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Long-term mortality among adults with or without asthma in the PAARC study

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ABSTRACT: The Pollution Atmosphérique et Affections Respiratoires Chroniques (PAARC; Air Pollution and Chronic Respiratory Diseases) study provided the opportunity to examine the 25-yr mortality of 940 asthmatic adults drawn from a large population-based sample of 14,267 adults investigated during 1974–1976 in seven French cities.

Vital statistics were collected in 2001 for the whole population. Multivariate survival analysis was used to assess exact survival rates in asthmatics and nonasthmatics taking relevant confounders into account.

On average, the mortality rates obtained were 10.4 and 6.9 deaths·1,000 person-yrs^{-1} in asthmatics and nonasthmatics, respectively. On univariate analysis, asthma increased the relative risk (RR) of death by 1.48 (95% confidence interval (CI) 1.29–1.69). The association between asthma and death had an RR of 1.16 (95% CI 0.99–1.37) when age, sex, educational level, smoking habits, occupational exposure and forced expiratory volume in one second (FEV_1) were taken into account. FEV_1 was an important contributive factor causing increased risk of death in both smokers and nonsmokers. For instance, in asthmatics, the numbers of deaths due to respiratory disease and cancer appeared excessive.

The present study suggests that asthmatics exhibit a higher risk of mortality.
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Mortality rates for asthma appear to have been increasing in industrialised countries but are now considered stable [1–4]. The reasons for this trend remain unclear since mortality due to many chronic diseases has decreased and physiopathological and therapeutic knowledge concerning asthma has improved [5].

Understanding concerning the long-term mortality of asthmatics is still inadequate and most studies have been unable to ascertain whether or not asthma shortens survival. Only few epidemiological data on the overall survival of adults with asthma are available. The results obtained have sometimes been contradictory. In particular, there is still controversy concerning the excessive risk of death from other lung diseases in asthmatics [6]. For example, LANGE *et al.* [7] concluded that, in the general population, self-reported asthma was associated with a slight excess of mortality, mainly due to respiratory diseases. In a community-based study, MARKOWE *et al.* [8] reported that mortality from all causes was higher in the asthmatic cohort. The predominant cause of excess mortality identified was respiratory diseases, more specifically asthma and chronic obstructive airway disease [8, 9]. SILVERSTEIN *et al.* [10] stated that survival among patients suffering from asthma but without any other lung disease was not significantly different from that expected. Risk factors and prognoses in asthmatics are not yet well established and reducing the risk of mortality due to asthma remains difficult. Some of the inconsistencies may result from misdiagnosis of asthma. Moreover, although many studies have controlled for the effects of age, sex and smoking [7, 10], other confounding factors, such as occupational and environmental factors, may also be important [11].

The 25-yr mortality of a large French cohort was studied in order to determine whether or not mortality was premature in asthmatics and to analyse the specific causes of death.

Methods

The Pollution Atmosphérique et Affections Respiratoires Chroniques (PAARC; Air Pollution and Chronic Respiratory

Diseases) study was conducted during 1974–1976 in 24 areas around seven French cities, in order to assess the relationship between chronic respiratory diseases and air pollutants. The inclusion criteria were described in a previous PAARC report [12, 13]. The PAARC study included adults aged 25–59 yrs. The household family had to be French. They had to have been living in the area for 3 yrs and be of a socioeconomical status other than that of manual workers (the potential occupational exposures could exert greater effect than that expected from air pollution). The PAARC study included 20,310 adults in its initial stage but 900 were excluded because of unreliable data. Vital status was sought for all subjects born in France (16,905 subjects) over 3 yrs (1995–1998) for each place of birth and data were completed using a computerised national register (National Register of People Identification (RNIPP)). Causes of death were obtained through a specialised department (Causes of Death) of the National Institute of Health and Medical Research (INSERM). They were coded according to the International Classification of Diseases eighth and ninth revisions (ICD-8 and ICD-9) and pooled into four categories: cardiovascular diseases, respiratory diseases, cancer, and other causes (including endocrine diseases, blood diseases, mental troubles, nervous system disease, infectious diseases, digestive system disease, genitourinary system diseases, skin diseases, osteoarticular system diseases, congenital anomaly, other morbid symptoms, trauma and poisoning). Causes of death from among the total available causes of deaths in asthmatic and nonasthmatic subjects and then respiratory *versus* nonrespiratory causes of death were compared using a global Chi-squared test.

