# World Journal of *Meta-Analysis*

World J Meta-Anal 2016 April 26; 4(2): 10-62





Published by Baishideng Publishing Group Inc



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SYSTEMATIC REVIEWS

# Environmental tobacco smoke exposure and lung cancer: A systematic review

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Author contributions: Lee PN, Fry JS and Forey BA planned the study; Hamling JS and Thornton AJ carried out the literature searches, assisted by Lee PN and Forey BA; Fry JS, Forey BA, Hamling JS and Thornton AJ carried out the data entry which was independently checked by one of these or Lee PN; Lee PN and Forey BA discussed any difficulties in interpreting published data or in the appropriate methods for derivation of RRs; Forey BA and Hamling JS conducted the main statistical analyses, and Fry JS the bias analyses along lines discussed and agreed with Lee PN; Lee PN drafted the paper, with the assistance of Thornton AJ, which was critically reviewed by the other authors.

**Conflict-of-interest statement:** Lee PN, Director of P.N. Lee Statistics and Computing Ltd., is an independent consultant in statistics and an advisor in the fields of epidemiology and toxicology to a number of tobacco, pharmaceutical and chemical companies including the sponsors of this study. Fry JS, Forey BA and Hamling JS are employees of, and Thornton AJ a consultant to, P.N. Lee Statistics and Computing Ltd.

Data sharing statement: Supplementary Files provide: (1) further information on the methods; (2) fuller description and results of the confounder/misclassification analyses; (3) description of reasons for rejection of some papers; and (4) fuller results of the main meta-analyses. Copies of the database files are available on request from the corresponding author at peterlee@ pnlee.co.uk.

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Received: November 24, 2015 Peer-review started: November 25, 2015 First decision: December 28, 2015 Revised: January 19, 2016 Accepted: March 9, 2016 Article in press: March 14, 2016 Published online: April 26, 2016

#### Abstract

**AIM:** To review evidence relating passive smoking to lung cancer risk in never smokers, considering various major sources of bias.

METHODS: Epidemiological prospective or case-control studies were identified which provide estimates of relative risk (RR) and 95%CI for never smokers for one or more of seven different indices of exposure to environmental tobacco smoke (ETS): The spouse; household; workplace; childhood; travel; social and other; and total. A wide range of study details were entered into a database, and the RRs for each study, including descriptions of the comparisons made, were entered into a linked database. RRs were derived where necessary. Results were entered, where available, for all lung cancer, and for squamous cell cancer and adenocarcinoma. "Most adjusted" results were entered based on results available, adjusted for the greatest number of potential confounding variables. "Least adjusted" results were also entered, with a preference for results adjusted at least for age for prospective studies. A pre-planned series of fixed-effects and random-effects meta-analyses were conducted. Overall analyses and analyses by continent were run for each exposure index, with results for spousal smoking given by sex, and results for childhood exposure given by source of ETS exposure. For spousal exposure, more extensive analyses provide

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results by various aspects of study design and definition of the RR. For smoking by the husband (or nearest equivalent), additional analyses were carried out both for overall risk, and for risk per 10 cigarettes per day smoked by the husband. These adjusted for uncontrolled confounding by four factors (fruit, vegetable and dietary fat consumption, and education), and corrected for misclassification of smoking status of the wife. For the confounding adjustment, estimates for never smoking women were derived from publications on the relationship of the four factors to both lung cancer risk and at home ETS exposure, and on the correlations between the factors. The bias due to misclassification was calculated on the basis that the proportion of ever smokers denying smoking is 10% in Asian studies and 2.5% elsewhere, and that those who deny smoking have the same risk as those who admit it. This approach, justified in previous work, balances higher true denial rates and lower risk in deniers compared to non-deniers.

**RESULTS:** One hundred and two studies were identified for inclusion, published in 1981 onwards, 45 in Asia, 31 in North America, 21 in Europe, and five elsewhere. Eightyfive were of case-control design and 17 were prospective. Significant (P < 0.05) associations were noted, with random-effects of (RR = 1.22, 95%CI: 1.14-1.31, n = 93) for smoking by the husband (RR = 1.14, 95%CI: 1.01-1.29, n = 45) for smoking by the wife (RR = 1.22, 95%CI: 1.15-1.30, n = 47) for workplace exposure (RR = 1.15, 95%CI: 1.02-1.29, n = 41) for childhood exposure, and (RR = 1.31, 95%CI: 1.19-1.45, n = 48) for total exposure. No significant association was seen for ETS exposure in travel (RR = 1.34, 95%CI: 0.94-1.93, n = 8) or in social situations (RR = 1.01, 95%CI: 0.82-1.24, n = 15). A significant negative association (RR = 0.78, 95%CI: 0.64-0.94, n = 8) was seen for ETS exposure in childhood, specifically from the parents. Significant associations were also seen for spousal smoking for both squamous cell carcinoma (RR = 1.44, 95%CI: 1.15-1.80, n = 24) and adenocarcinoma (RR = 1.33, 95%CI: 1.17-1.51, n = 30). Results generally showed marked heterogeneity between studies. For smoking by either the husband or wife, where 119 RR estimates gave an overall estimate of (RR = 1.21, 95%CI: 1.14-1.29), the heterogeneity was highly significant (P < 0.001), with evidence that the largest RRs were seen in studies published in 1981-89, in small studies (1-49 cases), and for estimates unadjusted by age. For smoking by the husband, the additional analyses showed that adjustment for the four factors reduced the overall (RR = 1.22, 95%CI: 1.14-1.31) based on 93 estimates to (RR = 1.14, 95%CI: 1.06-1.22), implying bias due to uncontrolled confounding of 7%. Further correction for misclassification reduced the estimate to a marginally non-significant (RR = 1.08, 95%CI: 0.999-1.16). In the fully adjusted and corrected analyses, there was evidence of an increase in Asia (RR = 1.18, 95%CI: 1.07-1.30, n = 44), but not in other regions (RR = 0.96, 95%CI: 0.86-1.07, n = 49). Studies published in the 1980's, studies providing dose-response data, and studies only providing results unadjusted for age showed elevated

RRs, but later published studies, studies not providing dose-response data, and studies adjusting for age did not. The pattern of results for RRs per 10 cigs/d was similar, with no significant association in the adjusted and corrected results (RR = 1.03, 95%CI: 0.994-1.07).

**CONCLUSION:** Most, if not all, of the ETS/lung cancer association can be explained by confounding adjustment and misclassification correction. Any causal relationship is not convincingly demonstrated.

Key words: Passive smoking; Lung neoplasms; Doseresponse; Meta-analysis; Review; Confounding factors (epidemiology); Misclassification

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**Core tip:** We present an up-to-date meta-analysis of the evidence relating non-smoker lung cancer to environmental tobacco smoke (ETS) exposure. We demonstrate a clear risk increase for spousal, at-home, workplace and total exposure, but not childhood exposure. For husband smoking, the relative risk (RR) is estimated as (RR = 1.22, 95%CI: 1.14-1.31). However, adjustment for confounding by education and dietary variables, and correction for misclassified wife's smoking reduces it to (RR = 1.08, 95%CI: 0.999-1.16). Given the other data limitations and biases we discuss, one cannot reliably conclude that any true ETS effect on lung cancer risk exists. Our results suggest caution in drawing inferences from weak epidemiological associations where known biases exist.

