SYSTEMATIC REVIEW

REVISED Epidemiological evidence relating environmental smoke to COPD in lifelong non-smokers: a systematic review [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Some evidence suggests environmental tobacco smoke (ETS) might cause chronic obstructive pulmonary disease (COPD). We reviewed available epidemiological data in never smokers.

Methods: We identified epidemiological studies providing estimates of relative risk (RR) with 95% confidence interval (CI) for various ETS exposure indices. Confounder-adjusted RRs for COPD were extracted, or derived using standard methods.

Meta-analyses were conducted for each exposure index, with tests for heterogeneity and publication bias. For the main index (spouse ever smoked or nearest equivalent), analyses investigated variation in RR by location, publication period, study type, sex, diagnosis, study size, confounder adjustment, never smoker definition, and exposure index definition.

Results: Twenty-eight relevant studies were identified; nine European or Middle Eastern, nine Asian, eight American and two from multiple countries. Five were prospective, seven case-control and 16 cross-sectional. The COPD definition involved death or hospitalisation in seven studies, GOLD stage 1+ criteria in twelve, and other definitions in nine. For the main index, random-effects meta-analysis of 33 heterogeneous ($p < 0.001$) estimates gave a RR of 1.20 (95%CI 1.08-1.34). Higher estimates for females (1.59, 1.16-2.19, $n=11$) than males (1.29, 0.94-1.76, $n=7$) or sexes combined (1.10, 0.99-1.22, $n=15$ where sex-specific not available), and lower estimates for studies of 150+ cases (1.08, 0.97-1.20, $n=13$) partly explained the heterogeneity. Estimates were higher for Asian studies (1.34, 1.08-1.67, $n=10$), case-

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Any reports and responses or comments on the article can be found at the end of the article.

control studies (1.55,1.04-2.32, n=8), and COPD mortality or hospitalisation (1.40,1.12-1.74, n=11). Some increase was seen for severer COPD (1.29,1.10-1.52, n=7). Dose-response evidence was heterogeneous. Evidence for childhood (0.88,0.72-1.07, n=2) and workplace (1.12,0.77-1.64, n=4) exposure was limited, but an increase was seen for overall adulthood exposure (1.20,1.03-1.39, n=17). We discuss study weaknesses that may bias estimation of the association of COPD with ETS.

Conclusions: Although the evidence suggests ETS increases COPD, study weaknesses and absence of well-designed large studies preclude reliable estimation of the effect. More definitive evidence is required.

Keywords

Passive smoking, COPD, Dose-response, Meta-Analysis, Review, Pulmonary Disease

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REVISED Amendments from Version 1**Abstract: Conclusions**

In the first sentence, “precludes reliable inference of causality” has been replaced by “preclude reliable estimation of the effect”.

Introduction

In line 2 it is made clear that the paper is about exposure to ETS “from cigarettes”.

Discussion paragraph 2

The old penultimate sentence reads “While the clear relationship of smoking with COPD makes it plausible that some effect will also be evident, exposure from ETS (ref) is much less than from active smoking, as noted in the Introduction.”

The old final sentence has been replaced by “Also, various limitations of the evidence discussed below make it difficult to estimate reliably the true effect of any causal relationship. However, one should also take into account the evidence of a relationship between ETS and wheezing (refs), a symptom of COPD”.

Discussion

A new paragraph has been inserted headed “Another relevant publication” which describes results from a recent study by Ukawa *et al.* and the effect it has on meta-analysis estimates.

Discussion: Conclusion

In the first sentence “...suggestive of a possible effect ..” has been replaced by “suggestive of an effect”. The next sentence now starts “However, the marginal ..” and ends with “make it difficult to obtain an accurate estimate of any possible effect” rather than “the evidence must be regarded as inadequate to infer a causal relationship.”

The number of references has been extended from 73 to 75.

Any further responses from the reviewers can be found at the end of the article

Introduction

This systematic review aims to present an up-to-date meta-analysis of available epidemiological evidence relating exposure to environmental tobacco smoke (ETS) from cigarettes to risk of chronic obstructive pulmonary disease (COPD) in lifelong non-smokers (“never smokers”). As described below, this review considers data from 28 longitudinal, case-control or cross-sectional studies^{1–28}.

It is long established that active smoking causes COPD, the U.S. Surgeon General concluding in 1964²⁹ that “cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis”. This opinion was echoed in their 2004 report³⁰, which felt the evidence “sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality”, a view confirmed by a recent systematic review³¹.

Sidestream smoke (released between puffs from the burning cone) contains similar chemicals to mainstream smoke (drawn and inhaled by smokers), but with different relative and absolute quantities of many individual constituents³². However, sidestream smoke, after mixing with aged exhaled mainstream smoke, is

diluted massively by room air before non-smokers inhale it. Smoke constituent levels in tissues of non-smokers are very much lower than in smokers, studies using cotinine typically indicating a relative exposure factor between 0.06% and 0.4%^{33–35}, with studies using particulate matter indicating a lower factor of 0.005% to 0.02%^{36–44}. Though an effect of ETS on COPD risk is plausible, it is difficult to establish this with certainty, as a threshold is a logical possibility. The same difficulty of establishing effects of ETS exposure on other diseases caused by smoking is also present, notably for lung cancer^{31,45}.

In 2006, a review by the U.S. Surgeon General of the association of COPD with ETS exposure⁴⁶ concluded that “the evidence is suggestive but not sufficient to infer a causal relationship between second-hand smoke exposure and risk for COPD”, the need for additional research also being highlighted. Although that review cited only nine of the 28 studies considered here^{1,3,5–10,13}, and although various new studies have appeared since then, no other fully comprehensive review of this subject appears to have been undertaken.

This review, which is essentially an update of the 2006 review⁴⁶ is an attempt to assess the epidemiological evidence currently available, restricting attention to studies of COPD in which its relationship to one or more ETS exposure indices has been studied in never smokers. This restriction to never smokers is necessary as there is a very strong association of COPD with smoking⁴⁶, and it is difficult to reliably detect any ETS effect where a history of smoking is present. This is because the extent of a smoker’s overall exposure to smoke constituents is determined largely by his own smoking habits and hardly at all by his much smaller ETS exposure, and also because smoking and ETS exposure are correlated (e.g. since smokers tend to marry smokers). Any errors in assessing smoking history are therefore likely to cause a residual confounding effect much larger than any plausible ETS effect⁴⁷.

As the 2006 US Surgeon General’s Report⁴⁶ notes “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”. That report goes on to state that “the hallmark of COPD is the slowing of expiratory airflow measured by spirometric testing, with a persistently low FEV₁ [forced expiratory volume in one second] and a low ratio of FEV₁ to FVC [forced vital capacity] despite treatment”. International guidelines⁴⁸ define COPD as post-bronchodilator FEV₁/FVC <0.70, with severity classified by subdividing FEV₁ as a percentage of predicted into four groups (≥80, <80, <50 and <30%). The term COPD was little used until the 1980s, and diagnoses commonly used earlier (e.g. chronic bronchitis and emphysema) do not correspond exactly to what is now termed COPD. The studies we selected for review used disease definitions close enough to COPD as now defined to reasonably allow overall assessment. Some studies present additional results using criteria corresponding to severer forms of the disease. While these data are presented here, they are not included in our detailed meta-analyses.

Materials and methods

This systematic review was conducted according to PRISMA guidelines⁴⁹.

Study inclusion and exclusion criteria

Attention is restricted to epidemiological longitudinal, case-control or cross-sectional studies which provide risk estimates for never (or virtually never) smokers for any of the following indices of ETS exposure: spouse, partner, cohabitant, at home, at work, in adulthood, in childhood.

The term COPD is relatively recent, so we also included studies with outcomes described otherwise. Following the strategy used in our review of smoking and COPD³¹, outcomes “could be based on International Classification of Diseases (ICD) codes, on lung function criteria, on a combination of lung function criteria and symptoms, or on combinations of diagnosed conditions....where diagnoses were extracted from medical records or reported in questionnaires”. Acceptable combinations of diagnosed conditions had to include both chronic bronchitis and emphysema, but could also additionally include asthma, acute and unqualified bronchitis or bronchiectasis. However, studies were rejected where results were only available for emphysema, for chronic bronchitis, for respiratory symptoms such as cough or phlegm, or for lung function criteria not equating to COPD. Over-broad definitions such as respiratory disease were also not accepted. Acceptable lung function criteria included those of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the European Respiratory Society, and the British and American Thoracic Societies,

Studies which provide near equivalent definitions of “never smokers” are also accepted; thus never smokers can include occasional smokers or smokers with a minimal lifetime duration of smoking or number smoked. Risk estimates may be based on relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs), and must either be provided directly or be capable of being estimated from the data provided.