Asthmatics were defined as subjects having responded positively to either the diagnostic question "have you ever had asthma?" or the symptomatic question "have you ever had attacks of breathlessness associated with wheezing?" during a face-to-face baseline interview conducted in 1974–1976. The validity of these questions has been assessed in previous studies [14]. Individual data were also collected during 1974–1976. The baseline variables studied were as follows. 1) Sex. 2) Education, defined in three levels: primary, secondary (technical school certificate) and tertiary (university). 3) Smoking habits, defined in five classes from the initial questionnaire: nonsmokers (people who had not smoked for 1 yr), former smokers (people who had stopped smoking for $\geqslant$1 month), light smokers (<10 g tobacco·day^{-1}), moderate smokers ($\geqslant$10 and $\leqslant$20 g tobacco·day^{-1}) and heavy smokers ($\geqslant$20 g tobacco·day^{-1}). 4) Forced expiratory volume in one second (FEV1), measured by vitalograph mobile spirometry [12] (on the basis of at least three graphs, the best FEV1 being selected) and expressed as a percentage of reference (predicted) values according to the recommendations of the European Respiratory Society [15]. Analysis was performed using FEV1 as a continuous variable and then categorising it according to the severity criteria of asthma (National Heart, Lung and Blood Institute (NHLBI)/World Health Organization (WHO) workshop report, 1995) as either less than or at least 80% predicted [16]. 5) Occupational exposure to gas, dust or vapour, defined using a job exposure matrix [17].

The study outcome was death. Adjusted mortality relative risk (RR) was estimated using a Cox proportional hazards regression model and the model with delayed entry to take into account left-truncation [18, 19]. A multivariate Cox model allowed the association between death and the different variables to be studied. Models were initially created for both sexes, then separately for males and females, and finally for nonsmokers, in order to study mortality caused by asthma rather than chronic bronchitis or smoking.

Results

Prevalence of asthma

Of the 16,905 subjects, the RNIPP revealed the vital status of 14,286; 2,533 had died (847 female) and 11,753 were still alive (6,636 female). It was not possible to gather information on the remaining 2,619 subjects (1,908 female). Unknown vital status occurred significantly more often among the females (66% due to not knowing their married name). Of the 14,286 subjects, >99% (14,267 subjects) answered questions about asthma; 940 claimed to be asthmatics, including 418 who responded positively to both questions relating to asthma. Asthma was identified in 6.4% (476) of females and 6.8% (464) of males.

Description of the population

Lung function was lower in asthmatics than in nonasthmatics (mean±SD FEV1 85.5±21.6 *versus* 93.7±18.0% pred, $p<1\times10^{-4}$). A mean FEV1 of <80% pred occurred in 61.7±14.7% of asthmatics and 66.7±12.1% of nonasthmatics. Otherwise, asthmatics differed from nonasthmatics only in educational level (table 1). Females exhibited a lower educational level than males (14.6 *versus* 9.7% were of primary educational level, $p<1\times10^{-4}$) and were less exposed to tobacco smoke (73.4 *versus* 25.6% were nonsmokers). The characteristics of asthmatics and nonasthmatics according to vital status are shown in table 2.

Mortality

The mean age at death was similar in asthmatics and nonasthmatics. There were 224 (23.8%) deaths in asthmatics and 2,171 (16.3%) in nonasthmatics, with mean incidence rates during follow-up of 10.4 and 6.9 deaths·1,000 person-yrs^{-1}, respectively ($p<1\times10^{-4}$). The risk of death was significantly higher in asthmatics than nonasthmatics ($p<1\times10^{-4}$, log-rank test) (fig. 1).

Risk factors for death

Subjects who died had reported significantly more asthma (RR 1.48, 95% confidence interval (CI) 1.29–1.69) and occupational exposure to gas, dust or vapour (RR 1.27, 95% CI 1.16–1.40) than survivors. They were more frequently male and former, current moderate and current heavy smokers. They showed lower FEV1 than survivors (RR 0.987, 95% CI 0.985–0.989) and, more frequently, an FEV1 of <80% pred (RR 1.59, 95% CI 1.45–1.75) (data not shown).