Lee PN, Fry JS, Forey BA, Hamling JS, Thornton AJ. Environmental tobacco smoke exposure and lung cancer: A systematic review. *World J Meta-Anal* 2016; 4(2): 10-43 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i2/10.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i2.10

#### INTRODUCTION

It has been widely accepted that environmental tobacco smoke (ETS) exposure increases lung cancer risk, based on various authoritative reviews<sup>[1]</sup>. However, it was suggested some years ago<sup>[2]</sup> that a substantial part, if not all, of the relationship may be due to bias resulting from confounding by other lung cancer risk factors, and misclassification of smoking habits, with some self-reported never smokers actually being smokers. While there have been various meta-analyses of the evidence in the last 20 years<sup>[3-10]</sup>. these are often limited to specific indices of exposure or regions, and typically do not include formal adjustments for potential biases. They also do not take into account all the more recent studies, with over 100 studies published by now, many relatively recent.

The objective of this review, therefore, is to present an up-to-date comprehensive meta-analysis of the



available evidence which relates ETS exposure to lung cancer risk among never smokers, considering exposure from various sources, and illustrating the potential magnitude of the bias that can arise from confounding and misclassification of smoking.

#### MATERIALS AND METHODS

#### Introduction

The analyses presented were conducted in three stages. First, results of meta-analysis are presented relating a range of indices of ETS exposure to risk of lung cancer. Second, for two indices (spousal smoking and amount smoked by the spouse), individual study estimates for females are adjusted for the effects of confounding for selected variables (fruit consumption, vegetable consumption, dietary fat consumption and education) and revised meta-analyses conducted. Third, further adjustments are made for the biasing effects of misclassification of smoking status. The materials and methods section is therefore divided accordingly.

#### Study inclusion and exclusion criteria

Attention was restricted to epidemiological prospective or case-control studies published up to and including July 2015, which involved five or more lung cancers, and which provided relative risk (RR) estimates for never (or virtually never) smokers for one or more defined ETS exposure types or dose-related ETS indices. The "exposure types" compare subjects exposed and unexposed to ETS from seven different sources: Spouse; household; workplace; childhood; travel; social and other; and total, the final category including biochemical assessments of exposure. The "dose-related indices" concern ETS exposure in terms of amount smoked, duration of smoking and the number of smokers the subject was exposed to. ETS exposure from pipe/cigar only was ignored. Note that the term "relative risk" is taken to include estimates of it, such as the odds ratio or hazard ratio.

Studies using near equivalent definitions of "never smokers" were accepted when stricter definitions were unavailable, so never smokers could include occasional smokers, those with a minimal lifetime duration of smoking or number smoked, or ex-smokers who had quit at least 20 years previously.

#### Literature searches

Up until July 2015 potentially relevant papers were regularly sought from MEDLINE searches (using search terms "tobacco smoke pollution" and "lung neoplasm"), from files on smoking and health which were collected for many years within our company, and from references which were cited in the papers obtained. At the end of the process no paper examined cited a possibly relevant paper which had not been previously examined.

#### Study identification

Relevant papers were separated into studies, noting where there were multiple papers per study or multiple studies per paper, and any overlaps between studies. Each study was uniquely referenced by a  $\leq$  6 character code, based on the name of the principal author, with a suffix indicating where the same author had reported on multiple studies.

#### Data recorded

Data were entered on a study database, and also on a linked RR database. The structure and content of the databases are described in www.pnlee.co.uk/ downloads/etslc/23482-supplementary file 1.pdf.

In brief, a study database record describes the study design, the available data and a previously described index of study quality<sup>[11]</sup>. Typically there are multiple records per study on the RR database, each record holding a detailed description of a specific comparison made and the corresponding RR and its 95%CI.

#### **RR** derivation

When available, adjusted RRs and CIs were entered. Unadjusted estimates were derived from the  $2 \times 2$  table, using standard methodology<sup>[12]</sup>, any differences between calculated and author-provided estimates being noted. Other methodologies were used where required to derive estimates, those more commonly used<sup>[13,14]</sup> being described in www.pnlee.co.uk/downloads/etslc/23482supplementary file 1.pdf.

#### Identifying the RRs to enter

RRs were entered, if available, relating to various predefined combinations of type of lung cancer, index of smoking, confounders considered, and strata. The combinations are described in the following sections.

**Type of lung cancer:** Results were entered for overall lung cancer, squamous cell carcinoma and adenocarcinoma, or their nearest equivalents for which data were available.

Smoking indices: The intention was to enter RRs comparing subjects exposed and unexposed to the various indices of ETS defined above. Though RRs for exposure to smoking by the spouse should ideally be derived from data only for married subjects, we also allowed RRs from studies where unmarried subjects were included in the reference group. Similarly, RRs for workplace exposure could include non-working subjects. For the "household" and "childhood" categories, RRs were entered for all possible sources recorded by the studies, but for the "travel" and "social" categories, if more than one index of exposure was available, only that representing the greatest number of exposed subjects was entered. RRs were entered for all available timings of adult exposure, but for childhood, only RRs for the earliest exposure were entered. "Total" exposure was defined as exposure to two or more types of exposure, or biochemical assessment of overall exposure. For doserelated exposure indices, RRs were entered for each level of exposure relative to a common base level. RRs were entered, where available, using denominators



representing both "no exposure to the specific type of ETS" and "no exposure to any ETS".

**Confounders:** For case-control studies, we entered results adjusted for the most potential confounders available, and also adjusted for fewest. For prospective studies, we entered results adjusted for age and the most confounders, and for age and the fewest, and unadjusted results were entered only where there were no age-adjusted results. We describe these alternative RRs as "most-adjusted" and "least-adjusted".

**Strata:** We only entered results stratified by sex or age. Combined sex results were only entered if results by sex were unavailable. We entered results for all ages and for separate age groups. Specifically for spousal exposure (or nearest equivalent - see "analyses conducted" below), where an adjusted RR was available only for combined sexes but numbers of cases and controls were given by sex, split-sex estimates were entered, assuming that the RR applied to each sex, with separate CIs estimated for males and females.

#### Meta-analyses

**Analyses conducted:** The series of meta-analyses conducted was pre-planned. For a given exposure type, a set of up to 20 analyses was conducted. Meta-analyses 1 and 2 used the overall data available, while meta-analyses 3 and 4 were separated by region (North America, Europe, Asia or other regions), with meta-analyses 1 and 3 using most-adjusted and 2 and 4 least-adjusted data. Analyses 5-20 were based on most-adjusted data only and studied variation by other factors, as described in www.pnlee.co.uk/downloads/ etslc/23482-supplementary file 1.pdf.

The primary index of exposure used was "spousal smoking (or nearest equivalent)" where, for studies which provided no results for spousal exposure, results for household, total or both spousal/home and other exposure were chosen instead. This identified a single exposure definition for each study. For overall lung cancer, the full set of 20 meta-analyses was carried out restricted to females, and unrestricted on sex. Further meta-analyses for the principal index of exposure corresponded to meta-analyses 1 to 4 only. These included analyses for spousal smoking (or nearest equivalent) for males, spousal smoking (specifically) for females, males and unrestricted on sex, and analyses for spousal smoking (or nearest equivalent) for squamous cell carcinoma and for adenocarcinoma, each for females, males and unrestricted on sex.