Literature searches

A PubMed search identified papers published up to June 2016 using the term “COPD AND (ENVIRONMENTAL TOBACCO SMOKE OR PASSIVE SMOKING OR SECOND-HAND SMOKE EXPOSURE OR INVOLUNTARY SMOKING)”, with restriction to humans. After rejecting papers that were clearly irrelevant based on the abstract, copies of the others were obtained for inspection. Other potentially relevant papers were obtained from reference lists in the 2006 Surgeon General report⁴⁶, an earlier review we conducted⁴⁷ and relevant review papers identified in the search. The complete list of potentially relevant papers were then looked at in detail to determine those which described studies satisfying the selection criteria, the rejected papers also including those where an alternative paper provided results from the same study that were more useful (e.g. based on a longer follow-up, a larger number of cases, or using a disease definition closer to COPD as currently defined).

Data recorded

Details were extracted from relevant publication on the following: study author; year of publication; study location; study design; sexes included; disease definition; number of cases; potential confounding variables considered; and never smoker definition. An effect estimate together with its associated 95% confidence interval (CI) was obtained, where available, for ETS exposure at home, at work, in adulthood, childhood, and from these sources combined. Choice between multiple definitions of COPD followed the rules of Forey *et al.*³¹, except that here we also obtained additional estimates, if available, for severer COPD. We preferred effect estimates where the denominator was with no (or minimal) exposure to the ETS type considered rather than with no exposure to any ETS. Effect estimates and 95% CIs extracted were sex-specific, if possible, and for longitudinal studies were for the longest follow-up available. Estimates adjusted for covariates, where available, were generally preferred to unadjusted estimates, except that results adjusted for symptoms or precursors of COPD were not considered. Where a study provided multiple adjusted estimates, we used that adjusted for most covariates. Dose-response data were also extracted, where available.

Derivation of effect estimates

For a study reporting effect estimates and CIs only by exposure level, that for the overall unexposed/exposed comparison was estimated using the Morris and Gardner method⁵⁰ for unadjusted data or the Hamling *et al.* method⁵¹ for adjusted data. These methods also allowed estimation of the significance of dose-related trends, if not given in the source publication.

Alternative types of effect estimates

As the great majority of effect estimates were ORs derived from case-control or cross-sectional studies, and as the RRs or HRs from longitudinal studies were all based on low incidences, where the OR would be virtually the same, all estimates were treated as if they were ORs. In the rest of this paper, we use OR rather than referring to specific types of effect estimate.

Meta-analyses

A pre-planned set of fixed-effect and random-effects meta-analyses were carried out using standard methods⁵². Heterogeneity was quantified by H , the ratio of the heterogeneity chi squared to its degrees of freedom. The I-squared statistic⁵³ is related to H by the formula $I^2 = 100 (H-1)/H$. Publication bias tests were also conducted using the Egger method⁵⁴.

Our main analyses included OR estimates for the exposure most closely equivalent to “spouse ever smoked” where results were provided or could be estimated. This selection was based on the source of exposure (spouse highest preference, then partner, cohabitant, home or work). Spousal smoking is traditionally used for studying possible ETS effects, it being clearly demonstrated that women married to a smoker have much higher cotinine levels than women married to a non-smoker⁵⁵. Apart from the meta-analyses using all available estimates, meta-analyses also investigated variation in the OR according to a list

of pre-defined factors, and using the following subsets: continent (North America, Asia, Europe, multicountry); publication period (1976–1990, 1991–2005, 2006–2016); study type (longitudinal, case-control, cross-sectional); sex (males, females, combined); diagnosis (mortality or hospitalisation, GOLD stage 1+, other); method of taking asthma into account (included as part of the COPD definition, adjusted for, asthmatic participants excluded, ignored); number of cases estimate based on (<50, 50–149, 150+ cases); extent of confounder adjustment (unadjusted for age, adjusted for age and at most four other variables, adjusted for age and five or more variables); never smoker definition (never smoked any product, never smoked but product unstated, other – including never cigarette smoker, occasional smoker or very short-term smoker); and definition of exposure index (spouse specifically, other exposure at home, other).

Meta-analyses were also carried out for the main index using the estimates for severer COPD, and also for other indices of exposure with sufficient data (workplace, overall adult – including at least home and work, childhood). Here, data were too limited to study variation in the OR by the subsets described above.

Results of the overall meta-analyses are displayed as forest plots. In each plot, individual estimates are listed in increasing order of the OR. For the main index, estimates are grouped by region. Random-effects estimates are also shown. The estimates are not only shown numerically, but in graphical form on a logarithmic scale, where the OR is shown as a square, the area of which is proportional to its inverse-variance weight. Arrows warn when the CI goes outside the range of the plot.

Study quality and risk of bias

We did not attempt to derive any overall score based on study quality and risk of bias for each individual study, as the relative importance of different sources of bias or poor study quality is difficult or impossible to assess accurately. Instead, we attempted to gain insight into this in two ways. First, as mentioned in the previous section, we carried out meta-analyses showing how the OR varied by some relevant aspects linked to study quality and bias, such as study size, study type, source of diagnosis, method of taking asthma into account, and extent of confounder adjustment. Second, we considered factors affecting quality and bias in the discussion section, including some factors that affected all or virtually all of the studies.

Results

Searches

The PubMed search produced 509 hits. As summarized in [Figure 1](#), Seventy-five were considered of potential relevance based on the abstracts, 15 of which proved to meet the inclusion criteria on examination of the papers themselves. Further examination of reference lists in reviews^{46,47,56–63} and in papers obtained identified a further 40 papers of potential relevance, 13 of which met the inclusion criteria. Of the 87 papers examined but not accepted, the most common reasons for rejection were no results for never smokers (38 papers), not COPD as defined (26), no control group or no results for unexposed participants (11) and better results for the same cohort given in another paper (9), some studies being rejected for more than one reason.

[Supplementary File 1](#) gives details of the studies rejected and fuller reasons for rejection.

Studies identified

[Table 1](#) gives details of the 28 epidemiological studies that met the inclusion criteria, including author, reference(s), publication year, location, design, sexes included, disease definition, account taken of asthma, and numbers of cases in never smokers. The studies are listed in chronological order of publication and are given consecutive identifying study numbers.

The included studies are mainly of representative populations, except that studies 18 and 26 have a large proportion with respiratory symptoms. Of the 28 studies, one was published in the 1970s, six in the 1980s, one in the 1990s, nine between 2000 and 2009 and 11 more recently.

Nine studies were conducted in Europe or the Middle East, subsequently referred to as “Europe” (two in England, and one each in Greece, Italy, Lebanon, Poland, Sweden, Switzerland and Turkey), while nine took place in Asia (five in China, and one each in Hong Kong, Japan, Korea and Taiwan), seven in North America (six in the USA and one in Canada) and one in South America (Brazil). Two studies presented combined results, one from 16 countries, the other from 14.

Five studies were longitudinal in design, with the length of follow-up varying from 12 to 39 years, one was a cross-sectional study analysed as a nested case-control study, 16 other studies were cross-sectional, with the remaining six of case-control design.

Most studies were of both sexes, though six studies considered only females.

Two studies considered those with a minimum age of 60, with a further 16 having a minimum age between 35 and 51. Other studies had a lower minimum age.

Definitions of outcome used varied by study. Seven studies required the case to have died or been hospitalised for COPD, while a further 12, mainly relatively recent cross-sectional studies, used COPD as defined by the GOLD stage 1+ criteria. The remaining nine studies used other definitions, as detailed in [Table 1](#). Five studies (17, 19, 20, 26, 28) also provided results for severer COPD (generally equivalent to GOLD 2+, see footnotes to [Table 1](#)).

Twenty-one studies ignored asthma in their outcome definition and analysis, with the remaining 12 studies equally divided into those that included asthma in their outcome definition, excluded asthmatics, or adjusted for asthma status in analysis.

Most studies were small, with ten studies considering less than 100 cases and only one study (15) more than 1000 cases.

[Table 2](#) gives the adjustment variables used and the definitions of never smokers used in the studies.

Figure 1. Flow-chart of study selection and exclusion criteria. The flow-chart shows the number of articles identified from the PubMed search and from reference lists of reviews and articles obtained, as well as showing those excluded, with reasons for exclusion. Note that some articles were excluded for multiple reasons.

Table 1. Studies providing evidence on COPD and ETS exposure in never smokers.

