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PULMONARY DISEASES

Air pollution in relation to manifestations of chronic pulmonary disease: A nested case–control study in Athens, Greece

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Abstract. Chronic pulmonary diseases are a major cause of morbidity and mortality worldwide. The present study is a case–control study nested in a defined cohort, undertaken in Athens, Greece, in order to investigate the association between long-term exposure to ambient air pollution and the development of chronic bronchitis, emphysema or chronic obstructive pulmonary disease (COPD). Individualized personal exposure assessment has been applied based on long-term residential and occupational subject history linked with geographical air pollution distribution. The first consecutive 3904 participants from the European Prospective Study into Cancer and Nutrition (EPIC), all residents of Athens, were asked to complete a questionnaire. One hundred and sixty-eight participants reporting a history of COPD symptomatology and 168 healthy controls recruited from the same study base individually matched for age and gender, were visited by a physician at their homes for conducting spirometry and a medical interview. Eighty-four of the 168 self-identified as cases were diagnosed as having chronic bronchitis, emphysema or COPD. Logistic regression models were used for statistical evaluation. Cases were more exposed to air pollution compared to controls. The estimated odds ratio (OR) indicates an increase of 37% in the risk of medically confirmed cases per exposure quartile ($p = 0.02$). When most of the subjects exposed are considered vs. all others, there is a twofold increase in disease risk ($p = 0.03$). Our findings provide evidence that long-term exposure to air pollution is an important factor in the development of chronic respiratory diseases.

Key words: Air pollution, Chronic bronchitis, Chronic health effects, Chronic obstructive pulmonary disease (COPD), Emphysema, Nested case–control study

Abbreviations: BS = black smoke; COPD = chronic obstructive pulmonary disease; EPIC = European Prospective Study into Cancer and Nutrition; OR = odds ratio; SES = socioeconomic status

Introduction

Chronic bronchitis and emphysema are major causes of respiratory morbidity often leading to chronic obstructive pulmonary disease (COPD) which is characterized by the presence of airflow obstruction. COPD is a major cause of morbidity and mortality worldwide [1]. Occurrence and mortality rates vary widely between countries and are increasing. In the United States [2] and the European Union, COPD is one of the five leading causes of death [3].

Cigarette smoking is the main known cause of chronic respiratory diseases and the exposure–response relationship between cigarette smoking and pulmonary function is well-established [4]. Because a small fraction of variation in pulmonary function can be explained by smoking, other factors, genetic or environmental, have been implicated in the pathogenesis of COPD [5, 6]. Although several studies have reported short-term associations between air pollution and daily admissions or emergency visits to hospitals for chronic bronchitis, emphysema or COPD exacerbation, the role of ambient air pollution exposure in the etiology of either chronic bronchitis, emphysema and COPD remains controversial [7–12].

Athens faces a serious air pollution problem, which has existed for about 30 years. Monitoring of pollutants, such as sulfur dioxide (SO_2) and black smoke (BS), started in the mid-seventies when 24-hour levels of BS and SO_2 often exceeded 500 $\mu g/m^3$ [13]. Between 1975 and 1982, a gradual reduction in the levels of SO_2 and to a lesser extent of BS occurred as a result of several measures implemented to improve the quality of heating and car fuel [14]. However, since 1982, pollution levels have stabilized, with an apparent change in pollutant profile towards a more pronounced photochemical component [15]. Several previous studies have shown effects of air pollution on the mortality [16] and morbidity [12, 17] from respiratory causes in the Greater Athens area.

The aim of the present study was to investigate the association between long-term exposure to ambient air pollution and chronic bronchitis, emphysema or COPD.

Participants and methods

Study subjects

In the early 1990s, the European Prospective Study into Cancer and Nutrition (EPIC) was initiated in seven European countries: France, Germany, Greece, Italy, Spain, The Netherlands and UK, with the major objective to collect data on diet, other lifestyle and environmental factors, anthropometry as well as biological samples in a cohort of about 400,000 healthy European adults [18]. In Greece, about 25,000 adults have already been enrolled in the project with an approximately equal proportion of men and women. These subjects will be followed up to investigate the incidence of and mortality from cancer and other diseases in relation to several individual characteristics, environmental exposures and biochemical markers.

