EPIDEMIOLOGICAL EVIDENCE ON ENVIRONMENTAL TOBACCO SMOKE AND COPD

1. This review summarizes evidence from the ten published epidemiological studies of chronic obstructive pulmonary disease (COPD) among adult lifelong non-smokers.[1-10]

2. As noted in the 2006 US Surgeon General's Report[11] "COPD is a non-specific term, defined differently by clinicians, pathologists, and epidemiologists, each using different criteria based on symptoms, physiologic impairment, and pathologic abnormalities." The report stated that "the hallmark of COPD is the slowing of expiratory airflow measured by spirometric testing, with a persistently low FEV_1 [forced expiratory volume in one second] and a low ratio of FEV_1 to FVC [forced vital capacity] despite treatment". International guidelines[12] define COPD as $FEV_1/FVC < 0.70$, with severity classified in four stages ($FEV_1 \geq 80\%$, $<80\%$, $<50\%$, $<30\%$ predicted). COPD is a term that was not used widely until the 1980s, and diagnoses commonly used in the past, such as chronic bronchitis and emphysema do not equate precisely to what is now termed COPD. The studies selected for review are those using disease definitions sufficiently close to COPD to allow overall assessment. Studies based on a definition of chronic bronchitis using only cough and persistent phlegm have not been included.

3. The restriction of attention to evidence in lifelong non-smokers is because of the known very strong association of COPD with smoking,[11] and the extreme difficulty in reliably detecting any effect of ETS in the presence of a history of smoking. This is partly because the total extent of a smoker's exposure to smoke constituents will be largely determined by his own smoking habits and little by his much smaller exposure to ETS, and partly because, since smoking and ETS exposure are correlated (e.g. smokers tend to marry smokers), any errors in the assessment of the smoking history are likely to cause a residual confounding effect substantially larger than any plausible effect of ETS.[13]

4. The overall evidence from the ten studies considered shows a statistically significant increased risk of COPD in relation to ETS exposure from the spouse or other household member, with a meta-analysis based on 14 independent estimates giving an overall relative risk estimate of 1.38 (1.14-1.68). There is also some evidence of a dose-response relationship, with three[5,9,10] of the six studies which investigated this reporting a statistically significant positive trend.

5. There are a number of limitations of the evidence which make it difficult to interpret this association and dose-response relationship as providing convincing evidence of a causal relationship:

   - None of the studies have validated the lifelong non-smoking status of their subjects. It is known that some current and past smokers deny smoking on interview,[14] and given that the smoking habits of spouses or household members tend to be considerably more similar than expected by chance,[13] misclassification of even a modest proportion of ever smokers as never smokers can cause bias, particularly where, as here, the association of COPD with smoking is so strong.[15]

- Most of the studies have made little or no adjustment for potential confounding variables, such as occupation, education, diet and family history of disease, which may differ between smoking and non-smoking households.[16] Failure to adjust for household size, where the index of exposure is based on presence of a smoker in the household, is also a common problem.
- A number of the studies involve quite few COPD cases. While this is not surprising, given that the great majority of COPD cases occur in current or former smokers, this limits the ability to detect potential effects reliably.
- All the three prospective studies reporting analyses[1,4,7] involve long periods of follow-up during which smoking by the subject or spouse was assumed to be unchanged. They also rely on death certificate diagnosis, known to be inaccurate, and do not detect deaths from COPD occurring outside the original study area.
- Three of the four case-control studies use control groups that may well be unrepresentative of the population from which the cases derived. Two studies[3,10] selected controls from visitors to the hospital where the cases were, while one study[9] used a bizarre methodology which involved the informant of a death identifying a "living person about the same age who was well known to the informant" as the control, and the informant being asked about the lifestyle 10 years earlier of the decedent and the control.
- Even given the restriction to the studies chosen, there is doubt about the appropriateness of the diagnostic criteria in some of the studies. For example, in one study,[5] the definition of disease used included asthma as well as chronic bronchitis and emphysema, with the diagnosis reported by the head of the household, and not necessarily made by a physician.
- It is also noteworthy that, with the exception of two studies,[2,8] none of the studies collected information on ETS exposure from sources other than in the home, and one of those[8] presented results only for a combined index of household and workplace exposure. Unlike the situation for lung cancer, there is thus essentially no information available on risk of COPD from exposure to ETS in the workplace or in childhood.

