UM, Umeå; UP, Uppsala; VE, Verona

$PM_{2.5}$ and lung function

There were no significant effects of $PM_{2.5}$ on lung function level (Tables 2 and 3), nor on change in lung function level over the follow-up period.[19] These null-findings were robust towards adjustment for covariates and within various sub-samples of participants analysed (Table 3; Table 1 in online supplement, and ref.[19]). As expected, age and height were strong predictors of lung function level (Table 2). For example, in women FEV1 was 25.5 ml lower for each additional year of age, whereas it was 31.8 ml higher for each additional centimeter of standing height. The negative effects of current smoking on lung function level were significant in men only, while for change in lung function this was the case in both sexes.

Height was the strongest confounder of the crude negative, though non-significant, association between $PM_{2.5}$ and lung function level. Including additional covariates had only minor influence on the $PM_{2.5}$ coefficients. As shown in the online supplement, other exposure metrics such as sulfur content on $PM_{2.5}$, light absorbance, or NO_2 were neither associated with lung function and these findings remained similar for seasonal means instead of the annual average (see supplement Table 2).

Neither the sub-sample analyses among never smokers, northern, central, or southern centres, centres that all used Biomedin spirometers, subjects who did not move between surveys (long term residents), and movers, (Table 3) nor any additional analyses substantially altered the coefficients for $PM_{2.5}$ (see online supplement starting on page 2, including Tables 1 and 8).

Table 2 Coefficients (*P*-values) for lung function level from main models[a] for complete samples, by sex

	Women (*N* = 2243)			**Men (*N* = 2031)**		
Variable	FEV1-level (ml)	FVC-level (ml)	FEV1/FVC-level[b]	FEV1-level (ml)	FVC-level (ml)	FEV1/FVC-level
Intercept	3349	4115	0.816	3967	4840	0.822
Age	−25.5 (<0.001)	−18.0 (<0.001)	−0.003 (<0.001)	−25.2 (<0.001)	−21.6 (<0.001)	−0.002 (0.001)
Height (cm)	31.8 (<0.001)	44.6 (<0.001)	−0.001 (<0.001)	41.6 (<0.001)	61.3 (<0.001)	−0.002 (<0.001)
Ex-smoker	36.5 (0.004)	55.2 (<0.001)	−0.003 (0.156)	1.5 (0.934)	13.4 (0.539)	−0.002 (0.308)
Current smoker	−9.1 (0.478)	23.2 (0.122)	−0.009 (<0.001)	−62.9 (0.001)	−54.0 (0.014)	−0.006 (0.008)
PM2.5 (μg/m^3)	9.3 (0.578)	−6.4 (0.782)	0.004 (0.194)	38.5 (0.097)	32.0 (0.316)	0.002 (0.577)

[a]Coefficients for lung function level are estimated in the same model as coefficients for change in lung function (see online supplement) and, therefore, adjusted for those variables. In addition coefficients for lung function level are adjusted for BMI and SES (coefficients not shown).
[b]Model did not converge. Estimates are based on iterative Estimation-maximization.

Table 3 $PM_{2.5}$ coefficients (*P*-values) for lung function level from sensitivity analyses using different adjustment variables and subsamples