Study No.	Author ^a	Year ^b	Location	Type ^c	Sexes included	Age range ^d	Definition of COPD used ^e	Accounting for asthma	No. of cases ^f
1	Lebowitz ¹	1976	USA	CS	M,F	15+	Asthma, bronchial trouble or emphysema (physician diagnosis, questionnaire report)	Included	246
2	Comstock ²	1981	USA	CS	M ^g	20+	FEV ₁ /FVC <0.70 (spirometry test ^h)	Ignored	30
3	Hirayama ³	1984	Japan	L15	F	40+	Emphysema or chronic bronchitis (mortality)	Ignored	130
4	Krzyzanowski ⁴	1986	Poland	L13	M,F	19–70	FEV ₁ <65% predicted (spirometry test ^h)	Ignored	37
5	Lee ⁵	1986	England	CC	M,F	35–74	Chronic bronchitis ⁱ (hospitalisation)	Ignored	26
6	Kalandidi ⁶	1987	Greece	CC	F	40–79	Chronic obstructive lung disease (hospitalisation)	Excluded ^j	103

Study No.	Author ^a	Year ^b	Location	Type ^c	Sexes included	Age range ^d	Definition of COPD used ^e	Accounting for asthma	No. of cases ^f
7	Sandler ⁷	1989	USA	L12	M,F	16+	Emphysema or bronchitis (mortality)	Ignored	19
8	Dayal ⁸	1994	USA	CS ^k	M,F	Adults	Chronic bronchitis, emphysema or asthma (diagnosis, questionnaire report)	Included	219
9	Forastiere ⁹	2000	Italy	CS ^l	F	25–74	COPD (physician diagnosis, questionnaire report)	Ignored	50
10	Enstrom ¹⁰	2003	USA	L39	M,F	31+	COPD (mortality)	Included	264
11	De Marco ¹¹	2004	16 countries	CS	M,F	20–44	COPD (GOLD stage 1+) ^h	Ignored	156
12	Celli ¹²	2005	USA	CS	M,F	30–80	FEV ₁ /FVC <0.70 (spirometry test ^h)	Ignored	414 ^m
13	McGhee ¹³	2005	Hong Kong	CC	M,F	60+	COPD (including pulmonary heart disease, mortality)	Ignored	138
14	Sezer ¹⁴	2006	Turkey	CC	F	38+	COPD (specialist clinic diagnosis)	Ignored	74
15	Xu ¹⁵	2007	China	CC	M,F	35+	COPD (hospital diagnosis of emphysema or chronic bronchitis, questionnaire report)	Ignored	1097
16	Yin ¹⁶	2007	China	CS	M,F	51+	COPD (GOLD stage 1+ but without bronchodilator)	Excluded	429
17	Zhou ¹⁷	2009	China	CS	M,F	40+	COPD (GOLD stage 1+) ^{n,o}	Ignored	644
18	Wu ¹⁸	2010	Taiwan	CC	F	40+	COPD (GOLD stage 1+)	Excluded	168
19	Jordan ¹⁹	2011	England	CS	M,F	40+	COPD (GOLD stage 1+ but without bronchodilator) ^p	Excluded	779 ^m
20	Lamprecht ²⁰	2011	14 countries	CS	M,F	40+	COPD (GOLD stage 1+) ^{n,q}	Adjusted	523
21	Chen ²¹	2012	China	CS	M,F	60+	COPD (physician diagnosis, questionnaire report)	Ignored	149
22	He ²²	2012	China	L17	M,F	51–87	COPD (mortality or GOLD stage 1+) ^y	Ignored	36
23	Waked ²³	2012	Lebanon	CS	M,F	40+	COPD (GOLD stage 1+)	Ignored	25
24	Moreira ²⁴	2013	Brazil	CS	F	40+	COPD (GOLD stage 1+)	Excluded	43
25	Eze ²⁵	2014	Switzerland	CS	M,F	18–65	COPD (GOLD stage 1+) ^h	Ignored	444
26	Hagstad ²⁶	2014	Sweden	CS	M,F	20–77	COPD (GOLD stage 1+)	Ignored	41 ^m
27	Kim ²⁷	2014	Korea	CS	M,F	40+	COPD (GOLD stage 1+ but without bronchodilator)	Adjusted	323
28	Tan ²⁸	2015	Canada	CS	M,F	40+	COPD (LLN, FEV ₁ /FVC <5th centile) ^s	Adjusted	161

^a First author and reference of principal publication

^b Year of publication

^c Study types are CC = case-control, CS = cross-sectional, L = longitudinal. For longitudinal studies, number of years follow-up is shown

^d Age at baseline for longitudinal studies

^e Definition of principal COPD outcome is shown. Definition of severer COPD used is shown in footnotes, along with alternative definitions for which results are available

^f Number of cases in lifelong non-smokers

^g Study also included females, but none had COPD

^h No mention of use of bronchodilator prior to spirometry

ⁱ Named as chronic bronchitis, but defined by authors as ICD 9th revision 491, 492, 496 so equates to COPD

^j Ignored for controls

^k Analysed as a nested CC study

^l Never smoking women had been identified by earlier studies in the same areas

^m Approximate estimate

ⁿ Severer outcome definition based on GOLD Stage 2+

^o Alternative results are also available for GOLD stage 0+

^p Severer outcome definition based on NICE criteria (FEV₁/FVC <0.7 and FEV₁ <80% predicted) described as equivalent to GOLD stage 2+ (no bronchodilator, omitting participants with diagnosis of asthma). Alternative results are also available based on the LLN criteria, for “clinically significant COPD” based on the LLN, GOLD and NICE criteria, and including participants with diagnosis of asthma

^q Alternative results are also available using the LLN criteria

^r Based on death certificate, supplemented by medical records for lung function if their death was not from COPD

^s Severer outcome definition is based on LLN criteria plus FEV₁ <80% predicted

Table 2. Potential confounding variables adjusted for and definition of never smoker.

Study No.	Author	Variables adjusted for	Definition of never smokers ^a
1	Lebowitz	None	Never NOS
2	Comstock	Age, education, number of bathrooms, persons/room, children in household, air conditioning, cooking fuel	Never cigarettes
3	Hirayama	Age of husband	Never cigarettes
4	Krzyzanowski	Age	Never NOS
5	Lee	Age, marital status (Table 3) Age (Table 5, Table 6 and Table 7)	Never NOS
6	Kalandidi	Age, occupation	Never NOS
7	Sandler	Age, housing quality, schooling, marital status	Never any product
8	Dayal	Age, sex, neighbourhood, heating, cooking	Never NOS
9	Forastiere	Age, center, age x center, education	Never cigarettes
10	Enstrom	Age ^b	Never any product ^c
11	De Marco	Sex, childhood respiratory infections, occupational exposure, socioeconomic status	Never smoked 20 packs of cigarettes or 360 g of tobacco in a lifetime, or at least 1 cigarette/day or 1 cigar/week for a year
12	Celli	Age, sex, race/ethnicity, BMI, education, poverty, urban residence, high risk industry, high risk occupation, biomass, allergy	Never smoked 100 cigarettes in lifetime
13	McGhee	Age, education (Table 3) Age, sex, education (Table 4)	Never NOS
14	Sezer	Wood ash, biomass ^d	Never NOS
15	Xu	Education, occupation, family income, cooking fuels, heating in winter, ventilating fans, occupational physical activity	Never NOS
16	Yin	Age, sex, education, occupational dust exposure, indoor air pollution	Never NOS
17	Zhou	Age, sex, education, BMI, family history of respiratory disease, biomass, heating fuel, ventilation in kitchen, childhood chronic cough, occupational exposures	Never NOS

Study No.	Author	Variables adjusted for	Definition of never smokers ^a
18	Wu	Age, height, education level, cooking status, burning incense, tea consumption	Never smoked, on average, more than 1 cigarette/day for a year
19	Jordan	Age, sex, year of study	Never smoked at least 1 cigarette/day
20	Lamprecht	None (COPD in Table 3) Age, education, occupational exposure, biomass fuel use, childhood hospitalisation, comorbidity, BMI (severer COPD in Table 3)	Never smoked more than 20 packs in lifetime or more than 1 cigarette/day for a year
21	Chen	None	Never cigarettes
22	He	Age, sex, marital status, occupation, education, alcohol, diastolic blood pressure, triglyceride and total cholesterol levels, BMI	Never smoked 100 cigarettes in lifetime
23	Waked	Age, sex, area of residence	Never NOS
24	Moreira	None	Never NOS
25	Eze	None	Never NOS
26	Hagstad	Age, sex, asthma, family history of obstructive airway disease, socioeconomic group (COPD in Table 3) None (severer COPD in Table 3 and Ever home/work and Childhood in Table 6)	Never smoked more than 1 cigarette/day for a year
27	Kim	Age, sex, previous diagnosis of asthma or tuberculosis, family income, education status	Never cigarettes
28	Tan	Age, education, childhood respiratory illness, heart disease, hypertension or diabetes, asthma, BMI, exposure to organic dust, inorganic dust, gases and vapours, biomass cooking and heating for ≥ 10 years, TB	Never smoked more than 1 cigarette/day for a year

^a Never any product = never smoked cigarettes, pipes or cigars; Never NOS = never smoked, product unspecified;

^b Results adjusted for more variables not used as adjustment included health status

^c Questions on pipe and cigar smoking were asked at baseline, but not at the follow-up interviews

^d The cases and controls were matched on age

Five studies (1, 20, 21, 24, 25) made no adjustment for any potential confounding variables, while some others made little or no adjustment for such variables as occupation, education, diet and family history of disease, which may differ between smoking and non-smoking households⁶⁴. Failure to adjust for household size, where the index of exposure is based on presence of a smoker in the household, was also common. Where adjustment was carried out, all but four studies considered age, although study 3 adjusted for the husband's age rather than the subject's.

Fifteen studies were of never smokers, though only three of these made it clear they were never smokers of cigarettes, pipes or cigars. Five studies were of never cigarette smokers (i.e. they may have included some pipe or cigar only smokers), the remaining eight allowing a minimal smoking history, such as smoking less than 1 cigarette a day or less than 100 cigarettes in life.