6. Despite these reservations and the various possibilities of bias, the association observed is stronger than seen for lung cancer or heart disease[17] and must be regarded as suggestive of a possible effect of ETS exposure on risk of COPD, especially given the strong association of smoking with the disease. However, in the absence of well designed large studies the evidence must be regarded as insufficient to infer a causal relationship.

THE DATA

Table 1 summarizes some relevant features of the ten studies selected, while Table 2, supported by Figure 1, presents relative risks comparing subjects exposed and unexposed to smoking by the spouse or other household member. Table 3 summarizes relevant dose-response findings.

The term "relative risk" is taken to include direct estimates of the relative risks from prospective studies, and indirect estimates (odds ratios) from case-control studies. Relative risk estimates and 95% confidence limits presented are adjusted for covariates if adjusted data are available, and otherwise are unadjusted. Where, for some studies, the source publication provides more than one adjusted estimate, the data that are normally presented are those adjusted for most covariates.

Some studies reported relative risks and confidence intervals only by level of the exposure of interest. Relative risks and confidence intervals for the overall exposed/unexposed comparison were then calculated using the method of Morris and Gardner[18] for unexposed data or the "effective numbers" method[19] for adjusted data. These adjusted risks and intervals were used to estimate corresponding "effective numbers" of cases and controls (or subjects at risk) at each level, which could then be combined to allow estimation of risks and intervals for overall exposure.[19]

The relative risks and 95% confidence intervals are plotted graphically in the figure. In the figure, each study is represented by a square and a horizontal line. The square indicates both the value of the relative risk estimate (by its position) and the size of the study (by the area of the square, which is proportional to the inverse of the variance of the relative risk estimate, and is thus closely related to the number of lung cancers studied). The horizontal line indicates the confidence interval. By this means of presentation, large studies, which contribute more to the overall evidence, have more visual impact than small studies. The result of random-effects meta-analysis of the studies is represented at the bottom of the figure by use of a diamond, the centre of the diamond representing the relative risk and the width of the diamond representing the confidence interval.

The tables and figures are based on results from a total of ten studies. An appendix explains why results from certain other publications, which might have been thought to cite relevant data, are not included in the tables and figures.

This work was supported by the tobacco industry. The accuracy of the material presented and the interpretation of the findings are the responsibility of the authors alone.

TABLE 1 Studies providing evidence on COPD and ETS exposure in lifelong never smokers

Study Ref	Author[a]	Year[b]	Location	Type[c]	Sexes included	Definition of disease	No. of cases[d]	Definition of exposure
1	Hirayama	1984	Japan	P15	F	Emphysema or chronic bronchitis (mortality)	130	Husband ever smoked
2	Lee	1986	England	CC	M,F	Chronic bronchitis (hospitalisation)	26	Spouse smoked in marriage[e]
3	Kalandidi	1987	Greece	CC	F	Chronic obstructive lung disease (hospitalisation)	103	Husband ever smoked
4	Sandler	1989	USA	P12	M,F	Emphysema or bronchitis (mortality)	19	Lived with a smoker
5	Dayal	1994	USA	CS[f]	M,F	Chronic bronchitis, emphysema or asthma (diagnosis, questionnaire report)	219	Lives with a smoker
6	Forastiere	2000	Italy	CS[g]	F	Chronic obstructive pulmonary disease (physician diagnosis, questionnaire report)	50	Ever married to a cigarette smoker
7	Enstrom	2003	USA	P39	M,F	Chronic obstructive pulmonary disease (mortality)	264	Spouse ever smoked
8	Celli	2005	USA	CS	M,F	Airway obstruction: $FEV_1/FVC < 0.70$ (spirometry test)	414[h]	Lives with a smoker who smokes in the home, or exposed at work at least 1 hour per day
9	McGhee	2005	Hong Kong	CC	M,F	Chronic obstructive pulmonary disease (mortality)	138	Lived with a smoker 10 yrs ago
10	Sezer	2006	Turkey	CC	F	Chronic obstructive pulmonary disease (specialist clinic diagnosis)	74	Lived with a smoker for 10 yrs

