EPIDEMIOLOGICAL EVIDENCE ON ENVIRONMENTAL TOBACCO SMOKE AND COPD

A Review with Meta-Analyses

Executive Summary

Results of 23 studies relating COPD to ETS exposure in never smokers have been published. This document presents a review of the evidence, with meta-analyses.

The studies varied in design, in the indices of ETS exposures considered, and in the definitions of COPD used. The main analyses compared subjects with ETS exposure and those with no or little exposure using an index of exposure most nearly equivalent to ever smoking by the spouse, and a definition of COPD which was the nearest available equivalent to GOLD stage 1+. Random-effects meta-analysis of 28 independent relative risk estimates gave a combined estimate of 1.19 (95% CI 1.06-1.33). The 28 estimates were heterogeneous ($p<0.05$). This is partly explained by variation by sex ($p<0.01$), with higher estimates for females (1.55, 1.11-2.18, n = 10) than for males (1.28, 0.92-1.77, n = 6) or sexes combined (1.07, 0.98-1.17, n = 12), and partly by variation by number of cases ($p<0.05$), with higher estimates for studies with <50 cases (1.24, 0.74-2.07, n=10) and with 50-149 cases (1.40, 1.19-1.66, n=10) than for studies with 150+ cases (1.06, 0.95-1.19, n=8). No significant evidence of variation was seen by continent, publication period, study type or diagnosis, though there was some indication that estimates were higher from studies in Asia (1.36, 1.07-1.73, n = 8), from case-control studies (1.55, 1.04-2.32, n = 8), and for COPD mortality or hospitalization (1.40, 1.13-1.75, n = 11). When attention was restricted to results for GOLD stage 2+ COPD, a non-significant increase in risk was seen (1.18, 0.95-1.47, n = 5).

Evidence of a dose-response relationship was also heterogeneous, with significant trends reported in some studies contrasting with a lack of relationship reported by other studies.

Data on other indices of ETS exposure was much more limited. Meta-analysis of available data (for GOLD stage 1+ COPD) on childhood ETS exposure (0.90, 0.74-1.09, n = 3), and on exposure at work during adulthood (1.20, 0.63-2.29, n = 3) showed no

significant increase in risk of COPD, but a significant ($p<0.05$) increase was seen (RR = 1.28, 1.06-1.55, n = 5) for a combined index of adulthood exposure.

Detailed examination of the evidence revealed a number of weaknesses. These include limited numbers of cases in many studies, failure to update smoking status in some prospective studies, inappropriate controls in some case-control studies, and inadequate control for potential confounding variables. The variability of the definition of COPD between studies is also a problem, as is the limited evidence for specific sources of ETS, and the failure to validate reported ETS exposure by biomarkers or air measurements in the home. As many of the studies collected ETS exposure from subjects who already had COPD, recall bias may arise. Also, failure to validate current and past smoking status of self-reported lifelong non-smokers is also important, and may result in overestimation of the true association of COPD with ETS.

Overall, 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 limitations in some of the studies, the evidence can be regarded as insufficient to infer a causal relationship.

Contents

Acknowledgement

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.

1. Introduction

This review considers results from 23 studies of ETS and COPD in lifelong non-smokers ("never smokers")[1-23]. It is an update of our previous reviews[24-26] but has been extended to include more detail on indices of exposure other than spousal.

In 2006, the U.S. Surgeon General published a review[27] of the association between COPD and ETS exposure, and concluded that "the evidence is suggestive but not sufficient to infer a causal relationship between second-hand smoke exposure and risk for COPD", and the need for further research in this area was also highlighted. Although various new studies have since been published, no other reviews of this subject appear to have been undertaken.

This review attempts to assess the available evidence to date. We restrict attention to epidemiological studies of COPD in which its relationship to one or more indices of ETS exposure has been studied in lifelong never smokers. The restriction to never smokers is appropriate because of the known very strong association of COPD with smoking[27], 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[28].

As noted in the 2006 US Surgeon General's Report[27] "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[29] 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 that are sufficiently close to COPD as currently defined, so as 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. Some of the studies presented additional results using criteria that relate to more severe forms of the disease. Although these data have been presented in the tables, they have not been included in the meta-analyses.

2. Methods

In March 2013, publications not included in our previous reviews[24-26] that described the results of epidemiological studies relating ETS exposure to the risk of COPD in never smoking subjects were sought from MEDLINE searches (using the search terms "COPD", "environmental tobacco smoke", "passive smoking", "secondhand smoke exposure" and "involuntary smoking" and the date range January 2010 to March 2013), and also from the extensive files on smoking and health accumulated by P N Lee Statistics and Computing Ltd, and reference lists of papers retrieved. As noted in the introduction, results had to be available for a disease definition sufficiently close to COPD as currently defined, so as to allow overall assessment. Acceptable definitions of COPD were as described in our review of smoking and COPD[30]. Thus studies were rejected (see section 7) where results were available only for emphysema, for chronic bronchitis, for respiratory symptoms such as cough or phlegm, or by lung function criteria not equivalent to COPD.

From these publications, details were extracted of the study location and design and of the potential confounding variables considered. Where available, estimates of the relative risk, together with the associated 95% confidence interval, were obtained relating to ETS exposure at home, at work, in adulthood, and in childhood. 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 or cross-sectional 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 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[31] for unadjusted data or the method of Hamling *et al*[32] for adjusted data.

Fixed effect and random effects meta-analyses were conducted using standard methods[33]. For the main index of exposure, one result was selected from each study for which an estimate of risk of exposure (versus no or minimal exposure from that source) was

provided or could be estimated. The selection was based on the source of exposure (spouse highest preference, then partner, cohabitant, home or work). This was intended to produce an index that was most closely equivalent to "spouse ever smoked". Spousal smoking is the index traditionally used for studying effects of ETS exposure, as it has been clearly demonstrated that women married to a smoker have a markedly higher ETS exposure, as measured by cotinine, than women married to a non-smoker[34]. Further meta-analyses were carried out for other indices of exposure considered by the studies where there were sufficient data to do so.

The relative risks and 95% confidence intervals are shown graphically in Figure 1. 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 23 studies. Section 7 explains why results from certain other publications, which might have been thought to provide relevant data, are not included in the tables and figure.

3. Results

3.1 The studies

Details of the 23 studies[1-23] included in this review are given in Table 1, where they are identified by the first author of the principal publication. The table shows that one study was published in the 1970s, six in the 1980s, one in the 1990s, nine between 2000 and 2009, and six subsequently. This suggests that there has been an increase in interest in the possible association between COPD and ETS exposure in recent years, or perhaps that older papers concentrated more on endpoints not broadly equivalent to COPD.

Eight of the studies[4-6,9,14,19,21,23] were conducted in Europe (two in England, and one each in Greece, Italy, Lebanon, Poland, Sweden and Turkey), while seven studies[3,13,15-18,22] took place in Asia (four in China, and one each in Hong Kong, Japan and Taiwan). Six of the studies[1,2,7,8,10,12] were conducted in the USA. One study[11] collected data from a total of 16 countries, while another[20] combined results from 14 countries.

Most studies were of both sexes, though five studies[3,6,9,14,18] only considered females.

Most of the studies were fairly small, with the number of cases being 100 or less in nine studies[2,4,5,7,9,14,20-23] and only one study[15] considering more than 1000 cases.

Five of the studies[3,4,7,10,22] were prospective in design, with the length of follow-up ranging from 12-39 years. One study[8] was a cross-sectional study analysed as a nested case-control study. Eleven other studies[1,2,9,11,12,16,17,19-21,23] were cross-sectional, while the remaining six studies[5,6,13-15,18] were of a case-control design.

The definitions of disease used varied between study. Seven studies[3,5-7,10,13,22] required the case to have died or been hospitalised for COPD, while a further eight[11,16-21,23], mainly relatively recent cross-sectional studies, used COPD as defined by the GOLD stage 1+ criteria. The remaining eight studies[1,2,4,8,9,12,14,15] used other definitions, as detailed in Table 1.

The potential confounding variables adjusted for in the analyses are listed in Table 2. Two of the studies[1,20] did not adjust their results for any potential confounders, and some 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[35]. 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. Where adjustment was carried out, all but four of the studies[3,11,14,15] considered age, although one of these studies[3] adjusted for the age of the husband (the source of the ETS exposure) rather than adjusting for the age of the wife (the subject).

