Residential air pollution does not modify the positive association between physical activity and lung function in current smokers in the ECRHS study

Elaine Fuertes[a,b,c,d,*], Iana Markevych[e,f], Deborah Jarvis[d,g], Danielle Vienneau[h,i], Kees de Hoogh[h,i], Josep Maria Antó[a,b,c], Gayan Bowatte[j], Roberto Bono[k], Angelo G. Corsico[l,m], Margareta Emtner[n], Thorarinn Gislason[o], José Antonio Gullón[p], Joachim Heinrich[d,e], John Henderson[q], Mathias Holm[r], Ane Johannessen[s,t], Bénédicte Leynaert[u,v], Alessandro Marcon[w], Pierpaolo Marchetti[w], Jesús Martínez Moratalla[x,y,z], Silvia Pascual[aa], Nicole Probst-Hensch[h,ab], José Luis Sánchez-Ramos[ac], Valerie Siroux[ad], Johan Sommar[ae], Joost Weyler[af], Nino Kuenzli[h,i], Bénédicte Jacquemin[a,b,c,ag,ah], Judith Garcia-Aymerich[a,b,c]

[a] ISGlobal, Barcelona, Spain
[b] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
[d] Population Health and Occupational Diseases, National Heart and Lung Institute, Imperial College London, London, United Kingdom
[e] Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Germany
[f] Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany
[g] MRC-PHE Centre for Environment and Health, Imperial College London, London, United Kingdom
[h] Swiss Tropical and Public Health Institute, Basel, Switzerland
[i] University of Basel, Basel, Switzerland
[j] Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, Australia
[k] Department of Public Health and Pediatrics, University of Turin, Turin, Italy
[l] Division of Respiratory Diseases, IRCCS Policlinico San Matteo Foundation, Pavia, Italy
[m] Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy
[n] Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden
[o] Department of Respiratory Medicine and Sleep, Landspitali University Hospital Reykjavik, Reykjavik, Iceland
[p] Department of Pneumology, Hospital San Agustín, Avilés, Asturias, Spain
[q] Population Health Sciences, Britsol Medical School, University of Bristol, Bristol, United Kingdom
[r] Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
[s] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[t] Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway
[u] Inserm, UMR 1152, Pathophysiology and Epidemiology of Respiratory Diseases, Paris, France
[v] University Paris Diderot Paris, UMR 1152, Paris, France
[w] Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University of Verona, Verona, Italy
[x] Servicio de Neumología del Complejo Hospitalario Universitario de Albacete, (CHUA), Albacete, Spain
[y] Servicio de Salud de Castilla – La Mancha (SESCAM), Spain
[z] Facultad de Medicina de Albacete, Universidad de Castilla - La Mancha, Albacete, Spain
[aa] Respiratory Department, Galdakao Hospital, OSI Barrualde-Galdakao, Biscay, Spain
[ab] Department Public Health, University of Basel, Basel, Switzerland
[ac] Department of Nursing, University of Huelva, Huelva, Spain
[ad] Institute for Advanced Biosciences, UGA-Inserm U1209-CNRS UMR 5309, Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health, Grenoble, France
[ae] Occupational and Environmental Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[af] Epidemiology and Social Medicine, University of Antwerp, Antwerp, Belgium
[ag] VIMA: Aging and Chronic Diseases, Epidemiological and Public Health Approaches, U1168, Institut Médical de Santé et Recherche Médicale, Villejuif, France
[ah] Unité mixte de recherche (UMR)-S1168, Université Versailles St-Quentin-en-Yvelines, Versailles, France

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ABSTRACT

Background: Very few studies have examined whether a long-term beneficial effect of physical activity on lung function can be influenced by living in polluted urban areas.

Objective: We assessed whether annual average residential concentrations of nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameters < 2.5 μm ($PM_{2.5}$) and < 10 μm (PM_{10}) modify the effect of physical activity on lung function among never- (N = 2801) and current (N = 1719) smokers in the multi-center European Community Respiratory Health Survey.

Methods: Associations between repeated assessments (at 27–57 and 39–67 years) of being physically active (physical activity: ≥2 times and ≥1 h per week) and forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were evaluated using adjusted mixed linear regression models. Models were conducted separately for never- and current smokers and stratified by residential long-term NO_2, $PM_{2.5}$ mass and PM_{10} mass concentrations (≤75th percentile (low/medium) versus > 75th percentile (high)).

Results: Among current smokers, physical activity and lung function were positively associated regardless of air pollution levels. Among never-smokers, physical activity was associated with lung function in areas with low/medium NO_2, $PM_{2.5}$ mass and PM_{10} mass concentrations (e.g. mean difference in FVC between active and non-active subjects was 43.0 mL (13.6, 72.5), 49.5 mL (20.1, 78.8) and 49.7 mL (18.6, 80.7), respectively), but these associations were attenuated in high air pollution areas. Only the interaction term of physical activity and PM_{10} mass for FEV_1 among never-smokers was significant (p-value = 0.03).

Conclusions: Physical activity has beneficial effects on adult lung function in current smokers, irrespective of residential air pollution levels in Western Europe. Trends among never-smokers living in high air pollution areas are less clear.

1. Introduction

Regular physical activity is known to reduce the risk of numerous non-communicable diseases, such as coronary heart disease, type 2 diabetes and several types of cancer (Lee et al., 2012). Evidence for a beneficial role in maintaining respiratory health in both healthy and sick populations is also building (Brumpton et al., 2017; Cheng et al., 2003; Jakes et al., 2002; Pelkonen et al., 2003; Watz et al., 2014), with some studies reporting stronger effects among current smokers (Fuertes et al., 2018; Garcia-Aymerich et al., 2007). This latter observation may be partly attributable to the anti-inflammatory effects of regular physical activity on the inflammatory burden of smokers who are at high risk of lower lung function (Gan et al., 2005; Kasapis and Thompson, 2005).