[a] First author of paper
[b] Year of publication
[c] Study types are CC = case-control, CS = cross-sectional, P = prospective. For prospective studies, number of years follow-up is shown
[d] Number of cases in lifelong non-smokers
[e] Additional results are also available for a combined index based on ETS exposure at home, at work, during travel and during leisure
[f] Analysed as a nested CC study
[g] Never smoking women had been identified by earlier studies in the same areas
[h] Approximate estimate

FIGURE 1 Relative risk of COPD among lifelong never smokers in relation to smoking by the spouse or household member

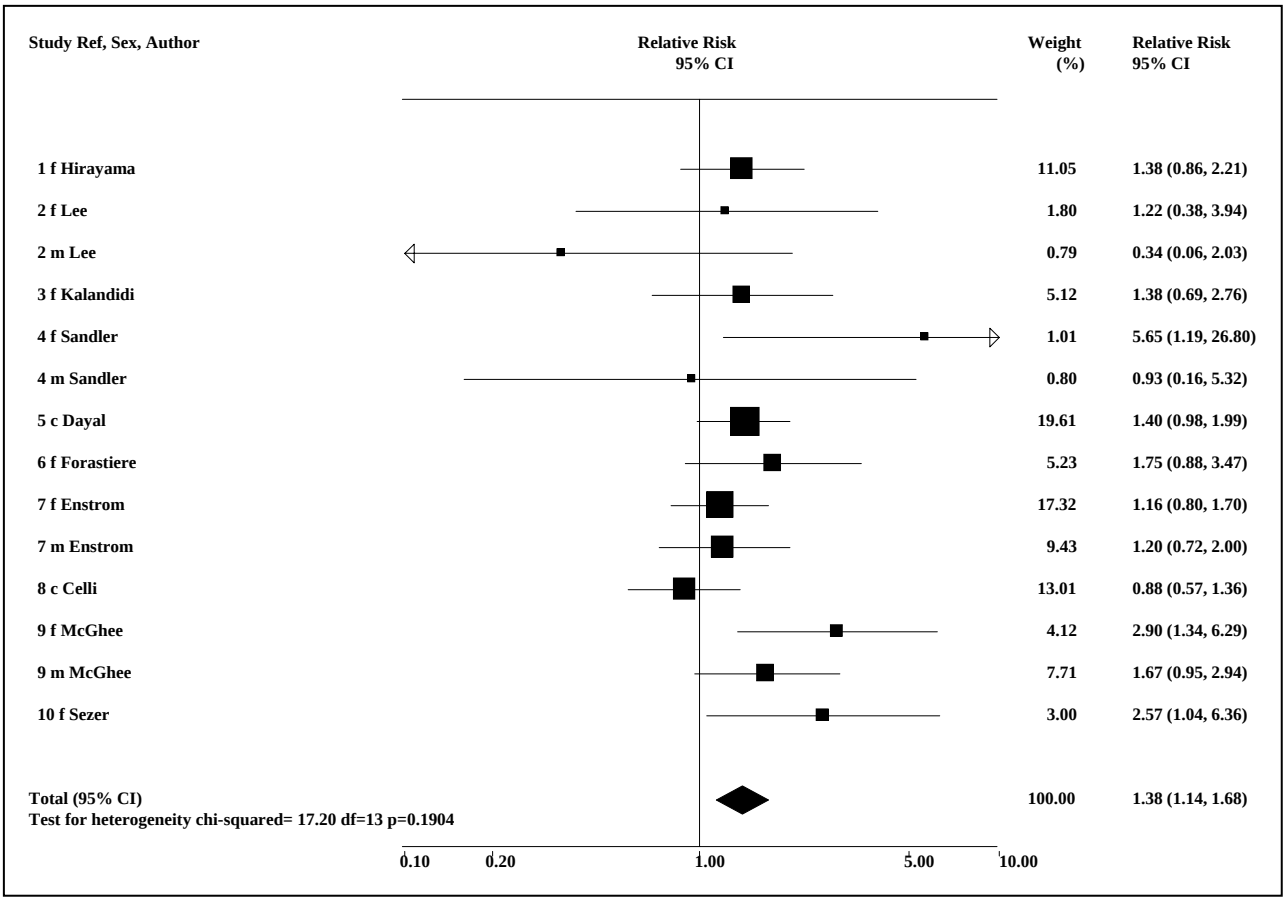

TABLE 2 Relative risk of COPD among lifelong never smokers in relation to smoking by the spouse or household member

Study Ref	Author	Type[a]	Sex	Number of cases Unexposed	Exposed	Relative risk (95% CI)	Factors adjusted for
1	Hirayama	P15	F	28	102	1.38 (0.86-2.21)[b]	Age of husband
2	Lee	CC	F	4	13	1.22 (0.38-3.94)[b]	Age, marital status
			M	8	1	0.34 (0.06-2.03)[b]	
3	Kalandidi	CC	F	13	90	1.38 (0.69-2.76)[b]	Age, occupation
4	Sandler	P12	F	2	11	5.65 (1.19-26.8)	Age, housing quality, schooling,
			M	4	2	0.93 (0.16-5.32)	marital status
5	Dayal	CS	M+F	74[c]	145[c]	1.40 (0.98-1.99)[b]	Age, sex, neighbourhood, heating, cooking
6	Forastiere	CS	F	11	39	1.75 (0.88-3.47)	Age, center, age x center, education
7	Enstrom	P39	F	45	128	1.16 (0.80-1.70)	Age, race, education, exercise,
			M	69	22	1.20 (0.72-2.00)	BMI, fruit/fruit juice, urbanization, health status
8	Celli	CS	M+F	327[c]	86[c]	0.88 (0.57-1.36)	Age, sex, race/ethnicity, BMI, education, poverty, urban residence, high risk industry, high risk occupation, biomass, allergy