The present study is nested in the EPIC cohort. The study base consists of all participants who were recruited in the EPIC project until 1996 and were residents of Greater Athens (n = 3904). The subjects were asked to complete a questionnaire 2 years after their enrollment. Two thousand and seventy (53%) responses were obtained. Out of these, 168 participants who reported a history of COPD, chronic bronchitis, emphysema or respiratory symptoms such as breathlessness, chronic cough and chronic phlegm production for at least 3 months per year for at least 2 years were included in the study as cases (case-series1). Subjects with a history of heart disease, asthma or episodic wheezing in childhood and adulthood or other respiratory diseases (bronchiectasis, tuberculosis, etc.) were excluded from the study. One hundred and sixty-eight controls without a history of respiratory disease and without any symptoms, individually matched for age and gender, were recruited from the same study base. All 336 participants were visited by a thoracic disease specialist (J.D.) at their homes for conducting spirometry and simultaneously completed an additional questionnaire by an interview. After conducting spirometry, case-series2 was defined as the subset of case-series1 that fulfilled the criteria for clinical diagnosis of chronic bronchitis, emphysema or COPD i.e. reporting of chronic cough and chronic phlegm production for at least 3 months per year for at least 2 years and/or doctor diagnosed chronic bronchitis or emphysema or COPD and/or FEV1/VC < 88 percent of that predicted for men and <89% of that predicted for women [3]. Case-series2 consisted of 84 cases exactly 50% of case-series1.

Detailed questionnaire

A detailed questionnaire that consisted of questions about respiratory symptoms such as cough, phlegm, shortness of breath, wheezing, chest tightness, medication use, residence, occupational history, smoking status and any other health problems was filled out by the thoracic disease specialist who visited the 336 participants at their homes. The physician interviewer was ignorant about the exposure and disease status of the subject, and he conducted the interview before performing spirometry.

Pulmonary function tests

Spirometry was performed using an autospiro AS-300 (mass flowmeter; Minato Medical Science Co., Osaka, Japan). According to the manufacturers, this spirometer has the same configuration and function as a RICO AS-500 that meets ATS standards [19]. The maneuvers were performed in a standardized manner with the subjects seated and wearing a noseclip. Subjects were instructed to abstain from inhaled bronchodilator use for 4 hours before testing. We used the best FEV_1 value out of three acceptable measures and the FEV_1/VC value from the best-test effort. Pulmonary function results are expressed as the percent of the predicted values. The predicted spirometric values are from the European Coal and Steel Community [20].

Air pollution exposure

Long-term retrospective personal exposure of each subject to air pollution was assessed on the basis of detailed information about their lifelong residential and employment addresses. In the absence of empirical information, we chose two exposure indicators for the analyses: (1) The exposure related to the most recent 5 years before the interview, considered to reflect shorter latency and (2) that related to the past 20 years, considered to reflect longer latency. The procedure of estimating personal exposure was done in two stages. Firstly, we assessed the geographical air pollution distribution in Athens assigning a pollution index to each area in the Athens basin and secondly, using this geographic pollution index, we assessed personal exposure based on the index of the areas of residences and employment addresses of each subject. More specifically, for the Greater Athens region (which is a basin surrounded by mountains and the sea and in which 40% of the Greek population lives), air pollution levels by borough were calculated on the basis of the average long-term concentrations of BS and nitrogen dioxide (NO_2), as recorded in 14 monitoring stations dispersed throughout the region. Geographical concentration patterns were based on data from a decade (1987–1997) but assumed to be the same during the 20 years for which exposure was