In addition to smoking, exposure to air pollution is also pro-inflammatory. It is thus conceivable that an individual's exposure to air pollution may influence how physical activity affects respiratory health. Short-term semi-controlled studies and panel studies have yielded equivocal evidence as to whether an interaction exists between air pollution and physical activity with respect to lung function (Giles et al., 2012; Jarjour et al., 2013; Kubesch et al., 2015; Laeremans et al., 2018a; Matt et al., 2016; Strak et al., 2012; Weichenthal et al., 2011; Sinharay et al., 2017) and very few studies have examined long-term effects. One long-term study in California, USA, found that children participating in sports were more likely to develop asthma (after five years of follow-up) than those not participating in sports, but only if they lived in areas with high ozone levels (McConnell et al., 2002). Another long-term study of elderly urban residents found that home outdoor nitrogen dioxide (NO_2) concentrations did not modify the beneficial association of increased participation in sports, cycling and gardening with total, cardiovascular and diabetes mortality, although effect estimates between cycling and gardening with respiratory mortality were attenuated in high NO_2 settings (Andersen et al., 2015). Finally, a recent study reported that lung function improved with physical activity at low, but not high, black carbon levels among a sample of 115 healthy non- or ex-smoking adults (Laeremans et al., 2018b). Similar long-term studies related to other inflammatory-associated conditions, such as cardiovascular risk factors (Endes et al., 2017; Sinharay et al., 2017), are also beginning to emerge.

Understanding the interplay between air pollution, physical activity and lung function is important to inform policy efforts aimed at increasing physical activity in urban areas. Although studies are beginning to quantify the levels at which air pollution may negate the health benefits of physical activity (Tainio et al., 2016), there is currently limited evidence on which to base guidelines that either encourage physical activity in all settings or promote behavioral changes when air quality is low (as currently suggested by some agencies (Centers for Disease Control and Prevention, 2015)). Given the general paucity of long-term studies and the fact that the few that do exist on respiratory health have been conducted in specific population subgroups (children (for asthma) and the elderly (for respiratory mortality)) or are based on small sample sizes, additional population-based studies are warranted.

In a previous analysis of the prospective multi-center European Community Respiratory Health Survey (ECRHS), we reported that increased physical activity was associated with higher average forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) among current smokers (Fuertes et al., 2018). It is of interest to see whether concomitant exposure to high residential air pollution concentrations may affect this relationship. Under the framework of the Ageing Lungs in European Cohorts (ALEC) consortium (www.alecstudy.org), we investigated whether the positive association between physical activity and FEV_1 and FVC is modified by home outdoor concentrations of NO_2, particulate matter with aerodynamic diameters smaller than 2.5 μm ($PM_{2.5}$) and particulate matter with aerodynamic diameters smaller than 10 μm (PM_{10}).

2. Material and methods

2.1. Participants

Over 18,000 participants were originally recruited (ECRHS I) from 30 centers in 14 countries in 1991–1993 using population-based registers (representative population-based arm), with an additional sampling of asthmatics (symptomatic arm) (Janson et al., 2001). Two follow-ups have since taken place: ECRHS II in 1999–2003 (27–57 years) and ECRHS III in 2010–2014 (39–67 years). At the original recruitment and at both follow-ups, extensive lifestyle and health information was collected using questionnaires. The current analysis is restricted to data from both study arms obtained during the first (ECRHS II) and second (ECRHS III) follow-ups, during which both physical activity and spirometry data were collected (Burney et al., 1994; The European Community Respiratory Health Survey II Steering Committee, 2002).

From the 10,217 subjects (from 26 centers in 12 countries) who participated in the first follow-up (ECRHS II), 2931 were ex-smokers and were excluded from the analysis. Of those remaining, 5636 had information on FEV_1 or FVC and physical activity at either the first or second follow-up. At least one air pollutant could be assigned to the address at the first follow-up for 4520 of these participants (from 19 centers in nine countries: Belgium, France, Germany, Italy, Norway, Spain, Sweden, Switzerland and the United Kingdom). Of these, 2801 and 1719 were never- and current smokers at the first follow-up, respectively, and make up the study population (flow chart provided in Fig. S1). Ethical approval was obtained by all centers from the appropriate ethics committees and participants provided written consent.

2.2. Lung function

Lung function without bronchodilation was assessed according to American Thoracic Society recommendations at both follow-ups (Miller et al., 2005). FEV_1 and FVC in absolute values (mL), repeatable to 150 mL from at least two of a maximum of five correct manoeuvres, were the outcomes in this analysis. Lung function decline (difference in FEV_1 and FVC between the two follow-ups) was not considered as an outcome in the current analysis as we found no evidence that lung function decline was associated with physical activity in our previous analysis (Fuertes et al., 2018). Different spirometers were used across centers at the first follow-up (ECRHS II) whereas all centers except two used the same spirometer at the second follow-up (ECRHS III; Fuertes et al., 2018). During the lung function testing, body weight and height were measured by trained research staff.

2.3. Physical activity

Leisure-time vigorous physical activity data were collected using self-completed questionnaires by asking participants how often (frequency) and for how many hours per week (duration) they usually exercised so much that they got out of breath or sweaty (Rovio et al., 2005; Washburn et al., 1990; World Health Organization, 2017). Based on this information, individuals were identified as physically active if they exercised with a frequency of at least two times per week and for a duration of at least 1 h a week, and non-active otherwise, at both follow-ups. This "active" variable thus represents a combination of physical activity frequency and duration and has been shown to be associated with FEV_1 and FVC (Fuertes et al., 2018) as well as reduced bronchial hyperresponsiveness (Shaaban et al., 2007) in the ECRHS. Additional data on socio-demographic and health factors were collected by questionnaires and during measurements at clinical visits during both follow-ups.

