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REVIEW

Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases

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Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. J. Trédaniel, P. Boffetta, R. Saracci, A. Hirsch. ©ERS Journals Ltd 1994.

ABSTRACT: Exposure to environmental tobacco smoke (ETS) is widespread in European countries, the most serious exposures occurring at home and in the workplace. Epidemiological studies have, essentially, addressed the association between ETS exposure and respiratory health in children, and increased risk of lung cancer among adult nonsmokers. Relatively few studies have been reported on ETS and adult non-neoplastic respiratory diseases.

On the basis of the available data, no definite conclusion (excluding the acute irritating effect of ETS on respiratory mucous membranes) can be drawn. Although biologically plausible, it remains controversial whether ETS exposure is associated with chronic respiratory symptoms and occurrence of chronic obstructive pulmonary disease, including asthma. Most of the studies that have used the most sensitive indicators of pulmonary function have suggested a negative impact of ETS exposure. However, if really present, the physiological significance of such small changes is unclear, and the relationship to long-term changes in lung function is not established. Moreover, the possibility of bias and confounding factors must be taken into account. Thus, there is a need for further epidemiological studies on ETS exposure and adult non-neoplastic respiratory disorders.
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Cigarette smoking has been identified as the single most important source of preventable morbidity and premature mortality [1–5].

Passive smoking, involuntary smoking, and exposure to environmental tobacco smoke (ETS), are used synonymously to describe the involuntary exposure of nonsmokers, both children and adults, to tobacco combustion products generated by smokers. ETS comprises the amount of tobacco smoke which is not inhaled by the smoker (sidestream smoke-SS), as well as the portion of inhaled smoke (mainstream smoke) which is not retained in the smoker's lung, and is exhaled into the environment. In enclosed spaces, smoke accumulates, and the concentration varies with the number of smokers, with the type of smoking, and with the characteristics of the room, especially the ventilation. Although the exposures to active smoke and ETS are not identical, the latter appears to include most tobacco combustion by-products, including irritants, and carcinogens [2, 6–8].

The level of exposure to ETS, based on biochemical markers, such as salivary and urinary concentrations of nicotine and cotinine, has been estimated to be equivalent to 0.1–2 cigarettes·day^{-1} [9–14]. The ubiquitousness of tobacco smoke in homes, workplaces, public areas (with especially high concentrations measured in bars or taverns [15]), and private establishments, makes exposure to ETS virtually unavoidable. For instance, in a population study of 37,881 nonsmokers and former smokers, 63% of the nonsmokers reported some daily exposure; 35% were exposed at least 10 h·week^{-1}, and 16% at least 40 h·week^{-1} [16]. During the study of health and the environment and evaluation of particulate matter in Tucson, Arizona, LEBOWITZ *et al.* [17] found that 39% of the population were exposed to ETS. To investigate to what extent questionnaires can indicate exposure levels to ETS, the International Agency for Research on Cancer (IARC) conducted a multicentre study, which included 1,369 nonsmoking women. Of the total, 20% of the subjects had nondetectable urinary cotinine levels, indicating that they were true unexposed nonsmokers. Analyses of self-report for these subjects revealed that 60% of them were not exposed outside the home, and 89% reported that they had no exposure from a husband who smoked [18].

During the last 15 yrs, attention has been focused on the potential health effects of ETS [19–22]. When this topic was first raised in the 1972 Report of the Surgeon General [23], only a handful of studies had addressed this issue, and provided limited information. The 1984 Report on Chronic Obstructive Lung Disease [24] devoted more attention to ETS. Recent assessments have definitely concluded that the involuntary inhalation of cigarette smoke by nonsmokers causes disease, most notably lung cancer (2, 25–28).

There is also cumulative evidence that parental smoking, especially of the mother, is associated with increased prevalence of respiratory symptoms, increased incidence of acute respiratory infections, and decreased lung function, with a small reduction in their rate of pulmonary growth and development in children of smoking parents [28, 29]. The combination of epidemiological studies with the demonstration of physiological changes with exposure to ETS, together with biochemical evidence that elements of ETS have adverse effects on the cardiovascular system, has been interpreted as supportive of the hypothesis that ETS may cause coronary heart disease [30, 31].

Conversely, the effects of ETS on the risk of non-neoplastic respiratory diseases in adults have not been fully clarified. Several reviews of the literature on ETS have addressed some aspects of this problem [19, 20, 22, 29, 32, 33], but a recent comprehensive review is lacking, particularly as ETS exposure in the workplace assumes increasing importance as an occupational health issue [34, 35]. The aim of this article is to review currently available data concerning ETS and lung function, respiratory symptoms, and respiratory diseases (excluding lung cancer) in nonsmoking adults.

Acute effects

The determination of acute effects of ETS is difficult, because the observed reactions, although immediate, are largely subjective [36]. Nonsmokers seem to react significantly more than do smokers [37].

The most common effect is tissue irritation, especially of the eyes, but also of the nose, throat and airways [37–39]. WEBER *et al.* [40] exposed 60 subjects to ETS in a climatic chamber: approximately one third of normal nonsmokers experienced eye irritation, headache, and rhinitis; the effects on throat and respiratory system were relatively small [40]. Acrolein was the most notable irritant measured. LEBOWITZ *et al.* [17] found an increased prevalence of acute respiratory symptoms as indoor ETS increases, especially in households from the lower socio-economic status. Complaints are especially marked amongst aircraft passengers [41–43].