The main analyses of ETS exposure use an index of ETS exposure that relates to smoking by the spouse or household member, or to the nearest equivalent available. As shown in Table 3, which lists the definitions of ETS exposure, five studies[3,5,6,9,10] restricted attention to smoking by the spouse only, while a further 11 studies[1,2,7,8,13,14,16,20-23] considered smoking by cohabitants too, although one of these studies[13] only included subjects who had lived with a smoker 10 years previously, and another[20] only considered ETS exposure in the home in the two weeks prior to the study. The remaining studies used an index of ETS that included exposure in the home and at work[4,12,17,18] or a combination of exposure from any source[11,15,19].

Five studies also presented separate results for other indices of ETS exposure, as shown in Table 6. Four studies[16,21-23] looked at exposure at work, and one[16] of these also presented results for combined exposure at home and at work. One study[5] produced a combined index of adulthood exposure at home or work, or during travel or leisure. Three studies[16,21,23] considered childhood ETS exposure, and one study[23] also looked at parental smoking during pregnancy.

Although the majority of studies presented results comparing subjects who were exposed or unexposed to ETS, some studies required a minimum level of exposure before a subject could be classified as exposed. In one study[19], exposure had to be for at least one hour per week, while another[12] specified living with a smoker who smoked in the home or exposure at work for at least one hour per day. In one study[22] exposure had to be for 15+ minutes per day at least once per week for two or more years, while in another[15] the minimum requirement was 15 minutes or more, three or more times per week. In one study[11] subjects were only considered to have been exposed if they reported four or more hours

exposure on most days or nights in the previous year. Finally, one study[14] required 10 years of exposure.

3.2 Relative risk estimates and meta-analyses

Table 3, 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), while Table 6 presents relative risks for other indices of exposure. Tables 4 and 7 give the results of various meta-analyses. Tables 5 and 8 summarize relevant dose-response findings.

3.2.1 Main index of exposure

From Table 3, it can be seen that of the 28 individual risk estimates given for an endpoint equivalent to GOLD stage 1+, 21 are above 1.00, with five of these being significantly so at $p<0.05$. Seven studies reported a negative association between ETS exposure and COPD, but in only one of these[4] did it reach statistical significance. In addition, four studies presented a total of five relative risk estimates for the GOLD stage 2+ definition, with three estimates above 1.00, one marginally significant, and two below 1.00.

Table 4 demonstrates that the overall evidence from the 23 studies considered shows some increased risk of COPD (GOLD stage 1+ or equivalent) in relation to ETS exposure from the spouse or other household member, with a random-effects meta-analysis based on 28 independent estimates giving an overall relative risk estimate of 1.19 (1.06-1.33). Although there was no significant evidence of heterogeneity by continent, a significant increase was only seen for Asia (1.36, 1.07-1.75, n = 8). There was no significant heterogeneity by period of publication or by study type, but there was marginal evidence ($p<0.1$) of heterogeneity by diagnosis, with estimates highest for definitions based on mortality or hospitalisation (1.40, 1.13-1.75). There was stronger evidence of heterogeneity by sex ($p<0.01$), with the combined relative risk estimate 1.55 (1.11-2.18, n = 10) for females, and also by numbers of cases, a marker of study size ($p<0.05$), with larger estimates of relative risk from smaller studies (1.24, 0.74-2.07 for less than 50 cases, and 1.40, 1.19-1.66 for 50-149 cases) than from larger studies (1.06, 0.95-1.19 for more than 150 cases). Based on the five estimates for more severe COPD (GOLD stage 2+), the combined estimate was a non-significant 1.18 (0.95-1.47).

There is also some evidence of a dose-response relationship, as shown in Table 5, with six[8,13,14,16,18,22] of the 10 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 years of ETS exposure at home and at work. One study[19], which found no relationship with COPD as defined by GOLD criteria, also presented dose-response relationships using other criteria equivalent to more severe forms of COPD but still failed to find a significant increase in risk with increasing exposure.

3.2.2 Other indices of exposure

Available results for other indices of exposure are given in Tables 6 and 8, with some meta-analyses presented in Table 7.

Workplace exposure

Four studies[16,21-23] examined the relationship between COPD risk and exposure in the workplace, with one of these studies[21] differentiating between current and previous places of employment. There were three RRs for definitions equivalent to GOLD stage 1+, one of which was a non-significant increase, and the other two non-significant reductions, the combined estimate being 1.20 (0.63-2.29). The results for GOLD stage 2+ also failed to provide evidence of a possible relationship between COPD risk and workplace ETS exposure. One study[16] examined the risk of COPD in relation to increasing exposure to ETS, and found no relationship when the number of smokers was considered, but a significant positive relationship when the number of years of exposure was examined.

Any adult exposure

Three studies[5,16,22] also used indices of exposure which were combinations of various sources of ETS, with two of these presenting results for men and women separately. All five RRs presented were above 1.00, one being statistically significant. When the results were combined by meta-analysis, the estimate of 1.28 (1.06-1.55) was also significantly increased. Two of the studies presented results for dose-response relationships, but only in one study[16] was a trend evident.

Childhood exposure

Three studies[16,21,23] presented results for ETS exposure during childhood, with one[23] of these collecting information on smoking by the subject's mother and father separately. There was no clear picture of an association, with none of the RRs reaching statistical significance, and the overall estimate for GOLD stage 1+ COPD being non-significantly reduced (RR = 0.90, 0.74-1.09, n = 3). Only one study[16] examined the risk of COPD in relation to increasing exposure to childhood ETS, but there was no evidence of a positive relationship. In reality, the RRs presented decreased as the number of smokers increased, but this failed to reach statistical significance.

Other sources of exposure

One study[23] collected information on smoking during pregnancy by the subject's mother and father separately, and although both RRs were above 1.00, neither was significantly so. There were too few results to produce an overall estimate of risk. The authors did not present any results relating to a possible dose-response relationship.

4. Discussion

Based on 28 estimates of the risk of COPD associated with ever having a spouse who smoked, or the nearest equivalent ETS exposure index available, random effects meta-analysis gave a significantly increased RR estimate of 1.19 (1.06-1.33). There was also some evidence of a dose-response relationship. However, there are a number of limitations of the evidence which make it difficult to interpret these findings as providing convincing evidence of a causal relationship, as summarized below.

Limited numbers of cases

Of the 23 studies, nine[2,4,5,7,9,14,20-23] involve less than 100 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.

Publication bias

The observation that relative risks are only modestly elevated for studies with larger numbers of cases is but are more elevated for smaller studies is consistent with some publication bias, authors tending to be more likely to report studies showing stronger relationships.

Misclassification of never smoking status

None of the studies have validated the lifelong non-smoking status of their subjects, although one study[18] did verify current active and passive tobacco smoke exposure, using urinary cotinine levels, in a random sample of participants. It is known that some current and past smokers deny smoking on interview[36], and given that the smoking habits of spouses or household members tend to be considerably more similar than expected by chance[28], misclassification of even a modest proportion of ever smokers as never smokers can cause bias[37], particularly where, as here, the association of COPD with smoking is strong[30].

Weaknesses in prospective studies

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. Only two of the prospective studies[4,22] collected information on smoking status at more than

one time point. None of the studies detected deaths from COPD occurring outside the original study area.

Inappropriate controls in case-control studies

Although three of the six case-control studies used population controls, three 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 attended by the cases. The final 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.

Inadequate control for potential confounding variables

As noted earlier, some studies made little or no adjustment for variables which may differ between smoking and non-smoking households. Adjustment for dietary variables and for education has been shown to explain a substantial part of the association of lung cancer with spousal smoking[35], and the same may apply to COPD.

Variation and appropriateness of diagnostic criteria

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. The varying definitions of disease used in the different studies add further uncertainty.

Misclassification of ETS exposure

While random errors in classifying ETS exposure will tend to underestimate the relationship between COPD and ETS, errors may not be random. Thus, of the 23 studies considered, 18 were of a case-control or cross-sectional design, where recall bias may exist if subjects with COPD tend to overestimate their ETS exposure relative to subjects who do not have COPD. ETS exposure was generally not validated by biochemical markers or air measurements in the home.

Limited evidence for specific sources of ETS

It is also noteworthy that only 12 studies[4,5,11,12,15-19,21-23] collected information on ETS exposure from sources other than in the home. Four of these[4,12,17,18] presented results only for a combined index of household and workplace exposure and a further three[11,15,19] 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. While there is much less published information available on risk of COPD from exposure to ETS specifically in the workplace or in childhood than there is on smoking by the spouse or cohabitants, the data that are available show no consistent relationship between COPD risk with these indices of exposure.