2.4. Air pollution exposure

We estimated NO_2, $PM_{2.5}$ mass and PM_{10} mass concentrations using existing land-use regression (LUR) models for Western Europe that are based on satellite- and ground-based measurements (de Hoogh et al., 2016; Vienneau et al., 2013). Briefly, information from > 1500 AIR-BASE monitoring sites that cover background, industrial and traffic environments were combined with spatial information on land-use characteristics, population density, road lengths, altitude, distance to sea and satellite-based air pollution measurements to create a single LUR model per pollutant that was applied and mapped on a 100 m grid across Western Europe. For NO_2, we a priori chose the LUR model derived using ground-based monitoring data from 2005 (2005–2007 are available (Vienneau et al., 2013)) as this corresponds best to the timing of the ECRHS II follow-up. For $PM_{2.5}$ and PM_{10}, only one LUR model is available for each pollutant, based on monitoring data from 2010 for $PM_{2.5}$ mass (de Hoogh et al., 2016) and 2007 for PM_{10} mass (Vienneau et al., 2013). Using these LUR models, we assigned individual-level air pollution estimates to all participants' home addresses

at ECRHS II (the first follow-up). As Switzerland was not included in the first European LUR models (Vienneau et al., 2013), both NO_2 and $PM_{2.5}$ estimates for Basel were taken from the 2010 models (PM_{10} data are not available for this center) (de Hoogh et al., 2016).

As a confirmatory analysis, we created a second set of indicators of NO_2, $PM_{2.5}$ mass and PM_{10} mass exposure using different LUR models developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE; Beelen et al., 2013; Cyrys et al., 2012; Eeftens et al., 2012a, 2012b), and also assigned these to all participants' home addresses at ECRHS II (the first follow-up). In contrast to the Western Europe-LUR models described above, the ESCAPE LUR models were developed to reflect the spatial variation of air pollution among individuals living in participating ESCAPE geographical areas. Hence, the monitoring sites used to develop the ESCAPE LUR models (40 and 20 sites for NO_2 and particulate matter, respectively, per geographical area) had a high density in the study areas and were selected to capture within-city variability in air pollution concentrations. However, given that ESCAPE-based estimates are only available for 15 (NO_2) and seven ($PM_{2.5}$ mass and PM_{10} mass) of the participating 19 ECRHS centers included in this analysis (see Table S1), which corresponds to 62% of participants for NO_2 and 30% of participants for $PM_{2.5}$ mass and PM_{10} mass, there are used here only for replication purposes.

2.5. Statistical analysis

Repeated cross-sectional associations between physical activity (active versus non-active) and FEV_1 and FVC were estimated using multivariable mixed linear regression models with random intercepts for subjects nested within centers (lme4 package (Bates et al., 2014) in the statistical program R, version 3.3.2 (R Core Team, 2012)). Mixed models account for repeated measurements, and thus subjects contributing physical activity and lung function data at either one or both time points (ECRHS II and III) were included. As associations between physical activity and lung function were only found among current smokers in our previous analysis (Fuertes et al., 2018), and thus smoking status is an important effect modifier in this relationship, all associations are presented separately for never-smokers and current smokers based on participants' responses at the first follow-up (ECRHS II). Ex-smokers (at ECRHS II) were excluded as this group represents a mix of recent and long-term quitters whose smoking-related systemic inflammatory state is uncertain.

Models were adjusted for the same covariates as in our previous analysis (Fuertes et al., 2018), which were selected because they were associated with both lung function and physical activity: age, age^2, height, weight, secondhand smoke exposure (all entered as both values assessed at the two different follow-ups), as well as sex, age completed full time education (17 years; 17–20 years; > 20 years) and occupation (management/professional/non-manual; technical/professional/non-manual; other non-manual; skilled manual; semi-skilled/unskilled manual; other/unknown, classified according to the International Standard Classification of Occupations-88 code (Office, 1991); all entered as the value assessed at the first follow-up). Models for current smokers were also adjusted for lifetime pack-years smoked (entered as both values assessed at the two different follow-ups). Numeric variables were mean centered over the data from both follow-ups (Schielzeth, 2010).

In the main analysis, all models were stratified by whether a participant's residence was in an area with low/medium (≤ 75 percentile of entire sample) versus high (> 75 percentile of entire sample) NO_2 concentrations, as has been done in a previous study (Andersen et al., 2015). The same approach was followed for $PM_{2.5}$ mass and PM_{10} mass. Models including an interaction term between physical activity and each air pollutant (as binary variables (≤ or > 75th percentile)) were also examined.

To test the sensitivity of our results to the air pollution categorization approach, we ran secondary analyses in which we re-defined the

low/medium versus high air pollution exposure areas using the 1) 90th percentile of the entire sample, 2) 75th percentile by geographical area (i.e. within study center, n = 19), and 3) 75th percentile of the entire sample based on the ESCAPE-based air pollution estimates.

The following additional sensitivity analyses were also run: 1) excluding participants who changed their place of residence between follow-ups, 2) excluding participants who changed their smoking status between follow-ups, 3) excluding groups with respiratory symptoms or disorders (chronic obstructive pulmonary disease (COPD, defined as FEV_1/FVC < Lower Limit of Normal predicted using the Global Lung Initative equations (Quanjer et al., 2012)), asthma and the symptomatic ECRHS study arm), and finally, 4) including the air pollutants as continuous variables instead of binary variables in the interaction term.