On multivariate analysis, in the whole population, asthmatics died more frequently than nonasthmatics (RR 1.16, 95% CI 0.99–1.37). The interaction between asthma and FEV1 was nonsignificant (p=0.0521).

In a second stage, analysis was performed by sex and asthmatics died more frequently than nonasthmatics, but this difference was nonsignificant (RR 1.15, 95% CI 0.95–1.39 in males; RR 1.21, 95% CI 0.89–1.66 in females) (table 3). There was no effect of occupational exposure on mortality in either males or females.

Finally, analysis was performed according to smoking status in order to study mortality caused by asthma and not by chronic bronchitis or smoking habit. Among nonsmokers, asthmatics died more frequently than nonasthmatics, but this difference was nonsignificant (RR 1.29, 95% CI 0.96–1.73).

When analysis was performed using FEV1 categorised as

Table 1. – Characteristics of asthmatics and nonasthmatics in the Pollution Atmosphérique et Affections Respiratoires Chroniques (Air Pollution and Chronic Respiratory Diseases) study (1974–2001)

	Asthmatics	Nonasthmatics	p-value
Subjects n	940	13327	
Males %	49.4	47.5	0.27
Age yrs	43.3±9.3	42.1±9.6	$<1\times10^{-4}$
Educational level %			
Primary	14.6	12.1	0.03
Secondary	50.0	53.9	
Tertiary	35.4	34.0	
Smoking habits 1974–1976 %			
Nonsmoker	49.2	50.7	0.08
Former smoker	12.8	10.9	
Current smoker			
<10 g tobacco·day^{-1}	11.0	11.5	
⩾10 and <20 g tobacco·day^{-1}	9.2	11.1	
⩾20 g tobacco·day^{-1}	17.8	15.8	
Occupational exposure (to gas, vapour or dust) %	24.9	23.4	0.33
FEV1 L·s^{-1}	2.7±0.9	3.0±0.8	$<1\times10^{-4}$
% pred	85.5±21.6	93.7±18.0	$<1\times10^{-4}$
FEV1<80% pred L·s^{-1}	1.9±0.6	2.1±0.6	
% pred	61.7±14.7	66.7±12.1	
Subjects n	295	2393	
FEV1⩾80% pred L·s^{-1}	3.1±0.7	3.2±0.7	
% pred	97.9±12.1	100.3±12.2	
Subjects n	565	9895	

Data are presented as absolute values, percentages or mean±SD. FEV1: forced expiratory volume in one second; % pred: percentage of the predicted value.

Table 2. – Characteristics of asthmatics and nonasthmatics in the Pollution Atmosphérique et Affections Respiratoires Chroniques (Air Pollution and Chronic Respiratory Diseases) study (1974–2001) according to vital status

	Uncensored			Censored		
	Asthmatics	Nonasthmatics	p-value	Asthmatics	Nonasthmatics	p-value
Subjects n	224	2171		716	11156	
Age at entry yrs	49.8	48.4	0.005	41.3	40.8	0.257
Age at exit yrs	65.6	65.0	0.369	67.0	66.5	0.198
Follow-up person-yrs	3400	34819		18064	280743	

less than or at least 80% pred, asthmatics died more frequently than nonasthmatics (RR 1.21, 95% CI 1.03–1.43 in the whole population; RR 1.22, 95% CI 1.01–1.48 in males; RR 1.23, 95% CI 0.90–1.67 in females; RR 1.32, 95% CI 0.98–1.76 in nonsmokers).

Causes of death

Asthma was reported as the cause of death of only seven adults (two asthmatics and five nonasthmatics). The distribution of cause of death was different among asthmatics (197 causes identified) and nonasthmatics (1,798 causes identified) ($p<1\times10^{-4}$). Asthmatics died from respiratory diseases more frequently than nonasthmatics (12.7% (n=25) *versus* 3.6% (n=64) of all available causes of death) and particularly from obstructive pulmonary disease (8.6% (n=17) *versus* 1.6% (n=29)) (table 4).