5. Summary and Conclusions

This review summarizes evidence from the 23 published epidemiological studies of chronic obstructive pulmonary disease (COPD) among adult lifelong non-smokers.

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.

6. Tables

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]
1	Lebowitz[1]	1976	USA	CS	M,F	Physician-confirmed asthma, bronchial trouble or emphysema	246
2	Comstock[2]	1981	USA	CS	M[e]	FEV_1/FVC <0.70 (spirometry test[f])	30
3	Hirayama[3]	1984	Japan	P15	F	Emphysema or chronic bronchitis (mortality)	130
4	Krzyzanowski[4]	1986	Poland	P13	M,F	Chronic obstructive pulmonary disease: FEV1 <65% predicted (spirometry test[f])	37
5	Lee[5]	1986	England	CC	M,F	Chronic bronchitis (hospitalisation)[g]	26
6	Kalandidi[6]	1987	Greece	CC	F	Chronic obstructive lung disease (hospitalisation)	103
7	Sandler[7]	1989	USA	P12	M,F	Emphysema or bronchitis (mortality)	19
8	Dayal[8]	1994	USA	CS[h]	M,F	Chronic bronchitis, emphysema or asthma (diagnosis, questionnaire report)	219
9	Forastiere[9]	2000	Italy	CS[i]	F	Chronic obstructive pulmonary disease (physician diagnosis, questionnaire report)	50
10	Enstrom[10]	2003	USA	P39	M,F	Chronic obstructive pulmonary disease (mortality)	264
11	De Marco[11]	2004	16 countries	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+[f])	156
12	Celli[12]	2005	USA	CS	M,F	Airway obstruction: FEV_1/FVC <0.70 (spirometry test[f])	414[j]
13	McGhee[13]	2005	Hong Kong	CC	M,F	Chronic obstructive pulmonary disease (mortality)	138
14	Sezer[14]	2006	Turkey	CC	F	Chronic obstructive pulmonary disease (specialist clinic diagnosis)	74
15	Xu[15]	2007	China	CC	M,F	Emphysema or chronic bronchitis (hospital diagnosis)	1097

Study Ref	Author[a]	Year[b]	Location	Type[c]	Sexes included	Definition of disease	No. of cases[d]
16	Yin[16]	2007	China	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+ but without bronchodilator)	429
17	Zhou[17]	2009	China	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+)	644
18	Wu[18]	2010	Taiwan	CC	F	Chronic obstructive pulmonary disease (GOLD stage 1+)	168
19	Jordan[19]	2011	England	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+ but without bronchodilator)	779[j]
20	Lamprecht[20]	2011	14 countries	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+)	523
21	Hagstad[21]	2012	Sweden	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+)	53
22	He[22]	2012	China	P17	M,F	Chronic obstructive pulmonary disease (mortality, GOLD stage 1+[k])	36
23	Waked[23]	2012	Lebanon	CS	M,F	Chronic obstructive pulmonary disease (GOLD stage 1+)	25

[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] Study also included females, but none had this outcome
[f] No mention of use of bronchodilator prior to spirometry
[g] Named as chronic bronchitis, but defined by authors[38] as ICD 491, 492, 496 so equates to COPD
[h] Analysed as a nested CC study
[i] Never smoking women had been identified by earlier studies in the same areas
[j] Approximate estimate
[k] Based on death certificate, supplemented by medical records

TABLE 2 Potential confounding variables adjusted for in results cited in Tables 3-7

Study Ref	Author	Factors adjusted for
1	Lebowitz	None
2	Comstock	Age, education, number of bathrooms, persons/room, children in household, air conditioning, cooking fuel
3	Hirayama	Age of husband
4	Krzyzanowski	Age
5	Lee	Age, marital status (Table 3) Age (Tables 4, 6 and 7)
6	Kalandidi	Age, occupation
7	Sandler	Age, housing quality, schooling, marital status
8	Dayal	Age, sex, neighbourhood, heating, cooking
9	Forastiere	Age, center, age x center, education
10	Enstrom	Age, race, education, exercise, BMI, fruit/fruit juice, urbanization, health status
11	De Marco	Sex, childhood respiratory infections, occupational exposure, socioeconomic status
12	Celli	Age, sex, race/ethnicity, BMI, education, poverty, urban residence, high risk industry, high risk occupation, biomass, allergy
13	McGhee	Age, education (Table 3) Age, sex, education (Table 6)
14	Sezer	Wood ash, biomass[a]
15	Xu	Education, occupation, family income, cooking fuels, heating in winter, ventilating fans, occupational physical activity
16	Yin	Age, sex, education, occupational dust exposure, indoor air pollution
17	Zhou	Age, sex, education, BMI, family history of respiratory disease, biomass, heating fuel, ventilation in kitchen, childhood chronic cough, occupational exposures
18	Wu	Age, height, education level, cooking status, burning incense, tea consumption
19	Jordan	Age, sex, year of study
20	Lamprecht	None (GOLD Stage 1+ in Table 3) Age, education, occupational exposure, biomass fuel use, childhood hospitalization, comorbidity, BMI (GOLD Stage 2+ in Table 3)
21	Hagstad	Age, sex, family history of OAD, area of domicile, asthma, SES (Table 3) None (Table 4)
22	He	Age, sex, marital status, occupation, education, alcohol, diastolic blood pressure, triglyceride and total cholesterol levels, BMI
23	Waked	Age, sex, area of residence

[a] The cases and controls were matched on age

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

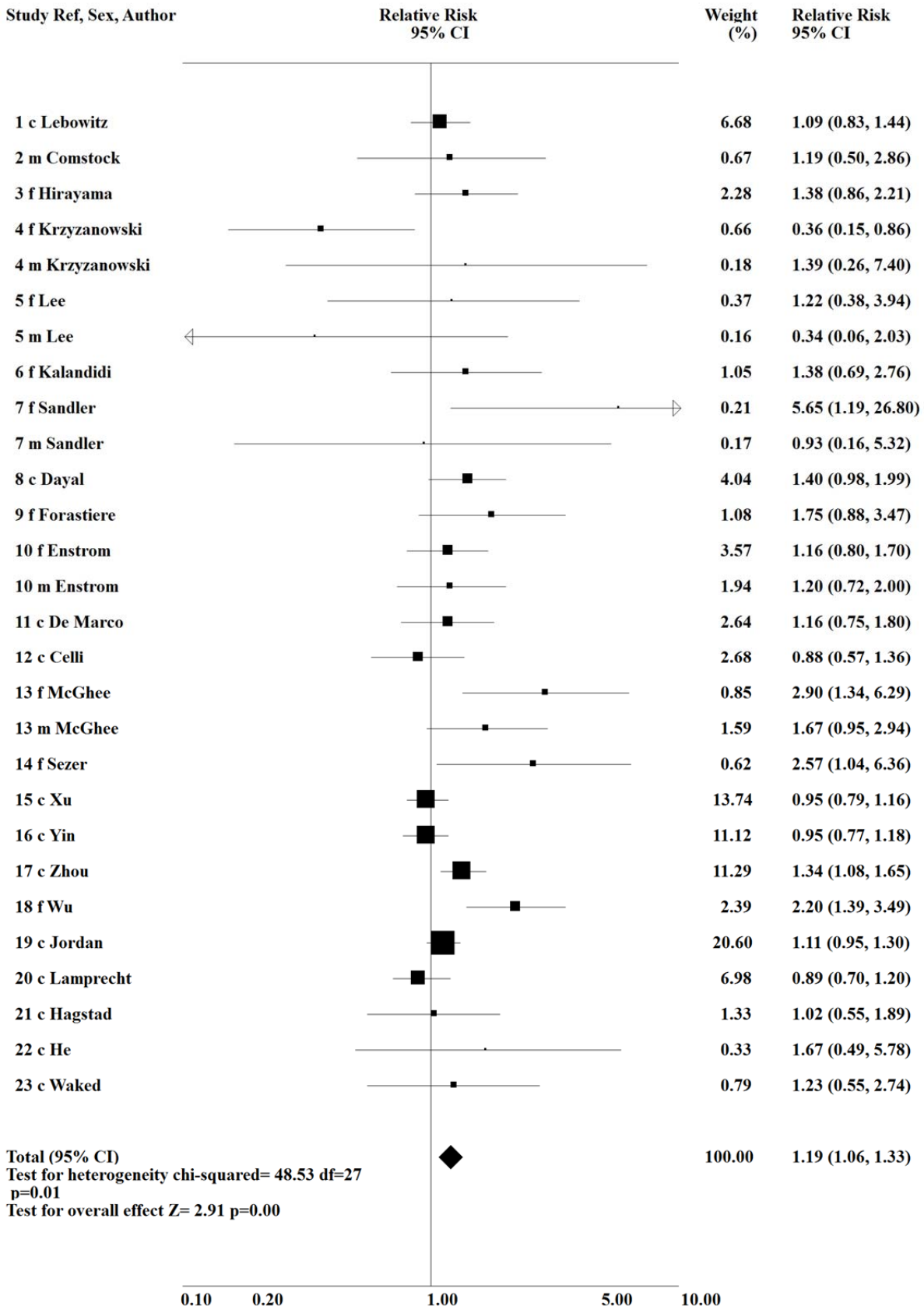

TABLE 3 Relative risk of COPD among lifelong never smokers in relation to smoking by the spouse or household member (or nearest available equivalent)