3. Results

3.1. Study population

Of the available study sample (2801 and 1719 never and current smokers, respectively), 1429 never-smokers and 799 current smokers contributed lung function and physical activity measurements at both time points. Compared to the never- and current smokers from centers in which air pollution exposure assessment was conducted (N = 5769), participants ultimately included in the analysis were more likely to be male and less likely to be exposed to secondhand tobacco smoke at the first follow-up.

The characteristics of the study population, comparing never- and current smokers, are presented in Table 1. The distributions of the air pollutants derived using the Western Europe-LUR model are presented per area in Fig. 1. Air pollution concentrations tended to be higher in more southern countries and lower in more northern countries as previously observed in other European studies (Cyrys et al., 2012; Eeftens et al., 2012b). Mean FEV_1 was lower among those living in areas of high, compared to low, NO_2 and PM_{10} mass concentrations for never-smokers only. Mean FVC was lower in areas of high, compared to low/

medium, NO_2 and PM_{10} mass concentrations among both never- and current smokers (Table S2). The percentage of physically active participants was higher among never-smokers compared to current smokers in nearly all cases, and among participants living in areas of low/medium air pollution concentrations compared to those living in areas of high air pollution concentrations (Table 2).

3.2. Effect modifying role of air pollution and smoking

Associations of physical activity with lung function in areas of low/medium and high air pollution concentrations are shown stratified by smoking status in Fig. 2. Among current smokers, being physically active was associated with higher average FEV_1 and FVC regardless of residential air pollution levels, with slightly larger effect estimates observed in areas with high NO_2 and $PM_{2.5}$ mass concentrations (Fig. 2). No interaction terms were significant (all p-values > 0.10).

Among never-smokers, physical activity was associated with higher average FVC among participants living in areas with low/medium (≤75th percentile) NO_2, $PM_{2.5}$ mass and PM_{10} mass concentrations, and higher average FEV_1 for those living in areas with low/medium PM_{10} mass. No clear beneficial effect of physical activity on FVC or FEV_1 was apparent in settings where any of these pollutants were high (> 75 percentile of concentrations). The interaction term of physical activity and PM_{10} mass was significant for FEV_1 (p-value = 0.031) and suggestive for FVC (p-value = 0.085). All other interaction terms had p-values > 0.10.

When using the 90th percentile (instead of the 75th percentile) to define areas of low/medium versus high air pollution, differences in the direction and size of the effect estimates of physical activity on lung function were more apparent, especially among never-smokers (Table 3). Being physically active in very high air pollution settings (> 90th percentile) appeared to be (non-significantly) negatively associated with FEV_1 and especially FVC among never-smokers. In contrast, among current smokers, the size of the positive effect of physical activity on lung function (especially FVC) appeared greater among

Table 1
Characteristics (n/N (%) or mean ± SD) of the study population, stratified by smoking status at the first follow-up.

		Never-smokers	Current smokers	p-Value[a]
Male sex		1238/2801 (44.2)	892/1719 (51.9)	< 0.001
Age in years (mean ± SD)		42.1 ± 7.2	42.1 ± 7.0	0.704
Height in cm (mean ± SD)		169.5 ± 10.1	169.5 ± 9.3	0.857
Weight in kg (mean ± SD)		73.2 ± 15.0	73.4 ± 15.2	0.631
BMI	Continuous, in kg/m² (mean ± SD)	25.4 ± 4.5	25.5 ± 4.5	0.657
	< 25 kg/m²	1414/2643 (53.5)	832/1630 (51.0)	0.275
	25–30 kg/m²	884/2643 (33.4)	580/1630 (35.6)	
	> 30 kg/m²	345/2643 (13.1)	218/1630 (13.4)	
Secondhand smoke exposure at home/work		691/2776 (24.9)	1173/1719 (68.2)	< 0.001
Age completed full time education	< 17 years	562/2773 (20.3)	493/1705 (28.9)	< 0.001
	17–20 years	904/2773 (32.6)	588/1705 (34.5)	
	> 20 years	1307/2773 (47.1)	624/1705 (36.6)	
Occupation	Management/professional/non-manual	814/2801 (29.1)	388/1719 (22.6)	< 0.001
	Technical/professional/non-manual	503/2801 (18.0)	262/1719 (15.2)	
	Other non-manual	730/2801 (26.1)	476/1719 (27.7)	
	Skilled manual	236/2801 (8.4)	225/1719 (13.1)	
	Semi-skilled/unskilled manual	255/2801 (9.1)	239/1719 (13.9)	
	Other/unknown	263/2801 (9.4)	129/1719 (7.5)	
Ever asthma		526/2798 (18.8)	240/1715 (14.0)	< 0.001
COPD[b]		137/2543 (5.4)	144/1588 (9.1)	< 0.001
Symptomatic study arm of ECRHS cohort		462/2801 (16.5)	310/1719 (18.0)	0.196
Lung function	FEV_1 in mL at ECRHS II (mean ± SD)	3500 ± 834	3422 ± 775	0.002
	FEV_1 in mL at ECRHS III (mean ± SD)	3066 ± 785	2929 ± 724	< 0.001
	FVC in mL at ECRHS II (mean ± SD)	4350 ± 1037	4330 ± 950	0.523
	FVC in mL at ECRHS III (mean ± SD)	3993 ± 995	3920 ± 912	0.064

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ECRHS = European Community Respiratory Health Survey; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; SD = standard deviation.

[a] Comparisons between never-smokers and current smokers were done using the Student's *t*-test for continuous variables and the chi-square test for categorical variables.