Using Cox analysis, it was found that asthmatics died more frequently from chronic obstructive pulmonary disease (COPD) than nonasthmatics (RR 3.53, 95% CI 1.73–7.19), taking into account sex, smoking habit and FEV1 (data not shown).

Discussion

The present findings suggest excessive mortality in asthmatics, particularly due to COPD. This finding is strengthened by the fact that the data are based on a 25-yr follow-up of a large sample of the French adult population. The study could have some limitations regarding data precision due to asthma definition, which can be problematic because of difficulties in the differential diagnosis of asthma and COPD overall in adults. Similarly, smoking habits, which are likely to have changed between the 1970s and the 1990s, and mortality data depend on death certificates, the reliability of which can be uncertain [20]. Moreover, selection bias must be considered when extrapolating the present results to the entire population. The study did not include people of foreign nationality, those born in foreign countries or the elderly. For some females, vital status could not be easily identified due to their change of family name after marriage. If being female, having a low educational level and being elderly make subjects more susceptible than others to death due to asthma, it is possible that this selection bias would have induced difficulty in demonstrating their effect [21].

Nevertheless, some comment can be made with regard to

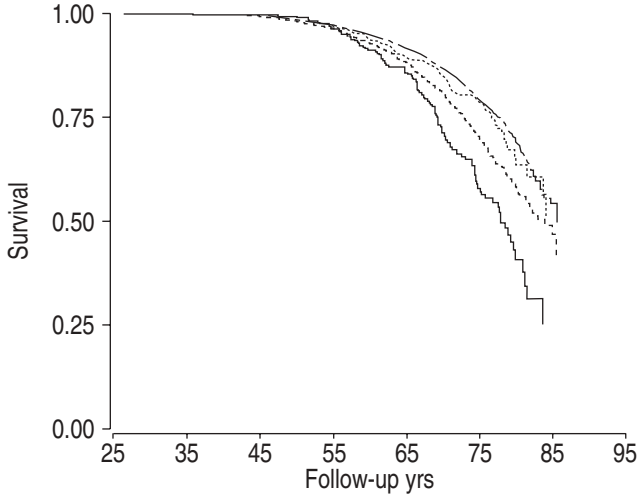

Fig. 1. – Survival of asthmatics (·····: forced expiratory volume in one second (FEV_1) $\geqslant$80% predicted; ——: FEV_1 <80% pred) and nonasthmatics (– – –: FEV_1 $\geqslant$80% pred; - - - - -: FEV_1 <80% pred) in the Pollution Atmosphérique et Affections Respiratoires Chroniques (Air Pollution and Chronic Respiratory Diseases) study (1974–1998). Log-rank test $p<1\times10^{-4}$.

these potential limitations. The definition of asthma used in the present study is the one commonly used in epidemiological studies; several studies have shown that the question "do you have asthma?" is very specific [22, 23], and VESTBO *et al.* [24] concluded that questions on breathlessness, compared to spirometric measurements, FEV_1 in particular, provide good validity [25]. Even if tobacco habits have changed between the 1970s and the 1990s, tobacco consumption has been taken into account both qualitatively (former and current smokers) and quantitatively (grams of tobacco per day). The loss of information on smoking habits was not relevant in the present study because people tend to quit smoking and it is uncommon to start smoking at the age chosen for recruitment (25–50 yrs); the strongly expected association of the smoking variables with specific causes of death (previous analysis by authors) showed the relevance of this indicator. Therefore, the analysis was restricted to nonsmokers in order to focus on asthma [26, 27] and the confusion bias reduced by controlling not only for the effects of age (left-truncated model), sex, educational level and smoking but also for other confounders such as occupational exposure. The PAARC population can be considered as representative of the urban nonmanual worker household population in France in the 1970s and provides original findings. Thus, in this 25-yr follow-up of a large sample of the French adult population, premature mortality was found in asthmatics, which could provide an answer to the questions of ULRIK [28] regarding mortality in asthma. A significant excess mortality was observed in asthmatic subjects, with an excess of death due to COPD in asthmatic subjects (ICD-9 codes 490–496). This finding supports the hypotheses of previous studies, according to which asthma is a risk factor for COPD and COPD a risk factor for mortality in asthma [29]. No significant excess in mortality from lung cancer was found among asthmatics, unlike in the studies of BOFFETTA *et al.* [6], HUOVINEN *et al.* [30] and WU *et al.* [31], in which the risk of death due to lung cancer adjusted for smoking was higher in males with asthma (RR 3.2, 95% CI 1.4–7.3). However, no long-term survival studies controlled for occupational exposure. Even if FEV_1 is known to be a predictive factor of mortality, this association has rarely been described in the long-term survival of asthmatic