Study Ref	Author	Type[a]	Sex	Definition of exposure	Number of cases		Relative risk (95% CI)
					Unexposed	Exposed	
Definition equivalent to GOLD stage 1+:							
1	Lebowitz	CS	M+F	Lives with current or ex smoker[b]	129	117	1.09 (0.83-1.44)[c]
2	Comstock	CS	M	Lives with a smoker	23	7	1.19 (0.50-2.86)[c]
3	Hirayama	P15	F	Husband ever smoked	28	102	1.38 (0.86-2.21)[c]
4	Krzyzanowski	P13	F	Exposure at home or workplace	26	6	0.36 (0.15-0.86)[c]
			M		3	2	1.39 (0.26-7.40)[c]
5	Lee	CC	F	Spouse smoked in marriage	4	13	1.22 (0.38-3.94)[c]
			M		8	1	0.34 (0.06-2.03)[c]
6	Kalandidi	CC	F	Husband ever smoked	13	90	1.38 (0.69-2.76)[c]
7	Sandler	P12	F	Lived with a smoker	2	11	5.65 (1.19-26.8)
			M		4	2	0.93 (0.16-5.32)
8	Dayal	CS	M+F	Lives with a smoker	74[d]	145[d]	1.40 (0.98-1.99)[c]
9	Forastiere	CS	F	Ever married to a cigarette smoker	11	39	1.75 (0.88-3.47)
10	Enstrom	P39	F	Spouse ever smoked	45	128	1.16 (0.80-1.70)
			M		69	22	1.20 (0.72-2.00)
11	De Marco	CS	M+F	4+ hours per day exposure on most days/nights in previous 12 months	129	27	1.16 (0.75-1.80)
12	Celli	CS	M+F	Lives with a smoker who smokes in the home, or exposed at work at least 1 hour per day	327[d]	86[d]	0.88 (0.57-1.36)
13	McGhee	CC	F	Lived with a smoker 10 yrs ago	15	27	2.90 (1.34-6.29)
			M		69	27	1.67 (0.95-2.94)
14	Sezer	CC	F	Lived with a smoker for 10 yrs	13[e]	61	2.57 (1.04-6.36)[c]
15	Xu	CC	M+F	Spent 15+ minutes, 3+ times per week in room with smoker at any time in life	Total 1097		0.95 (0.79-1.16)
16	Yin	CS	M+F	Lives with a smoker	195	234	0.95 (0.77-1.18)[c]
17	Zhou	CS	M+F	Exposure at home or workplace	119[d]	525[d]	1.34 (1.08-1.65)[c]
18	Wu	CC	F	Exposure at home (including childhood) or workplace	41	127	2.20 (1.39-3.49)[c]
19	Jordan	CS	M+F	1+ hours of exposure per week	Total 779[d]		1.11 (0.95-1.30)[c]

Study Ref	Author	Type[a]	Sex	Definition of exposure	Number of cases		Relative risk (95% CI)
					Unexposed	Exposed	
20	Lamprecht	CS	M+F	Exposure at home in previous 2 weeks	423	100	0.89 (0.70-1.20)[c]
21	Hagstad	CS	M+F	Lives with a smoker	Total 53		1.02 (0.55-1.89)
22	He	P17	M+F	Exposure at home for 15+ minutes per day, 1+ days per week for 2+ years	10	4	1.67 (0.49-5.78)[f]
23	Waked	CS	M+F	Lives with a smoker	Total 25		1.23 (0.55-2.74)[c]
GOLD stage 2+ definition[g]							
17	Zhou	CS	M+F	Exposure at home or workplace	89	379	1.27 (1.00-1.63)[c]
19	Jordan	CS	M+F	1+ hours of exposure per week	Total 334[d]		1.13 (0.84-1.51)[c,h]
20	Lamprecht	CS	F	Exposure at home in previous 2 weeks	Total 159		1.53 (0.98-2.41)
			M		Total 67		0.97 (0.40-2.40)
21	Hagstad	CS	M+F	Lives with a smoker	Total 27		0.49 (0.20-1.23)[i]

[a] Study types are CC = case-control, CS = cross-sectional, P = prospective. For prospective studies, number of years follow-up is shown
[b] Separate results also available for lived with current smoker or lived with exsmoker
[c] RR and/or CI estimated from data provided
[d] Approximate estimates
[e] Includes up to 10 years exposure
[f] Compares exposed at home only to unexposed. Excludes those exposed at work
[g] GOLD Stage 2+ results not included in the meta-analysis or figure 1
[h] RR based on NICE criteria
[i] Compared with no airway obstruction

TABLE 4 Meta-analyses of COPD[a] risk among lifelong never smokers in relation to smoking by the spouse or household member (or nearest available equivalent)

		Fixed-effect	Random-effects	Heterogeneity[b]		
Subgroup	N[c]	Relative risk (95% CI)	Relative risk (95% CI)	Chisquared	DF[d]	p[e]
All	28	1.13 (1.05-1.21)	1.19 (1.06-1.33)	48.53	27	<0.01
By continent						
USA	8	1.16 (0.99-1.36)	1.16 (0.99-1.36)	6.88	7	NS
Asia	8	1.16 (1.04-1.29)	1.36 (1.07-1.73)	24.57	7	<0.01
Europe[f]	10	1.12 (0.98-1.29)	1.14 (0.87-1.51)	13.69	9	NS
Multicountry	2	0.96 (0.76-1.20)	0.96 (0.76-1.21)	1.02	1	NS
			Between continents	*2.36*	*3*	*NS*
By publication period						
1976-1990	10	1.12 (0.91-1.37)	1.11 (0.81-1.52)	13.68	9	NS
1991-2005	8	1.29 (1.09-1.52)	1.31 (1.07-1.59)	9.56	7	NS
2006-2012	10	1.09 (1.00-1.19)	1.15 (0.98-1.35)	22.41	9	<0.01
			Between periods	*2.88*	*2*	*NS*
By study type						
Prospective	8	1.18 (0.93-1.49)	1.17 (0.82-1.67)	11.83	7	NS
Case-control	8	1.20 (1.02-1.40)	1.55 (1.04-2.32)	23.51	7	<0.01
Cross-sectional	12	1.10 (1.01-1.20)	1.11 (1.01-1.21)	12.30	11	NS
			Between types	*0.89*	*2*	*NS*
By sex						
Males	6	1.28 (0.92-1.77)	1.28 (0.92-1.77)	3.25	5	NS
Females	10	1.50 (0.23-2.83)	1.55 (1.11-2.18)	22.14	9	<0.01
Both	12	1.07 (0.09-1.16)	1.07 (0.98-1.17)	12.78	11	NS
			Between sexes	*10.37*	*2*	*<0.01*
By diagnosis						
Mortality or hospitalization	11	1.39 (1.13-1.70)	1.40 (1.13-1.75)	10.99	10	NS
GOLD Stage 1+[g]	8	1.12 (0.02-1.23)	1.15 (0.97-1.36)	16.27	7	<0.05
Other	9	1.05 (0.93-1.20)	1.10 (0.88-1.39)	16.13	8	<0.05
			Between diagnoses	*5.14*	*2*	*<0.1*
By number of cases						
<50	10	1.25 (0.89-1.76)	1.24 (0.74-2.07)	18.42	9	<0.05
50-149	10	1.40 (1.19-1.66)	1.40 (1.19-1.66)	9.24	9	NS
150+	8	1.07 (0.98-1.16)	1.06 (0.95-1.19)	12.00	7	NS
			Between numbers	*8.87*	*2*	*<0.05*
All (GOLD stage 2+)	5	1.20 (1.02-1.42)	1.18 (0.95-1.47)	5.44	4	NS