PIMM *et al.* [44] exposed 20 nonsmoking adults to ETS for 2 h on alternate days. Maximal expiratory flow at 25% forced vital capacity (MEF_{25}) decreased slightly with smoke exposure. No other consistent changes in lung function were observed. Despite the small amount of physiological change, most subjects found the exposure to cigarette smoke unpleasant. Similar results were found by SHEPHARD *et al.* [45], who exposed 23 young healthy adults to 2 h of ETS and observed a small (3–4%) decrease of dynamic lung volumes. BASCOM *et al.* [46] exposed 10 historically ETS-sensitive and 11 historically ETS-nonsensitive subjects to 15 min of clean air, followed by 15 min of a high concentration of ETS. Pulmonary function changes were of a small magnitude (<7%) in both groups. However, sensitive subjects showed significant decrements in forced volume capacity (FVC), forced expiratory volume in one second (FEV_1), and mean expiratory flow during the middle half of the FVC ($FEF_{25–75}$) after smoke. The $FEF_{25–75}$ continued to remain significantly decreased 20 min after cessation of exposure.

Chronic respiratory symptoms

There are no studies of chronic ear, nose and throat symptoms in adults exposed to ETS. Nearly 25% of 10,000 nonsmoking office-workers reported exacerbation of pre-existing pulmonary conditions, when working with a smoker [47].

Few studies have addressed the effect of ETS exposure on chronic respiratory symptoms (persistent cough, phlegm, wheezing) in nonsmoking adults with ETS exposure. They are summarized in table 1.

LEBOWITZ and BURROWS [48] studied chronic respiratory symptoms in a community population of 3,484 individuals from Tucson, Arizona; 1,258 adults were lifelong nonsmokers. There was no significant trend in their symptoms in relation to the smoking status of other family members.

As part of a large survey in three USA towns, SCHILLING *et al.* [56] studied respiratory symptoms, diseases and lung function in 376 white families. Symptom prevalence in nonsmokers was unrelated to whether or not their spouses smoked. The records of 1,724 residents of Washington County, Maryland were analysed to evaluate the effects of ETS exposure [49]. The frequency of major respiratory symptoms (cough, phlegm, wheeze, breathlessness, chest illness) showed no evidence of an association with the presence of a cigarette smoker in the household.

KAUFFMANN *et al.* [50, 51] conducted a parallel analysis on two large female populations, enrolled, respectively, in the US Six Cities study (2,200 women) [57] and the French PAARC study (3,855 women) [58]. One thousand nine hundred and twenty seven women (32%) were exposed to ETS from their current spouse. Over all, a weak association was found between ETS exposure and respiratory symptoms, which was of borderline signification for wheeze and dyspnoea. No association was observed with cough or phlegm production.

A prospective cohort study was carried out in an urban West Scotland population, the members of which were homogeneous for social class and ethnic group [52, 59]. From the original cohort, 243 men and 1,295 women were ETS exposed. For each of the four respiratory symptoms studied (infected sputum, persistent sputum, dyspnoea and hypersecretion) the rates in the ETS exposed group were nonsignificantly higher than those in the control group (unexposed nonsmokers).

SCHWARTZ and ZEGER [53, 54] re-examined the data originally obtained from a cohort of 100 student nurses in Los Angeles [60, 61] recruited for a diary study of acute effects of air pollution. Diaries were completed weekly, for as long as 3 yrs. Controlling for active smoking, a smoking room-mate increased the risk of an episode of phlegm (relative risk (RR)=1.41) but not of cough.

Table 1. – Studies of environmental tobacco smoke (ETS) and chronic respiratory symptoms

First author Year, Country [Ref.]	ETS exposed subjects	Measure of risk	Categories	Results				
				Cough	Phlegm	Wheeze	Dyspnoea	Colds
LEBOWITZ 1976, USA [4]	1258	Prevalence rate %	Smoker	6.8	8.6	4.5		
			Ex-smoker	8.1	6.5	5.5		
			Nonsmoker	10.3	8.6	4.4		
COMSTOCK 1981, USA [49]	539 (426 M, 113 F)	RR	Male	0.96	0.90	1.04		
			Female	0.17	0.72	1.45		
KAUFFMAN 1989, USA/ France [50, 51]	1476 French + 451 USA	RR	France	1.35 (0.8–2.4)	0.77 (0.3–2.0)	1.03 (0.8–1.4)	1.17 (0.8–1.6)	
			USA	1.4 (0.6–2.1)	1.65 (0.7–3.8)	1.35 (1.0–1.9)	1.35 (0.7–2.6)	
HOLE 1989, Scotland [52]	1538 (243 M, 1295 F)	RR			1.21 (0.8–1.8)		1.09 (0.8–1.4)	
SCHWARTZ 1990, USA [53, 54]	100	RR			1.41 (1.1–1.9)			
WHITE 1991, USA [55]	80	Prevalence rate %	Exposed	70	67.5		67.5	85
			Unexposed	25	20		15	20

RR: relative risk.

WHITE *et al*. [55] reported a study investigating the effects of workplace ETS exposure on the prevalence and symptoms of respiratory illness among 40 ETS exposed and 40 unexposed nonsmokers. Passive smokers experienced more respiratory symptoms than nonsmokers, namely chronic cough (70 *versus* 25%), chronic phlegm (68 *versus* 20%), shortness of breath (68 *versus* 15%), and chest illnesses (85 *versus* 20%). Passive smokers missed twice as many workdays due to chest illness during an average 12 month period than did nonsmokers ($p<0.05$).