Main exposure index

The main meta-analyses use an exposure index that relates as closely as possible to ever smoking by the spouse. **Table 3** shows the definitions of ETS exposure used for the main index. This was based on smoking by the spouse for five studies, and on smoking by cohabitants for a further 13 (although study 13 only included participants who had lived with a smoker 10 years previously, and study 20 only considered ETS exposure in the home in the two weeks prior to the study). For the remaining studies, the index was based on exposure in the home and at work (studies 4, 12, 17, 18 and 27) or on a combination of exposure from any source (studies 11, 15, 19, 21 and 25).

Although most studies presented results comparing participants who were exposed or unexposed to ETS, some required a minimum level before a subject could be classified as exposed. In study 19, exposure had to be for at least one hour per week, while study 12 specified living with a smoker who smoked in the home or exposure at work for at least one hour per day. In studies 20 and 28, exposure had to have been in the previous two weeks, while participants in study 25 had to have had regular exposure in the previous year. In study 22 exposure had to be for 15+ minutes per day at least once per week for two or more years, while in study 15 the minimum requirement was 15 minutes or more, three or more times per week. In study 11, participants were only considered to have been exposed if they reported four or more hours of exposure on most days or nights in the previous year. Finally, study 14 required 10 years of exposure.

Table 3, supported by **Figure 2**, also presents the ORs for the main exposure index, while **Table 4** presents the results of meta-analyses, and **Table 5** the dose-response data.

From **Table 3** it can be seen that, of the 33 individual OR estimates given for COPD, 24 are above 1.00, seven of these increases being significant at $p < 0.05$. Eight studies reported an OR below 1.00, but only in study 4 for females was the reduction statistically significant. Study 25 reported an OR of 1.00, while study 24, excluded from the meta-analyses, did not present an OR but

reported no significant relationship with duration or type of exposure. In addition, five studies presented a total of seven OR estimates for severer COPD, with five estimates above 1.00 (one significantly so and one marginally significant) and two non-significantly below 1.00.

Table 4 demonstrates that the overall evidence for the main exposure index shows some increased risk of COPD, with the random-effects OR, based on 33 independent estimates, being 1.20 (95% CI 1.08-1.34) with no clear evidence of publication bias ($0.05 < p < 0.1$), but clear heterogeneity ($p < 0.001$). The largest contributors to this were the high ORs for studies 18 and 21 and in females for study 13 and the low OR in females for study 4.

Although there was no significant heterogeneity by continent, a significant increase was seen for North America (1.19, 1.01-1.41, $n = 10$) and Asia (1.34, 1.08-1.67, $n = 10$), but not for other locations. There was no significant heterogeneity by period of publication or study type. There was evidence of heterogeneity by sex ($p < 0.01$), with a significant increase only for females (1.59, 1.16-2.19, $n = 11$). There was no heterogeneity by aspects of diagnosis, although the estimates were highest for definitions based on mortality or hospitalisation (1.40, 1.12-1.74, $n = 11$). However, there was significant heterogeneity ($p < 0.001$) by numbers of cases, with larger ORs from studies of less than 50 cases (1.26, 0.83-1.92, $n = 11$) and from studies of 50-149 cases (1.62, 1.35-1.96, $n = 9$) than for studies of 150 or more cases (1.08, 0.97-1.20, $n = 13$). There was no significant evidence of heterogeneity by extent of confounder adjustment, or by how never smokers or the exposure index were defined. For all these subgroup analyses, there was little evidence of publication bias, but evidence of heterogeneity in some subgroups.

The combined OR for severer COPD was significant (1.29, 1.10-1.52, $n = 7$).

There was also evidence of a dose-response relationship, as shown in **Table 5**, with six of 11 studies investigating this reporting a statistically significant positive trend. Study 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. Study 19, which found no relationship with the main COPD outcome, also presented dose-response relationships for severer COPD, again finding no significant increase in risk with increasing exposure.

Other exposure indices

Five studies also presented additional results for other indices of ETS exposure, as shown in **Table 6**. Four studies (16, 22, 23, 26) looked at exposure at work, all but study 23 also presenting results for combined exposure at home and at work. Study 5 produced a combined index of adulthood exposure at home or work, or during travel or leisure. Three studies (16, 23, 26) considered childhood ETS exposure, study 23 studying exposure from both the mother and the father, and also looking at parental smoking during pregnancy.

Table 3. COPD among never smokers and smoking by the spouse or household member^a.

Study No.	Author	Type ^b	Sex	Definition of exposure ^c	Number of cases		Odds ratio (95% CI) ^d
					Unexposed	Exposed	
COPD:							
1	Lebowitz	CS	M+F	Lives with ever smoker ^e	129	117	1.09 (0.83-1.44)
2	Comstock	CS	M	Lives with a smoker	23	7	1.19 (0.50-2.86)
3	Hirayama	L15	F	Husband ever smoked	28	102	1.38 (0.86-2.21)
4	Krzyzanowski	L13	F	Exposure at home or workplace	26	6	0.36 (0.15-0.86)
			M		3	2	1.39 (0.26-7.40)
5	Lee	CC	F	Spouse smoked in marriage	4	13	1.22 (0.38-3.94)
			M		8	1	0.34 (0.06-2.03)
6	Kalandidi	CC	F	Husband ever smoked ^e	13	90	1.38 (0.69-2.76)
7	Sandler	L12	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 ^g	145 ^g	1.40 (0.98-1.99)
9	Forastiere	CS	F	Ever married to a cigarette smoker	11	39	1.75 (0.88-3.47)
10	Enstrom	L39	F	Spouse ever smoked ^e	45	128	1.13 (0.80-1.58)
			M		69	22	1.27 (0.78-2.08)
11	De Marco	CS	M+F	4+ hours per day exposure on most days/nights in previous 12 months	129	27	1.14 (0.74-1.77)
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 ^g	86 ^g	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 at least 10 yrs	13	61	2.57 (1.04-6.36)
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	Lived with a smoker	195	234	0.95 (0.77-1.18)
17	Zhou	CS	M+F	Exposure at home or workplace	119 ^g	525 ^g	1.34 (1.08-1.65)
18	Wu	CC	F	Exposure at home (including childhood) or workplace	41	127	2.20 (1.39-3.49)
19	Jordan	CS	M+F	1+ hours of exposure per week	Total 779 ^g		1.11 (0.95-1.30)

Study No.	Author	Type ^b	Sex	Definition of exposure ^c	Number of cases		Odds ratio (95% CI) ^d
					Unexposed	Exposed	
20	Lamprecht	CS	M+F	Exposure at home in previous 2 weeks	423	100	0.89 (0.70-1.20) ^f
21	Chen	CS	M+F	Exposure at home, workplace or other places	85	64	1.82 (1.30-2.54) ^f
22	He	L17	M+F	Exposure at home for 15+ minutes per day, 1+ days per week for 2+ years ^h	10	4	1.67 (0.49-5.78)
23	Waked	CS	M+F	Lives with a smoker	Total 25		1.23 (0.55-2.74) ^f
24	Moreira	CS	F	Lives with a smoker	Total 43		No significant difference in number of years exposure, or proportion exposed to straw cigarettes ⁱ
25	Eze	CS	M+F	Exposure at home, workplace or other places in previous year	293	151	1.00 (0.81-1.24) ^f
26	Hagstad	CS	M+F	Ever lived with a smoker ^j	25	64	1.38 (0.84-2.27)
27	Kim	CS	M+F	Exposure at home or workplace	248	75	0.85 (0.60-1.21) ^f
28	Tan	CS	F	Lived with a smoker in previous 2 weeks	M&F 94	M&F 12	2.20 (1.03-4.71)
			M				1.01 (0.27-3.76)
Severer COPD^k:							
17	Zhou	CS	M+F	Exposure at home or workplace ⁱ	89	379	1.27 (1.00-1.63) ^f
19	Jordan	CS	M+F	1+ hours of exposure per week	Total 334 ^g		1.13 (0.84-1.51) ^f
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)
26	Hagstad	CS	M+F	Ever lived with a smoker ^j	11	35	2.46 (1.24-4.88) ^f
28	Tan	CS	F	Lives with a smoker	M&F 94	M&F 4	1.65 (0.46-5.88)
			M				0.69 (0.08-6.31)

^a Or nearest equivalent to spouse or household member (see text and Table)

^b Study types are CC = case-control, CS = cross-sectional, L = longitudinal. For longitudinal studies, number of years follow-up is shown

^c Comparison is with those not exposed as defined, except where indicated otherwise

^d RRs from longitudinal studies are taken as being equivalent to ORs

^e Separate results also available for current smoker and exsmoker

^f OR and/or CI estimated from data provided

^g Approximate estimates

^h Compares exposed at home only to unexposed. Excludes those exposed at work

ⁱ A straw cigarette is a handful of tobacco, wrapped in a corn husk; study not included in meta-analysis

^j Compared to subjects not exposed to any source of ETS; results also available for current or former exposure

^k Results not included in the meta-analysis in [Figure 2](#)

Figure 2. Forest plot for the main index, by region. Individual study estimates of the OR and its 95%CI are shown separately by region, sorted in increasing order of OR. These are shown as numbers, and also graphically on a logarithmic scale. Random-effects estimates of ORs and 95% CIs are also shown for each region combined and overall. Studies are identified by the study number shown in Table 1. In the graphical representation, ORs are indicated by a square, with the area of the square proportional to the weight.