[a] Definition of COPD nearest equivalent to GOLD stage 1+ unless stated. Data as shown in Table 3
[b] Heterogeneity relates to variation between studies within subgroup, except for results given in italics which relate to heterogeneity between subgroups
[c] N number of estimates in meta-analysis
[d] DF degrees of freedom
[e] p expressed as <0.001, <0.01, <0.05, <0.1 or NS (p≥0.1)
[f] Includes one study from Turkey and one from Lebanon
[g] Excluding mortality (study 22)

TABLE 5 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	Exposure Level	No. of cases	Relative risk (95% CI)	Trend p[b]
Definition equivalent to GOLD stage 1+:								
3	Hirayama	P15	F	Husband	Never smoked	28	1.00	
					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	
					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	
					≤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
			M	Wife	Per level[f]	91	1.05 (0.88-1.24)	NS
13	McGhee	CC	M+F	Cohabitants	No smoker	84	1.00	
					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	
					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	
					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)	++
18	Wu	CC	F	Lifetime cohabitants and co-workers	No exposure	41	1.00	
					<32 years	58	1.86 (1.10-3.17)c	
					32+ years	69	2.53 (1.51-4.26)c	+[h]
19	Jordan	CS	M+F	Any exposure	Total	779[d]		
					No exposure		1.00	
					1-19 hours/wk		1.11 (0.94-1.31)	
					20+ hours/wk		1.10 (0.81-1.49)	NS
22	He	P17	M+F	Cohabitants and co-workers	Score 0[i]	10	1.00	
					Score 1-2	8	1.52 (0.57-4.04)	
					Score 3-4	13	2.32 (0.98-5.50)	
					Score 5-6	5	5.01 (1.65-15.24)	++
GOLD stage 2+ definition:								
19	Jordan	CS	M+F	Any exposure	Total	779[d]		
					No exposure		1.00[j]	
					1-19 hours/wk		1.10 (0.81-1.49)	
					20+ hours/wk		1.33 (0.74-2.38)	NS

[a] Study types are CC = case-control, CS = cross-sectional, P = prospective. For prospective studies, number of years follow-up is shown
[b] NS p≥0.05, + p<0.05, ++ 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] Trend estimate from data provided
[i] Sum of scores for exposure at home (0 = no exposure, 1 = <4 pack years, 2 = 4 to <8 pack years, 3 = ≥8 pack years) and at work (0 = no exposure, 1 = <5, 2 = 5 to <15, 3 = ≥15, calculated from (pack years x smokers x hours/day)/100
[j] Using NICE criteria

TABLE 6 Relative risk of COPD among lifelong never smokers in relation to other indices of ETS exposure

Study				Number of cases			Relative risk	Meta-
Ref	Author	Type[a]	Sex	Unexposed	Exposed	Index of exposure[b]	(95% CI)	analysis[c]
Definition equivalent to GOLD stage 1+:								
5	Lee	CC	F	7	5	Combined index of adulthood exposure at home, work, during travel and leisure	1.04 (0.34-3.20)[d]	A
			M	1	3		1.18 (0.19-7.42)[d]	A
16	Yin	CS	M+F	225	204	Childhood – home	0.87 (0.71-1.06)[d]	C
				240	187	Adulthood – work	0.96 (0.78-1.19)[d]	W
				191[e]	238	Adulthood - home and/or work (hours)	1.24 (1.01-1.51)[d]	A
22	He	P17	M+F	10	26	Workplace[f]	2.52 (1.00-6.38)	W
			M	8	15	Adulthood – home and/or work	2.15 (0.86-5.39)	A
			F	2	11		3.31 (0.69-15.82)	A
23	Waked	CS	M+F	Total 25		During pregnancy: mother	1.59 (0.51-4.92)[d]	
						During pregnancy: father	1.69 (0.73-3.90)[d]	
						Childhood: mother	1.17 (0.39-3.52)[d]	C
						Childhood: father	1.36 (0.61-3.07)[d]	C
						Workplace	0.75 (0.18-3.14)[d]	W
GOLD stage 2+ definition:								
21	Hagstad	CS	M+F	Total 27		Childhood	0.62 (0.28-1.35)[d]	
						Current workplace	0.21 (0.05-0.88)[d]	
						Previous workplace	1.09 (0.47-2.52)[d]	

[a] Study types are CC = case control, CS = cross-sectional, P = prospective. For prospective studies, number of years follow-up is shown
[b] Comparison is with no exposure of the type specified, except where indicated otherwise
[c] Meta-analysis the RR is included in Table 5 – A = Any adult, C = Childhood and W = Workplace
[d] RR and/or CI estimated from data provided
[e] Includes up to 2 years of exposure of 40 hours per week
[f] Compares exposed at work only to unexposed. Excludes those exposed at home

TABLE 7 Meta-analyses of COPD[a] risk among lifelong never smokers in relation to other indices of ETS exposure

		Fixed-effect	Random-effects	Heterogeneity		
Index of exposure	N[b]	Relative risk (95% CI)	Relative risk (95% CI)	Chisquared	DF[c]	p[d]
Workplace	3	1.00 (0.82-1.23)	1.20 (0.63-2.29)	4.12	2	NS
Any adult[e]	5	1.28 (1.06-1.55)	1.28 (1.06-1.55)	2.88	4	NS
Child	3	0.90 (0.74-1.09)	0.90 (0.74-1.09)	1.33	2	NS

[a] Definition of COPD equivalent to GOLD stage 1+. Data as shown in Table 4
[b] N number of estimates in meta-analysis
[c] DF degrees of freedom
[d] p expressed as <0.001, <0.01, <0.05, <0.1 or NS ($p \geq 0.1$)
[e] Index includes "home or workplace" or combined index of any adulthood exposure

TABLE 8 Dose-response evidence for COPD among lifelong never smokers in relation to other indices of exposure

Study Ref	Author	Type[a]	Sex	Exposure Source	Level	No. of cases	Relative risk (95% CI)	Trend p[b]
5	Lee	CC	F	Combined index of home, work, during travel + leisure	Score 0-1[c]	7	1.00	
					Score 2-4	4	1.05 (0.29-3.75)	
					Score 5-12	1	1.03 (0.12-8.85)	NS[d]
			M		Score 0-1	1	1.00	
					Score 2-4	2	0.83 (0.07-9.56)	
					Score 5-12	1	1.90 (0.11-32.61)	NS[d]
16	Yin	CS	M+F	Childhood	No smoker	225	1.00	
					1 smoker	157	0.89 (0.72-1.10)	
					2+ smokers	47	0.81 (0.58-1.12)	NS
				Co-workers	No smoker	240	1.00	
					1 smoker	15	0.88 (0.51-1.52)	
					2+ smokers	172	0.97 (0.78-1.20)	NS
					<2 years of 40 hours/wk	286	1.00	
					2-5 years of 40 hours/wk	65	1.35 (1.01-1.80)	
					5+ years of 40 hours/wk	78	1.50 (1.14-1.97)	++
				Cohabitants + co-workers	<2 years of 40 hours/wk	191	1.00	
					2-5 years of 40 hours/wk	82	0.95 (0.72-1.24)	
					5+ years of 40 hours/wk	156	1.48 (1.18-1.85)	++

[a] Study types are CC = case-control, CS = cross-sectional, P = prospective. For prospective studies, number of years follow-up is shown
[b] NS = $p \geq 0.05$, + = $p < 0.05$, ++ = $p < 0.01$
[c] Based on sum of 0 = not at all, 1 = little, 2 = average, 3 = a lot for each source of exposure
[d] Trend estimated from data provided

7. Studies/analyses not included in tables and figure

In preparing the tables and figure in this document certain papers which might be thought to provide 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[39], 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[40], USA : Results given for comparison of lowest vs highest quartile of FEV_1, which does not equate to COPD.

- Hirayama *et al* 1987[41], Japan : Gives less complete results than presented in the paper used[3].