Lung function testing

It is important to appreciate whether or not healthy adults exposed to ETS may have changes in pulmonary function that may eventually lead them to the development of a chronic obstructive pulmonary disease (COPD). A number of studies have been published on the effects of ETS and pulmonary function in adults. However, these investigations were often initiated within the framework of research projects not primarily concerned with ETS. As a result, certain reservations must be made regarding the relevance of some of the findings, due to the low sensitivity and low power of these studies. In particular, the older studies used spirometric tests of low sensitivity, such as FEV_1 and FVC, which depend mainly on the total airway resistance and elastic recoil of the lung, and are not disturbed even in the presence of early small airways dysfunction, possibly representing the initial reaction of the bronchopulmonary system to the active inhalation of tobacco smoke. However, many recent studies have assessed the potential effects of ETS on small airways function by means of sensible parameters, such as mean forced expiratory flow during the middle half of the forced vital capacity (FEF_{25-75}) and the end of the FVC (FEF_{75-85}).

A number of studies (table 2) have failed to detect an association between ETS exposure and lung function. SCHILLING *et al*. [56] analysed the FEV_1 in 330 families. In the families in which only one subject smoked (114 pairs), the nonsmoker's lung function was similar to that in which neither spouse smoked. The results for residual FVC and flow rates showed similar trends.

COMSTOCK *et al*. [49] analysed the possible effects of household tobacco smoke on FEV_1 and the ratio between FEV_1 and forced vital capacity (FEV_1/FVC) among 1,724 residents of Washington County, Maryland. In the subgroup of 93 nonsmokers who lived with a smoker, the lung function tests were similar to those observed in 325 unexposed nonsmokers.

As part of a case-control study of 20–39 year old nonsmoking female participants in the Tecumseh Community Health Study, JONES *et al*. [62] showed no significant effect on FEV_1 from exposure to smokers in the home.

Table 2. – Studies of environmental tobacco smoke (ETS) and lung function - negative results

First author Year, Country [Ref.]	Subjects	Pulmonary function measures	Results
SCHILLING 1977, USA [56]	330 families (114 with one smoker)	FVC, FEV_1	No effect of the spouse's smoking status on the pulmonary function
COMSTOCK 1981, USA [49]	418 nonsmokers: 93 living with a smoker	FVC, FEV_1 FEV_1/FVC	RR associated with a smoker in the household: FEV_1 <80%: 1.42 FEV_1/FVC <70%: 1.19
JONES 1983, USA [62]	213 women, aged 20–39 yrs	FEV_1	% of women living with a smoker at home: low FEV_1: 32.2% high FEV_1: 39.8%
LEBOWITZ 1984, USA [63]	271 families	FVC, FEV_1 MEF_{50} MEF_{75}	No effect of the spouse's smoking status on the pulmonary function
LEBOWITZ 1984, USA [64, 65]	117 families	PEF	No effect of ETS exposure on PEF, even in asthmatic subjects
KENTNER 1984, Germany [66]	1351 white collar: 383 ETS exposed	FVC $FEF_{25–75}$ $FEF_{75–85}$	No effect of ETS exposure on the pulmonary function
LAURENT 1992, France [67]	14 male prisoners	FVC, FEV_1 MEF_{25} MEF_{75}	No effect of daily ETS exposure of 13 h during a month

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; MEF_{50} and MEF_{75}: maximal expiratory flow at 50 and 75% of FVC, respectively; $FEF_{25–75}$ and $FEF_{75–85}$: forced expiratory flow during the middle half of FVC and at end FVC, respectively; PEF: peak expiratory flow; RR: relative risk.

LEBOWITZ *et al*. [63] analysed the family aggregation of pulmonary function measurements in the nuclear families of the Tucson Epidemiological Study of Airways Obstructive Diseases. There were 271 parental pairs and their children who had satisfactory pulmonary function data. No relationship was found between fathers' or mothers' smoking and their spouses' pulmonary function, judged on FVC, FEV_1, maximum expiratory flow at 50% (MEF_{50}) and 75% (MEF_{75}) of FVC. In another analysis, 117 families (229 adults and children) were randomly selected and were studied over a 2 yr period, using daily symptom diaries and peak expiratory flow (PEF) meters [64, 65]. There were no effects of ETS exposure on PEF (or symptoms) in adults.

KENTNER *et al*. [66] carried out an investigation involving 1,351 white collar workers, in Northern Bavaria. Information about active smoking and ETS exposure - including exposure at home and in the workplace - was obtained by a standardized questionnaire. FVC, $FEF_{25–75}$, and $FEF_{75–85}$, and maximal mid-expiratory flow (MMEF) were determined. In this study, passive smokers showed no decrease in their ventilatory parameters.

On their arrival in prison, 14 volunteer male, nonsmoking prisoners were put into a cell that was already occupied by three smokers [67]. Mean daily duration of ETS exposure was 13 h. No significant difference could be demonstrated on FEV_1, FVC, MEF_{75}, and MEF_{25} between the first and the 30th day of their imprisonment.