Table 4. Meta-analyses of COPD^a risk among never smokers and smoking by spouse or household member^b.

		Fixed-effect	Random-effects	Publication bias	Heterogeneity ^c	
Subgroup	N ^d	Odds ratio (95% CI)	Odds ratio (95% CI)	p ^e	Chisquared per DF ^f	p ^g
All COPD	33	1.14 (1.07-1.21)	1.20 (1.08-1.34)	<0.1	1.99	<0.001
<i>By continent</i>						
North America	10	1.19 (1.02-1.38)	1.19 (1.01-1.41)	NS	1.08	NS
Asia	10	1.18 (1.07-1.30)	1.34 (1.08-1.67)	<0.1	3.83	<0.001
Europe ^h	11	1.10 (0.98-1.24)	1.14 (0.93-1.39)	NS	1.53	NS
Multicountry	2	0.95 (0.76-1.20)	0.95 (0.76-1.20)	-	0.90	NS
			<i>Between continents</i>		1.13	NS
<i>By publication period</i>						
1976–1990	10	1.12 (0.91-1.37)	1.11 (0.81-1.52)	NS	1.52	NS
1991–2005	8	1.28 (1.09-1.50)	1.30 (1.07-1.59)	<0.1	1.40	NS
2006–2015	15	1.11 (1.03-1.20)	1.19 (1.03-1.37)	<0.1	2.70	<0.001
			<i>Between periods</i>		1.18	NS
<i>By study type</i>						
Longitudinal	8	1.18 (0.94-1.47)	1.18 (0.83-1.67)	NS	1.71	NS
Case-control	8	1.20 (1.02-1.40)	1.55 (1.04-2.32)	NS	3.36	<0.01
Cross-sectional	17	1.12 (1.04-1.21)	1.14 (1.02-1.27)	NS	1.72	<0.05
			<i>Between types</i>		0.34	NS
<i>By sex</i>						
Males	7	1.29 (0.94-1.76)	1.29 (0.94-1.76)	NS	0.55	NS
Females	11	1.50 (1.25-1.81)	1.59 (1.16-2.19)	NS	2.40	<0.01
Both	15	1.08 (1.01-1.16)	1.10 (0.99-1.22)	NS	1.81	<0.05
			<i>Between sexes</i>		5.57	<0.01
<i>By diagnosis</i>						
Mortality ⁱ or hospitalisation	11	1.37 (1.13-1.66)	1.40 (1.12-1.74)	NS	1.13	NS
GOLD Stage 1+	10	1.09 (1.01-1.19)	1.11 (0.97-1.27)	NS	2.22	<0.05
Other	12	1.15 (1.02-1.29)	1.23 (0.97-1.56)	NS	2.54	<0.01
			<i>Between diagnoses</i>		2.24	NS
<i>By method for taking asthma into account</i>						
Included	4	1.19 (1.00-1.41)	1.19 (1.00-1.41)	NS	0.45	NS
Adjusted for	4	0.94 (0.77-1.15)	1.00 (0.72-1.39)	NS	1.76	NS
Excluded	4	1.11 (0.99-1.26)	1.24 (0.93-1.65)	NS	3.63	<0.05
Ignored	21	1.18 (1.08-1.30)	1.27 (1.07-1.50)	NS	2.08	<0.01
			<i>Between methods</i>		1.49	NS

		Fixed-effect	Random-effects	Publication bias	Heterogeneity ^c	
Subgroup	N ^d	Odds ratio (95% CI)	Odds ratio (95% CI)	p ^e	Chisquared per DF ^f	p ^g
<i>By number of cases estimate is based on</i>						
<50	11	1.29 (0.97-1.71)	1.26 (0.83-1.92)	NS	1.85	<0.05
50–149	9	1.62 (1.35-1.96)	1.62 (1.35-1.96)	NS	0.53	NS
150+	13	1.07 (1.00-1.15)	1.08 (0.97-1.20)	NS	1.97	<0.05
			<i>Between numbers</i>		8.65	<0.001
<i>By extent of confounder adjustment</i>						
Unadjusted for age	6	1.11 (0.98-1.25)	1.15 (0.94-1.42)	NS	2.55	<0.05
Adj. for age+ <5 variables	18	1.16 (1.05-1.28)	1.26 (1.06-1.49)	NS	1.75	<0.05
Adj. for age+ 5+ variables	9	1.13 (1.00-1.27)	1.20 (0.95-1.53)	NS	2.61	<0.01
			<i>Between groups</i>		0.16	NS
<i>By definition of never smoker</i>						
Never any product	4	1.22 (0.93-1.61)	1.28 (0.88-1.87)	NS	1.34	NS
Never, product unstated	15	1.10 (1.01-1.20)	1.16 (0.99-1.36)	NS	2.15	<0.01
Other	14	1.17 (1.06-1.30)	1.25 (1.05-1.50)	NS	2.18	<0.01
			<i>Between definitions</i>		0.63	NS
<i>By definition of exposure</i>						
Spouse specifically	7	1.26 (1.02-1.55)	1.26 (1.02-1.55)	NS	0.60	NS
Other lives with smoker	15	1.14 (1.02-1.29)	1.31 (1.08-1.59)	<0.01	1.85	<0.05
Other	11	1.11 (1.03-1.21)	1.13 (0.95-1.34)	NS	3.31	<0.001
			<i>Between definitions</i>		0.55	NS
All severer COPD	7	1.29 (1.10-1.52)	1.29 (1.10-1.52)	NS	0.94	NS

^a Definition of COPD as shown in the body of Table 1, severer COPD in footnotes to Table 1. Data as shown in Table 3

^b Or nearest equivalent to spouse or household member (see text and Table 3)

^c Heterogeneity relates to variation between studies within subgroup, except for results given in italics which relate to heterogeneity between subgroups

^d N number of estimates in meta-analysis

^e Egger test p expressed as <0.001, <0.01, <0.05, <0.1 or NS (p≥0.1)

^f DF degrees of freedom

^g p expressed as <0.001, <0.01, <0.05, <0.1 or NS (p≥0.1)

^h Includes one study from Turkey and one from Lebanon

ⁱ Including study 22

The ORs for these other exposure indices are supported by Figure 3 (workplace) and Figure 4 (overall adult), while Table 7 presents the results of meta-analyses. Note that Figure 4, and the meta-analyses for overall adult exposure, consider not only the ORs indicated in Table 6, but also include estimates from

Table 3 for those ten studies (4, 11, 12, 15, 17, 18, 19, 21, 25, 27) for which the exposure was at least from home and work.

Of the four ORs included in the meta-analysis of COPD for exposure at work, two were above 1.00, one of borderline

Table 5. Dose-response evidence for COPD among never smokers for smoking by spouse or household member.

Study No.	Author	Type ^a	Sex	Exposure Source	Level	No. of cases	Odds ratio (95% CI) ^b	Trend p ^c
COPD:								
3	Hirayama	L15	F	Husband	Never smoked	28	1.00	NS
					Ex smoker or 1–19/day	65	1.29 (0.79–2.12) ^d	
					20+/day	37	1.60 (0.92–2.78) ^d	
6	Kalandidi	CC	F	Husband	Never smoked	13	1.00	NS
					Daily consumption ≤1 pack/day	35	2.5 (1.3–5.0)	
					≥1 pack/day	37	1.5 (0.8–2.7)	NS
					Lifelong consumption ≤300,000 cigs	52	1.30 (0.64–2.64) ^d	
8	Dayal	CS	M+F	Cohabitants	300,000+ cigs	38	1.70 (0.72–4.03) ^d	NS
					No smoker	74 ^e	1.00	++
					≤1 pack/day ⁱ	76 ^e	1.16 (0.78–1.72)	
10	Enstrom	L39	F M	Husband Wife	>1 pack/day ⁱ	69 ^e	1.86 (1.21–2.86)	
					Per level ^g	173	0.99 (0.92–1.06)	NS
13	McGhee	CC	M+F	Cohabitants	Per level ^g	91	1.06 (0.91–1.25)	NS
					No smoker	84	1.00	++
14	Sezer	CC	F	Cohabitants	1 smoker	54 ^h	1.85 (1.14–3.00)	
					2+ smokers		2.51 (1.22–5.18)	
					<10 years	13	1.00	++
					10–19 years	12	1.19 (0.58–5.68)	
16	Yin	CS	M+F	Cohabitants	20–29 years	20	2.46 (0.83–7.33)	
					30+ years	29	4.96 (1.65–14.86)	
					No smoker	195	1.00	NS
					1 smoker	201	0.96 (0.77–1.20)	
18	Wu	CC	F	Lifetime cohabitants and co-workers	2+ smokers	33	0.92 (0.62–1.36)	
					<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	+ ⁱ
					<32 years	58	1.86 (1.10–3.17) ^d	
					32+ years	69	2.53 (1.51–4.26) ^d	