- Kalandidi *et al* 1990[42], Greece : Gives essentially the same data as that presented in the letter used[6].

- Pope and Xu 1993[43], 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[44], 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[45], 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[46], USA : Based on same subjects as[47], therefore doubtful that analysis reported is restricted to never smokers.

- Dennis *et al* 1996[48], Colombia : No analyses restricted to never smokers.

- Piitulainen *et al* 1998[49], 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[47], USA : No analyses restricted to never smokers.

- Birring *et al* 2002[50], England : No control group

- Garcia-Aymerich *et al* 2003[51], Spain : No control group. No analyses restricted to never smokers.

- Fidan *et al* 2004[52], Turkey : Uses coffeehouse employment as surrogate measure of ETS exposure. No analyses restricted to never smokers.

- Nihlen *et al* 2004[53], Sweden : No analyses restricted to never smokers.

- Svanes *et al* 2004[54], 17 countries in 3 continents : "Chronic bronchitis" (both regular cough and regular phlegm) does not equate to COPD

- Upton *et al* 2004[55], 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[56], 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[57], USA : No analyses restricted to never smokers.

- Kotaniemi *et al* 2005[58], Finland : No analyses restricted to never smokers.

- Vineis *et al* 2005[59], 6 European countries : No analyses restricted to never smokers.

- Wang *et al* 2005[60], China : No details of ETS exposure available for control subjects.

- Xu *et al* 2005[61], China : No analyses restricted to never smokers.

- Amigo *et al* 2006[62], Chile : No analyses restricted to never smokers.

- Eisner *et al* 2006[63], USA : No control group.

- Jindal *et al* 2006[64], 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[65], Poland : No analyses restricted to never smokers.

- Mohangoo *et al* 2006[66], Netherlands : No analyses restricted to never smokers.

- Price *et al* 2006[67], USA : Never smokers not studied.

- Sunyer *et al* 2006[68], 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[69], USA : No unexposed group.

- Eisner *et al* 2007[70], 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[71], 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[72], Poland : No analyses restricted to never smokers.

- Osman *et al* 2007[73], Scotland : No control group and no analyses restricted to never smokers.

- Simoni *et al* 2007[74], 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[75], India : Smoking habits of individuals not assessed, families being classified as containing or not containing a smoker.

- Beyer *et al* 2008[76], Germany : No control group. Study of exacerbation rate in subjects with pre-existing disease.

- Lamprecht et al 2008[77], Austria : Presents data for subset of subjects included in paper used for this study[20].

- Nataraja 2008[78], China : Gives less complete data than paper already used for this study[16].

- Vierikko *et al* 2008[79], 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[80], 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[81], USA : No control group. Analyses not restricted to never smokers. Results for short-term ETS exposure already reported for this study[63].

- Evans and Chen 2009[82], Canada : Presents results for endpoint of self-reported physician-diagnosed chronic bronchitis, which does not equate to COPD.

- Lai *et al* 2009[83], 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[84], Poland : Study of COPD prevalence in subjects with severe peripheral arterial disease. No analyses restricted to never smokers.

- Lam *et al* 2010[85], China : ETS exposure only considered as potential confounder in analyses for other exposures.

- Lovasi *et al* 2010[86], USA : Endpoint of emphysema only.

- Naiman *et al* 2010[87], Canada : ETS exposure only considered as potential confounder in analyses for other exposures.

- Roche *et al* 2010[88], France : Endpoint of chronic bronchitis only. No analyses restricted to never smokers.

- Tiberti *et al* 2010[89], Italy : No analyses restricted to never smokers.

- Zhou *et al* 2010[90], China : No analyses restricted to never smokers.

- Al Zaabi *et al* 2011[91], UAE : No analyses restricted to never smokers.

- Beatty *et al* 2011[92], USA : No analyses restricted to never smokers for endpoint of COPD, only chronic bronchitis.

- Hersh *et al* 2011[93], USA : No analyses restricted to never smokers.

- Yin *et al* 2011[94,95], China : ETS exposure only considered as potential confounder in analyses for other exposures.

- González-Garcia *et al* 2012[96], Colombia : No control group. Participants selected for tobacco smoke exposure.

- Hooper *et al* 2012[97], 14 countries : No analyses restricted to never smokers. Data already presented for this study[20].

- Johannessen *et al* 2012[98], Norway : No analyses restricted to never smokers.

- Salameh *et al* 2012[99], Lebanon : Case group includes COPD but is mostly made up of chronic bronchitis cases and results not given separately for COPD. No analyses restricted to never smokers.

8. References

1. Lebowitz MD, Burrows B. Respiratory symptoms related to smoking habits of family adults. *Chest* 1976;**69**:48-50.

2. Comstock GW, Meyer MB, Helsing KJ, Tockman MS. Respiratory effects of household exposures to tobacco smoke and gas cooking. *Am Rev Respir Dis* 1981;**124**:143-8.

3. Hirayama T. Lung cancer in Japan: effects of nutrition and passive smoking. In: Mizell M, Correa P, editors. *Lung cancer: causes and prevention, Proceedings of the International Lung Cancer Update Conference, New Orleans, Louisiana, March 3-5, 1983*. Deerfield Beach, Florida: Verlag Chemie International, Inc, 1984;175-95.

4. Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with change in ventilatory function and the development of chronic obstructive pulmonary disease in a 13-year follow-up of the Cracow study. Risk of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;**134**:1011-9.

5. Lee PN, Chamberlain J, Alderson MR. Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. *Br J Cancer* 1986;**54**:97-105.

6. Kalandidi A, Trichopoulos D, Hatzakis A, Tzannes S, Saracci R. Passive smoking and chronic obstructive lung disease [Letter]. *Lancet* 1987;**2**:1325-6.

7. Sandler DP, Comstock GW, Helsing KJ, Shore DL. Deaths from all causes in non-smokers who lived with smokers. *Am J Public Health* 1989;**79**:163-7.

8. Dayal HH, Khuder S, Sharrar R, Trieff N. Passive smoking in obstructive respiratory diseases in an industrialized urban population. *Environ Res* 1994;**65**:161-71.

9. Forastiere F, Mallone S, Lo Presti E, Baldacci S, Pistelli F, Simoni M, *et al*. Characteristics of nonsmoking women exposed to spouses who smoke: epidemiologic study on environment and health in women from four Italian areas. *Environ Health Perspect* 2000;**108**:1171-89.

10. Enstrom JE, Kabat GC. Environmental tobacco smoke and tobacco related mortality in a prospective study of Californians, 1960-98. *BMJ* 2003;**326**:1057-61. Full version available at http://bmj.com/cgi/content/full/326/7398/1057

11. de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, *et al*. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. *Thorax* 2004;**59**:120-5.

12. Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. *Am J Med* 2005;**118**:1364-72.

13. McGhee SM, Ho SY, Schooling M, Ho LM, Thomas GN, Hedley AJ, *et al*. Mortality associated with passive smoking in Hong Kong. *BMJ* 2005;**330**:287-8.

14. Sezer H, Akkurt I, Guler N, Marakoğlu K, Berk S. A case-control study on the effect of exposure to different substances on the development of COPD. *Ann Epidemiol* 2006;**16**:59-62.

15. Xu F, Yin X, Shen H, Xu Y, Ware RS, Owen N. Better understanding the influence of cigarette smoking and indoor air pollution on chronic obstructive pulmonary disease: a case-control study in Mainland China. *Respirology* 2007;**12**:891-7.

16. Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, *et al*. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. *Lancet* 2007;**370**:751-7.

17. Zhou Y, Wang C, Yao W, Chen P, Kang J, Huang S, *et al*. COPD in Chinese nonsmokers. *Eur Respir J* 2009;**33**:509-18.

18. Wu C-F, Feng N-H, Chong I-W, Wu K-Y, Lee C-H, Hwang J-J, *et al*. Second-hand smoke and chronic bronchitis in Taiwanese women: a health-care based study. *BMC Public Health* 2010;**10**:44.

19. Jordan RE, Cheng KK, Miller MR, Adab P. Passive smoking and chronic obstructive pulmonary disease: cross-sectional analysis of data from the Health Survey for England. *BMJ Open* 2011;**1**:e000153.

20. Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, *et al*. COPD in never smokers: results from the population-based Burden of Obstructive Lung Disease study. *Chest* 2011;**139**:752-63.