In contrast to these negative studies, a number of investigations have detected an association between ETS exposure and pulmonary function. They are summarized in table 3. Three early studies [68–70] had found no difference between ETS exposed and unexposed nonsmokers, either in FVC or in FEV_1, but significantly lower values for $FEF_{25–75}$ and $FEF_{75–85}$ in passive smokers. WHITE and FROEB [71] provided data on 2,100 asymptomatic adults enrolled in a physical fitness programme. $FEF_{25–75}$ and $FEF_{75–85}$ appeared to be significantly lower among ETS exposed individuals than in unexposed nonsmokers. In addition, values in passive smokers were not significantly different from those in light (1–10 cigarettes per day) smokers and in smokers who did not inhale. Using the data of the French Cooperative Study PAARC, which in 1975 surveyed more than 7,800 adult residents

Table 3. – Studies of environmental tobacco smoke (ETS) and lung function - positive results

First author Year, Country [Ref.]	Subjects	Pulmonary function measures	Results
WHITE 1980, USA [71]	2100 subjects: 400 ETS exposed (200 males & 200 females)	FVC, FEV_1, FEF_{25-75}, FEF_{75-85}	For males % predicted: NS: FVC 102, FEV_1 103, FEF_{25-75} 104, FEF_{75-85} 120 PS: 99, 98, 91, 95 LS: 95, 97, 89, 77
KAUFFMANN 1983, France [72, 73]	5266 households - 750 ETS unexposed -530 ETS exposed } ≥40 yrs	FVC, FEV_1, FEF_{25-75}	FEF_{25-75} Men: Unexposed 3.58±1.17, Exposed 3.02±0.84 Women: 2.74±0.99, 2.57±0.87
SALEM 1984, Egypt [74]	196 NS 400 PS 202 S	FEV_1, PEF, $Paco_2$	NS: PEF 487.7, Pao_2 93.02, $Paco_2$ 37.0 PS: 472.8, 91.5, 39.0 S: 455.5, 87.0, 42.6
BRUNEKREEF 1985, The Netherlands [75]	163 NS women (97 available for final analysis)	FVC, FEV_1, PEF, MEF, MEF_{50}, MEF_{25}, MMEF	Women aged 40–60 yrs FEV_1: Unexposed 2.82±0.29, Exposed 2.63±0.35 PEF: 8.12±0.83, 6.79±1.01 MEF_{75}: 6.96±1.24, 5.89±1.19
SVENDSEN 1987, USA [76]	1245 never smoker men: - 959 married to NS wife - 286 married to S wife	FEV_1	Wife: Baseline n / mean; All visits n / mean NS: 514, 3591.9, 257, 3491.3 1–19·day^{-1}: 66, 3412.1, 31, 3263.3 ≥20·day^{-1}: 96, 3548.8, 50, 3489.0 All S: 162, 3493.1, 81, 3403.3
MASI 1988, Canada [77]	293 NS young adults	FVC, MEF_{50}, MEF_{75}, FEF_{25-75}, DLCO	Inverse relationship between ETS exposure and: - flow volume curve in men - DLCO in women
HOLE 1989, Scotland [52]	- 1538 ETS exposed - 917 unexposed	FEV_1	Unexposed 2.31, Exposed 2.23
MASJEDI 1990, Iran [78, 79]	- 167 men -108 women	FVC, FEV_1, PEF, FEF_{25-75}	For males % predicted FVC: Unexposed 102.1, Exposed 97.5 FEV_1: 102.6, 96.9 FEF_{25-75}: 104.3, 94.4

NS: nonsmoker; PS: passive smoker; S: smoker; LS: light smoker; $Paco_2$: arterial carbon dioxide tension; MMEF: maximal mid-expiratory flow; Pao_2: arterial oxygen tension; DLCO: diffusing capacity of the lungs for carbon monoxide. For further abbreviations see legend to table 2.

of seven cities throughout the country, KAUFFMANN and co-workers [72, 73] analysed an homogeneous group of 5,266 households, where both spouses were interviewed and no other adult was living. Restricting the comparison to subjects aged 40 yrs or more, *i.e.* presumably exposed for at least 15 yrs, and living with a current smoker of at least 10 g·day^{-1}, a decrease in FEV_1 and FEF_{25-75} was found in both sexes. Furthermore, in the more homogeneous group of women without paid work (*i.e.* presumably not exposed to workplace smoking) a dose-effect relationship, according to the amount of tobacco smoked by their husbands, was evident.

An Egyptian study compared 990 subjects, according to their smoking habits [74]. ETS exposed subjects had a decrease in all ventilatory parameters studied. Blood gas levels were estimated in 223 subjects; ETS exposed subjects presented a significant increase in arterial carbon dioxide tension ($Paco_2$). Moreover, after voluntary exposure to ETS during 30 min, a significant decrease in peak expiratory flow (PEF), and definite subjective reactions, namely, tightness of chest (25%), cough (18%), dyspnoea (9%), wheezing (5%), were observed.

BRUNEKREEF *et al.* [75] investigated the association between pulmonary function and exposure to ETS in the home, in a sample of 173 adult, nonsmoking women living in a rural area of The Netherlands.