9	McGhee	CC	F	15	27	2.90 (1.34-6.29)	Age, education
			M	69	27	1.67 (0.95-2.94)	
10	Sezer	CC	F	13[d]	61	2.57 (1.04-6.36)[b]	Wood ash, biomass[e]

[a] Study types are CC = case-control, CS = cross-sectional, P = prospective. For prospective studies, number of years follow-up is shown
[b] RR and/or CI estimated from data provided
[c] Approximate estimates
[d] Includes up to 10 years exposure
[e] The cases and controls were matched on age

TABLE 3 Dose-response evidence for COPD among lifelong never smokers in relation to smoking by the spouse or household member

Study				Exposure		No. of	Relative risk	Trend	Factors
Ref	Author	Type[a]	Sex	Source	Level	cases	(95% CI)	p[b]	adjusted for
1	Hirayama	P15	F	Husband	Never smoked	28	1.00		Age of husband
					Exsmoker or 1-19/day	65	1.29 (0.79-2.12)[c]		
					20+/day	37	1.60 (0.92-2.78)[c]	NS	
3	Kalandidi	CC	F	Husband	Never smoked	13	1.00		Age, occupation
					Lifelong consumption				
					≤300,000 cigs	52	1.30 (0.64-2.64)[c]		
					300,000+ cigs	38	1.70 (0.72-4.03)[c]	NS	
5	Dayal	CS	M+F	Cohabitants	No smoker	74[d]	1.00		Age, sex, neighbourhood, heating, cooking
					≤1 pack/day[e]	76[d]	1.16 (0.78-1.72)		
					>1 pack/day[e]	69[d]	1.86 (1.21-2.86)	+	
7	Enstrom	P39	F	Husband	Per level[f]	173	0.98 (0.91-1.06)	NS	Age, race, education, exercise, BMI, fruit/fruit juice, urbanization, health status
			M	Wife	Per level[f]	91	1.05 (0.88-1.24)	NS	
8	McGhee	CC	M+F	Cohabitants	No smoker	84	1.00		Age, sex, education
					1 smoker	54[g]	1.85 (1.14-3.00)		
					2+ smokers	…	2.51 (1.22-5.18)	+	
9	Sezer	CC	F	Cohabitants	<10 years	13	1.00		Wood ash, biomass[h]
					10-19 years	12	1.19 (0.58-5.68)		
					20-29 years	20	2.46 (0.83-7.33)		
					30+ years	29	4.96 (1.65-14.86)	+	