	Women				**Men**			
Effects on level	*N*	FEV1 β (*P*)	FVC β (*P*)	FEV1/FVC[a] β (*P*)	N	FEV1 β (*P*)	FVC β (*P*)	FEV1/FVC β (*P*)
Sub-models								
Crude	2250	−24.2 (0.33)	−54.9 (0.09)	0.006 (0.06)	2040	−24.0 (0.49)	−57.8 (0.21)	0.005 (0.26)
Height only	2250	11.2 (0.50)	−5.3 (0.82)	0.004 (0.18)	2040	38.3 (0.09)	29.9 (0.34)	0.002 (0.56)
Minimal	2245	11.2 (0.50)	−5.4 (0.81)	0.004 (0.18)	2037	38.8 (0.09)	30.5 (0.33)	0.002 (0.56)
Main	2243	9.3 (0.58)	−6.4 (0.78)	0.004 (0.19)	2031	38.5 (0.10)	32.0 (0.32)	0.002 (0.58)
Centre level adj.	2243	19.7 (0.23)	2.6 (0.90)	0.005 (0.14)	2031	39.7 (0.14)	25.1 (0.43)	0.004 (0.37)
Age squared	2245	10.3 (0.53)	−7.0 (0.76)	0.004 (0.18)	2037	38.2 (0.09)	29.7 (0.33)	0.003 (0.55)
Maximal	2227	9.0 (0.58)	−6.4 (0.78)	0.004 (0.24)	2018	39.2 (0.09)	31.1 (0.33)	0.002 (0.55)
Centre specific adj. for height and BMI	2243	−6.0 (0.79)	−24.4 (0.40)	0.003 (0.38)	2031	37.2 (0.13)	24.8 (0.41)	0.004 (0.33)
Sub-samples								
Never smokers	1007	4.6 (0.81)	−9.7 (0.70)	0.003 (0.33)	745	14.1 (0.59)	−4.7 (0.89)	0.004 (0.44)
Northern centres	871	59.5 (0.41)	76.9 (0.34)	−0.001 (0.95)	716	79.2 (0.41)[a]	168.9 (0.14)	−0.007 (0.70)
Central centres	618	105.3 (0.48)	153.3 (0.54)[a]	−0.005 (0.85)	541	107.6 (0.31)[a]	201.2 (0.44)[a]	−0.015 (0.73)[a]
Southern centres	755	8.2 (0.69)	−15.1 (0.56)	0.006 (0.05)	774	20.8 (0.58)	−8.5 (0.85)	0.006 (0.24)
Biomedin spiro.	1122	14.4 (0.48)	−9.8 (0.76)	0.007 (0.07)	1057	27.6 (0.43)[a]	−4.7 (0.92)[a]	0.006 (0.26)
Long term residents	1132	23.3 (0.24)	9.6 (0.73)	0.005 (0.15)	956	36.2 (0.08)	17.9 (0.54)	0.004 (0.43)
Movers	1108	−9.2 (0.66)	−26.2 (0.32)	0.003 (0.35)	1074	28.2 (0.38)	27.0 (0.52)[a]	0.001 (0.87)

Crude = intercept, $PM_{2.5}$.
Height only = crude + height.
Minimal = crude + smoking status (never, ex, current).
Main = crude + body mass index (BMI), socio-economic status (SES).
Age squared = crude + age^2.
Centre level adj. = main + centre means of 'Education level (age)', 'Proportion of non-manual professions', 'ETS'.
Maximal = main + long and short term respiratory symptoms, exercise, trucks at home, height squared Centre specific adj. for height, BMI = main + centre × height + centre × BMI.
Coefficients are per 10 μg/m^3 $PM_{2.5}$. Units for FEV1 and FVC are ml.
[a]Models did not converge. Estimates are based on iterative Estimation-Maximization.

Discussion

ECRHS is the first trans-European study to investigate long-term air pollution and lung function. No significant associations between $PM_{2.5}$ and lung function levels were found across the 21 communities, despite sufficient statistical power. These null findings for cross-sectional effects stand in contrast to findings of two European multi-centre studies, SAPALDIA[4] and SALIA.[5] On the other hand, ECRHS was underpowered to detect effects on lung function decline. The observed average decline (25 ml/a and 33 ml/a in FEV1, for women and men, respectively; see Table 1) was comparable to other studies.[20] The significantly detectable size of air pollution effects on lung function decline was equivalent to smoking 16 and 23 pack years, in women and men, respectively (ECRHS data). As emphasized in the recent SAPALDIA analyses, there is a need for more powerful studies to investigate effects of air pollution on lung function decline, and availability of individual level long-term exposure data appears to be crucial.[6]

Our inability to refute the null hypothesis imposes a challenge in the interpretation of the data. The findings either reflect no adverse effects of urban background air pollution on lung function, or are the result of biases toward the null due to some unresolved methodological issues. It is inherently impossible to 'prove' the null hypothesis, thus, one can only speculate about which of the two possible interpretations is appropriate. Related to the possibility of methodological limitations, factors that may have led to systematic misclassification of centre estimates are the primary concern, since we measured air pollution at the centre level. In the following we address the potential for misclassification of lung function and air pollution, as well as confounding separately.

Lung function assessment

Lung function measurements followed a standardized protocol and fulfilled the ATS criteria for reproducibility. Subjects were advised not to smoke or use respiratory medication 1 h before the examination. Individuals who had a respiratory infection in the 3 weeks previous to examination were asked to return at a later point, if possible. Adjustment for short-term effects of air pollution was not feasible, however, because daily air pollution data was not available (84 out of 365 days).[12]

Spirometry was conducted by well-trained local personnel, and calibration of spirometers was part of the protocol. Nonetheless, the use of different equipment is a potential source of error in cross community comparisons of lung function.[21] As can be seen in Figures 2 and 3, type of spirometer was associated with air pollution levels, but centre means of lung function did not depend on the device used.