Table 4. – Studies of environmental tobacco smoke (ETS) and chronic obstructive pulmonary diseases (COPD)

First author Year, Country [Ref.]	Subjects	Results
SIMECEK 1980, Czechoslavakia [80]	80690 NS >18 yrs (23473 men 57217 women)	Higher prevalence of chronic bronchitis among ETS exposed subjects in the home (p<0.005)
HIRAYAMA 1981, Japan [81]	91540 NS wives ≥40 yrs; Follow-up 1966–1979	66 deaths by emphysema or asthma. RR according to husband's smoking habits: NS: 1.0; ES or 1–19 cg·day^{-1}: 1.29; ≥20 cg·day^{-1}: 1.49; p: 0.474
LEE 1986, England [82]	26 COPD NS hospital in-patients	RR according to husband's smoking habits: - NS: 1.0 - S: 0.83 (95% CI 0.31–2.20)
SANDLER 1989, USA [83]	19035 NS identified in 1963; mortality associated with ETS exposure: 1963–1975	RR (95% CI) All diseases: Men 1.44 (0.75–2.75); Women 1.21 (0.87–1.69) COPD: Men 0.93 (0.16–5.32); Women 5.65 (1.19–26.8) Other: Men 1.53 (0.76–3.07); Women 1.08 (0.76–1.54)
KALANDIDI 1990, Greece [84, 85]	103 COPD NS hospital in-patients, women 40–79 yrs	RR (90% CI) according to the smoking status of the spouse: -average daily number of cigarettes: NS: 1.0; ES: 0.6 (0.3–1.30); 1–20: 2.4 (1.3–4.5); ≥21: 1.4 (0.8–2.6) - lifelong total number of cigarettes (thousands) NS: 1.0; <300: 1.3 (0.8–2.4); >300: 1.8 (0.9–3.6)

cg: cigarettes; ES: ex-smokers; CI: confidence interval. For further abbreviations see legend to tables 2 and 3.

On cross-sectional analyses, in the subgroup of women aged 40–60 yrs, PEF, FEV_1 and MEF_{75} appeared to be significantly decreased, but no trend with level of exposure was shown.

Men aged 35–57 yrs were recruited in 18 US cities, and seen annually over 6–8 yrs for cardiovascular and other disease risk factors assessment and a medical examination [76]. Pulmonary function testing was conducted at screening, and at each annual examination. Among the participants who had never smoked, 286 were married to a smoker and 959 to a nonsmoker. Men with smoking wives had significantly lower levels of pulmonary function at baseline, as measured by FEV_1. However, the difference was only about 100 ml (3,493 ml *versus* 3,591 ml).

MASI *et al*. [77] studied lung function of 293 nonsmoking volunteers of both sexes, 15–35 years old, from Montreal, Canada. Small airways abnormality, as noted by a decrease in $FEF_{25-75\%}$, MEF_{50}, and MEF_{75}, were reported in men passively exposed to cigarette smoke (measured as persons × yrs, or packs per day × persons × yrs). A decrease of the diffusing capacity of the lung in relation to cumulative ETS exposure at work was found among women.

Participants in the West Scotland study showed that mean FEV_1 was significantly higher in controls than in ETS exposed individuals [52]. Highly exposed passive smokers had significantly lower adjusted FEV_1 when compared with those with low exposure. No significant difference was found between passive smokers with low exposure and controls.

MASJEDI and co-workers [78, 79] assessed the effects of exposure to ETS on pulmonary function of nonsmoking Iranian men and women. Of the 275 subjects examined, 132 (48%) were ETS exposed, and had significant reductions in FEV_1, FVC and FEF_{25-75}. This decrease was greatest among men exposed at the workplace, whereas men exposed to ETS only at home had smaller and nonsignificant reductions in the three parameters studied. No significant difference in pulmonary function was found among the 54 women exposed to ETS, but only eight women had ETS exposure at work.

Finally, LEBOWITZ and co-workers [17] recently observed that morning PEF is decreased in subjects sleeping in bedrooms where cigarettes are smoked.

Chronic obstructive pulmonary disease (COPD)

Few studies have examined the possible association between exposure to ETS and development of COPD. They are summarized in table 4.

A study of chronic bronchitis in Czechoslovakia recorded the data obtained for the adult population of three West Bohemian districts in 1972–1975 [80]. A total of 80,690 nonsmoking adults was examined. Subjects exposed at home to ETS suffered more frequently from manifestations of chronic bronchitis (however, limited information was provided on the results).

In an analysis of mortality among Japanese nonsmoking wives of smokers, HIRAYAMA [81] presented relative risks of death for nonsmoking women, according to their husbands' smoking habits. Based on a total of 66 deaths, a positive trend, although not significant, was observed for emphysema and asthma.

As a part of a hospital case-control study carried out in England, no relationship was found between an index of cumulative ETS exposure or the smoking status of the spouse and risk of chronic bronchitis [82].

SANDLER *et al*. [83] investigated the 1963–1975 mortality of 27,891 smokers and 19,035 nonsmokers resident in Washington County, Maryland. Subjects were classified according to their 1963s smoking status. Among nonsmokers, there were 1,248 men and 9,551 women married to a smoker. Mortality from respiratory diseases was higher among the ETS exposed subjects than among unexposed nonsmokers. The trend was stronger for emphysema and bronchitis among women, and for other respiratory diseases among men.

In 1982, KALANDIDI *et al*. [84, 85] undertook a study to investigate the association between ETS and COPD in Greek women, aged 40–79 yrs. One hundred and three incident cases, who had never smoked, and 179 nonsmoking control women were interviewed regarding the smoking habits of their husbands. Relative risks of (hospitalization for) COPD were studied by average daily number of cigarettes, as well as total life-long number of cigarettes smoked by the husband. In both instances, there were statistically significant linear trends between amount of tobacco smoked by the husband and risk of COPD for the wife.

A study of US Seventh-day Adventists noted that living with a smoker for 10 yrs increased the risk of COPD by 7%, whereas a similar occupational exposure increased the risk by 11% [86].