[b] Defined as pre-bronchodilator FEV1/FVC < Lower Limit of Normal predicted using the Global Lung Initiative (Quanjer et al., 2012).

NO$_2$
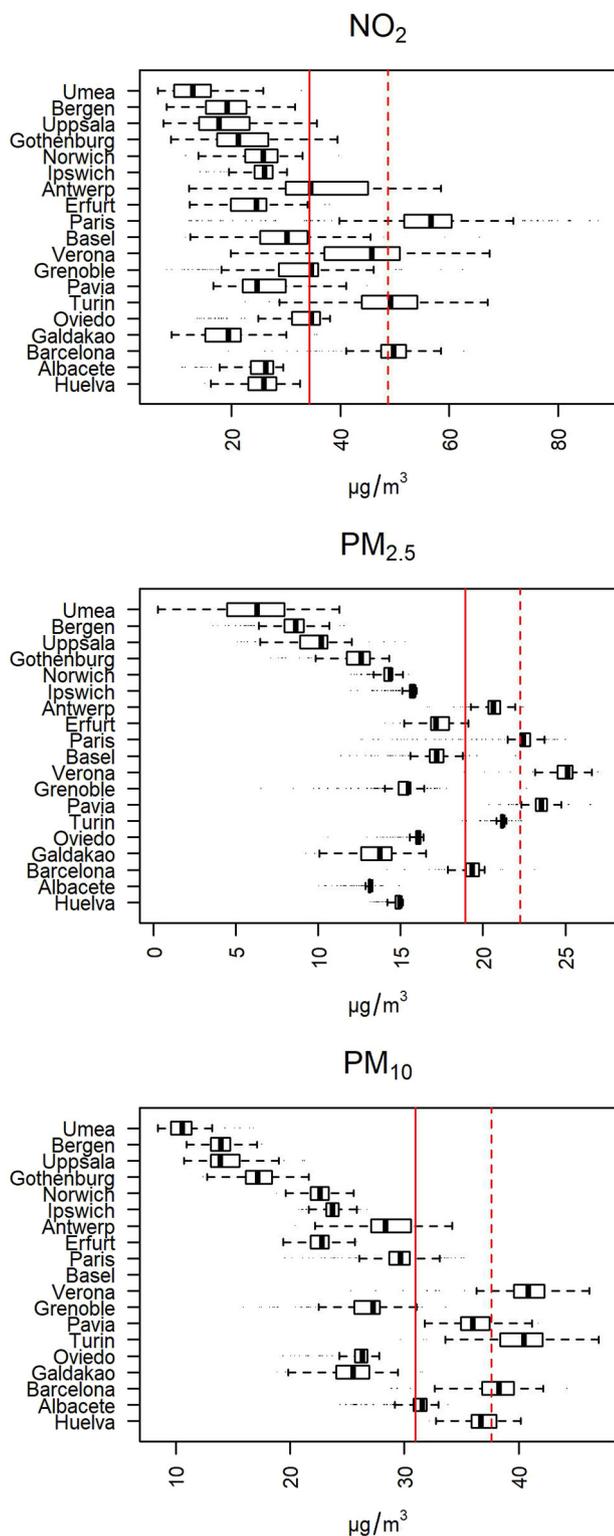

PM$_{2.5}$

PM$_{10}$

Fig. 1. Distribution of NO$_2$, PM$_{2.5}$ mass and PM$_{10}$ mass concentrations per geographical area, ranked north (top) to south (bottom). For each area, the median value is indicated by the black line and the box summarizes the 25th to 75th percentiles. The solid vertical bar represents the overall 75th percentile while the dashed vertical bar represents the overall 90th percentile.

those living in very high air pollution settings (> 90th percentile), but differences between air pollution groups were not significant.

When using the 75th percentile of the air pollutants in each geographical area (instead of the whole sample) to dichotomize the study areas, no consistent evidence of effect modification by air pollution

Table 2
Number and percentage (n/N (%)) of physically active participants at each follow-up, per smoking status and air pollution concentration level at ECRHS II.

		Never-smokers		Current smokers	
		Active at ECRHS II	Active at ECRHS III	Active at ECRHS II	Active at ECRHS III
NO$_2$	≤75th percentile	896/2107 (42.5)	629/1359 (46.3)	375/1243 (30.2)	253/733 (34.5)
	> 75th percentile	215/656 (32.8)	129/437 (29.5)	127/459 (27.7)	66/269 (24.5)
	p-Value[a]	< 0.001	< 0.001	< 0.001	0.003
PM$_{2.5}$ mass	≤75th percentile	868/2094 (41.5)	645/1409 (45.8)	362/1260 (28.7)	273/784 (34.8)
	> 75th percentile	243/669 (36.3)	113/387 (29.2)	140/442 (31.7)	46/218 (21.1)
	p-Value[a]	0.021	< 0.001	< 0.001	< 0.001
PM$_{10}$ mass	≤75th percentile	839/2001 (41.9)	588/1330 (44.2)	359/1179 (30.4)	245/728 (33.7)
	> 75th percentile	169/533 (31.7)	103/309 (33.3)	143/521 (27.4)	74/272 (27.2)
	p-Value[a]	< 0.001	< 0.001	0.002	0.061

ECRHS = European Community Respiratory Health Survey; NO$_2$ = nitrogen dioxide; PM$_{2.5}$ = particulate matter with aerodynamic diameters smaller than 2.5 μm; PM$_{10}$ = particulate matter with aerodynamic diameters smaller than 10 μm.