estimated. A line for zero air pollution was drawn at the highest points of the surrounding mountains. For each borough, the calculated air pollution level was the average of the measurements of the three nearest stations, or the two nearest and the zero air pollution line, weighted by the inverse of the distance from the borough's center to the measurement points. Our subjects declared their residence or employment addresses in 43 boroughs within the Athens basin for which NO_2 levels were available. In 35 of these, BS was also assessed. The rank correlation between the two pollutants was 0.90. We classified the boroughs into five categories based on the quintiles of the NO_2 distribution. The boroughs in category 5 were the most polluted with mean annual BS levels between 34 and 79 $\mu g/m^3$ and mean annual NO_2 levels between 50 and 80 $\mu g/m^3$. Boroughs in category 4, 3, 2 were progressively less polluted (with BS levels from 25 to 34 $\mu g/m^3$ and NO_2 from 40 to 50 $\mu g/m^3$ in the fourth category; smoke between 13 and 24 $\mu g/m^3$ and NO_2 between 23 and 35 $\mu g/m^3$ in the third; and smoke less than 13 $\mu g/m^3$ and NO_2 less than 23 $\mu g/m^3$ in the least polluted category). A map of the greater Athens area with borders of boroughs and pollution categories is included (Figure 1). Past residence in rural or semi-urban areas was considered as category 1, whereas past residence in other cities of Greece was classified into category 2 or 3 according to the recorded or presumed level of air pollution. Then, for every individual, an index was calculated as the time-weighted average of the pollution categories of areas where he/she spent time as a resident or an employee. A 40-hour workweek was assumed for individuals working outside their homes whilst for other individuals, including housewives, their residence formed the only basis for estimating their air pollution exposure. When all subjects had their air pollution exposure assessed, always regardless of case–control status, they were distributed into four groups based on the marginal quartiles of the personal air pollution exposure distribution.

Statistical analyses

χ^2-test for the linear trend was used to evaluate any differences in the distribution of smoking habits or level of education (as an index of socioeconomic status, SES) across quartiles of air pollution exposure. Conditional and unconditional logistic regression models were used for the statistical evaluation adjusting for age, gender, smoking habits and education [21].

Results

In Table 1, the age and gender distribution of the entire cohort, the two case-series (original 168 case-series1; after conducting spirometry and the medical interview 84 case-series2) as well as the controls are shown. Cases were as expected older than the original cohort.

In Table 2, socio-demographic and smoking characteristics of the two case-series as well as of the controls subjects are shown. Current smoking was as expected more prevalent in case-series2 (50%), followed by case-series1 (41%) and the comparison series (27%) and the opposite trend is observed for non-smokers. Controls were somewhat more educated.

In Table 3, the distribution of subjects by smoking habits and the level of education across quartiles of air pollution is presented. The differences between current and ex-smokers on the one hand and non-smokers on the other are not statistically significant ($p > 0.10$) but less educated subjects tend to be more exposed ($p = 0.02$).

In Table 4, ventilatory function data for the three comparison groups are shown. Although the FEV_1/VC ratio in the percent predicted is within the normal range, the differences between the control group and both case-series are statistically significant for all respiratory function indices studied. The average values among the three groups display a decreasing trend with respect to each respiratory parameter. After conducting spirometry, we were able to diagnose COPD cases according to the European Respiratory Society's criteria [3]. These cases were too few ($n = 31$) to allow separate analysis.

In Table 5, the two case-series and the controls are classified according to their exposure to outdoor air pollution in the most recent 20 years and the most recent 5 years. Controls are less exposed to the highest quartile of air pollution during the last 20 years (11% in controls, 16% in case-series1 and 19% in case-series2). The same pattern is evident with respect to the recent 5 years (the corresponding figures are 16% for controls, 23% for case-series1 and 32% for case-series2).