Asthma

The evidence regarding ETS exposure producing pulmonary changes leading to bronchospasm in asthmatic patients is sparse [87]. A broad range of respiratory tract illnesses (including asthma) and functional alterations has been attributed to the exposure of infants and children to parental (especially maternal) cigarette smoking [88]. However, the effect of ETS in adult asthmatic subjects is difficult to study and less well understood, despite the fact that many patients regard ETS as a major exacerbating factor [89].

A few observational studies are available. PIPES [90] observed that 15% of patients with respiratory allergies gave a history of their respiratory allergy being precipitated or aggravated by exposure to tobacco smoke. SPEER [36] reported results of an investigation using a questionnaire given to 191 allergic nonsmokers and 250 nonallergic nonsmokers. Allergic patients experienced more nasal symptoms, headache, cough, wheezing, sore throat and hoarseness than nonallergic patients. Similarly, WEBER and FISCHER [91] reported more irritation at work among those employees suffering from hayfever exposed to ETS, as compared to non-exposed employees. In a survey of 111 asthmatic patients, 78% reported that cigarette smoke aggravated their asthma, and one third of these were exposed at home [92].

Relevant experimental studies are summarized in table 5. SHEPHARD *et al*. [93] exposed 14 asthmatic patients - whose baseline pulmonary function demonstrated slight previous airflow obstruction (FEV_1 74% predicted) - to a 2 h ETS exposure. Shortness of breath, wheezing, or tightness in the chest were experienced by five subjects. No significant changes of dynamic lung volumes were observed between sham and smoke exposure periods.

DAHMS *et al*. [94] exposed 10 asthmatic patients and 10 control subjects to ETS for an hour. The control subjects showed no change in pulmonary function, whereas the asthmatic group demonstrated a significant linear decrease in pulmonary function during the ETS exposure.

WIEDEMAN *et al*. [95] investigated the effect of acute ETS exposure both on lung function and airway reactivity (assessed by methacholine inhalation challenge testing) in a group of nine young, nonsmoking, stable asthmatic patients. Subjects were exposed for one hour to a high level of cigarette smoke. No decrease in FEV_1 or MEF_{50} was observed, but FVC showed a small but significant decrease. There was also a slight, although significant, decrease in nonspecific bronchial reactivity, the clinical significance of which is unclear.

Suggestion can induce an attack of asthma [98]. Most of the previous studies were not able to exclude the possibility that changes in pulmonary function in asthmatic subjects were emotionally related to cigarette smoke. Therefore, URCH *et al*. [96] tested this hypothesis in 24 adult nonasthmatic nonsmokers and 16 asthmatic nonsmokers. They argued that if physiological responses were dominant, changes in pulmonary function should show a dose-response relationship to ETS, whereas, if psychological reactions were dominant, any dose-response gradient would be less obvious, and subjects would have correlations between functional changes and specific measures of suggestibility. Subjects were exposed for one hour to a high ETS concentration (heavy smoke), a lower concentration (moderate smoke), or control. Cigarette smoke was generated by a cigarette smoking machine, located outside the exposure chamber, but visible to the subjects. During control exposure, the cigarettes were smoked but the smoke was diverted from the exposure chamber. Serial pulmonary function tests (FVC, FEV_1, MEF_{50}, MEF_{75}, and $FEF_{50–75}$) were performed. Asthmatics showed significant dose-response relationships for MEF_{50} at 5 min of exposure, and for FVC and FEV_1 at 30 min of exposure; results that support a physiological rather than psychological explanation of the findings.

It has been suggested that ETS is a stimulus of airway hyperresponsiveness [99]. LEBOWITZ *et al*. [17] stated that, after adjustment for age and sex, bronchial responsiveness is related to ETS in homes. KNIGHT and BRESLIN [99] exposed six asthmatic patients to one hour of ETS. At the end of the exposure, FEV_1 had fallen

Table 5. – Studies of environmental tobacco smoke (ETS) and asthma

First author Year, Country [Ref.]	Patients n	Exposure	Results
SHEPHARD 1979, USA [93]	14	14.6 m³, 2 h CO: 24 ppm	% of sham exposure: FVC 100.6±50; FEV_1 101.4±7.9; MEF_{25} 124.8±85; MEF_{50} 99.6±26.9
DAHMS 1981, USA [94]	10 10 controls	30 m³, 1 h	% change from pre-exposure value: 15' / 30' / 45' / 60' / p FVC -7.45 / -10.9 / -16.2 / -20.0 / <0.01 FEV_1 -8.6 / -12.9 / -17.5 / -21.4 / <0.01 FEF_{25-75} -10.9 / -18.4 / -19.2 / <0.01
WIEDEMANN 1986, USA [95]	9	4.25 m³, 1 h CO: 50 ppm	Pre-smoke / Post-smoke / p FVC 4.65±0.58 / 4.56±0.60 / 0.01 FEV_1 3.46±0.65 / 3.45±0.63 MEF_{50} 3.46±1.14 / 3.42±1.02 PD_{20} FEV_1 0.25±0.22 / 0.79±1.13 / 0.043 CoHB % 1.71±0.89 / 2.57±1.05 / 0.001
URCH 1988, Canada [96]	16 24 controls	14.6 m³, 1 h CO: 31 or 17 ppm	% change from pre-exposure value after 30' exposure: Sham / Moderate / Heavy FVC 0 / -41 / -105 FEV_1 +23 / +4 / -71
STANKUS 1988, USA [97]	21	26 m³, 2 h	7 out of 21 subjects experienced a significant decline (20%) in FEV_1