[a] Study types are CC = case-control, CS = cross-sectional, P = prospective. For prospective studies, number of years follow-up is shown

[b] + = trend $p<0.05$, NS = trend $p\geq0.05$

[c] RR and/or CI estimated from data provided

[d] Approximate estimates

[e] Sum of smoking levels for all cohabitants

[f] For husband smoking, there were 8 levels: never, former, current pipe/cigar and current cigs/day 1-9, 10-19, 20, 21-39 and 40+. For wife smoking there were 7 levels, with no level for pipe/cigar

[g] Number of cases is for the exposed groups combined

[h] The cases and controls were matched on age

Note : Study 2 (Lee) also reported a non-significant trend using an index based on exposure at home, at work, during travel and during leisure and an analysis involving only 16 COPD cases

APPENDIX

STUDIES/ANALYSES NOT INCLUDED IN TABLES AND FIGURES

In preparing the tables and figures in this document certain papers which might be thought to cite relevant data have not been referred to. For each of these papers, this appendix notes the authors, date of publication and country and the reasons for not referring to them.

- Hirayama *et al* 1981,[20] Japan: Only results for emphysema and asthma combined given, with results for a more appropriate index **(**emphysema and chronic bronchitis) available elsewhere[1].

- Hirayama *et al* 1987,[21] Japan: Gives less complete results than presented in the paper used.[1]

- Kalandidi *et al* 1990,[22] Greece : Gives essentially the same data as that presented in the letter used.[3]

- Robbins *et al* 1993,[23] USA : This study describes results of a study in non-smokers relating definite symptoms of airway obstructive disease to ETS exposure. 15% of subjects had a history of past smoking. There is a statement that analyses were repeated using only data for never smokers, but detailed results are not given.

- Leuenberger *et al* 1994,[24] Switzerland : Presents results relating various chronic respiratory symptoms to ETS in never smokers, but none of these symptoms can be equated to COPD.

- Piitulainen *et al* 1998,[25] Sweden : A study of alpha 1-antitrypsin deficient non-smokers which mainly concerns lung function, the definition of chronic bronchitis used (daily cough with phlegm at least 3 months per year) not involving reduced lung function.

- Svanes *et al* 2004,[26] 17 countries in 3 continents : None of the respiratory symptom or lung function endpoints considered equates to COPD.

- Eisner *et al* 2005,[27] USA : No analyses restricted to never smokers.

- Vineis *et al* 2005,[28] 6 European countries : No analyses restricted to never smokers.

- Xu *et al* 2005,[29] China : No analyses restricted to never smokers.

- Jindal *et al* 2006,[30] India : The definition of COPD used “Presence of cough with expectoration for more than three months in a year for the past two or more years” is actually a definition of the chronic bronchitis syndrome and not of COPD, as it does not involve reduced lung function.

- Kałucka 2006,[31] Poland: No analyses restricted to never smokers.

- Simoni *et al* 2007,[32] Italy : Presents results for workplace exposure, in addition to spousal exposure previously reported for this study.[6] However, the outcomes presented are less appropriate (OLD including asthma, and various respiratory symptoms).

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