EPIDEMIOLOGICAL EVIDENCE ON ENVIRONMENTAL TOBACCO SMOKE AND COPD

1. This review summarizes evidence from the 18 published epidemiological studies of chronic obstructive pulmonary disease (COPD) among adult lifelong non-smokers.[1-18]

2. As noted in the 2006 US Surgeon General's Report[19] "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[20] define COPD as post-bronchodilator 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 as currently defined, to allow overall assessment. In particular, studies based on a definition of chronic bronchitis using only persistent cough and phlegm, or based on FEV_1/FVC as a continuous variable, 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,[19] 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.[21]

4. The overall evidence from the 18 studies considered shows some increased risk of COPD in relation to ETS exposure from the spouse or other household member, with a random-effects meta-analysis based on 23 independent estimates giving an overall relative risk estimate of 1.19 (1.04-1.35), and estimates similar for studies in Europe (1.16, 0.75-1.81, n=8), USA (1.16, 0.99-1.35, n=8), Asia (1.23, 0.98-1.54, n=6), and the single multicountry study (1.16, 0.75-1.80). There is also some evidence of a dose-response relationship, with four[8,13,14,16] of the seven studies which investigated this reporting a statistically significant positive trend. One of these studies[16] reported no trend in relation to the number of smokers in the household, but did report positive dose-response relationships for hours of ETS exposure at home and at work.

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,[22] and given that the smoking habits of spouses or household members tend to be considerably more similar than expected by chance,[21] 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.[23]
- Many 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.[24] 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.
- Three of the prospective studies[3,7,10] reported analyses involving long periods of follow-up during which smoking by the subject or spouse was assumed to be unchanged. They also relied on death certificate diagnosis, known to be inaccurate, and did not detect deaths from COPD occurring outside the original study area. Only one of the prospective studies[4] collected information on smoking status at more than one time point. This study based diagnosis on spirometry tests, but used different criteria from the GOLD guidelines[20] published later.
- Three of the five case-control studies used control groups that may well be unrepresentative of the population from which the cases derived. Two studies[6,14] selected controls from visitors to the hospital where the cases were, while one study[13] 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,[8] 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 only seven studies[4,5,11,12,15,16,18] collected information on ETS exposure from sources other than in the home, but three of these[4,12,18] presented results only for a combined index of household and workplace exposure and a further two[11,15] presented results only for total exposure irrespective of location, results we have used in our analyses as the nearest available equivalent to smoking by the spouse or household member. Unlike the situation for lung cancer, there is very little published information available on risk of COPD from exposure to ETS in the workplace or in childhood.

6. The evidence may 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, given the marginal significance of the meta-analysis, the absence of well designed and fully reported large studies, and the limitations noted above, the evidence must be regarded as insufficient to infer a causal relationship.

THE DATA

Table 1 summarizes some relevant features of the 18 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 (or nearest available equivalent). 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[25] for unadjusted data or the method of Hamling *et al*[26] for adjusted data.

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 COPD cases 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 figure are based on results from a total of 18 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 figure.