[a] Comparison between low and high air pollution areas.

concentrations was observed (Table 4). Re-defining the air pollution categories using the ESCAPE-LUR data (see Table S3), as well as excluding movers (see Table S4), those who changed their smoking status (see Table S5), those with COPD, those reporting asthma and the ECRHS symptomatic study arm in separate analyses (latter results not shown) did not largely change the direction of the effect estimates or main conclusions of the study, although the effect estimates tended to be attenuated in several cases. Finally, including the air pollutants as continuous variables rather than as binary variables in the interaction term did not yield different results, with suggestive/significant interactions observed among never-smokers and no interactions observed among current smokers (see Table S6).

4. Discussion

In this multi-center European analysis, a positive association between physical activity and better lung function was observed among current smokers, irrespective of residential air pollution levels. However, associations between physical activity and better lung function appeared attenuated among never-smokers living in areas with high residential air pollution levels, particularly for FVC.

4.1. Interpretation

Engaging in physical activity, especially of the more vigorous kind as assessed in this study, may lead to increased minute ventilation, alterations in breathing (from predominantly nasal to predominantly oral breathing, deeper inhalation) and impairments of nasal defenses, all of which may increase an individual's air pollution dose (Giles and Koehle, 2014). This increase in pollutant exposure could partly counteract the overall benefits of physical activity on respiratory health, as has been suggested by short-term studies (e.g. Matt et al., 2016; Sinharay et al., 2017). This mechanism is supported by the results observed among never-smokers in the current study, among whom positive associations between physical activity and FEV$_1$ and FVC were observed only in areas of low/medium air pollution concentrations. The apparent attenuation of associations in high air pollution settings could be one reason why we did not find consistent associations between physical activity and lung function among never-smokers in our
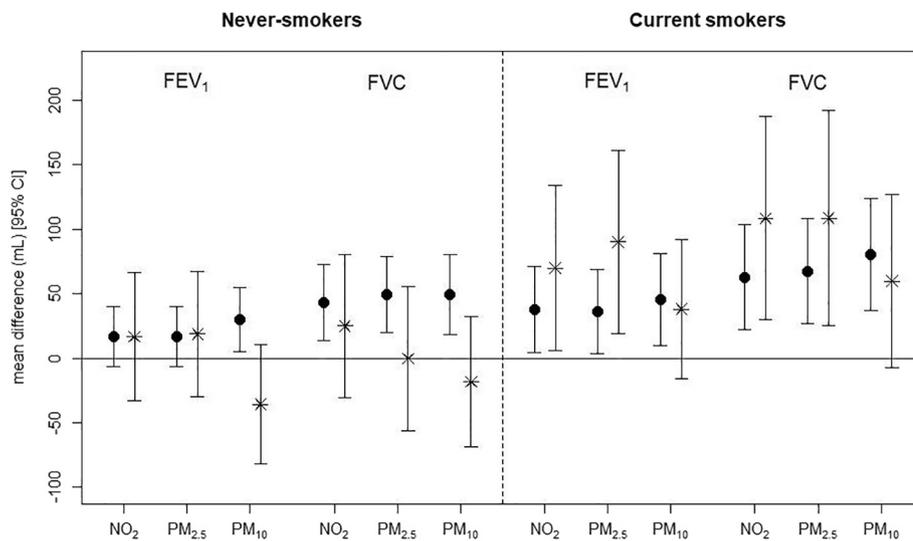
Fig. 2. Adjusted difference in mean FEV_1 and FVC, comparing physically active to non-physically active individuals, living in low/medium (filled circles) versus high (stars) air pollution areas (based on overall 75th percentile), stratified by smoking status. Positive values represent higher lung function in the active group. Models are adjusted for sex, age, age^2, height, weight, secondhand smoke exposure, age completed full time education and occupation. Models for current smokers are additionally adjusted for lifetime pack-years smoked.

previous analysis in which air pollution was not considered as a potential confounder/effect modifier (Fuertes et al., 2018).

In contrast, physical activity was positively associated with FEV_1 and FVC irrespective of air pollution levels among current smokers. This is a potentially important public health finding, as it suggests that regular physical activity should be encouraged among current smokers regardless of air pollution levels in their surroundings. Current smokers may benefit the most from the anti-inflammatory effects of regular physical activity, possibly because of their high systemic inflammatory burdens (Fuertes et al., 2018; Garcia-Aymerich et al., 2007), which could cancel out any negative effects of air pollution. It is difficult to support this hypothesis with comparisons from past studies as most examined short-term effects of air pollution and excluded smokers a priori.

The only existing adult longitudinal cohort study that considered an effect modifying role of long-term residential air pollution on the relationship between physical activity and respiratory health reported that the beneficial associations between cycling and gardening with respiratory mortality among elderly urban residents tended to be

attenuated in high NO_2 settings (no differences were found for total, cardiovascular and diabetes mortality) (Andersen et al., 2015). Although these associations were extensively adjusted for personal smoking behavior, effect modification by smoking was not examined. A second recent study reported that the beneficial effects of physical activity on lung function were reduced with high black carbon exposure, estimated as the average of three week-long personal monitoring campaigns (Laeremans et al., 2018b). As this published study was restricted to 115 healthy, active, non-smokers, it is difficult to compare its results with those of the current study, as our results appear to suggest that different effects may predominate depending on an individual's systemic inflammatory burden. Additional long-term studies that incorporate biological markers and consider subgroups with various systemic inflammatory states are required to clarify these findings.