PD_{20} FEV_1: provocative dose of methacholine causing a 20% decrease in FEV_1; CoHB: carboxyhaemoglobin; ': minutes. For further abbreviations see legend to table 2.

by 11%, and 4 h after exposure, bronchial reactivity to inhaled histamine was increased. STANKUS *et al.* [97] exposed 21 historically ETS sensitive subjects for 2 h intervals, at two distinct smoke levels. Seven of the 21 subjects (33%) experienced a significant (>20%) and reproducible decline in FEV_1. Rechallenge studies of these subjects, 24 months later, confirmed the previous observations, and suggested that ETS sensitivity remains unchanged for relatively long (at least 2 yrs) periods of time in most smoke-sensitive subjects with asthma [100]. No classic late-phase pulmonary response (at 5–6 h after exposure) was observed, showing that cigarette-smoke sensitivity apparently differs from the classic immediate and late asthmatic responses induced by allergen-inhalation challenge. Pretreatment with albuterol, cromolyn, and a combination of albuterol and cromolyn, 30 min before ETS exposure significantly diminished airway reactivity to ETS. The same group demonstrated that almost one third of smoke-sensitive subjects with asthma and one fifth of smoke-sensitive subjects without asthma have a marked increase in bronchial hyperreactivity 6 h after ETS exposure [101]. DANUSER *et al.* [102] exposed 10 hyperreactive subjects to ETS, and observed a significant decrease of FEV_1, FVC, and MEF_{50}; a dose-response relationship was found for symptoms. However, these results were not confirmed by MAGNUSSEN and co-workers [103, 104], who exposed asthmatic adults to ETS followed by bronchoprovocation test with methacholine.

Finally, the studies on the possible allergenic action of tobacco smoke present a confusing pattern [105]. The fact that there are some indications that tobacco dust may have negative health effects [106] has sometimes been taken to mean that tobacco smoke is also allergenic. No experimental evidence has been presented to support this hypothesis [107]. A study of both allergic and non-allergic subjects revealed that intolerance to tobacco smoke was common in both groups; the effect of tobacco smoke appeared to be of an irritative rather than an allergic character [36]. BASCOM *et al.* [46] who studied upper respiratory tract sensitivity, noted an increased responsiveness to ETS in historically ETS sensitive subjects. An allergic, IgE-mediated, mechanism seemed unlikely, since no histamine was detected, suggesting that activation of mast cells was not occurring. Further evidence against the allergenic role of tobacco smoke includes the fact that smoke causes the same types of reaction in both allergic and nonallergic individuals, few allergic patients have positive skin tests to tobacco [97, 101], and, finally, that smoke does not provoke such nonrespiratory conditions as the allergic dermatoses or gastrointestinal allergy.

Discussion

Involuntary smoking produces unpleasant symptoms in many individuals. The acute irritating effect of ETS on respiratory mucous membranes is well-established. These subjective complaints may be sufficient reason

for legal regulation of smoking in confined public places. Conversely, no definite conclusion can be drawn from the studies that have investigated chronic respiratory symptoms in relation to ETS exposure. It remains controversial whether acute passive smoking is associated with important pulmonary physiological hazards. Most of the studies that have used the most sensitive indicators of pulmonary function have suggested an effect of ETS exposure; however, a number of negative studies did not support this hypothesis, and dose-response relationships have not been described [108]. The physiological significance of the small changes in pulmonary function observed in some positive studies, is unclear [19]. Most of the available studies are cross-sectional, and the relationship to long-term changes in lung function is not established. Improved characterization of susceptible subgroups is needed [29].

Four out of five studies offer support to the hypothesis of an association between ETS exposure and risk of COPD. However, excluding the study by KALANDIDI *et al.* [85], they have provided limited information, and were based on a small number of subjects; thus, these results have to be interpreted with caution. For example, the hospital-based study from England, in which no clear association between ETS exposure and COPD risk was found [82], was based on only 26 COPD cases, who were reduced to 16 in the analysis by cumulative ETS exposure. Conflicting evidence exists on the association in asthmatic patients between ETS exposure and appearance of symptoms and functional abnormalities (including change in bronchial responsiveness). Psychological factors do not seem to be involved, as well as any potential allergenic role of SS.

Bias and confounding factors

Considering that the association between ETS and non-neoplastic respiratory effects in adults, if it exists, is at least weak, one must wonder whether chance could explain the reported findings. Most of the studies which we have reviewed, especially the early ones, although suggestive of a positive effect, have had several deficiencies, which can substantially bias study results, increasing the difficulty of interpretation, especially if the likely effect of ETS is small [109, 110]. In particular, statistical considerations must be taken into account: by convention, a probability value less than 5% is deemed statistically significant. However, the p-value is a measure of the probability that the finding is due to chance, and it reflects the size of the sample studied. Thus, the absence of statistical significance for an association between an exposure and a disease may not necessarily be indicative of the absence of an association [111], but may reflect an inadequate sample size [22]. Considering the fact that, if real, the association between ETS exposure and adult respiratory non-neoplastic lung diseases is weak, it is therefore not surprising that the available studies, most of which have included a small number of subjects, could not achieve the level of the statistical significance.

Of particular concern, as a possible source of bias, are former and current smokers who report themselves as nonsmokers and, thus, may have been at higher risk than true nonsmokers, because of a history of smoking, and not because of exposure to ETS. Hence, a health effect from active smoking may be contaminating, and falsely increasing, the evaluation of the risk of ETS if this misclassification is more important among cases than controls. The recognized concordance of smoking habits in married couples is of particular concern [112]: a woman who claims to be a nonsmoker is more likely to be, or to have been, an actual smoker if married to a smoker, than if married to a nonsmoker. Conversely, misreporting among controls - and unrecognized exposure due to background ETS artificially elevates the proportion of exposed controls relative to cases, and contributes to underestimation of risk. It is plausible that the first hypothesis is most commonly implied in the studies on ETS and respiratory diseases.