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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	Lebowitz	1976	USA	CS	M,F	Physician-confirmed asthma, bronchial trouble or emphysema	246	Lives with current or ex smoker[e]
2	Comstock	1981	USA	CS	M[f]	FEV_1/FVC <0.70 (spirometry test[g])	30	Lives with a smoker
3	Hirayama	1984	Japan	P15	F	Emphysema or chronic bronchitis (mortality)	130	Husband ever smoked
4	Krzyza-nowski	1986	Poland	P13	M,F	Chronic obstructive pulmonary disease: FEV1 <65% predicted (spirometry test[g])	37	Exposure at home or workplace
5	Lee	1986	England	CC	M,F	Chronic bronchitis (hospitalisation)[h]	26	Spouse smoked in marriage[i]
6	Kalandidi	1987	Greece	CC	F	Chronic obstructive lung disease (hospitalisation)	103	Husband ever smoked
7	Sandler	1989	USA	P12	M,F	Emphysema or bronchitis (mortality)	19	Lived with a smoker
8	Dayal	1994	USA	CS[j]	M,F	Chronic bronchitis, emphysema or asthma (diagnosis, questionnaire report)	219	Lives with a smoker
9	Forastiere	2000	Italy	CS[k]	F	Chronic obstructive pulmonary disease (physician diagnosis, questionnaire report)	50	Ever married to a cigarette smoker
10	Enstrom	2003	USA	P39	M,F	Chronic obstructive pulmonary disease (mortality)	264	Spouse ever smoked
11	De Marco	2004	16 countries	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+[g])	156	4+ hours per day exposure on most days/nights in previous 12 months
12	Celli	2005	USA	CS	M,F	Airway obstruction: FEV_1/FVC <0.70 (spirometry test[g])	414[l]	Lives with a smoker who smokes in the home, or exposed at work at least 1 hour per day
13	McGhee	2005	Hong Kong	CC	M,F	Chronic obstructive pulmonary disease (mortality)	138	Lived with a smoker 10 yrs ago
14	Sezer	2006	Turkey	CC	F	Chronic obstructive pulmonary disease (specialist clinic diagnosis)	74	Lived with a smoker for 10 yrs
15	Xu	2007	China	CC	M,F	Emphysema or chronic bronchitis (hospital diagnosis)	1097	Spent 15+ minutes, 3+ times per week in room with smoker
16	Yin	2007	China	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+ but without bronchodilator)	429	Lives with a smoker[m]
17	Lamprecht	2008	Austria	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+)	108	Lives with a smoker
18	Zhou	2009	China	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+)	644	Exposure at home or workplace

[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]	Separate results also available for lived with current smoker or lived with exsmoker
[f]	Study also included females, but none had this outcome
[g]	No mention of use of bronchodilator prior to spirometry
[h]	Named as chronic bronchitis, but defined as ICD 491, 492, 496[27] so equates to COPD
[i]	Additional results are also available for a combined index based on ETS exposure at home, at work, during travel and during leisure
[j]	Analysed as a nested CC study
[k]	Never smoking women had been identified by earlier studies in the same areas
[l]	Approximate estimate
[m]	Additional results are also available for exposure during childhood and at work