Study No.	Author	Type ^a	Sex	Exposure Source	Level	No. of cases	Odds ratio (95% CI) ^b	Trend p ^c
19	Jordan	CS	M+F	Any exposure	Total No exposure 1–19 hours/wk 20+ hours/wk	779 ^e	1.00 1.11 (0.94–1.31) 1.10 (0.81–1.49)	NS
22	He	L17	M+F	Cohabitants and co-workers	Score 0 ^f Score 1–2 Score 3–4 Score 5–6	10 8 13 5	1.00 1.52 (0.57–4.04) 2.32 (0.98–5.50) 5.01 (1.65–15.24)	++
27	Kim	CS	M+F	Home or workplace	Total No exposure ≤6 hours/day >6 hours/day	323	1.00 0.83 (0.58–1.19) 1.75 (0.47–6.59)	NS
Severer COPD:								
19	Jordan	CS	M+F	Any exposure	Total No exposure 1–19 hours/wk 20+ hours/wk	334 ^e	1.00 1.10 (0.81–1.49) 1.33 (0.74–2.38)	NS

^a Study types are CC = case-control, CS = cross-sectional, L = longitudinal. For longitudinal studies, number of years follow-up is shown

^b RRs from longitudinal studies are taken as being equivalent to ORs

^c NS p≥0.05, + p<0.05, ++ p<0.01

^d OR and/or CI estimated from data provided

^e Approximate estimates

^f Sum of smoking levels for all cohabitants

^g 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, as for husband except with no level for pipe/cigar

^h Number of cases is for the exposed groups combined

ⁱ Trend estimated from data provided

^j 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)

statistical significance, and two were below 1.00, the combined estimate being 1.12 (0.77–1.64). Note that in study 26 there was a choice of workplace OR estimates, with the meta-analysis including that for current exposure. Using estimates for previous or ever exposure would not have affected the conclusion that there was no clear relationship of COPD to workplace ETS exposure.

Of the 17 ORs included in the meta-analysis for overall adult exposure, 12 were above 1.00, five significantly so, with one equal to 1.00, and four less than 1.00. The combined estimate of 1.20 (1.03–1.39) was also significantly increased.

There was no clear association of COPD with childhood ETS exposure, with none of the ORs shown in Table 6 being significant. Only two estimates could be included in the meta-analysis, giving an overall estimate of 0.88 (0.72–1.07).

There was no significant evidence of publication bias for workplace or adult exposure, the data being too limited to assess this for childhood exposure. However, there was evidence of heterogeneity (p<0.01) for overall adult ETS exposure.

The limited further dose-response data shown in Table 8 added little to the data already shown in Table 5.

Discussion

We rejected papers for various appropriate reasons. These included the following: failing to give results for an endpoint equivalent to COPD; giving results only for COPD exacerbation or prognosis; not presenting results for never smokers; describing studies without a control group; not presenting results for those unexposed to ETS; and presenting less useful results than reported in another publication.

Twenty-eight epidemiological studies did qualify for inclusion, and from 33 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 OR estimate of 1.20 (1.08–1.34). There was also some evidence of dose-response. While the clear relationship of smoking with COPD³¹ makes it plausible that some effect will also be evident for ETS, one must emphasize that exposure is much less than from active smoking, as noted in the Introduction. Also, various limitations of the evidence,

Table 6. Odds ratio for COPD among never smokers for other indices of ETS exposure.

Study No.	Author	Type ^a	Sex	Number of cases		Index of exposure ^b	Odds ratio (95% CI) ^c	Meta-analysis ^d
				Unexposed	Exposed			
COPD:								
5	Lee	CC	F	7	5	Combined index of adulthood exposure at home, work, during travel and leisure ^e	1.04 (0.34-3.20) ^f	A
			M	1	3		1.18 (0.19-7.42) ^f	A
16	Yin	CS	M+F	225	204	Childhood – home	0.87 (0.71-1.06) ^f	C
				240	187	Adulthood – work	0.96 (0.78-1.19) ^f	W
				191	238	Adulthood - home and/or work ^g	1.24 (1.01-1.51) ^f	A
22	He	L17	M+F	10	26	Workplace ^h	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) ^f	
						During pregnancy: father	1.69 (0.73-3.90) ^f	
						Childhood: mother	1.17 (0.39-3.52) ^f	C
						Childhood: father	1.36 (0.61-3.07) ^f	
						Workplace	0.75 (0.18-3.14) ^f	W
26	Hagstad	CS	M+F	25	78	Previous workplace ⁱ	1.42 (0.86-2.33)	
				25	14	Current workplace ⁱ	1.17 (0.58-2.36)	W
				25	10	Previous and current workplace ⁱ	1.74 (0.77-3.91)	
				25	5	Ever at home and both previous and current workplace ⁱ	3.80 (1.29-11.20)	
				25	3	Currently at home and both previous and current workplace ⁱ	5.73 (1.46-22.50)	
				25	115	Ever at home and/or work ⁱ	1.87 (1.20-2.91) ^f	A
Severer COPD:								
26	Hagstad	CS	M+F	Total 27		Childhood ⁱ	0.62 (0.28-1.35) ^f	

^a Study types are CC = case control, CS = cross-sectional, L = longitudinal. For longitudinal studies, number of years follow-up is shown^b Comparison is with no exposure of the type specified, except where indicated otherwise^c RRs from longitudinal studies are taken as being equivalent to ORs^d A = Any adult, C = Childhood and W = Workplace indicate estimates included in Table 7 meta-analysis^e Comparison is with those with no exposure of any of the four types, or at most little exposure from one of them^f OR and/or CI estimated from data provided^g Comparison is with those with <2 years of 40 hours per week exposure^h Compares exposed at work only to unexposed. Excludes those exposed at homeⁱ Comparison group is subjects not exposed to ETS from any source^j From 65

Figure 3. Forest plot for workplace exposure. Individual study estimates of the OR and its 95%CI are shown sorted in increasing order of OR. These are shown as numbers, and also graphically on a logarithmic scale. Random-effects estimates of ORs and 95%CI are also shown. Studies are identified by the study number shown in Table 1. In the graphical representation, ORs are indicated by a square, with the area of the square proportional to the weight.

Figure 4. Forest plot for overall adult exposure. Individual study estimates of the OR and its 95%CI are shown sorted in increasing order of OR. These are shown as numbers, and also graphically on a logarithmic scale. Random-effects estimates of ORs and 95%CI are also shown. Studies are identified by the study number shown in Table 1. In the graphical representation, ORs are indicated by a square, with the area of the square proportional to the weight.

Table 7. Meta-analyses of COPD^a risk among never smokers for other indices of ETS exposure.

Index of exposure	N ^b	Fixed-effect	Random-effects	Publication bias	Heterogeneity	
		Odds ratio (95% CI)	Odds ratio (95% CI)	p ^e	Chi squared per DF ^d	p ^e
Workplace	4	1.01 (0.83-1.23)	1.12 (0.77-1.64)	NS	1.43	NS
Overall adult ^f	17	1.16 (1.07-1.25)	1.20 (1.03-1.39)	NS	2.65	<0.001
Child ^g	2	0.88 (0.72-1.07)	0.88 (0.72-1.07)	-	0.27	NS

^a Definition of COPD as shown in the body of Table 1. Data as shown in Table 6 excluding severer COPD^b Number of estimates in meta-analysis^c Egger test p expressed as <0.001, <0.01, <0.05, <0.1 or NS (p≥0.1)^d Degrees of freedom^e p expressed as <0.001, <0.01, <0.05, <0.1 or NS (p≥0.1)^f Index includes "home or workplace" or combined index of any adulthood exposure. Note that this meta-analysis not only includes those estimates marked with an A in Table 6, but also includes estimates from Table 3 for studies 4, 11, 12, 15, 17, 18, 19, 21, 25 and 27^g Preferring exposure from the mother in study 23. Estimates would be 0.89 (0.74-1.08) fixed and 0.91 (0.70-1.18) random, preferring exposure from the father**Table 8. Dose-response evidence for COPD among never smokers for other indices of exposure.**

Study No.	Author	Type ^a	Sex	Exposure Source	Level	No. of cases	Odds ratio (95% CI)	Trend p ^b
5	Lee	CC	F	Combined index of adulthood exposure at home, work, during travel and 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 and 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^b NS = p≥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

discussed below, make it difficult to estimate reliably the true extent of any causal relationship. However, one should also take into account the evidence of a relationship between ETS and wheezing^{46,66}, a symptom of COPD.

Few cases

Though four studies involved more than 500 cases, with the maximum 1097 in study 15, as many as ten of the 28 studies involved less than 100 cases, the quite small number of cases making it difficult to detect potential effects reliably.

Publication bias

The observation that ORs are only modestly raised for studies with larger numbers of cases but are greater for smaller studies suggests the possibility of publication bias, with authors being more likely to report stronger relationships. However formal tests for publication bias⁵⁴ showed no clear evidence of its existence. One must note, though, that various large longitudinal studies, e.g. 67–70, reported results relating ETS to smoking-related diseases such as lung cancer or heart disease, but did not do so for COPD. If any relationship had been seen, these studies might well have been reported.