Table 6 shows the results of multiple logistic regression evaluating the effects of exposure to air pollution on the risk of developing chronic bronchitis, emphysema or COPD, alternatively comparing the two case-series to the control group and always adjusting for age, gender, smoking habits and education as an index of SES. The estimated odds ratios (OR) are all above the value of 1 and consistently higher when the most recent 5-year exposure is considered rather than the 20-year exposure and when case-series2 is compared rather than case-series1. We present results from both conditional and unconditional logistic regressions, which are consistent. The OR per quartile of exposure in the recent 5 years and risk of medically confirmed respiratory disease is 1.37 (95% CI: 1.05–1.79, $p = 0.02$) in the unconditional regression results and of similar magnitude (1.39, 95% CI: 0.97–1.97) but not statistically significant at the nominal level in the conditional ($p = 0.07$). The

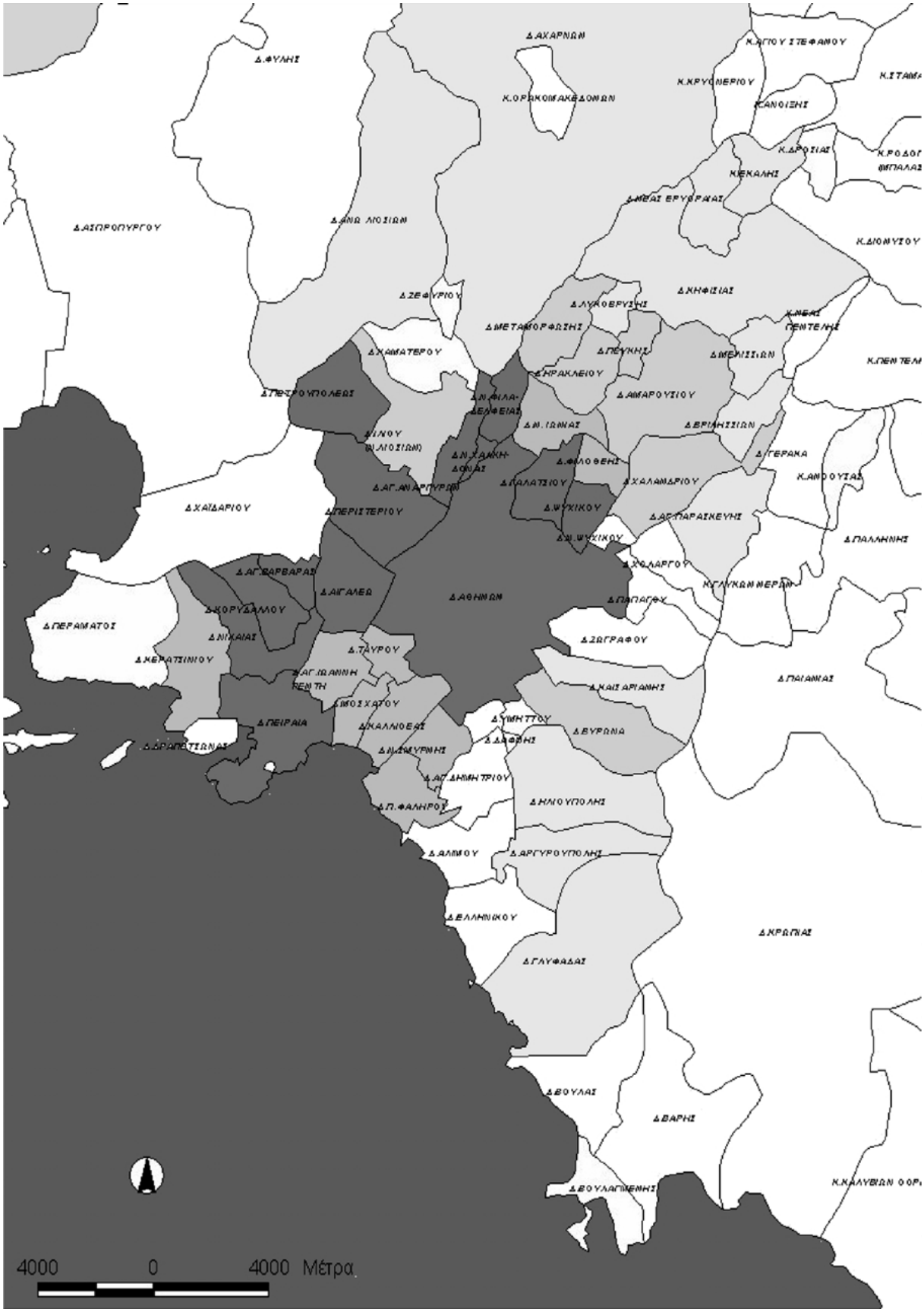

Figure 1. Map of the Greater Athens Region illustrating pollution categories 2–5 (5: darker, highest pollution; 2: lighter, lowest pollution). Category 1 was assigned only to areas outside Athens. Boroughs in white represent areas not assigned to a pollution category as no study subject had ever resided or worked in these.