Analyses for the other types of exposure were run only for overall lung cancer, without restriction on sex, and were equivalent to meta-analyses 1-4 only. The childhood and household exposure analyses were run using alternative indices, depending on the available data, as described in www.pnlee.co.uk/downloads/etslc/ 23482-supplementary file 1.pdf. **Selecting RRs for the meta-analyses:** In selecting RRs to include we tried to include all relevant data once only. Where a study had multiple RRs, that used is chosen by an order of preference specific to the meta-analysis. Order of preference may be needed for exposure status and timing, and for the unexposed base. As RR definitions may be sex-specific, the RRs selected may differ by sex. Results for sexes combined are only considered in the absence of sex-specific results.

#### Conducting the meta-analyses for exposure indices:

We conducted fixed-effect and random-effects metaanalysis of study-specific data for the various exposure indices studied as described elsewhere<sup>[13]</sup>. Heterogeneity was measured by H, the ratio of heterogeneity  $\chi^2$  to degrees of freedom. H relates to  $I^2$  statistic<sup>[15]</sup> by  $I^2 = 100$ (H - 1)/H. For all meta-analyses, results of publication bias tests using the Egger method<sup>[16]</sup> were also given.

Results are displayed in forest plots. Within each plot, studies are identified by their reference code, and listed in order of RR. Most of the plots are also grouped by region. The study estimates are shown both as numbers and in graphical form logarithmically. In the latter representation an RR is shown as a square, the area of which is proportional to its weight, its inversevariance. Arrows warn if the CI goes outside the range of the plot. Random-effects estimates are also presented, overall or by region, shown by a diamond whose width indicates the 95%CI.

Carrying out meta-analyses for number of cigarettes smoked by the husband: The methods used are as described elsewhere<sup>[17]</sup>, and are summarized here. The underlying model assumes that, when comparing two groups differing in exposure by dose d, log RR is estimated by  $\beta d$ . For each study, given data at each level of exposure consisting of the dose level, the number of cases, and the number of controls (or subjects at risk),  $\beta$  and its standard error (SE $\beta$ ) are estimated by the method of Greenland and Longnecker<sup>[18]</sup>, This can be applied to studies with only two levels (unexposed and exposed), and also to confounder-corrected RRs and 95%CIs, by estimating pseudo-counts using the method of Hamling<sup>[14]</sup>. Estimates of  $\beta$  and SE $\beta$  from each study are then meta-analysed as described above. The method of estimating midpoint doses for intervals such as 1-19 or 20+ cigarettes per day is as described previously<sup>[17]</sup>.

The series of meta-analyses conducted for the estimates of  $\beta$  was similar to that for the exposure indices as described above.

#### Adjustment for bias due to confounding

The potential confounding variables considered (consumption of fruit, consumption of vegetables, consumption of dietary fat, and education) and the methods used to adjust for them are as described in a previous publication<sup>[19]</sup> and in

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an unpublished updated analysis conducted in 2006<sup>[20]</sup>. The methods are summarized briefly below.

Estimating the relationship between the four potential confounding variables considered and the risk of lung cancer in never smoking females: The database of studies relating lung cancer risk in never smokers to the four potential confounding variables used in  $2001^{[19]}$  and updated in  $2006^{[20]}$  was used, restricting attention to never smoking females. Exp( $\beta$ ), the increase in risk per dose unit (SDs for dietary variables, years for education), was estimated using methodology equivalent to that described in the previous section. Methods for assigning midpoint dose values for grouped dietary data (*e.g.*, by quintiles), and for education groups were as before<sup>[19]</sup>.

Estimating the differences in fruit, vegetable and fat consumption and in education associated with ETS exposure: The database of studies comparing the distribution of the four potential confounding variables set up in  $2001^{[19]}$  and updated in  $2006^{[20]}$  was used, with attention restricted to never smoking females. For each potential confounding variable, we estimated the difference,  $\delta$ , in relation to marriage to, or living with, a smoker, in units of SDs for the dietary variables and years for education, using the methodology described earlier<sup>[19]</sup>. These study-specific estimates of  $\delta$  were then combined using random-effects meta-analysis.

# **The basic method for confounder adjustment:** As described earlier<sup>[19]</sup> we assume that the logarithm of L, the lung cancer risk, is linearly related to *n* explanatory factors $x_i$ by:

$$\log L = \beta_0^* + \sum_i \beta_i^* x_i \tag{1}$$

 $Exp(\beta_0^*)$  is the background risk that is expected for zero exposure to each factor. Exp  $(\beta_i^*)$  is the multiplicative risk increase expected per unit increase in exposure to the i<sup>th</sup> factor.

Should data relating lung cancer to the factors be available only univariately the relationship with each factor would be formulated as:

$$\log L = \beta_0 + \beta_i x_i \tag{2}$$

where  $exp(\beta)$  is the RR for a unit dose increase associated with factor i that is not adjusted for the other risk factors.

The  $\beta_i$  and the  $\beta_i^*$  are related by the matrix equation:  $B^* = S^{-1}C^{-1}SB$  (3)

Here B\* and B are the n  $\times$  1 vectors of and  $\beta_i$ , S the n x n standard deviation (SD) matrix,  $s_i$  and C the n x n correlation matrix  $c_i$ .

Given B, C and S, we can estimate B\*. In our context, there are five factors. i = 1 represents ETS with I = 2...5 the three dietary variables and education. Thus exp( $\beta_i$ ) is the unadjusted risk increase for each unit of increase in ETS exposure, and exp( $\beta_i^*$ ) the adjusted risk increase. The joint confounding effect of the four variables is estimated as exp( $\beta_i$ )/exp( $\beta_i^*$ ).

Relationship of the factors to lung cancer risk: Estimates of  $\beta_i$  are generally those described in the subsection "carrying out meta-analyses for number smoked by the husband". However, the basic method assumes that  $\beta_i$  is unadjusted for any of the four potential confounding variables. Where  $\beta_i$  is adjusted for one or more of the variables, we first back-corrected it in order to take out the effect of the adjustment as described earlier<sup>[19]</sup>. This back-correction procedure avoids double-adjustment for the same factor. Back-correction was also carried out in the following cases: For fruit consumption, where the RR estimate had already been adjusted for vitamin C; for dietary fat, where the RR estimate had already been adjusted for energy intake, for meat, or for cholesterol; and for education, where the RR estimate had already been adjusted for income, for socioeconomic status, or for ownership of a colour TV.

**Standard deviations:** We estimated  $s_1$ , the SD for ETS, directly for each study from the population data by level of exposure as described elsewhere<sup>[17]</sup>.  $s_2$ ,  $s_3$  and  $s_4$ , the SDs for the dietary variables are 1, since they are measured in units of SD. We took the SD for education as 2.435 years<sup>[20]</sup>.

**Correlations:** If i = j,  $c_{ij} = 1$ . To quantify other correlations, we used the formula:  $C_{ij} = \delta_j s_1/d_1 (average) s_j$  (4)

Here  $\delta_j$  is a common estimate of the difference in exposure to variable j for living with a smoker (see the sub-section "estimating the differences in fruit..."). s<sub>1</sub> and s<sub>j</sub> are as described above, and d<sub>1</sub>(average) is the mean ETS exposure for exposed never smokers. Where studies have more than one exposure level, we estimated d<sub>1</sub>(average) by weighting on the number of exposed subjects.