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

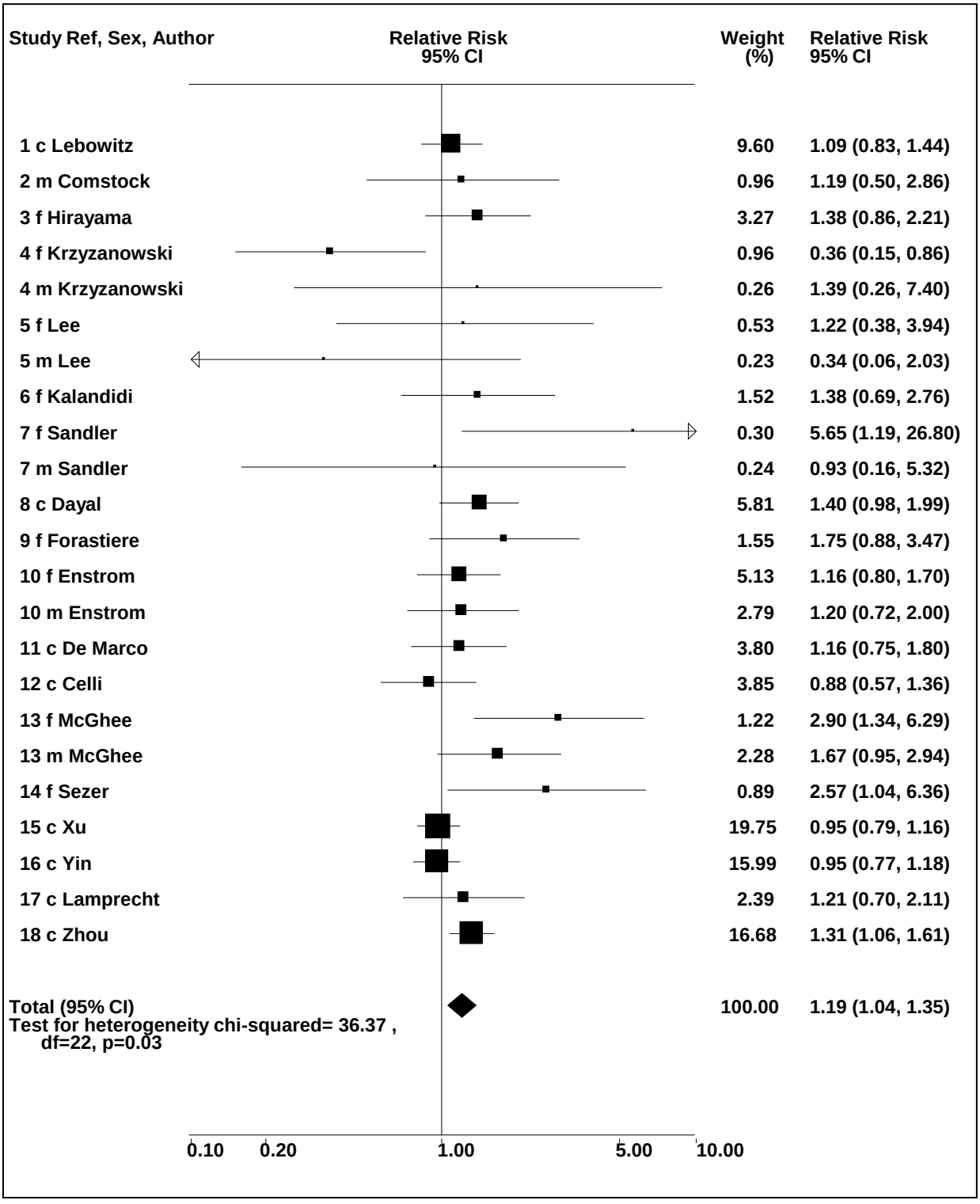

TABLE 2 Relative risk of COPD among lifelong never smokers in relation to smoking by the spouse or household member (or nearest available equivalent)

Study Ref	Author	Type[a]	Sex	Number of cases Unexposed	Exposed	Relative risk (95% CI)	Factors adjusted for
1	Lebowitz	CS	M	129	117	1.09 (0.83-1.44)[b]	None
2	Comstock	CS	M	23	7	1.19 (0.50-2.86)[b]	Age, education, number of bathrooms, persons/room, children in household, air conditioning, cooking fuel
3	Hirayama	P15	F	28	102	1.38 (0.86-2.21)[b]	Age of husband
4	Krzyzanowski	P13	F	26	6	0.36 (0.15-0.86)[b]	Age
			M	3	2	1.39 (0.26-7.40)[b]	
5	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]	
6	Kalandidi	CC	F	13	90	1.38 (0.69-2.76)[b]	Age, occupation
7	Sandler	P12	F	2	11	5.65 (1.19-26.8)	Age, housing quality, schooling, marital status
			M	4	2	0.93 (0.16-5.32)	
8	Dayal	CS	M+F	74[c]	145[c]	1.40 (0.98-1.99)[b]	Age, sex, neighbourhood, heating, cooking
9	Forastiere	CS	F	11	39	1.75 (0.88-3.47)	Age, center, age x center, education
10	Enstrom	P39	F	45	128	1.16 (0.80-1.70)	Age, race, education, exercise, BMI, fruit/fruit juice, urbanization, health status
			M	69	22	1.20 (0.72-2.00)	
11	De Marco	CS	M+F	129	27	1.16 (0.75-1.80)	Sex, childhood respiratory infections, occupational exposure, socioeconomic status
12	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
13	McGhee	CC	F	15	27	2.90 (1.34-6.29)	Age, education
			M	69	27	1.67 (0.95-2.94)	
14	Sezer	CC	F	13[d]	61	2.57 (1.04-6.36)[b]	Wood ash, biomass[e]
15	Xu	CC	M+F	Total 1097		0.95 (0.79-1.16)	Education, occupation, family income, cooking fuels, heating in winter, ventilating fans, occupational physical activity
16	Yin	CS	M+F	195	234	0.95 (0.77-1.18)[b]	Age, sex, education, occupational dust exposure, indoor air pollution
17	Lamprecht	CS	M+F	89	19	1.21(0.70-2.11)[b]	None
18	Zhou	CS	M+F	119[c]	525[c]	1.31(1.06-1.61)	Age, sex, education, BMI, family history of respiratory disease, biomass, heating fuel, ventilation in kitchen, childhood chronic cough, occupational exposures