21. Hagstad S, Ekerljung L, Lindberg A, Backman H, Rönmark E, Lundbäck B. COPD among non-smokers - report from the obstructive lung disease in Northern Sweden (OLIN) studies. *Respir Med* 2012;**106**:980-8.

22. He Y, Jiang B, Li LS, Li LS, Ko L, Wu L, *et al*. Secondhand smoke exposure predicted COPD and other tobacco related mortality in a 17-years cohort study in China. *Chest* 2012;**142**:909-18.

23. Waked M, Salame J, Khayat G, Salameh P. Correlates of COPD and chronic bronchitis in nonsmokers: data from a cross-sectional study. *Int J Chron Obstruct Pulmon Dis* 2012;**7**:577-85.

24. Lee PN, Forey BA. *Epidemiological evidence on environmental tobacco smoke and COPD*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2007. www.pnlee.co.uk/Report.htm [Download LEE2007C]

25. Lee PN, Thornton AJ. *Epidemiological evidence on environmental tobacco smoke and COPD*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2009. www.pnlee.co.uk/Reports.htm [Download LEE2009B]

26. Lee P, Forey B, Thornton A. *Epidemiological evidence on environmental tobacco smoke and COPD*. Sutton, Surrey: P N Lee Statistics and Computing Ltd; 2011. www.pnlee.co.uk/Reports.htm [Download LEE2011A]

27. US Surgeon General. *The health consequences of involuntary exposure to tobacco smoke. A report of the Surgeon General*. Atlanta, Georgia: US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006. http://www.surgeongeneral.gov/library/reports/index.html

28. Lee PN. *Environmental tobacco smoke and mortality. A detailed review of epidemiological evidence relating environmental tobacco smoke to the risk of cancer, heart disease and other causes of death in adults who have never smoked*. Basel: Karger; 1992.

29. Global Initiative for Chronic Obstructive Disease. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2006. Executive summary*. Medical Communications Resources, Inc.; 2006, (Revised 2006). http://www.goldcopd.org/

30. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm Med* 2011;**11**:36.

31. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. *BMJ* 1988;**296**:1313-6.

32. Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Stat Med* 2008;**27**:954-70.

33. Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. *J Clin Epidemiol* 1991;**44**:127-39.

34. Lee PN. Uses and abuses of cotinine as a marker of tobacco smoke exposure. In: Gorrod JW, Jacob P, III, editors. *Analytical determination of nicotine and related compounds and their metabolites*. Amsterdam: Elsevier, 1999;669-719.

35. Fry JS, Lee PN. Revisiting the association between environmental tobacco smoke exposure and lung cancer risk. II. Adjustment for the potential confounding effects of fruit, vegetables, dietary fat and education. *Indoor Built Environ* 2001;**10**:20-39.

36. Lee PN, Forey BA. Misclassification of smoking habits as determined by cotinine or by repeated self-report - a summary of evidence from 42 studies. *J Smoking-Related Dis* 1995;**6**:109-29.

37. Lee PN, Forey BA. Misclassification of smoking habits as a source of bias in the study of environmental tobacco smoke and lung cancer. *Stat Med* 1996;**15**:581-605.

38. Alderson MR, Lee PN, Wang R. Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked. *J Epidemiol Community Health* 1985;**39**:286-93.

39. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *Br Med J* 1981;**282**:183-5.

40. Jones JR, Higgins ITT, Higgins MW, Keller JB. Effects of cooking fuels on lung function in nonsmoking women. *Arch Environ Health* 1983;**38**:219-22.

41. Hirayama T. Passive smoking and cancer: an epidemiological review. *Gann Monogr Cancer Res* 1987;**33**:127-35.

42. Kalandidi A, Trichopoulos D, Hatzakis A, Tzannes S, Saracci R. The effect of involuntary smoking on the occurrence of chronic obstructive pulmonary disease. *Soz Praventivmed* 1990;**35**:12-6.

43. Pope CA, III, Xu X. Passive cigarette smoke, coal heating, and respiratory symptoms of nonsmoking women in China. *Environ Health Perspect* 1993;**101**:314-6.

44. Robbins AS, Abbey DE, Lebowitz MD. Passive smoking and chronic respiratory disease symptoms in non-smoking adults. *Int J Epidemiol* 1993;**22**:809-17.

45. Leuenberger P, Schwartz J, Ackermann-Liebrich U, Blaser K, Bolognini G, Bongard JP, *et al*. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA study). *Am J Respir Crit Care Med* 1994;**150**:1222-8.

46. Knutsen SF, Abbey D, Burchette R, Peters J. Passive smoking, chronic respiratory disease symptoms and lung function [Abstract]. *Epidemiology* 1995;**6**:13S.

47. Berglund DJ, Abbey DE, Lebowitz MD, Knutsen SF, McDonnell WF. Respiratory symptoms and pulmonary function in an elderly nonsmoking population. *Chest* 1999;**115**:49-59.

48. Dennis RJ, Maldonado D, Norman S, Baena E, Martinez G. Woodsmoke exposure and risk for obstructive airways disease among women. *Chest* 1996;**109**:115-9.

49. Piitulainen E, Tornling G, Eriksson S. Environmental correlates of impaired lung function in non-smokers with severe α_1-antitrypsin deficiency (PiZZ). *Thorax* 1998;**53**:939-43.

50. Birring SS, Brightling CE, Bradding P, Entwisle JJ, Vara DD, Grigg J, *et al*. Clinical, radiologic, and induced sputum features of chronic obstructive pulmonary disease in nonsmokers: a descriptive study. *Am J Respir Crit Care Med* 2002;**166**:1078-83.

51. Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003;**58**:100-5.

52. Fidan F, Cimrin AH, Ergor G, Sevinc C. Airway disease risk from environmental tobacco smoke among coffeehouse workers in Turkey. *Tob Control* 2004;**13**:161-6.

53. Nihlén U, Nyberg P, Montnémery P, Löfdahl C-G. Influence of family history and smoking habits on the incidence of self-reported physician's diagnosis of COPD. *Respir Med* 2004;**98**:263-70.

54. Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P. Parental smoking in childhood and adult obstructive lung disease: results from the European Community Respiratory Health Survey. *Thorax* 2004;**59**:295-302. Additional tables available from www.thoraxjnl.com/supplemental

55. Upton MN, Davey Smith G, McConnachie A, Hart CL, Watt GCM. Maternal and personal cigarette smoking synergize to increase airflow limitation in adults. *Am J Respir Crit Care Med* 2004;**169**:479-87.

56. Behrendt CE. Mild and moderate-to-severe COPD in nonsmokers: distinct demographic profiles. *Chest* 2005;**128**:1239-44.

57. Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, Blanc PD. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. *Environ Health* 2005;**4**:7-14.

58. Kotaniemi J-T, Sovijärvi A, Lundbäck B. Chronic obstructive pulmonary disease in Finland: prevalence and risk factors. *COPD* 2005;**2**:331-9.

59. Vineis P, Airoldi L, Veglia F, Olgiati L, Pastorelli R, Autrup H, *et al*. Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former and never smokers in the EPIC prospective study. *BMJ* 2005;**330**:277-80.

60. Wang X, Zhou Y, Zeng X, Liu S, Qiu R, Xie J, *et al*. (Study on the prevalence rate of chronic obstructive pulmonary disease in northern part of Guangdong province). *Zhonghua Liu Xing Bing Xue Za Zhi* 2005;**26**:211-3.

61. Xu F, Yin X, Zhang M, Shen H, Lu L, Xu Y. Prevalence of physician-diagnosed COPD and its association with smoking among urban and rural residents in regional mainland China. *Chest* 2005;**128**:2818-23.

62. Amigo H, Erazo M, Oyarzun M, Bello S, Peruga A. Tabaquismo y enfermedad pulmonar obstructiva crónica: determinación de fracciones atribuibles (Smoking and chronic obstructive pulmonary disease: attributable risk determination). *Rev Med Chil* 2006;**134**:1275-82.

63. Eisner MD, Balmes J, Yelin EH, Katz PP, Hammond SK, Benowitz N, *et al*. Directly measured secondhand smoke exposure and COPD health outcomes. *BMC Pulm Med* 2006;**6**:12.

64. Jindal SK, Aggarwal AN, Chaudhry K, Chhabra SK, D'Souza GA, Gupta D, *et al*. A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. *Indian J Chest Dis Allied Sci* 2006;**48**:23-9.