To quantify the correlations between the potential confounding variables we used averaged data from seven databases, the five used in 2001<sup>[19]</sup> and two additional US databases (NHIS2000, NHANES III), as described in www.pnlee.co.uk/downloads/etslc/23482-supplementary file 2.pdf.

## Adjustment for bias due to misclassification of smoking status

How the bias arises and what it depends on: Estimates of the RR of lung cancer in self-reported never smoking women associated with marriage to a smoker may be biased if a proportion of the women are actually current or ex-smokers. This bias arises because smokers marry smokers more often than is expected by chance. Misclassified smokers are therefore commoner among those married to a smoker. As shown by Lee and Forey<sup>[21]</sup>, the bias depends mainly on the rate of misclassification, the active smoking risk, the degree to which smoking by spouses is concordant, and the proportions of smokers among subjects and their spouses.



**Correction method used:** We use the Lee and Forey<sup>[21]</sup> method for bias correction, assuming joint effects of active smoking and ETS exposure are additive, and the published extension of the method<sup>[22]</sup>.

**Concordance ratio:** The concordance ratio is defined as the odds of the husband smoking if the wife ever smoked divided by the odds if the wife never smoked. From an earlier review<sup>[23]</sup> we used an estimate of 3.0.

**Study-specific data on active smoking RRs:** For each study, estimates were made of the active smoking RR, derived if possible from the source paper itself or another paper using the same study population. Otherwise they were derived from studies in that country, from estimates presented by the EPA<sup>[24]</sup> or by other methods, as described in www.pnlee.co.uk/ downloads/etslc/23482-supplementary file 2.pdf.

**Misclassification rates:** Misclassified smokers have a lower lung cancer risk than non-misclassified smokers. To take this into account, we followed precedent<sup>[21,22]</sup> in carrying out the misclassification correction on the basis that those who deny smoking have the same risk as those who admit it, but using lower misclassification rates (10% for Asia, and 2.5% elsewhere) than are observed. Support for the use of these rates is provided elsewhere<sup>[21-23,25,26]</sup>.

**Application of the method:** RRs for spousal smoking and for amount smoked by the spouse, were calculated: (1) with no adjustment for confounding or correction for misclassification; (2) with adjustment for confounding and no correction for misclassification; and (3) with adjustment for confounding and correction for misclassification.

#### RESULTS

#### Studies identified

There were 102 studies which met the inclusion criteria. Some studies were noted to have overlaps with other studies. However, as all overlaps were minor and could not be disentangled, it was decided to ignore them. Tables 1 and 2 give study details including reference(s), location, design, dates, numbers of cases in never smokers, definition of never smoking, ETS exposure measures considered, adjustment variables used, extent of histological confirmation of cases, whether results are available by histological type, and availability of doseresponse data. www.pnlee.co.uk/downloads/etslc/ 23482-supplementary file 3.pdf describes why other publications which could be thought possibly relevant are not considered in our analyses.

Of the 102 studies, 31 were conducted in North America (including 26 in United States), 45 in Asia (including 23 in China, 10 in Japan and 6 in Hong Kong), 21 in Europe (4 in Sweden being the most for any country), and 5 in other locations (including two international studies). Eighty-five studies were of case-control design and 17 were prospective. Twenty-six studies were published in 1981-1989, 28 in 1990-1999, 32 in 2000-2009 and 16 in or after 2010.

In general, the total number of cases per study was small, with 20 studies based on less than 50 cases, and 29 considering 50-99. Twenty-four studies examined 100-199 cases, 18 200-399 cases, with only 11 based on 400 or more cases.

The most commonly studied index was smoking by the spouse, considered by 55 studies. Smoking by a cohabitant was considered by 47 studies, workplace smoking by 40, and childhood exposure by 41. Travel and social exposures were considered by 5 and 11 studies respectively, and total exposure by 51.

#### Effect estimates

In what follows, meta-analysis RRs referred to in the text, tables and figures are based on "most-adjusted" estimates, meta-analysis RRs based on "least-adjusted" estimates usually being very similar. The results highlighted are drawn from more detailed analyses for all the exposure indices made available in www.pnlee. co.uk/downloads/etslc/23482-supplementary file 4.pdf, which also shows the "preferences" used in each analysis. This includes some analyses based on "leastadjusted" estimates, and also gives estimates for each individual study included in an analysis. Significance is taken to be at P < 0.05 unless otherwise stated. RRs and 95%CIs are normally shown to 2 decimal places. Exceptionally, they are shown to 3 decimal places for the analyses investigating bias due to confounding and misclassification, to show the effects of adjustment and correction more clearly.

#### Smoking by the spouse

Ninety-three studies provided results relating lung cancer in women to husband's smoking (or nearest equivalent), with 19<sup>[27-45]</sup> giving significantly raised RRs and 51 non-significantly raised RRs. In contrast 18 studies showed a negative relationship, significant in three studies<sup>[46-48]</sup>. Five studies gave a RR of 1.00. Two studies could not be included in the meta-analysis, one study<sup>[49]</sup> reporting no significant effect of passive smoking but giving no further details, with another<sup>[50]</sup> only giving an odds ratio of 2.2 (1.4-3.7) for greater than 40 smoker-years exposure to passive smoking. There was marked heterogeneity (P < 0.001) between the individual study estimates. However, fixedeffect (1.19, 95%CI: 1.14-1.24) and random-effects estimates (1.22, 1.14-1.31) were similar. Based on the Egger test there was no clear evidence of publication bias (0.05 < P < 0.1). Further analyses of these data are given in the section "smoking by the husband detailed analyses" below.

Forty-five studies considered smoking by the wife (or nearest equivalent). Twenty-eight RRs were raised, three<sup>[28,39,51]</sup> significantly. Fifteen studies reported a negative association, significant in one study<sup>[47]</sup>. One