Table 1. Age and gender distribution of the entire cohort, the 168 case-series1 (defined on the basis of a self-administered questionnaire), 84 case-series2 (diagnosed after conducting spirometry and the medical interview) and 168 controls

	Cohort, N (%)	Case-series1, N (%)	Case-series2, N (%)	Controls, N (%)
Age (years)				
>34	367 (9%)	4 (2%)	2 (2%)	4 (2%)
35–39	623 (16%)	15 (9%)	3 (4%)	15 (9%)
40–44	786 (20%)	26 (15%)	13 (15%)	26 (15%)
45–49	739 (19%)	32 (19%)	14 (17%)	31 (18%)
50–54	547 (14%)	33 (20%)	17 (20%)	34 (20%)
55–59	453 (12%)	19 (11%)	11 (13%)	19 (11%)
60–64	247 (6%)	20 (12%)	10 (12%)	19 (11%)
65–69	108 (3%)	14 (8%)	10 (12%)	15 (9%)
70+	34 (1%)	5 (3%)	4 (5%)	5 (3%)
Gender				
Women	2303 (59%)	114 (68%)	58 (69%)	114 (68%)
Men	1601 (41%)	54 (32%)	26 (31%)	54 (32%)

Table 2. Sociodemographic and smoking characteristics of 168 case-series1 (defined on the basis of a self-administered questionnaire), 84 case-series2 (diagnosed after conducting spirometry and medical interview) and 168 controls

	Case-series1	Case-series2	Controls
Duration of residence in Athens (years)*	35.45 ± 14.21	38.00 ± 13.85	35.08 ± 12.60
	N (%)	N (%)	N (%)
Smoking			
Non-smokers	65 (39%)	25 (30%)	81 (48%)
Exsmokers	34 (20%)	17 (20%)	42 (25%)
Current smokers	69 (41%)	42 (50%)	45 (27%)
Current workplace			
Office (indoors)	131 (78%)	64 (76%)	145 (87%)
Home	19 (11%)	10 (12%)	12 (7%)
Factory	7 (4%)	2 (2%)	4 (2%)
Outdoor urban	6 (4%)	6 (8%)	5 (3%)
Outdoor rural and others	5 (3%)	2 (2%)	2 (1%)
Education			
Elementary	12 (7%)	7 (8%)	8 (5%)
Secondary	55 (33%)	31 (37%)	53 (31%)
College/University	101 (60%)	46 (55%)	107 (64%)

* Data are presented as mean ± standard deviation.

Table 3. Quartiles of exposure to air pollution (in the recent 5 years) by smoking habits of all subjects

	Smoking habits			Education	
	Never smokers	Exsmokers	Current smokers	Elementary Secondary	College University
Air pollution exposure (recent 5 years)					
First quartile (lowest)	26 (18%)	19 (25%)	26 (23%)	17 (13%)	54 (26%)
Second quartile	44 (30%)	21 (28%)	35 (31%)	41 (32%)	59 (28%)
Third quartile	49 (34%)	20 (26%)	29 (25%)	40 (31%)	58 (28%)
Fourth quartile (highest)	27 (18%)	16 (21%)	24 (21%)	30 (24%)	37 (18%)
Total	146	76	114	128	208

estimated OR indicates an increase of 37% per increase of exposure by one quartile. When the most subjects exposed are considered (highest quartile vs. all others), there is a twofold increase in disease risk, which is also statistically significant in the unconditional regression ($p = 0.03$).