Table 3. – Risk factors for death (multivariate analysis) in the Pollution Atmosphérique et Affections Respiratoires Chroniques (Air Pollution and Chronic Respiratory Diseases) study (1974–2001)

	Whole population	Males	Females	Nonsmokers
Subjects n	11103	5939	5164	5207
Asthma	1.162 (0.986–1.369)	1.148 (0.946–1.394)	1.215 (0.890–1.658)	1.288 (0.961–1.725)
Female sex	0.583 (0.519–0.656)			0.642 (0.541–0.763)
Educational level (*versus* primary)				
Secondary	1.032 (0.903–1.180)	1.022 (0.870–1.201)		0.948 (0.754–1.191)
Tertiary	0.869 (0.751–1.006)	0.857 (0.721–1.018)		0.756 (0.582–0.983)
Smoking habit (*versus* nonsmokers)				
Former smokers	1.183 (1.009–1.386)	1.267 (1.049–1.530)	1.018 (0.688–1.507)	
Current smokers				
<10 cigarettes·day^{-1}	1.125 (0.951–1.332)	1.172 (0.949–1.447)	1.144 (0.844–1.550)	
$\geqslant$10 and <20 cigarettes·day^{-1}	1.631 (1.397–1.904)	1.779 (1.476–2.144)	1.253 (0.873–1.779)	
$\geqslant$20 cigarettes·day^{-1}	2.626 (2.302–2.994)	2.771 (2.357–3.258)	2.352 (1.758–3.173)	
FEV_1 (continuous)	0.999 (0.986–0.991)	0.988 (0.985–0.990)	0.991 (0.937–0.995)	0.993 (0.989–0.997)

Data are presented as relative risk (95% confidence interval). FEV_1: forced expiratory volume in one second.

Table 4. – Cause of death of asthmatics and nonasthmatics and association between asthma and death in the Pollution Atmosphérique et Affections Respiratoires Chroniques (Air Pollution and Chronic Respiratory Diseases) study (1974–1998)

Cause of death	Asthmatics %	Nonasthmatics %	RR (95% CI)$^{\#}$
Subjects n	197	1798	
Cardiovascular system diseases	29.44	24.97	1.380 (0.997–1.909)
Respiratory system diseases	12.69	3.56	2.800 (1.580–4.964)
Obstructive pulmonary disease	8.63	1.61	3.527 (1.730–7.192)
Cancer	38.58	47.61	1.064 (0.812–1.395)
Lung cancer	10.15	8.79	1.382 (0.816–2.339)

RR: relative risk; CI: confidence interval. $^{\#}$: adjusted for age, sex, educational level, smoking habit, occupational exposure and forced expiratory volume in one second where appropriate.

subjects [32, 33]. Like the present authors, LANGE *et al.* [7] observed that self-reported asthma was associated with poorer survival and higher risk of death from pulmonary diseases. They also stressed the role of an FEV1 of <80% pred as a predictor of mortality, but its role was similar in asthmatics and nonasthmatics. The mortality rate from all causes in the present study is comparable to those reported in previous studies; MARKOWE *et al.* [8] found increased mortality from all causes (RR 1.6, 95% CI 1.3–2.0) and HUOVINEN *et al.* [30] found an age-adjusted RR of 1.5 (95% CI 1.1–2.1).

In conclusion, the present study suggests excessive mortality in asthmatics, particularly due to chronic obstructive pulmonary disease. Smoking habits, social class and occupational exposure did not fully explain this excess of mortality [34], but a decrease in forced expiratory volume in one second increased the risk of death even in nonsmokers. Therefore, an implication of this study is that mortality in asthmatics could be diminished by avoiding lung function decrease, thus stressing the usefulness of monitoring forced expiratory volume in one second in asthmatics.

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