#### Table 1 Selected details of the 102 studies in publication date order

Study ref	Main ref	Other ref	Location	Study design <sup>1</sup>	5	Study dates <sup>2</sup>		Total cases	Never smoker criteria <sup>3</sup>
GARFI1	[75]	[104]	United States	Р	1959 -	1960,	1971	153	Dur 6 mo
CHAN	[105]	[106,107]	Hong Kong	CC	1976 -	1977		84	
CORREA	[67]		United States	CC	1979 -	1982		32	
TRICHO	[27]	[108,109]	Greece	CC	1978 -	1982		77	
BUFFLE	[110]		United States	CC	1976 -	1980		52	
HIRAYA	[28]	[111-120]	Japan	Р	1965 -	1966,	1981	264	
KABAT1	[53]		United States	CC	1971 -	1980		76	
GARFI2	[121]	[122]	United States	CC	1971 -	1981		134	
LAMW	[29]		Hong Kong	CC	1981 -	1984		75	
WU	[123]		United States	CC	1981 -	1982		31	
AKIBA	[68]		Japan		1971 -	1980		113	
LEE	[124]		United Kingdom		1979 -	1982		4/	
GAO	[125]		China	CC CC	1979 -	1982		19	
GAO HUMBI 1	[120]		United States		1964 -	1966		240	Dur6mo
KOO	[127]	[129_133]	Hong Kong		1981 -	1983		28 88	N20
LAMT	[30]	[127-155]	Hong Kong	CC CC	1983 -	1986		199	Occ (1 vr)
PERSHA	[134]	[135]	Sweden	CC	1961 -	1980		77	
BUTLER	[136]	[]	United States	Р	1976 -	1976.	1982	8	
GENG	[31]	[137]	China	CC	1983 -	1983		54	
INOUE	[138]		Japan	CC	1973 -	1983		28	
SHIMIZ	[70]		Japan	CC	1982 -	1985		90	
CHOI	[139]		South Korea	CC	1985 -	1988		88	
HOLE	[140]	[141]	Scotland	Р	1972 -	1976,	1985	9	
SCHOEN	[142]		United States	CC	1982 -	1983		116	
SVENSS	[143]	[144]	Sweden	CC	1983 -	1985		34	Occ
JANERI	[72]	[145]	United States	CC	1982 -	1985		191	N100
KALAND	[32]		Greece	CC	1987 -	1989		91	
SOBUE	[146]	[147]	Japan	CC	1986 -	1988		144	
WU-WIL	[46]		China	CC	1985 -	1987		417	
LIUZ	[148]	[149,150]	China	CC	1985 -	1986		54	1sm
BROWN2	[151]	[152-155]	United States	CC	1986 -	1991		432	17400 F
STOCKW	[58]	[156]	United States	66	1987 -	1991		210	N100, Dur 6 mo
DU	[52]	[157-159]	China		1986 -	1986		75	
EONTHA	[100]	[1/1 1/4]	United Chatan	CC 66	1985 -	1984		38	N100 Dun (
FUNIHA	[33] [165]	[161-164]	United States		1986 -	1988		60	N100, Dur 6 mo
DEWAAR	[165]	[167]	Netherlands		1900 -	1980		23	Cot
KABAT2	[168]	[169 170]	United States		1983 -	1990		110	Cor
SCHWAR	[57]	[10),110]	United States	CC	1984 -	1987		257	
SUN	[60]		China	CC	NA	1707		230	
WANGS	[34]		China	CC	NA			82	
WANGT	[171]		China	CC	1992 -	1994		135	
CARDEN	[73]	[172,173]	United States	Р	1982 -	1982,	1989	362	
ZHENG	[35]		China	CC	1990 -	1993		94	Non
AUVINE	[174]		Finland	CC	1986 -	1992		44	
BOFFET	[66]	[175-180]	West Europe	CC	1988 -	1994		640	N400
SHEN	[181]	[182-185]	China	CC	1993 -	1993		70	
ZARIDZ	[36]	[186-188]	Russia	CC	1991 -	1993		189	
BOFFE2	[189]		Europe	CC	1994 -	1996		70	N400
JEE	[190]		South Korea	Р	1992 -	1994,	1997	79	Occ, Dur 1 yr
RAPITI	[61]		India	202	1991 -	1992	1000	58	N400
SPEIZE	[191]		United States	P	1982 -	1982,	1992	35	Duridana
LEECH	[34]	[102 104]	Cnina		1992 -	1994		268	Dur 6 mo
MALATS	[37]	[192-194]	Furono/Brazil		1992 - NA	1998		120	N400
WANGI	[195]	[190]	China		1994 -	1998		233	Dur 6 mo
IOHNSO	[198]	[199-201]	Canada	CC CC	1994 -	1997		255 71	N100
LAGARD	[202]	[203]	Sweden	CC	1980 -	1995		433	Occ (1 vr)
NISHIN	[204]	[_~~]	Iapan	Р	1984 -	1984.	1992	24	
OHNO	[205]		Japan	CC	NA	,		191	N365
RACHTA	[63]	[206]	Poland	CC	1991 -	1997		54	Dur 6 mo
ENSTRO	[207]	[208]	United States	Р	1959 -	1960,	1998	256	
ZATLOU	[64]	[209,210]	Czech Republic	CC	1998 -	2002		84	N100
IARCKR	[1]	[180]	Germany	CC	1990 -	1996		123	Dur 6 mo, N400
MCGHEE	[211]		Hong Kong	CC	1998 -	1998		324	
EPICA	[212]	[213-216]	Western Europe	Р	1993 -	1998,	2000	59	



FANG	[38]	[216]	China	CC	2001 -	2004		157	
FRANCO	[71]	[216]	Mexico	CC	2000 -	2002		94	
GORLOV	[55]	[217-222]	United States	CC	1995 -	2003		193	N100
NEUBER	[49]		United States	CC	1994 -	1997		56	N100, Dur 6 mo
RYLAND	[223]		Sweden	CC	1989 -	1994		49	
WEN	[56]	[224-227]	China	Р	1997 -	2000,	2004	106	
YU	[228]	[228-230]	Hong Kong	CC	2002 -	2004		213	N400, Dur 1 yr
ZEKA	[59]		East Europe, United Kingdom	CC	1998 -	2002		223	N100
HILL1	[231]		New Zealand	Р	1981 -	1981,	1984	147	Occ
HILL2	[231]		New Zealand	Р	1996 -	1996,	1999	234	Occ
LOPEZC	[232]		Spain	CC	2000 -	2005		36	N100
ASOMAN	[233]		United States	CC	1992 -	NA		138	Occ (1 yr)
GALLEG	[51]		Mexico	CC	2003 -	2007		32	
KURAHA	[234]		Japan	Р	1990 -	1993,	2004	109	
PANDEY	[50]		Nepal	CC	NA			268	
YANG	[39]	[65,221,235,236]	United States	CC	1997 -	2008		297	N100
OLIVOM	[65]	[237]	United States	CC	NA			45	N100
TSE	[238]	[239]	China	CC	2004 -	2006		132	N400, Dur 1 yr
LIANG	[40]		China	CC	2004 -	2007		226	
BRENNE	[47]		Canada	CC	1997 -	2002		156	N100
JIANG	[41]		China	CC	2009 -	2009		145	
EPICC	[240]	[212]	Western Europe	Р	1992 -	1998,	2006	98	
KIYOHA	[241]		Japan	CC	1996 -	2008		153	
HE	[242]	[243]	China	Р	1976 -	1994,	2011	16	N100
LIM	[74]	[244-246]	China	CC	1996 -	2008		433	Occ (1 yr)
LIN	[42]		China	CC	2006 -	2010		226	
FERREC	[247]		Chile	CC	2007 -	2010		59	
ALZOUG	[48]	[248,249]	Canada	CC	1996 -	2000		44	N100
GELAC	[43]		Taiwan	CC	2002 -	2009		1540	Occ
MASJED	[44]	[250]	Iran	CC	2002 -	2005		81	Dur 6 mo
REN	[251]		China	CC	2002 -	2012		764	
SEKI	[252]		Japan	CC	1997 -	2009		431	
WHIOS	[253]	[254]	United States	Р	1993 -	1998,	2009	200	
ILCCO	[45]	[69]	International	CC	1984 -	2014		2504	N100
TORRES	[255]	[256]	Spain	CC	2011 -	2013		192	N100
			-						

<sup>1</sup>Study design is coded as P: Prospective; CC: Case control; <sup>2</sup>Study dates are given as Start year, End year, Final follow-up year (prospective studies only); <sup>3</sup>Inclusion of "near equivalents" to never smokers, coded as Dur: Includes those who smoked up to a number of months (mo) or years (yr); N: Includes those who smoked up to a number of cigarettes in their lifetime; Occ: Includes occasional smokers; Occ (1 yr): Includes those who smoked occasionally for up to 1 year; Non: Described as "non-smokers" and assumed from context to mean never smokers; 1sm: Study included 1 smoker; Cot: Excluded selfreported never smokers with urinary cotinine > 100 ng/mg.