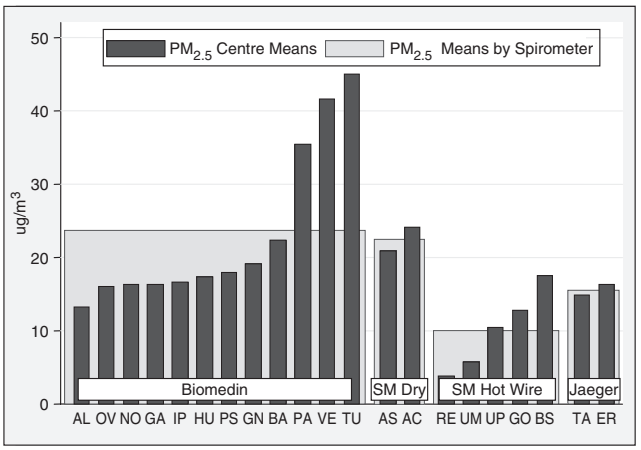

Figure 2 $PM_{2.5}$ levels across ECHRS centres by type of spirometer used. Wide grey bars in the background reflect mean $PM_{2.5}$ levels across centres using the same type of spirometer. Narrow black bars in the foreground represent centre $PM_{2.5}$ levels. *Note:* Biomedin, Biomedin Baires water seal volume displacement spirometer; SM Dry, SensorMedics dry seal volume displacement spirometer (changed to Jaeger Masterscope at follow-up); SM Hot Wire, SensorMedics heated wire flow sensing spirometer; Jaeger, Jaeger Pneumotach. Al, Albacete; AC, Antwerp City; AS, Antwerp South; BA, Barcelona; BS, Basel; GA, Galdakao; GN, Grenoble; GO, Gothenburg; HU, Huelva; IP, Ipswich; NO, Norwich; OV, Oviedo; RE, Reykjavik; PA, Pavia; PS, Paris; TA, Tartu; TU, Turin; UM, Umeå; UP, Uppsala; VE, Verona

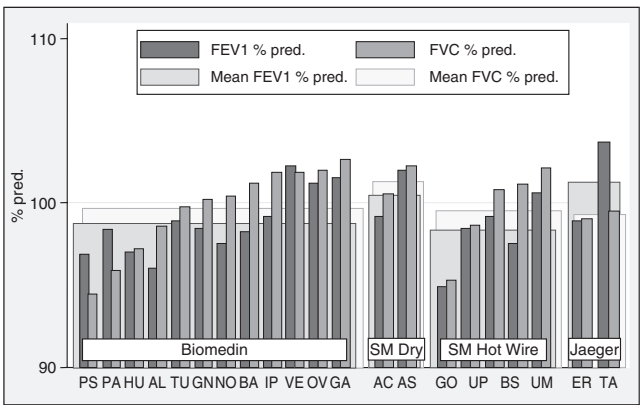

Figure 3 Lung function levels across ECHRS centres by type of spirometer used. Wide, bright bars in the background reflect mean lung function levels (percentage of predicted values) across centres using the same type of spirometer. Slim, dark bars in the foreground represent centre means of percentage of predicted lung function. Prediction equations used adjusted for sex, height and age. *Note:* See Figure 2

We conducted several sensitivity analyses based on spirometry related factors. However, limiting our analyses to centres that used Biomedin spirometers, adjustment for short-term respiratory symptoms, or inclusion of measurements not in compliance with

ATS criteria did not affect our findings. Moreover, results did not change using simpler, cross-sectional models, such as for example some similar to those used in the cross-sectional analyses of SAPALDIA[4] (see online supplement).

Subjects lost to follow-up might differ from those investigated, which may lead to biased centre mean lung function estimates. As shown in the online supplement, extensive investigations indicate loss to follow-up being an unlikely explanation for the null-findings.