Although smoking was not a confounder in this investigation, we have modeled the data taking into

Table 4. Ventilatory function of 168 case-series1 (defined on the basis of a self-administered questionnaire), 84 case-series2 (diagnosed after conducting spirometry and the medical interview) and 168 controls

	Controls		Case-series1		Case-series2	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Respiratory parameter (in % predicted)						
FVC	116.53	(114.34–118.72)	108.54	(105.95–111.13)	103.59	(99.67–107.51)
FEV_1	109.61	(107.38–111.84)	99.12	(96.15–102.09)	90.98	(86.38–95.58)
FEV_1/VC	102.23	(100.40–104.06)	98.15	(95.86–100.44)	94.37	(90.27–98.47)

Table 5. Index of exposure to air pollution for the most recent 20 and 5 years of 168 case-series1 (defined on the basis of a self-administered questionnaire), 84 case-series2 (diagnosed after conducting spirometry and the medical interview) and 168 controls

	Air pollution exposure (recent 20 years)			Air pollution exposure (recent 5 years)		
	Controls	Case-series1	Case-series2	Controls	Case-series1	Case- series2
First quartile (lowest)	27 (16%)	26 (15%)	8 (10%)	40 (24%)	31 (18%)	10 (12%)
Second quartile	68 (40%)	63 (38%)	29 (34%)	50 (30%)	50 (30%)	27 (32%)
Third quartile	55 (33%)	52 (31%)	31 (37%)	50 (30%)	48 (29%)	20 (24%)
Fourth quartile (highest)	18 (11%)	27 (16%)	16 (19%)	28 (16%)	39 (23%)	27 (32%)
Total	168	168	84	168	168	84

Table 6. Results of conditional and unconditional logistic regression evaluating the effects of exposure to air pollution for cases (series1 and series2 alternatively) vs. controls, adjusting for age, gender, smoking habits and education (as an index of SES)

Air pollution variable	Case-series1[a] vs. controls		Case-series2[b] vs. controls		Case-series2[c] vs. controls	
	OR	95% CI	OR	95% CI	OR	95% CI
Recent 20 years						
Linear trend (per quartile)	1.10	(0.84–1.43)	1.31	(0.95–1.79)	1.34	(0.89–2.01)
Most exposed[d] vs. all others	1.39	(0.73–2.67)	1.46	(0.67–3.19)	1.31	(0.52–3.28)
Recent 5 years						
Linear trend (per quartile)	1.18	(0.94–1.49)	1.37	(1.05–1.79)	1.39	(0.97–1.97)
Most exposed[d] vs. all others	1.46	(0.82–2.59)	2.01	(1.05–3.86)	1.89	(0.83–4.31)

[a] Conditional logistic regression of 168 cases vs. 168 matched controls.
[b] Unconditional logistic regression of 84 cases vs. 168 controls.
[c] Conditional logistic regression of 84 cases vs. 84 matched controls.
[d] Persons exposed to the highest quartile vs. all others.

account the duration of smoking and, in a different model, extent of smoking. As expected, the results concerning air pollution in relation to either case-series1 or case-series2 (in comparison to controls) were essentially identical.

Discussion

This is a case–control study nested in a cohort exploring the association of outdoor air pollution and the development of chronic bronchitis, emphysema and COPD. Historically, Athens has been considered as one of the most polluted European cities [22], and previous studies have consistently shown air pollution effects on the total as well as on respiratory morbidity [12, 17] and mortality [16, 23, 24]. Although the epidemiological evidence has been particularly strong and relevant for short-term effects [25–27], information on long-term consequences of chronic exposure to air pollution is rather scarce. Two large cohort studies in the US have reported long-term effects on mortality (including elevated risks for cardiopulmonary mortality) [28, 29] whilst the evidence for effects on morbidity is more fragmented. A number of studies that have been conducted so far [30–33] provide evidence for association between air pollution levels and decrements in lung function, implying that exposure to high ambient pollution levels during adulthood may be a risk factor for COPD. The Swiss

Study on Air Pollution and Lung Disease in Adults (SAPALDIA) published a 3.14% decrease in the mean FVC for a 10 $\mu g/m^3$ increase in the long-term levels of ambient particulate matter (PM) lower than 10 μg (PM_{10}) [34]. Due to the ubiquity of air pollution exposure, this 'small' effect is considered to have a large public health impact [35]. When the investigators [36] decided to focus on respiratory symptoms, they found positive associations between annual mean concentrations of NO_2, TSP or PM_{10} and reported increased prevalence of chronic phlegm production, chronic cough, breathlessness at rest during the day or at night, and dyspnea on exertion.