#### Table 2 Further details of the 102 studies

Ref.	ETS exposures <sup>1</sup>	Adjustment variables used <sup>2</sup>	Extent (%) of histological confirmation	Results by histological type	Dose-response results available <sup>3</sup>
GARFI1	s	7	NA		Yes
CHAN	s	0	80		
CORREA	s c <sup>4</sup>	1	97		Yes
TRICHO	s	0	27	Yes	Yes
BUFFLE	h	0	100		Yes
HIRAYA	s	2	NA		Yes
KABAT1	s h w	4	100		
GARFI2	s h w c o tot	4	100	Yes	Yes
LAMW	s tot	1	100	Yes	
WU	s w c tot <sup>4</sup>	2	100	Yes	
AKIBA	s c	6	53		Yes
LEE	s h w tr o tot	3	38	Yes	
BROWN1	tot	3	100	Yes	
GAO	s h c tot	2	43		Yes
HUMBL1	s	2	100		Yes
KOO	s h w c tot	5	97	Yes	Yes
LAMT	s	0	100	Yes	Yes
PERSHA	s c	2	83	Yes	Yes
BUTLER	s	2	100		
GENG	s	0	85		Yes
INOUE	s	3	NA		Yes
SHIMIZ	s h w	3	100		
CHOI	s	0	100		Yes



HOLE	h	2	NA		Yes
SCHOFN	s	-	100		100
SVENISS	h c tot	1	70		
LANEDI		1	100	N	V
JANERI	snwco	3	100	Yes	Yes
KALAND	s h w	5	48	Yes	Yes
SOBUE	s h c	3	100		
WU-WIL	shwc	5	42		
LIUZ	h	3	17		
BROWN2	s h w c	2	76	Yes	Yes
STOCKW	s h w <sup>4</sup> c o <sup>4</sup> tot	3	100	Yes	Yes
DU	e .	2	NA	100	Ves
	3	2	22		Voc
LIUQ	5	5	52	N/	Tes
FONTHA	s h w c o tot	10	100	Yes	Yes
LAYARD	s	3	NA		Yes
DEWAAR	tot	0	71		Yes
KABAT2	s h w c tr o tot	6	100		Yes
SCHWAR	h w	2	100		
SUN	s h w c hw tot	2	100	Yes	
WANGS	tot	0	100		
WANGT	S W C	1	57		Ves
CARDEN	- have a test	1	DI A		Y
CARDEN	S II W O LOL	0	INA 02	X	res
ZHENG	h	2	82	Yes	Yes
AUVINE	tot	1	NA		
BOFFET	s h w c tr o tot	7	96	Yes	Yes
SHEN	tot	9	100	Yes	Yes
ZARIDZ	s h w c	2	100	Yes	Yes
BOFFE2	s w c tot	5	100	Yes	Yes
IEE	S	5	0		Yes
RAPITI	swetr	3	100	Vos	Ves
CDELZE	5 W C L	1	100	105	105
SPEIZE	tot	1	100	N	N
ZHUNG	s n w c tot	/	57	Yes	Yes
LEECH	s h w c tot	7	100		Yes
MALATS	s tot	2	100		Yes
WANGL	h c	6	32		Yes
JOHNSO	h w c tot	4	100		Yes
LAGARD	h tot	6	100		
NISHIN	s h	7	NA		
OHNO	swctrotot	2	100		Yes
PACHTA	3 w c u o tot	2	100	Voc	105
ENCTRO	C .	21	100 NIA	Tes	
ENSIRO	s	8	INA 100	N	
ZAILOU	c tot	3	100	Yes	
IARCKR	s w c	2	100		Yes
MCGHEE	h	2	0		Yes
EPICA	h w tot	7	NA		
FANG	tot	8	100		Yes
FRANCO	h	2	100		
GORLOV	h w hw tot	4	100		
NEUBER	$tot^4$	3	100		
RYLAND	hw	3	98		
WENI		0	NA		Vac
VILIN	s w c tot	3	100		Tes
YU	tot	20	100		Yes
ZEKA	W	4	NA		Yes
HILL1	h	9	NA		
HILL2	h	9	NA		
LOPEZC	tot	0	100		
ASOMAN	h w o	0	100		
GALLEG	tot	0	100		
KURAHA	swchwtot	5	90	Yes	Yes
PANDEV	s tot	0	NA	100	Vec
VANC	c tot	5	IN/A		Tes
IANG	c tot	5	INA 100	N	
OLIVOM	С	4	100	Yes	
TSE	h w tot	9	100	Yes	Yes
LIANG	c tot	0	100		
BRENNE	h w c tot	3	100		Yes
JIANG	tot	17	100	Yes	
EPICC	с	10	NA		Yes
KIYOHA	S	0	100		
HE	tot	0	88		Vec
LIM	101 L	9	00		res
	n	0	90		V
	tot	9	100		Yes
FERREC	c tot⁼	3	72		



ALZOUG	s h w c tot	3	NA	Yes	Yes
GELAC	s h w hw tot	6	100		Yes
MASJED	s h w o tot	4	100	Yes	
REN	tot	5	100		
SEKI	s	7	94	Yes	
WHIOS	h4 w <sup>4</sup> c <sup>4</sup> tot	0	0		4
ILCCO	h w c tot	3	100	Yes	Yes
TORRES	h	2	99		Yes

<sup>1</sup>ETS exposure measures reported, coded as s: Spousal; h: Household; w: Work; c: Childhood; hw: Exposure at both home and work; tr: Travel; o: Social/ other; tot: Total exposure. Codes marked 4 represent exposures for which the only result presented is a statement that no association was found; <sup>2</sup>Number of factors adjusted for, excluding sex; <sup>3</sup>Coded as yes: Dose response result presented; <sup>4</sup>The only dose response result presented is a statement that no dose response was found. NA: Not available.

study found no association. One study<sup>[52]</sup> reported ETS was not statistically associated with lung cancer, but gave no further details and could not be included in the meta-analysis. Heterogeneity between studies was not significant, and fixed-effect (1.15, 1.03-1.28) and random-effects estimates (1.14, 1.01-1.29) were similar. There was no evidence of publication bias (P > 0.1).

Results by sex, separated by region, are given as forest plots in Figure 1 (husband smoking) and Figure 2 (wife smoking).

Further meta-analyses were carried out on results for smoking by either the husband or the wife (or nearest equivalent), based on 119 RR estimates. Details are given in Table 3, along with estimates split by various other factors. Overall, a fixed-effect RR (1.18, 1.14-1.23) and a random-effects RR (1.21, 1.14-1.29) were estimated, with marked heterogeneity between studies (P < 0.001). When the studies were examined according to various factors, there was evidence of heterogeneity between factor levels for publication date (P < 0.01), study size (P < 0.01) and age adjustment (P < 0.05), with the largest RRs seen for early (1981-1989) studies, small studies (1-49 cases) and estimates unadjusted for age. There was no significant heterogeneity by location, study type, reporting of dose-response results, or use of spouse as the index of exposure. There was no clear evidence of publication bias (0.05 < P < 0.1).