Misclassification of smoking status

No study validated the lifelong non-smoking status of their participants, although study 18 did verify current active and passive exposure in a random sample of participants by measuring urinary cotinine levels. As some current and past smokers deny smoking when interviewed⁷¹, and as the smoking habits of spouses or household members are clearly correlated⁴⁷, misclassification of even a few ever smokers as never smokers can cause relevant bias⁷², especially when, as is the case with COPD, the association with smoking is strong³¹.

Weaknesses in longitudinal studies

All the longitudinal studies considered involved follow-up for at least 12 years. Of the five studies, three (studies 3, 7 and 10) assumed spousal smoking was unchanged during follow-up, only studies 4 and 22 collecting information on smoking status at multiple time points.

All these studies only considered COPD deaths which occurred in the original study area.

Inappropriate controls in case-control studies

Although three case-control studies used population controls, the remaining three used control groups unlikely to be representative of the population from which the cases derived. Studies 6 and 14 used visitors to the hospital attended by the cases, and study 13 used as a control a person identified by the informant of a death as a “living person about the same age who was well known to the informant”, the informant then being asked about the lifestyle 10 years earlier of both decedent and control.

Weakness of cross-sectional studies

Over half of the studies were of cross-sectional design, a design limited by difficulties in determining whether ETS exposure or disease onset occurred first.

Poor control for potential confounding variables

As noted above, some studies made little or no adjustment for variables likely to differ between smoking and non-smoking households. Though ORs for the main exposure index did not vary significantly by extent of adjustment, it should be noted that adjustment for dietary variables and education explains a substantial part of the association of lung cancer with spousal smoking⁴⁵. The same may be the case for COPD.

Variation and appropriateness of diagnostic criteria

Definitions of COPD used were all consistent with the inclusion criteria. However, they still varied somewhat between study, further adding uncertainty to the meta-analysis results. Even given the inclusion criteria, there are doubts about the appropriateness of the diagnostic criteria used in some studies. In study 8, for example, the definition included asthma as well as chronic bronchitis and emphysema, the diagnosis being reported by the head of the household, and not necessarily made by a doctor.

Misclassification of ETS exposure

While random errors in determining ETS exposure led to underestimation of the relationship of COPD with ETS, errors may not be random. Twenty-three of the 28 studies considered were of case-control or cross-sectional design, where recall bias may exist if those with COPD tend to overestimate their ETS exposure compared to those without COPD. Exposure was generally not validated by biochemical markers or air measurements taken at home.

Limited evidence for some sources of ETS

Only 15 studies (4, 5, 11, 12, 15–19, 21–23, 25–27) provided data on ETS exposure from sources other than the home. Five (4, 12, 17, 18, 27) presented results only for a combined household and workplace exposure index, with a further five (11, 15, 19, 21, 25) only presenting results for total exposure irrespective of location, results used in our analyses as the nearest equivalent which was available to smoking by the spouse or household member. While there are far less available data on risk of COPD from ETS exposure specifically in the workplace or in childhood than on smoking in the home, the available data show no clear relationship of risk with these less studied exposure indices.

Comparison with other recently published reviews

A review in 2007⁷³ considered that “ETS exposure may be an important cause of COPD”. However, this conclusion was based on only six studies, one examining absolute risk of COPD in relation to changes in tobacco consumption, and one comparing lung function of employees in bars and restaurants before and after a smoking ban. Also it seemed that at least some of the others considered were not restricted to never smokers.

A review in 2010⁶⁰ meta-analysed results from 12 studies and gave an overall estimate of 1.56 (1.40–1.74), somewhat higher than our estimate. Not all of the studies included were of COPD, some being based on chronic bronchitis symptoms. Also, some studies were based on current non-smokers rather than on lifelong never smokers.

In 2013, Bentayeb *et al.*⁶¹ reviewed evidence on indoor air pollution and respiratory health in those aged over 65 years. After considering 33 papers (only one¹⁶ presenting relevant results on ETS and COPD risk in non-smokers), they reported that the most consistent relationship found was between ETS exposure and COPD risk. However, the findings did not allow causal inference due to heterogeneity of the studies considered, measurement errors in exposure assessment, variable outcome definition, and lack of information on lifetime exposure to air pollution. The authors concluded that more investigations are needed to understand the relationship of indoor air pollution to respiratory health in the elderly.

A review in 2014⁷⁴ reached similar conclusions, the authors stating that “second-hand exposure to tobacco smoke has also been shown to be associated with the risk of COPD, although more robust evidence needs to be generated”. These conclusions were derived from only eight studies, some concerned with respiratory symptoms rather than COPD. Also, one study did not restrict any analyses to never smokers.

A review in 2015⁶² included only five studies in the meta-analyses. The estimated risk of COPD in ETS-exposed participants was higher than we estimated, being 1.66 (1.38-2.00) for both sexes combined, 1.50 (0.96-2.28) for males and 2.17 (1.48-3.18) for females. However, these estimates were based on, respectively, three, one and one estimates, the authors examining three further studies but not including them in their meta-analysis due to low study quality. However, two of the studies they did include were not based on lifelong never smokers. Many other studies that might have been included were not. The authors noted that “the few existing studies on second-hand smoke exposure and COPD differ considerably, although the results indicate a positive association” and that “further research is needed, to provide more adequate primary studies which account for confounding and other biases”.

A review in 2016⁶³ of “the effects of smoking on respiratory health” also considered effects of ETS exposure. However, only three studies were cited, two not satisfying our inclusion

criteria. Noting the variability in the results, the authors only pointed to the need for additional studies.

It is clear that the present review includes far more studies relating ETS exposure to risk of COPD in never smokers than considered by others.

Another relevant publication

In response to a comment from a reviewer (Dr Maio), we updated our searches by a further two years. While this identified an additional 99 publications, only one⁷⁵ satisfied our inclusion criteria. That paper reported age and sex adjusted hazard ratio estimates by level of ETS exposure, which, when combined, gave an exposed/unexposed estimate of 2.25 (95% CI 1.05-4.82). Including this estimate, based on only 33 COPD cases, had little effect on the meta-analysis results shown in Table 4. Thus, the overall random-effects estimate of 1.20 (95% CI 1.08-1.34) for all COPD was changed only to 1.22 (1.09-1.36), while that for Asia was changed only from 1.34 (1.08-1.67) to 1.38 (1.11-1.72).

Conclusion

The evidence may be regarded as suggestive of an effect of ETS exposure on risk of COPD, especially given the strong association of smoking with the disease. However, the marginal significance of the meta-analyses, the absence of well-designed and fully reported large studies, and the limitations noted above make it difficult to obtain an accurate estimate of the true magnitude of any possible effect. More definitive studies are required to reach a firmer conclusion.

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Supplementary material

Supplementary file 1: Rejected studies: In preparing the tables and figures in this document, certain papers that 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.

[Click here to access the data.](#)

Supplementary file 2: PRISMA checklist

[Click here to access the data.](#)

Supplementary file 3: Forest plots in Excel

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Yousser Mohammad

National Center for Research in Chronic Respiratory Diseases and Comorbidities, Tishreen University School of Medicine, Tishreen University, Latakia, Syria

I find it is now definitely acceptable for indexing. I have nothing to add.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 30 Dec 2019

Peter Lee, P.N. Lee Statistics and Computing Ltd, Sutton, UK

I thank Dr Mohammad, and am glad he is now happy with the paper.

Competing Interests: As previously described

Reviewer Report 20 December 2019

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Sara Maio

Pulmonary Environmental Epidemiology Unit, CNR Institute of Clinical Physiology, Pisa, Italy

I would like to thank you the authors for their replies.

As regards my comment about the number of aspects and subsets, I agree with the authors that detailed information is essential to get a good insight of the described topic; however, on the other side, this could make text reading less smooth. Maybe, some aspects could be inserted in an online supplement.

However, I keep thinking that it is not to overlook the results about the dose-response evidence or the findings of the whole sample meta-analysis (OR 1.20); instead, it seems that the main message of the review is in favor of an absence of relationship between ETS and COPD. And this aspect is reinforced from the paragraph "Comparison with other recently published reviews", in which the reviews, reporting a significant association between ETS and COPD, are all discussed in terms of limitations and not to compare your positive results with those of other authors.

I agree with the authors that it is difficult to define a causal relationship basing on the published evidences; but, on the other side, I think that the possible relationship between ETS and COPD should be better highlighted. The 2017 Global Burden of Disease study clearly reported that second-hand smoke is a risk factor for COPD deaths and DALYs.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 30 Dec 2019

Peter Lee, P.N. Lee Statistics and Computing Ltd, Sutton, UK

I thank the reviewer for the comments.

As regards the comment about numbers of aspects and subsets, we have left the paper as it is. As a reader our strong preference is to have all the material to be considered in one place, without having to go backwards and forwards between the main paper and supplementary files. Readers can always skip reading information they are not interested in if they wish to.