[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 in adulthood

Study Ref	Author	Type[a]	Sex	Exposure Source	Level	No. of cases	Relative risk (95% CI)	Trend p[b]	Factors adjusted for
3	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	
6	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	
8	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)	+	
10	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	
13	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)	+	
14	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)	+	
16	Yin	CS	M+F	Cohabitants	No smoker	195	1.00		Age, sex, education, occupational dust exposure, indoor air pollution
					1 smoker	201	0.96 (0.77-1.20)		
					2+ smokers	33	0.92 (0.62-1.36)	NS	
					<2 years of 40 hours/wk	273	1.00		
					2-5 years of 40 hours/wk	73	1.11 (0.84-1.47)		
					5+ years of 40 hours/wk	83	1.60 (1.23-2.10)	++[i]	

[a] Study types are CC = case-control, CS = cross-sectional, P = prospective. For prospective studies, number of years follow-up is shown
[b] NS = trend p≥0.05, + = trend p<0.05, ++ = trend p<0.01
[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
[i] Trend estimated from data provided

Notes: 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

Study 16 (Yin) also reported non-significant trends associated with the number of smokers living in the same household in childhood and at work. However they also reported significant trends with hours of exposure at work (p=0.002) and with total hours adulthood home and work exposure (p=0.001)

APPENDIX

STUDIES/ANALYSES NOT INCLUDED IN TABLES AND FIGURE

In preparing the tables and figure 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. However papers excluded because they give results for symptoms or lung function parameters which do not equate to COPD are not mentioned in this appendix (except where the symptoms are equivalent to chronic bronchitis).

- Hirayama *et al* 1981,[28] Japan : Only results for emphysema and asthma combined given, with results for a more appropriate index (emphysema and chronic bronchitis) available elsewhere[3].

- Jones *et al* 1983, [29] USA : Results given for comparison of lowest vs highest quartile of FEV_1, which does not equate to COPD.

- Hirayama *et al* 1987,[30] Japan : Gives less complete results than presented in the paper used.[3]

- Kalandidi *et al* 1990,[31] Greece : Gives essentially the same data as that presented in the letter used.[6]

- Pope and Xu 1993,[32] China : "Chest illness" defined as chest illness with increased cough or phlegm during the last 3 years does not equate to COPD.

- Robbins *et al* 1993,[33] 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,[34] Switzerland : "Chronic bronchitis symptoms" (cough or phlegm for 3 months per year for more than 2 years) does not equate to COPD.

- Knutsen *et al* 1995,[35] USA : Based on same subjects as [36], therefore doubtful that analysis reported is restricted to never smokers.

- Piitulainen *et al* 1998,[37] 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) does not equate to COPD.

- Berglund *et al* 1999,[36] USA : No analyses restricted to never smokers.

- Birring *et al* 2002,[38] England : No control group

- Garcia-Aymerich *et al* 2003,[39] Spain : No control group. No analyses restricted to never smokers.

- Fidan *et al* 2004,[40] Turkey : Uses coffeehouse employment as surrogate measure of ETS exposure. No analyses restricted to never smokers.

- Nihlen *et al* 2004,[41] Sweden : No analyses restricted to never smokers.