It should be noted that the study results were less consistent when the air pollution categories were defined according to the 75th percentile of each geographical area rather than of the entire sample. The geographical area-specific categorization has the advantage of comparing individuals from the same centers that live in different air

Table 3
Adjusted difference in mean FEV_1 and FVC, comparing physically active to non-physically active individuals, living in low/medium versus high air pollution areas (based on overall 90th percentile), stratified by smoking.[a]

		Never-smokers						Current smokers					
		FEV_1			FVC			FEV_1			FVC		
		N	Mean difference (mL) (95% CI)	p-Value[b]	N	Mean difference (mL) (95% CI)	p-Value[b]	N	Mean difference (mL) (95% CI)	p-Value[b]	N	Mean difference (mL) (95% CI)	p-Value[b]
NO_2	≤90th percentile	2506	21.6 (−0.2, 43.4)	0.160	2487	47.3 (20.3, 74.2)	0.027	1496	43.1 (12.2, 74.0)	0.747	1488	67.3 (30.1, 104.5)	0.388
	>90th percentile	251	−23.4 (−103.8, 57.1)		250	−54.5 (−149.5, 40.5)		198	88.9 (−17.7, 195.5)		197	157.8 (12.4, 303.3)	
$PM_{2.5}$ mass	≤90th percentile	2493	22.2 (0.4, 44.0)	0.140	2474	45.8 (18.8, 72.8)	0.027	1508	38.9 (7.9, 69.8)	0.303	1500	65.8 (28.4, 103.3)	0.202
	>90th percentile	264	−35.5 (−113.8, 42.8)		263	−40.0 (−129.8, 49.8)		186	114.7 (6.2, 223.2)		185	177.3 (35.0, 319.7)	
PM_{10} mass	≤90th percentile	2289	22.9 (−0.2, 46.0)	0.053	2280	45.4 (16.9, 73.9)	0.041	1502	40.1 (9.0, 71.2)	0.433	1495	65.9 (28.1, 103.7)	0.272
	>90th percentile	233	−34.9 (−104.9, 35.1)		230	−47.5 (−124.1, 29.0)		190	125.4 (31.8, 219.0)		188	138.1 (9.4, 266.8)	

CI = confidence interval; FEV = forced expiratory volume in 1 s; FVC = forced vital capacity; N = number of participants; NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter with aerodynamic diameters smaller than 2.5 μm; PM_{10} = particulate matter with aerodynamic diameters smaller than 10 μm.

[a] Association estimates represent the mean difference in lung function between active and non-active subjects (with positive values representing higher lung function in the active group), adjusted for sex, age, age^2, height, weight, secondhand smoke exposure, age completed full time education and occupation. Models for current smokers are additionally adjusted for lifetime pack-years smoked.

[b] For interaction term of physical activity and air pollutant (≤ versus > 90th percentile).

Table 4
Adjusted difference in mean FEV_1 and FVC, comparing physically active to non-physically active individuals, living in low/medium versus high air pollution areas (based on area-specific 75th percentile), stratified by smoking.[a]

		Never-smokers						Current smokers					
		FEV_1			FVC			FEV_1			FVC		
		N	Mean difference (mL) (95% CI)	p-Value[b]	N	Mean difference (mL) (95% CI)	p-Value[b]	N	Mean difference (mL) (95% CI)	p-Value[b]	N	Mean difference (mL) (95% CI)	p-Value[b]
NO_2	≤75th percentile	2094	31.5 (7.7, 55.2)	0.022	2076	51.4 (21.1, 81.8)	0.184	1247	53.4 (20.1, 86.7)	0.366	1242	77.5 (36.2, 118.7)	0.687
	> 75th percentile	663	−33.6 (−78.9, 11.6)		661	−9.3 (−59.2, 40.6)		447	9.9 (−55.8, 75.6)		443	57.7 (−19.9, 135.2)	
$PM_{2.5}$ mass	≤75th percentile	2068	14.2 (−10.1, 38.5)	0.664	2055	33.7 (3.3, 64.0)	0.489	1270	51.0 (17.2, 84.9)	0.405	1263	79.8 (38.7, 120.9)	0.840
	> 75th percentile	689	20.8 (−22.2, 63.8)		682	45.4 (−5.1, 95.9)		424	6.5 (−55.7, 68.7)		422	36.3 (−42.3, 114.9)	
PM_{10} mass	≤75th percentile	1928	24.5 (−0.3, 49.3)	0.087	1916	38.1 (6.8, 69.4)	0.582	1237	41.4 (6.7, 76.2)	0.878	1230	69.4 (27.7, 111.2)	0.837
	> 75th percentile	594	−8.3 (−56.6, 39.9)		594	24.8 (−27.2, 76.8)		455	46.2 (−11.5, 103.9)		453	77.3 (4.7, 149.8)	

CI = confidence interval; FEV = forced expiratory volume in 1 s; FVC = forced vital capacity; N = number of participants; NO2 = nitrogen dioxide; PM2.5 = particulate matter with aerodynamic diameters smaller than 2.5 μm; PM10 = particulate matter with aerodynamic diameters smaller than 10 μm.

[a] Association estimates represent the mean difference in lung function between active and non-active subjects (with positive values representing higher lung function in the active group), adjusted for sex, age, age^2, height, weight, secondhand smoke exposure, age completed full time education and occupation. Models for current smokers are additionally adjusted for lifetime pack-years smoked.

[b] For interaction term of physical activity and air pollutant (≤ versus > 75th percentile).

pollution settings, which makes confounding by city/area-level factors less likely. However, using this approach leads to different cut-offs being used to define a high air pollution setting (ranging from 16.2 μg to 60.4 μg for Umeå and Paris, respectively), which may explain why the results were less consistent.

4.2. Strengths and limitations

This study is the first to examine whether associations between repeated measurements of physical activity and lung function differ according to long-term residential air pollution concentrations. Its strengths include the repeated clinical visits, the high quality FEV_1 and FVC measurements (collected approximately ten years apart) and the large number of participating individuals and (mainly urban) centers.