We have however made a number of changes to the main messages put over. As shown in the red-lining these appear at the end of the abstract, near the end of the discussion section, and in the conclusions section. We now make it clear that the overall association with the main ETS exposure index, coupled with the dose-response evidence, and the evidence on smoking and COPD, provides strong evidence of a possible causal relationship, and note that this is consistent with the Global Burden of Disease 2017 statement that ETS is a risk factor. However we make it clear that one cannot go further based on the evidence - one cannot definitively conclude that ETS causes COPD - still less get very accurate estimation of its possible effect.

I hope that these alterations are sufficient to remove the reviewer's reservations.

Competing Interests: As previously described.

Version 1

Reviewer Report 22 November 2019

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Yousser Mohammad

National Center for Research in Chronic Respiratory Diseases and Comorbidities, Tishreen University School of Medicine, Tishreen University, Latakia, Syria

The review is interesting, because it highlights methodological issues and gaps in surveys assessing the impact of environmental tobacco smoke on COPD incidence. These gaps and inconsistencies in surveys, lead to inadequacy on assessing the impact, and showing non-confirmative results (OR, RR, etc) on the association between ETS exposure and COPD.

I recommend it for indexing with minor changes.

However, the article should address three additional paragraphs or remark on:

1. Public health message of awareness, it should address that, even if non association is found between ETS and COPD, it is still that ETS kills 90,0000 people per year and it is a global public health issue. Haahtela et al. Helsinki by nature. The nature step for respiratory health, Clinical and Transitional Allergy¹.
2. Should mention water pipe because it is wide spreading: Yousser Mohammad, Rafea Shaaban, Bassam Abou Al-Zahab, Nikolai Khaltayev, Jean Bousquet, Basim Dubaybo. Impact of active and passive smoking as risk factors for asthma and COPD in women presenting to primary care in Syria: first report by the WHO-GARD survey group². WHO Advisory note 2015: waterpipe tobacco smoking: health effects, research needs and recommended actions by regulators – 2nd ed. World Health Organization. II.WHO Study Group on Tobacco Product Regulation. ISBN 978 92 4 150846 9 (NLM classification: QV 137)³.
3. Should discuss the difference in the quality of ETS

Not only nicotine but how the smoke is modified in the air and becoming may be more harmful to small airways:

- Lower ignition temperature
- Particles become smaller

- Higher proportion of CO, VOC

Ref found in the article: Mohammad Y. Passive smoking interference with wheezing and asthma Short Review of current knowledge⁴.

Wirth et al. Respiratory diseases related to passive smoking⁵.

Beside that, in one study⁶ the duration of exposure is 2 weeks, maybe we should omit it.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Passive smoking, Chronic Respiratory Diseases, impact of conflict

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 13 Dec 2019

Peter Lee, P.N. Lee Statistics and Computing Ltd, Sutton, UK

Reply to Yousser Mohammad

Dr Mohammad suggests that I should cite a statement by WHO that ETS is responsible for about 900,000 deaths per year from all causes combined. We would rather not do this for two reasons. First, the paper is specifically about ETS and COPD, so does not need to stray into the relationship between ETS and other causes of death. Secondly, estimation of the effect of ETS on overall mortality is extremely complex and citation of a single estimate is questionable. We have in fact published widely on the evidence relating ETS to other diseases, such as lung cancer (Lee *et al.*, 2016a; Lee *et al.*, 2002), other cancers (Lee, 2002; Lee and Hamling, 2006; Lee and Hamling, 2016; Lee *et al.*, 2016b), stroke (Lee and Forey, 2006; Lee *et al.*, 2017b), heart disease (Lee *et al.*, 2017a), and asthma (Lee and Forey, 2007), and find little evidence of an effect as large as WHO claims. For lung cancer, for example, we concluded (Lee *et al.*, 2017b) that any causal relationship is not convincingly demonstrated, as most, if not all, of the relationship with ETS can be explained by confounding adjustment and misclassification correction.

Dr Mohammad also suggests that I mention waterpipes. We would prefer not to do this as the paper is about ETS exposure from conventional cigarettes and as we have not formally reviewed the evidence relating to waterpipes. We have made it clearer in the introduction that the paper concerns ETS from cigarettes.

He also suggests that we should discuss differences in the quality of ETS. We assume that he is pointing out that ETS from various products may not have the same composition or effects as from conventional cigarettes. But we are not concerned with ETS from products other than cigarettes.

He suggests that we refer to evidence relating ETS to wheezing and asthma. While the paper he cites does not actually mention COPD, we do now include a statement in the text at the end of paragraph 2 of the discussion.

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Competing Interests: See the statement in the paper

Reviewer Report 11 May 2018

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Sara Maio

Pulmonary Environmental Epidemiology Unit, CNR Institute of Clinical Physiology, Pisa, Italy

The review could be of interest but some some major revisions are needed.

In particular, it would be important to update the papers selected for the revision because many other scientific evidences were published after June 2016.

Moreover, too many aspects and subsets are taken into account; they did not add information and they make the paper hard to read and the message not clear.

As regards to the subsets chosen for the meta-analysis, it would be important to take into account the publication period before and after the smoking ban, because it determined a variation in the exposure of the people to passive smoke and the related effects.

In the discussion, section "publication bias", it was reported that "One must note, though, that various large longitudinal studies, e.g. 66–69, reported results relating ETS to smoking-related diseases such as lung cancer or heart disease, but did not do so for COPD. If any relationship had been seen, these studies might well have been reported."

The reviewer thinks that this sentence is too strict and not supported by evidences.

Overall the discussion seems to set up versus a negative approach against the results of the other published reviews; on the other side, it did not discuss the results regarding the negative effect of exposure to ETS found using meta-analyses. The reviewer thinks that it is not to overlook the results about the dose-response evidence or the findings of the whole sample meta-analysis (OR 1.20) etc...

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

No

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 15 May 2018

Peter Lee, P.N. Lee Statistics and Computing Ltd, Sutton, UK

Dear Dr Maio,

I thank you for your comments which I respond to below on behalf of my co-authors. The text of the paper has not yet been altered as the editorial team advise that I wait for the additional referee reports before doing so.

Updating selected papers You say that "many other scientific evidences were published after June 2016. However, we have updated our searches to cover more recent papers, and only found one paper which satisfied the inclusion criteria. This was a report by Ukawa et al in 2017 (International Journal of Public Health, vol 62, pp 489-494) which presented results for at home passive smoking exposure from the Japan Collaborative cohort study, based

only on 33 cases. Rather than updating the whole range of analysis results, we intend simply to refer to this additional study, and the effect it had on the overall effect estimate, in a comment at the end of the discussion section. If you think there are other important papers we have missed please let us know what they are.

Too many aspects and subsets are taken into account We have published a number of previous reviews of the relationship of passive smoking to other diseases, and this style has never before been criticized. In our view it is important to fully describe how the association of interest varies by the source of exposure and by study characteristics, and also by the definition of disease. One cannot get a good insight without these details.

Taking into account the publication period before and after the smoking ban You say "the smoking ban" but there are many smoking bans, different in type and different in timing. In the US for example different states, and different locations within states, brought in bans at different times. When one also considers the long latent period of COPD, with deaths post-ban perhaps due to exposures pre-ban, and the fact that in some studies some COPD cases occur pre-ban and some post-ban, we did not consider it useful to attempt the required analysis.

Publication bias We made the point (also made in other passive smoking reviews) that some large cohort studies are known to have published positive relationships relating passive smoking to other diseases when they did not publish results relating passive smoking to COPD. Surely it is quite likely that they did not find a positive relationship for COPD? In my view large cohort studies ought to publish passive smoking results for all diseases with sufficient cases, but often they do not. Our comment is supported by the evidence as to what has and has not been published - though this does not prove that all such studies found no positive association with COPD, the likelihood is there. The argument is similar to the general one for publication bias. We don't generally have evidence that papers showing no association are less likely to be submitted or accepted than papers finding an association, but it is highly plausible.

Negative approach against other reviews We state the reasons why these other reviews are limited.

Overlooking evidence suggesting an association, such as the dose-response results and the overall meta-analysis results In paragraph 2 of the discussion we refer to the overall meta-analysis results and the dose-response results, and then go on to discuss why these results are only suggestive of a causal relationship. The overall association of 1.20 with passive smoking at home, though highly statistically significant, is quite small in magnitude, and it is certainly possible that it may be explicable in terms of bias. In our review of passive smoking and lung cancer (World Journal of Meta-Analysis, 2017, 4, 10-43) we were able to demonstrate quite clearly that a similar sized association could plausibly be explained by a combination of uncontrolled confounding and misclassification of smoking status. Though the data for COPD are not extensive enough to readily allow such adjustments, we would be extremely nervous in saying that the association is more than suggestive of a causal relationship. Nevertheless, we will look again at the wording we have used and try to make our argument clearer.

Conclusions drawn not adequately supported by the results presented This really relates to the previous point. We believe our conclusions are supported by the results.

We would be happy to hear your reactions to our replies.

Yours sincerely

Peter Lee (and co-authors)

Competing Interests: Our competing interests have already been described in the paper itself

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