In addition, most available studies had a poor definition of exposure, that may lead to non-differential misclassification, and to underestimation of existing associations.

However, available data suggest that misclassification of smoking status is not likely to explain the excess risk. FONTHAM *et al.* [113] found that 0.8% of lung cancer cases, 2.6% of colon cases, and 2% of population controls had very high cotinine levels, suggesting that they were actually current smokers. The International Agency for Research on Cancer (IARC) conducted a study explicitly designed to elucidate this methodological issue, in 13 centres from 10 countries, [18], and found a very high correlation between self-reported smoking habits and urinary cotinine, and indication that no more than 2–3% of self-reported "nonsmoker" were actually likely to be smokers. Finally, one must stress that because there is widespread exposure to ETS, this upward potential bias is counterbalanced by the downward bias from background ETS exposure to the supposedly unexposed group.

Very little data are available on the possible confounding effect of other risk factors. Most studies did not account for multipollutant exposures. Occupation and social class, in particular, have to be taken into account. Indeed, it has been suggested that smokers are over-represented in industrial jobs, and that there is a distinct pattern tying the social class and occupation of members of the household to different smoking patterns [114]. It is therefore conceivable that nonsmokers living with smokers could be more frequently exposed to toxic materials, that are carried into the home by members who have jobs at which they are exposed to hazardous substances. Another possibility is that ETS exposure in the workplace is an indicator of exposure to other irritants and toxic products. Also, families of industrial workers are likely to be located in areas subjected to higher levels of air pollutants, that could be related to the occurrence of COPD.

Criteria for a causal association

Criteria to consider in judging whether an association observed between some factor and disease is one of cause and effect have been extensively discussed [115, 116]:

- consistency cannot be judged to exist for the studies reviewed, where results are divergent between time and countries;
- the weakness of positive associations, when found, argues against strength of association;
- as most of the studies dealing with ETS exposure and adult non-neoplastic respiratory diseases were conducted in the USA, it is difficult to argue in favour of a generalization of the results;
- a dose-response relationship has not been considered in the majority of the studies. Few studies attempted to characterize exposure more specifically than using the numbers of smokers at home. Adults may have been exposed to ETS as children, and as adults either in the home or in the workplace environment, or both. The exposure time may be many decades. No study has so far considered the combined effect of these circumstances [117]. Aspects of ETS exposure, such as ventilation, room size, number of rooms in the home, duration of contact with the active smokers, that may strongly influence total exposure, have not been taken into consideration, and may explain the differences in the results. Recent studies [118] suggest that smoking by spouses contributes a large proportion of lifetime exposure to ETS, but that other sources can be important contributors. Thus, the fact that many studies took into account only the spouse's smoking status can partially explain the negativity of the findings;
- biological plausibility: combustion of tobacco products indoors contaminates air with nearly 4,000 chemicals [2]. The sidestream smoke has been documented to contain virtually all of the same compounds that have been identified in the mainstream smoke inhaled by smokers [7]. Because of the lower temperature in the burning cone of the smouldering cigarette, most partial pyrolysis products are enriched in sidestream as compared to mainstream smoke. Obviously, sidestream smoke is diluted in a considerably large volume of air, which reduces the concentrations inhaled by the involuntary smoker in comparison to those inhaled by the active smoker. Nevertheless, involuntary smoking is accompanied by exposure to many of the toxic agents generated by tobacco combustion. Furthermore, the intake of tobacco smoke components by nonsmokers has been confirmed by studies using biological markers, such as cotinine. Thus, it is biologically plausible to assume that ETS exposure is a risk factor for lung disease in nonsmokers.

ETS exposure during childhood is known to cause childhood respiratory diseases. Such diseases may also be reflected in decreased respiratory health in adulthood. These effects have not been accounted for in the studies of ETS exposure and lung function in adults, but it is likely that they would lead to underestimation of the effects of ETS in the adult studies [28].

Conclusion

The ubiquitousness of tobacco smoke in homes, workplaces, and public and private areas has until recently made exposure to ETS virtually unavoidable [16]. Involuntary exposure to tobacco smoke has only in the last decade been intensively investigated as a risk factor for disease in nonsmokers. Consequently, the evidence concerning ETS is more limited in scope than for active smoking, and controversy remains regarding the association of ETS with certain diseases [119]. Recent evidence suggests that passive smoking has subtle effects on the respiratory health of nonsmoking adults [28]; hence, exposure to ETS has, at the minimum, an adverse effect on the health of adults with pre-existing respiratory conditions, and is largely followed by acute irritant effects on healthy adults. Moreover, the potentially adverse effect of ETS exposure on respiratory condition is strongly plausible, according to biological considerations. However, if real, its long-term clinical significance is unclear, and supposed to be weak.

Considering the large number of studies which have resulted in widely divergent findings, methodologically improved studies with larger sample sizes are needed [29, 120]. However, full resolution would seem unnecessary for the evolution of a public policy on ETS, an air pollutant with a readily controllable source. One must not forget that ETS exposure is definitely considered as harmful to children, and as an environmental lung carcinogen for adults [27, 28].

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