- Svanes *et al* 2004,[42] 17 countries in 3 continents : "Chronic bronchitis" (both regular cough and regular phlegm) does not equate to COPD

- Upton *et al* 2004,[43] UK : Results for endpoint of COPD available for ever smokers only, none of the measures of lung function considered for never smokers equates to COPD.

- Behrendt 2005, [44] USA : Provides results for ETS exposure at home and at work, and by severity of COPD, in addition to results already included from this study[12], but non-smoker definition includes former smokers up to 5 pack-years.

- Eisner *et al* 2005,[45] USA : No analyses restricted to never smokers.

- Kotaniemi *et al* 2005,[46] Finland : No analyses restricted to never smokers.

- Vineis *et al* 2005,[47] 6 European countries : No analyses restricted to never smokers.

- Wang *et al* 2005,[48] China : No details of ETS exposure available for control subjects.

- Xu *et al* 2005,[49] China : No analyses restricted to never smokers.

- Amigo *et al* 2006,[50] Chile : No analyses restricted to never smokers.

- Eisner *et al* 2006,[51] USA : No control group.

- Jindal *et al* 2006,[52] 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 does not equate to COPD.

- Kałucka 2006,[53] Poland : No analyses restricted to never smokers.

- Mohangoo *et al* 2006,[54] Netherlands : No analyses restricted to never smokers.

- Price *et al* 2006,[55] USA : Never smokers not studied.

- Sunyer *et al* 2006,[56] 10 European countries : definition of chronic bronchitis used (chronic phlegm for more than three months each year) does not equate to COPD.

- Ebbert *et al* 2007,[57] USA : No unexposed group.

- Eisner *et al* 2007,[58] USA : Describes longitudinal decline in lung function rather than incidence of COPD. Includes smokers with less than 10 pack years or who quit 20 or more years ago.

- Hill *et al* 2007,[59] New Zealand : Presents data for an endpoint of respiratory deaths which, although it includes COPD, is too wide to be considered in this review.

- Kalucka 2007,[60] Poland : No analyses restricted to never smokers.

- Osman *et al* 2007,[61] Scotland : No control group and no analyses restricted to never smokers.

- Simoni *et al* 2007,[62] Italy : Presents results for workplace exposure, in addition to spousal exposure previously reported for this study.[9] However, the outcomes presented are less appropriate (OLD including asthma, and various respiratory symptoms).

- Sur and Mukhopadhyay 2007,[63] India : Smoking habits of individuals not assessed, families being classified as containing or not containing a smoker.

- Beyer *et al* 2008,[64] Germany : No control group. Study of exacerbation rate in subjects with pre-existing disease.

- Nataraja 2008,[65] China : Gives less complete data than paper already used for this study.[16]

- Vierikko *et al* 2008,[66] Finland : Presents data for endpoint of emphysema only in asbestos-exposed workers. No analyses restricted to never smokers except statement that no significant differences were found.

- Vozoris and Lougheed 2008,[67] Canada: Presents data for endpoints of self-reported physician-diagnosed chronic bronchitis and emphysema which cannot be combined due to lack of information on cases with both conditions.

- Eisner *et al* 2009,[68] USA : No control group. Analyses not restricted to never smokers. Results for short-term ETS exposure already reported for this study. [51]

- Evans and Chen 2009,[69] Canada : Presents results for endpoint of self-reported physician-diagnosed chronic bronchitis, which does not equate to COPD.

- Lai *et al* 2009,[70] Hong Kong : Adolescent subjects. Endpoint of respiratory symptoms (persistent cough or sputum for 3 consecutive months in past 12 months) does not equate to COPD.

- Sleszycka *et al* 2009,[71] Poland : Study of COPD prevalence in subjects with severe peripheral arterial disease. No analyses restricted to never smokers.

- Lam *et al* 2010,[72] China : ETS exposure only considered as potential confounder in analyses for other exposures.

- Lovasi *et al* 2010,[73] USA : Endpoint of emphysema only.

- Zhou *et al* 2010,[74] China : No analyses restricted to never smokers.

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