Characterization of exposure

ECRHS conducted the first standardized trans-European $PM_{2.5}$ measurement campaign.[12] Other lung function studies, such as SAPALDIA[4] or the Southern California Children's Health Study[3] successfully used central monitors, similar to the method in ECRHS. The vast majority of studies which linked long term air pollution to health outcomes also used central monitors.[2]

This approach assumes that one monitor per city provides an unbiased estimate of the average community exposure to background pollution, in other words a pollution mix of low spatial variability not immediately affected by local sources. $PM_{2.5}$ varies relatively little in space, and even less does its sulfur content,[22] which was available from elemental analysis.[15] Using sulfur instead of $PM_{2.5}$ did not alter our results, nor did NO_2, light absorbance or any other available exposure metrics (see online supplement; Pearson correlation $PM_{2.5}$—sulfur: $r = 0.87$). We measured a range of other constituents of air pollution which are more likely to be influenced by nearby sources, such as NO_2,[16] reflectance (soot),[15] or oxidative properties of $PM_{2.5}$.[23] Using these exposure markers did not result in any significant associations with lung function (see Table 2 in the online supplement). $PM_{2.5}$ may have been overestimated where monitors were located close to roads (<15 m). The exclusion of these centres (Pavia, Turin, Verona, Antwerp City), however, did not affect our results.

$PM_{2.5}$ measures the mass concentration of a mixture of particles of various sizes and composition, including hundreds of chemical substances. Since the mass of particles only serves as a proxy for unknown causal agents, unmeasured variations in the latter across cities could be a source of bias towards null. As shown earlier, $PM_{2.5}$ constituents vary across ECRHS centres, and correlations between constituents across cities vary as well.[15,23]

Another limitation of our study is the lack of past pollution data. In several studies annual means of particulate matter varied little over several years.[4,5] Historic air pollution data for ECRHS cities were scarce and could not be used in quantitative analyses.[24] Exclusion of Erfurt, where dramatic declines in pollution occurred after the German reunification, did not alter our findings. Findings from SAPALDIA indicate that historic pollution trends may be crucial for pollution effects on lung function decline. In that study, baseline levels of exposure were highly correlated with the change in air quality during follow-up across eight Swiss communities.[25]

All the above mentioned factors may have introduced considerable random error in our exposure estimates and thereby contributed to the observed null-findings.

There are three more fundamental limitations associated with the use of central monitors. First, to observe significant exposure contrasts comparisons across vast geographic areas or between urban and rural communities are required, introducing heterogeneity in the studied populations and increasing potential for confounding. Second, the few pollutants measured at central monitors may not be the most health relevant ones. Third, spatial heterogeneity of the health relevant pollution fraction may be substantial and therefore poorly characterized by central monitors.

Since the planning of ECRHS in the early 1990s, several studies found associations between markers of within-community exposure contrasts and various respiratory health outcomes including mortality.[5,9,26–28] Most of these studies use proximity of subjects' homes to traffic or residential NO_2 measurements.[29,30] These exposure measures may reflect a different, more toxic type of pollution, in particular fresh tailpipe emissions such as ultra-fine particles. Concentrations of many of these (unmeasured) pollutants can be an order of magnitude higher along busy roads.[31] Living along street canyons or narrow but busy roads is common in European cities underscoring the need for local exposure characterization.

In ECRHS measurements of residential outdoor NO_2 were conducted over one or two 2-week periods for a sub-sample of participants ($N = 1634$) (Figure 4). Due to the lack of repeated measurements long-term estimates based on the measured levels were of limited precision, and no effect of residential NO_2 on lung function could be detected. However, these measurements clearly point out the large within-community contrasts for NO_2, which are likely to exceed between-community contrasts observed for $PM_{2.5}$. Figure 4 raises considerable doubts about the assumption inherent to the cross-community comparison, namely of ranking community means of subjects' true individual exposures adequately when assessing exposure at the community level. Substantial within-community contrasts in true individual exposures are detrimental to this type of analyses.

Confounding

ECRHS is well suited to adjust for potential confounders on the individual level, such as physiological characteristics, tobacco smoke and other exposures, socio-economic variables, and various measures of respiratory health. Height was by far the strongest