Results for smoking by the spouse (or nearest equivalent) were also examined by histological type of cancer, with Figure 3 (squamous cell carcinoma) and Figure 4 (adenocarcinoma) showing forest plots by region. The analysis of squamous cell carcinoma, based on 24 RR estimates, showed a significant (P < 0.001) positive association and heterogeneity (P < 0.001), overall estimates being 1.41 (1.24-1.59, fixed-effect) and 1.44 (1.15-1.80, random-effects). No significant variation by region was seen. For adenocarcinoma, the 30 RR estimates were again heterogeneous (P < 0.01), with the meta-analysis showing significantly raised RRs, of 1.23 (1.15-1.32, fixed-effect) and 1.33 (1.17-1.51, random-effects). The heterogeneity was partly due to differences (P < 0.001) by region, with little increase seen in North American and European studies (randomeffects RRs 1.08, 0.96-1.22 for North America; 1.11,

0.82-1.49 for Europe), but a clear increase for Asia (random-effects RR 1.70, 1.35-2.15).

#### Workplace ETS exposure

For lung cancer and workplace ETS exposure, 47 RR estimates were available (Figure 5). Of these, 37 were raised, with estimates from six studies<sup>[33,45,53-56]</sup> being significant, and another<sup>[57]</sup> of borderline significance. This contrasted with nine studies, where RRs were non-significantly below 1.00, and one showing no association. Two other studies<sup>[58,59]</sup>, neither of which reported an association, could not be included in the meta-analysis, due to providing insufficient detail. Overall, there was a significant positive relationship, whether based on fixed-effect (1.21, 1.14-1.28) or random-effects RRs (1.22, 1.15-1.30). There was no evidence of heterogeneity or publication bias. Studies conducted in North America (1.21, 1.08-1.37), Europe (1.18, 1.01-1.39) and Asia (1.33, 1.20-1.47) all showed a significantly increased random-effects RR.

#### Childhood ETS exposure

Results for childhood ETS exposure are given, by region, in Figure 6, with further meta-analyses given in Table 4. For childhood exposure from any cohabitant, 41 RR estimates were available. Of these, 21 were raised, eight significantly<sup>[37,39,60-65]</sup>. In contrast 18 RR estimates were below 1.00, one<sup>[66]</sup> significantly so, while two were equal to 1.00. In addition, three studies<sup>[67-69]</sup> found no relationship but provided insufficient detail for inclusion in the meta-analysis. Although meta-analysis suggested a positive relationship with the risk of lung cancer, this only just reached statistical significance (fixed-effect RR = 1.08, 1.01-1.15; random-effects RR = 1.15, 1.02-1.29). There was significant heterogeneity between the studies (P < 0.001), and heterogeneity between the continents (P < 0.05), with a significant increase seen in Asia (random-effects RR = 1.31, 1.02-1.67), but not in North America (RR = 1.06, 0.89-1.28) or Europe (RR = 1.02, 0.81-1.29).

Based on nine RR estimates, meta-analysis showed no evidence of any relationship specifically with maternal smoking in childhood, with the fixed-effect estimate 0.96 (0.77-1.20) and the random-effects estimate 0.98 (0.77-1.25). There was also no association specifically with paternal smoking in childhood (fixed-effect model

Ref.	Random RR 95%CI	Weight (%)	Random RR 95%CI
N America			
ALZOUG	<b>B</b>	0.21	0.39 (0.15, 0.98)
BRENNE		0.88	0.40 (0.25, 0.63)
LAYARD		0.43	0.58 (0.30, 1.13)
JANERI	<b></b>	0.86	0.75 (0.47, 1.20)
KABAT1	<b>B</b>	0.15	0.79 (0.25, 2.45)
BUFFLE	<b>B</b>	0.26	0.80 (0.34, 1.90)
WHIOS		0.68	0.88 (0.52, 1.49)
ASOMAN		0.16	0.93 (0.31, 2.78)
FNSTRO		1 54	0.94 (0.66, 1.33)
BROWN2		4 59	1.00(0.80, 1.33)
SCHOEN		1.03	1.00(0.00, 1.20) 1.07(0.70, 1.64)
KABAT2		0.55	1.07(0.70, 1.04) 1.08(0.60, 1.94)
		1.05	1.00(0.00, 1.94)
		1.05	1.10(0.72, 1.00) 1.15(0.62, 2.10)
GURLUV		0.52	1.15 (0.63, 2.10)
GARFII		1.84	1.17 (0.85, 1.61)
JUHNSU		0.44	1.20 (0.62, 2.30)
CARDEN		1.5/	1.20 (0.80, 1.60)
WU	<b>B</b>	0.21	1.20 (0.50, 3.30)
GARFI2		1.09	1.23 (0.81, 1.87)
FONTHA	— <u>—</u>	4.07	1.29 (1.04, 1.60)
SPEIZE	•	0.08	1.50 (0.30, 6.30)
STOCKW	<b></b>	0.43	1.60 (0.80, 3.00)
BROWN1	<b>_</b>	0.09	1.68 (0.39, 6.90)
FRANCO		0.46	1.80 (0.95, 3.42)
YANG		0.53	2.00 (1.10, 3.63)
BUTLER		0.09	2.02 (0.48, 8.56)
CORREA		0.22	2.07 (0.81, 5.25)
HUMBL1		0.16	2.20 (0.76, 6.56)
GALLEG		0.04	8.00 (0.85, 75.31)
		7	
Subtotal (95%CI		24.24	1.07 (0.94, 1.23)
Europe	<b>_</b>		
ZATLOU		0.28	0.48 (0.21, 1.09)
TORRES		0.99	0.71 (0.46, 1.10)
IARCKR		0.83	0.80 (0.50, 1.30)
EPICA		0.21	0.84 (0.33, 2.17)
LOPEZC		0.00	0.99 (0.00, 509.87)
LEE		0.19	1.00 (0.37, 2.71)
BOFFE2		0.42	1.00 (0.50, 1.90)
BOFFET	— —	3.61	1.11 (0.88, 1.39)
LAGARD		1.89	1.15 (0.84, 1.58)
PERSHA		0.63	1.20 (0.70, 2.10)
SVENSS	<b></b>	0.21	1.36 (0.53, 3.49)
RYLAND		0.24	1.37 (0.57, 3.30)
MALATS		0.43	1.50 (0.77, 2.91)
ZARIDZ		1.40	1.53 (1.06, 2.21)
HOLE		0.04	1.89 (0.22, 16.12)
TRICHO		0.63	2.08 (1.20, 3.59)
KALAND		0.43	2.11 (1.09, 4.08)
DFWAAR		0.15	2.57 (0.84, 7.85)
		0.15	
Subtotal (95%CI		12.60	1.17 (0.99, 1.39)
Asia			
WI I-W/TI		4 50	0 70 (0 60 0 90)
CHAN		-1.J3 0 63	0 75 (0 43 1 30)
SHEN		. 0.05	0.75 (0.31, 1.78)
JILIN	0.10 0.20 1.00 5.00 10	).00	