65. Kałucka S. Występowanie POChP w rodzinie osoby palącej papierosy (The occurrence of chronic obstructive pulmonary disease (COPD) in cigarette smoking families). *Przegl Lek* 2006;**63**:848-57.

66. Mohangoo AD, van der Linden MW, Schellevis FG, Raat H. Prevalence estimates of asthma or COPD from a health interview survey and from general practitioner registration: what's the difference? *Eur J Public Health* 2006;**16**:101-5.

67. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, *et al*. Symptom-based questionnaire for identifying COPD in smokers. *Respiration* 2006;**73**:285-95.

68. Sunyer J, Jarvis D, Gotschi T, Garcia-Esteban R, Jacquemin B, Aguilera I, *et al*. Chronic bronchitis and urban air pollution in an international study. *Occup Environ Med* 2006;**63**:836-43.

69. Ebbert JO, Croghan IT, Schroeder DR, Murawski J, Hurt RD. Association between respiratory tract diseases and secondhand smoke exposure among never smoking flight attendants: a cross-sectional survey. *Environ Health* 2007;**6**:28.

70. Eisner MD, Wang Y, Haight TJ, Balmes J, Hammond SK, Tager IB. Secondhand smoke exposure, pulmonary function, and cardiovascular mortality. *Ann Epidemiol* 2007;**17**:364-73.

71. Hill SE, Blakely T, Kawachi I, Woodward A. Mortality among lifelong nonsmokers exposed to secondhand smoke at home: cohort data and sensitivity analyses. *Am J Epidemiol* 2007;**165**:530-40.

72. Kałucka S. Nastepstwa biernego tytoniu palenia w środowisku domowym (Consequences of passive smoking in home environment). *Przegl Lek* 2007;**64**:632-41.

73. Osman LM, Douglas JG, Garden C, Reglitz K, Lyon J, Gordon S, *et al*. Indoor air quality in homes of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;**176**:465-72.

74. Simoni M, Baldacci S, Puntoni R, Pistelli F, Farchi S, Lo Presti E, *et al*. Respiratory symptoms/diseases and environmental tobacco smoke (ETS) in never smoker Italian women. *Respir Med* 2007;**101**:531-8.

75. Sur D, Mukhopadhyay SP. A study on smoking habits among slum dwellers and the impact on health and economics. *J Indian Med Assoc* 2007;**105**:492-6, 498.

76. Beyer D, Mitfessel H, Gillissen A. Einfluss einer elterlichen passivrauchexposition im kindes- und jagendalter auf lungenfunktion und exazerbationstrate bei COPD-patienten (Parental smoking and passive smoke exposure in childhood promotes the COPD exacerbation rate). *Pneumologie* 2008;**62**:520-6.

77. Lamprecht B, Schirnhofer L, Kaiser B, Buist S, Studnicka M. Non-reversible airway obstruction in never smokers: results from the Austrian BOLD study. *Respir Med* 2008;**102**:1833-8.

78. Nataraja A. Passive smoking exposure is associated with an increased risk of COPD. *Thorax* 2008;**63**:48.

79. Vierikko T, Järvenpää R, Uitti J, Virtema P, Oksa P, Jaakkola MS, *et al*. The effects of secondhand smoke exposure on HRCT findings among asbestos-exposed workers. *Respir Med* 2008;**102**:658-64.

80. Vozoris N, Lougheed MD. Second-hand smoke exposure in Canada: prevalence, risk factors, and association with respiratory and cardiovascular diseases. *Can Respir J* 2008;**15**:263-9.

81. Eisner MD, Jacob PI, Benowitz NL, Balmes J, Blanc PD. Longer term exposure to secondhand smoke and health outcomes in COPD: impact of urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. *Nicotine Tob Res* 2009;**11**:945-53.

82. Evans J, Chen Y. The association between home and vehicle environmental tobacco smoke (ETS) and chronic bronchitis in a Canadian population: the Canadian Community Health Survey, 2005. *Inhal Toxicol* 2009;**21**:244-9.

83. Lai H-K, Ho S-Y, Wang M-P, Lam T-H. Secondhand smoke and respiratory symptoms among adolescent current smokers. *Pediatrics* 2009;**124**:1306-10.

84. Śleszycka J, Woźniak K, Banaszek M, Wiechno W, Domagała-Kulawik J. Czestość wystepowania oraz trudności w diagnozowaniu POchP u chroych na zaawansowana miażdzyce zarostowa tetnic konczyn dolnych (Prevalence and difficulties in chronic obstructive pulmonary disease diagnosis in patients suffering from severe peripheral arterial disease). *Pol Merkur Lekarski* 2009;**27**:92-6.

85. Lam K-BH, Jiang CQ, Jordan RE, Miller MR, Zhang WS, Cheng KK, *et al*. Prior TB, smoking, and airflow obstruction: a cross-sectional analysis of the Guangzhou Biobank Cohort Study. *Chest* 2010;**137**:593-600.

86. Lovasi GS, Diez-Roux AV, Hoffman EA, Kawut SM, Jacobs DR, Jr., Barr RG. Association of environmental tobacco smoke exposure in childhood with early emphysema in adulthood among nonsmokers: the MESA-Lung Study. *Am J Epidemiol* 2010;**171**:54-62.

87. Naiman A, Glazier RH, Moineddin R. Association of anti-smoking legislation with rates of hospital admission for cardiovascular and respiratory conditions. *CMAJ* 2010;**182**:761-7.

88. Roche N, Gaillat J, Garre M, Meunier JP, Lemaire N, Bendjenana H. Acute respiratory illness as a trigger for detecting chronic bronchitis in adults at risk of COPD: a primary care survey. *Prim Care Respir J* 2010;**19**:371-7.

89. Tiberti S, Masedu F, Valenti M. BPCO: studio trasversale di prevalenza e programma di screening in un'area a rischio nel delta del Po (COPD: cross-sectional study and screening in the Po River delta (Italy)). *Ann Ig* 2010;**22**:583-99.

90. Zhou Y, Hu G, Wang D, Wang S, Wang Y, Liu Z, *et al*. Community based integrated intervention for prevention and management of chronic obstructive pulmonary disease (COPD) in Guangdong, China: cluster randomised controlled trial. *BMJ* 2010;**341**:c6387.

91. Al Zaabi A, Asad F, Abdou J, Al Musaabi H, Al Saiari MB, Buhussien ASM, *et al*. Prevalence of COPD in Abu Dhabi, United Arab Emirates. *Respir Med* 2011;**105**:566-70.

92. Beatty AL, Haight TJ, Redberg RF. Associations between respiratory illnesses and secondhand smoke exposure in flight attendants: A cross-sectional analysis of the Flight Attendant Medical Research Institute Survey. *Environ Health* 2011;**10**:81.

93. Hersh CP, Hokanson JE, Lynch DA, Washko GR, Make BJ, Crapo JD, *et al*. Family history is a risk factor for COPD. *Chest* 2011;**140**:343-50.

94. Yin P, Jiang Y, Zhang M, Li YC, Wang LM, Zhao WH. (Association between frequency of fruit and vegetable intake and chronic obstructive pulmonary disease). *Zhonghua Yu Fang Yi Xue Za Zhi* 2011;**45**:707-10.

95. Yin P, Zhang M, Li Y, Jiang Y, Zhao W. Prevalence of COPD and its association with socioeconomic status in China: findings from China Chronic Disease Risk Factor Surveillance 2007. *BMC Public Health* 2011;**11**:586.

96. González-García M, Torres-Duque CA, Bustos A, Jaramillo C, Maldonado D. Bronchial hyperresponsiveness in women with chronic obstructive pulmonary disease related to wood smoke. *Int J Chron Obstruct Pulmon Dis* 2012;**7**:367-73.

97. Hooper R, Burney P, Vollmer WM, McBurnie MA, Gislason T, Tan WC, *et al*. Risk factors for COPD spirometrically defined from the lower limit of normal in the BOLD project. *Eur Respir J* 2012;**39**:1343-53.

98. Johannessen A, Bakke PS, Hardie JA, Eagan TML. Association of exposure to environmental tobacco smoke in childhood with chronic obstructive pulmonary disease and respiratory symptoms in adults. *Respirology* 2012;**17**:499-505.

99. Salameh P, Salame J, Khayat G, Akhdar A, Ziadeh C, Azizi S, *et al*. Exposure to outdoor air pollution and chronic bronchitis in adults: a case-control study. *Int J Occup Environ Med* 2012;**3**:165-77.