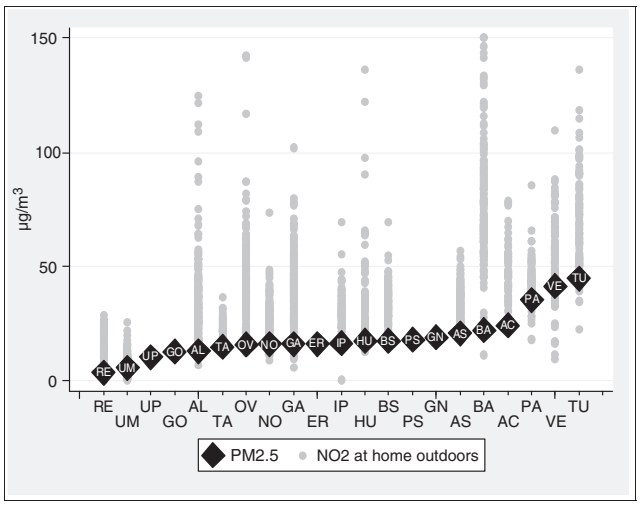

Figure 4 Distribution of $PM_{2.5}$ annual means across the 21 centres of ECRHS. The distribution of 2-week NO_2 at home outdoor measurements for a sub-sample of participants ($N = 1634$) is plotted as well (where available) to illustrate potential within city variability of NO_2 (Distribution of 2-week NO_2 measurements reflects spatial and temporal variability). *Note:* See Figure 1

predictor of lung function. Since air pollution was assessed on the centre level, the distribution of $PM_{2.5}$, lung function, and potential confounders across centres is of particular relevance.

Air pollution concentrations and lung function levels roughly follow a north-south gradient across Europe, with the highest pollution levels in northern Italy (Turin, Pavia, Verona) and Spain (Barcelona), and bigger lungs in northern Europe. This crude negative association is confounded by height, as can be seen from Table 3, because people in northern Europe are taller (Mean difference ~ 5 cm). The relatively high negative correlation between height and $PM_{2.5}$ across centres (Pearson $r = -0.46$, Table 1) poses a challenge to disentangle a potential, small effect of $PM_{2.5}$ from the strong effect of height on lung function levels. We conducted numerous additional analyses using various ways of adjustment for height, none of which yielded a significant association between $PM_{2.5}$ and lung function.[19]

Identifying and controlling for other factors that might act as confounders or effect modifiers on the centre level is challenging. Centre means of socioeconomic status (proportion of manual profession), level of education (age at the end of education) and exposure to environmental tobacco smoke showed correlations with $PM_{2.5}$ of similar magnitude as height, but the effects of their adjustment on $PM_{2.5}$ coefficients were small. Similarly, diet may have played a role as an uncontrolled community-level confounder; however, dietary data were not available for this analysis. Furthermore, unknown genetic factors which influence lung function or defense mechanisms could have acted as confounders or effect modifiers.

Stratification by numerous potentially confounding or modifying factors did not alter our findings (see online supplement Table 1). Since it is difficult to assess the degree of confounding that remains even after stratification, we conclude that comparisons across more homogeneous populations or within cities or communities would be clearly preferable to reduce the chance of confounding. This may explain the discrepancy between our results and those of SAPALDIA and SALIA.[4,5] The latter studies compared across far more homogenous populations than is the case for ECRHS.

Modeling approach

In our main models we assessed the effect of air pollution on lung function levels and linear decline in lung function simultaneously. To investigate the sensitivity of our results towards different modeling approaches we conducted multiple additional analyses, including separate cross-sectional models at baseline and follow-up, pooling men and women, log transformation, and non-linear parameters for age and height, among others (see online supplement). None of these models led to significant alterations of the null findings.

Conclusions

Urban background air pollution measured as city specific annual mean $PM_{2.5}$ levels was not significantly associated with lung function in this large longitudinal study across 21 European study centres.

We believe that these null findings provide important lessons relevant to the interpretation of this and other studies and the planning of future investigations of chronic effects of air pollution. The large geographical range of ECRHS, once seen as a major strength, came along with a significant diversity in exposure and health relevant characteristics across the studied populations.

The community-based exposure characterization led to considerable potential for exposure misclassification without capturing large contrasts of traffic-related pollution within European cities. Moreover, the heterogeneity of the studied populations and their living environments, and the correlation of air pollution, lung function and various potential confounders along a common north–south gradient within Europe decreased our ability to identify potential effects of air pollution on lung function. We conclude that these inherent limitations need to be resolved in future investigations to more conclusively distinguish between a true null effect and biases toward the null.

Recent developments of spatial analysis technologies (Geographic information systems, modeling capacities, etc.) offer promising tools to (retrospectively) derive

individual exposure estimates of spatially heterogeneous pollutants, such as traffic exhaust. Future analyses of ECRHS health data could therefore offer the unique opportunity to investigate long-term effects of traffic-related pollution, as well as the modifying role of local or regional factors across Europe, as done previously for acute air pollution effects.[32]

Supplementary Data

Supplementary data are available at *IJE* online.

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