An advantage of the present study is that it is nested in a large, well-established cohort. The EPIC study which has been recruiting subjects uses standardized protocols and questionnaires. The study design substantially reduces the possibility of selection bias. This study also has the advantage of examining long-term effects of air pollution with individualized estimates of exposure to pollution. Studies testing similar hypotheses have generally relied on ecological fixed site air pollution measurements and have focused on comparing different population groups. Results of studies of the latter type may theoretically be confounded by various unidentified factors operating at the group level. In the present study, individuals from the same population are compared, and their personal long-term exposure to air pollutants was estimated regardless of their case–control status. The fact that all subjects are current residents of Athens, obviously restricts the exposure range. It should be noted, however, that air pollution levels in the most polluted area category clearly exceed the WHO mean annual guideline values (50 $\mu g/m^3$ for BS and 40–50 $\mu g/m^3$ for NO_2 [37, 38]), whereas the least polluted areas had levels below 15 $\mu g/m^3$ for BS and 25 $\mu g/m^3$ for NO_2.

Every effort was made to have individual exposure estimates that were as accurate as possible. Nevertheless, our air pollution exposure assessment is a proxy to the true exposure. A lack of detailed historical data on air pollution, especially for the remote end of the 20-year period by geographical area, and the limited information on past time activity patterns limits the accuracy of our estimates. The resulting misclassification, however, is likely to be non-differential with a tendency to reduce elevated ORs towards the null. Moreover, the study participants were unaware of the working hypothesis.

The population of our study was relatively young and health conscious and therefore did not include many individuals with seriously compromised health. This reduces the number and severity of our cases and consequently, the power of our study. However, we believe that the advantages of the study design with respect to bias elimination compensate for the above weakness. The operational definition of COPD in our investigation does not strictly correspond to the clinical definition of this condition, because technical and financial reasons precluded the undertaking of a reliable reversibility test. However, this can only introduce non-differential misclassification in the response variable, the general consequence of which is a reduction of the statistical power of the study rather than the introduction of bias.

An interesting finding of the present study is the apparent linear trend between levels of air pollution exposure and prevalence of respiratory morbidity expressed as simple bronchitis, emphysema or COPD. With respect to exposure during the last 5 years, the odds of those most exposed vs. all others to become cases were doubled (OR: 2.01, 95% CI: 1.05–3.86, $p = 0.03$). Our results are consistent with those of previous studies [26, 39] that have used different exposure estimates. Tzonou et al. [12] found that residents of Athens who have lived all their lives in urban areas (mostly in Athens) have a twofold greater risk of COPD compared with people who have lived exclusively or partly in rural areas before settling in Athens. In the 1979 National Health Insurance Survey [26, 40] an increase in annual mean TSP of 100 $\mu g/m^3$ was associated with an 80% increase in the odds of reporting emphysema, chronic bronchitis or asthma. When Schwartz [41] examined the adverse health effects of exposure to airborne particles at concentrations seen in urban areas he found that a 10 $\mu g/m^3$ increase in TSP was associated with an increased risk of chronic bronchitis (OR: 1.07) and of a respiratory diagnosis of the examining physician in the First National Health and Nutrition Examination Survey (OR: 1.06). Plots of the relative odds by quartiles of TSP exposure, adjusting for covariates, showed dose-dependent increases in risk with increasing exposure.

In our study, we fail to show a statistically significant association of outcome with the 20-year air pollution exposure. This may reflect a genuine phenomenon or the fact that during the last 5 years measurements of air pollution and the estimated personal exposure were more accurate, thus reducing the extent of misclassification.

We conclude that our findings provide consistent and apparently unbiased evidence that chronic exposure to air pollution is an important factor in the occurrence of COPD.

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