The assignment of two sets of residential air pollution exposures using harmonized and validated LUR models is a further strength. The general consistency of the results obtained when the low/medium versus high air pollution areas were defined using exposures estimated by a single LUR developed for all of Western Europe (the primary models, Fig. 2) compared to when using area-specific ESCAPE LUR models (Table S3) is somewhat remarkable considering the differences in the two models and the number of participants with available data. The Western Europe LUR model covers a much larger area and estimates exposures at a 100×100 m grid level resolution using an extensive routine monitoring network. In contrast, the ESCAPE LUR models have a higher resolution because of their purposely designed measurement campaign which aimed more specifically at capturing within-area contrasts.

Study limitations include the fact that we used an annual average of air pollution concentrations estimated to the home address as a surrogate for personal exposure. We thus did not consider exposures that occurred away from the home, during commutes or indoors, which may have biased our results. We also had no information as to where participants were physically active. If those living in areas of high air pollution were more likely to seek out low air pollution areas in which to be physically active, we would expect to see similar patterns between never-smokers and current smokers. This was however not the case, as some associations between physical activity and lung function tended to be attenuated among only never-smokers living in high air pollution

areas. The differences in pattern between these two subgroups suggest a different predominant biological mechanism or a lifestyle factor that has not been controlled for.

We were unable to consider the composition of $PM_{2.5}$ or PM_{10}, which can vary significantly over geographical areas (Götschi et al., 2005) and may be as or more important for health than PM concentrations (Traversi et al., 2009). It is also possible that our findings cannot be extrapolated to areas in which air pollution concentrations can be substantially higher. A recent effort at quantifying this issue concluded that the benefits of active travel outweighed the harm caused by air pollution on all-cause mortality in all but the most extreme air pollution concentrations (Tainio et al., 2016). Finally, air pollution data measured in 2005 (NO_2), 2007 (PM_{10} mass) and 2010 ($PM_{2.5}$ mass) for the Western Europe LUR models and between 2008 and 2010 for the ESCAPE LUR models were used to develop the LUR regression models that were applied to home addresses in 1999–2003, under the implicit assumption that the spatial variability in the air pollutants would not have changed over this time period. Studies conducted in Europe and Canada have demonstrated that LUR models for NO_2 are temporally stable over 7–12 years (Cesaroni et al., 2012; Eeftens et al., 2011; Wang et al., 2013), which supports this assumption.

We have previously shown that smoking status is a strong effect modifier of the association between physical activity and lung function (Fuertes et al., 2018; Garcia-Aymerich et al., 2007), and we thus a priori conducted all analyses separately for never- and current smokers. This led to numerous statistical tests, which we chose not to adjust for multiple testing as this analysis tested an a priori hypothesis (Perneger, 1998). Correcting for multiple testing may also lead to conservative results if exposures are highly correlated (Bland and Altman, 1995), as is the case in this study. Although we were able to control for many potential confounders, residual confounding can never be completely excluded. Notably, we did not have information on short-term air pollution exposures at the time of spirometry for many areas. We adjusted all models for weight but chose a priori not to explore BMI as a potential effect modifier as we found no evidence to suggest this was necessary in our previous analysis on physical activity and lung function in the ECRHS cohort (Fuertes et al., 2018). Nonetheless, we cannot exclude the possibility that BMI may be important, given that obesity is associated with chronic low-grade inflammation and also has a

probable link to physical activity, air pollution and lung function (e.g. Schikowski et al., 2013). Furthermore, our results may be subject to selection bias as participants included in this analysis (N = 4520) were more likely to be male and less likely to be exposed to secondhand tobacco smoke at the first follow-up compared to all current and never smokers from centers in which air pollution exposure assessment was conducted (N = 5769).

Finally, it is important to note that our (questionnaire-based) assessment of physical activity captured only vigorous physical activity that occurred during leisure time. We had no information on occupation-related or less vigorous types of physical activity which do not lead to breathlessness or sweating (e.g. brisk walking, gardening, light bicycling). As the relative importance of different modes, frequencies, duration and intensities of physical activity on the various anti-inflammatory mechanisms is presently unknown (Gleeson et al., 2011), we cannot assess the appropriateness of our available physical activity measure in this regard or how our results might be affected.

4.3. Public health relevance and conclusions

Understanding how the environment may affect the influence of physical activity on respiratory health is of large public health importance given that many people (72% of the population of the European Union (European Environment Agency, 2017)) live in urban areas, and some of these areas continue to experience levels that exceed World Health Organization recommendations (World Health Organization Regional Office for Europe, 2006). Furthermore, many forms of physical activity occur outdoors (cycling, walking, running) and active transport is promoted as a method of reducing traffic-related air pollution levels in urban settings as well as physical inactivity (de Nazelle et al., 2011; Rojas-Rueda et al., 2016).

Overall, our study shows that physical activity is positively associated with better lung function in current smokers, largely irrespective of residential air pollution levels in Western Europe. Our results thus reinforce the public health message that physical activity is beneficial for health, including respiratory health. However, our data do suggest that there may be some attenuation of this effect among never-smokers living in high air pollution settings. If true, policies aimed at controlling air pollution levels would ensure maximal benefit from physical activity promotion policies.

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Conflict of interest

During the conduct of the study, Dr. Demoly reports consulting fees from ALK, Stallergenes Greer, Circassia, Chiesi, ThermofisherScientific and Menarini; Dr. Corsico reports grants from Chiesi Farmaceutici and from GlaxoSmithKline Italy; Professor Jarvis reports grants from the MRC, European Commission and Asthma UK; and Professor Henderson reports grants from the MRC, Wellcome and the European Commission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.07.032.

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