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Ref.			Random RR 95%CI		Weight (%)	Random RR 95%CI
1 11 17					0.21	0 77 (0 20 1 06)
					1.10	(0.50, 1.90)
KIVOLIA					1.10	1.00(0.07, 1.49)
					0.32	1.01(0.47, 2.17)
WANGL					0.70	1.03 (0.60, 1.70)
SHIMIZ					0.70	1.08 (0.64, 1.82)
DU					0.67	1.09 (0.64, 1.85)
WEN					1.25	1.09 (0.74, 1.61)
ZHONG					1.91	1.10 (0.80, 1.50)
WANG T					0.73	1.11 (0.67, 1.84)
LIM					3.96	1.12 (0.90, 1.40)
SOBUE					1.39	1.13 (0.78, 1.63)
SUN			——————————————————————————————————————		1.35	1.16 (0.80, 1.69)
REN			-		5.00	1.20 (0.99, 1.46)
RAPITI				_	0.24	1.20 (0.50, 2.90)
KURAHA			— — — <u>_</u>		0.83	1.26 (0.78, 1.03)
GELAC			<b>–</b>		5.87	1.30 (1.09, 1.56)
GAO			<b></b>		1.17	1.30 (0.87, 1.94)
SEKI					2.47	1.31 (0.99, 1.72)
YU				-	0.43	1.35 (0.70, 2.63)
MCGHEE					1.26	1.38 (0.94, 2.04)
LIANG					1.48	1.45 (1.01, 2.07)
HIRAYA					1.49	1.45 (1.02, 2.08)
AKIBA				_	0.64	1.50 (0.93, 2.76)
CHOI				_	0.59	1 63 (0 92 2 87)
KOO					0.47	1 64 (0.87, 3.09)
LAMT					1 51	1 65 (1 16 2 35)
					0.20	1 72 (0 77 3 87)
					0.29	1.72 (0.77, 3.67)
					0.50	1.72(0.93, 3.16)
					0.75	1.77 (1.07, 2.92)
NISHIN					0.20	1.80 (0.67, 4.60)
				-	1.37	1.8/(1.29, 2.71)
					0.40	2.01(1.01, 4.00)
					0.50	2.01(1.09, 5.72)
					0.04	2.07 (0.23, 10.34)
GENG					0.40	2.16 (1.08, 4.29)
INOUE			•		0.13	2.25 (0.77, 8.85)
JIANG			<b>-</b>		0.39	2.27 (1.13, 4.53)
LIN					1.12	2.50 (1.66, 3.77)
ZHENG					0.27	2.52 (1.09, 5.85)
WANGS				Ļ	0.38	2.53 (1.26, 5.10)
Subtotal (95%CI)			•		50.03	1.33 (1.20, 1.46)
Other						
HTLL 1						
TICCO					0 38	1 00 (0 49 2 01)
HTLL 2					12.16	1.00 (0.45, 2.01)
TILLZ					0.50	1.20(1.00, 1.50)
Subtotal (95%CI)					0.59	1.30 (0.76, 2.41)
			$\bullet$		13.13	1.20 (1.07, 1.35)
Total (95%CI)					100.00	1.22 (1.14, 1.31)
	0 10	0.20	1.00	E 00 1		
	0.10	0.20	1.00	5.00 1	0.00	

Figure 1 Forest plots for smoking by husband, by region. Estimates of the random-effects RR and its 95%Cl are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%Cls and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1. In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk

0.90, 0.80-1.00; random-effects model 1.00, 0.78-1.29), based on 11 estimates. However, meta-analysis of the eight estimates specifically considering parental smoking during childhood gave a reduced RR (0.78, 0.64-0.94 for both models). There was no significant heterogeneity for

maternal smoking or parental smoking, but there was for paternal smoking (P < 0.001) due to an atypically high estimate of 12.64 (4.89-32.68) for females in one study<sup>[61]</sup>.

None of the analyses of childhood exposure showed any significant evidence of publication bias.

Ref.	Random RR 95%CI	Weight (%)	Random RR 95%CI
N America			
ALZOUG		0.54	0.39 (0.09, 1.63)
BRENNE		2.35	0.40 (0.20, 0.80)
BUFFLE		0.71	0.51 (0.14, 1.79)
ENSTRO		2.64	0.63 (0.33, 1.22)
JANERI	∎	1.48	0.75 (0.31, 1.78)
ASOMAN	<b>B</b>	0.58	0.93 (0.23, 3.70)
KABAT1	<b></b>	0.43	1.00 (0.20, 5.07)
SCHWAR		3.04	1.10 (0.60, 2.03)
CARDEN		3.74	1.10 (0.60, 1.80)
GORLOV		1.55	1.41 (0.60, 3.30)
LAYARD	<b></b>	1.16	1.47 (0.55, 3.94)
KABAT2		1.49	1.60 (0.67, 3.82)
FRANCO		1.73	1.80 (0.80, 4.03)
CORREA		0.41	1.97 (0.38, 10.32)
YANG	,	3.27	2.00 (1.11, 3.59)
HUMBI 1		0.36	4 08 (0 70 23 91)
GALLEG		0.29	8 00 (1 13 56 52)
OALLEO	,	0.25	0.00 (1.13, 50.52)
Subtotal (95%CI)	▲	25.77	1.11 (0.82, 1.49)
		25177	1111 (0102) 1113)
Furone			
		0.30	0.40 (0.10, 3.00)
		1 35	0.40(0.10, 5.00) 0.69(0.28, 1.74)
TOPPES		1.55	0.05(0.20, 1.74)
EDICA	<b>_</b>	1.55	0.71(0.50, 1.07)
		0.48	0.04(0.10, 5.00)
		0.20	0.99(0.09, 10.71)
		9.23	1.15 (0.81, 1.65)
		0.75	1.30 (0.38, 4.39)
RYLAND		1.25	1.37 (0.53, 3.53)
BOFFEI		3.19	1.47 (0.81, 2.66)
MALAIS	<b>B</b>	0.68	1.50 (0.41, 5.43)
HOLE		0.20	3.52 (0.32, 38.65)
Subtotal (95%CI)		19.25	1.12 (0.88, 1.43)
Asia			
WANGL	<b></b>	1.19	0.56 (0.20, 1.40)
ZHENG	<b>B</b>	0.90	0.67 (0.22, 2.04)
MASJED		0.13	0.70- (0.04, 13.34)
TSE		5.50	0.90 (0.57, 1.41)
KIYOHA		4.02	1.01 (0.59, 1.71)
SEKI		0.63	1.29 (0.34, 4.91)
MCGHEE		4 76	1 34 (0.82, 2.17)
AKIBA		0.54	1.80 (0.39, 6.96)
HE	<b>_</b>	0.56	1 86 (0 45, 7 73)
ΗΓΡΑΥΔ	<b></b>	1 97	2 25 (1 05 4 76)
ITANG		0.67	2.23(1.03, 4.70)
		0.07	2.27(0.02, 0.27) 2 73 (0 49 15 21)
GELAC		0.50	$5 22 \cdot (0.75, 13.21)$
OLEAC		0.12	5.22 (0.25, 105.12)
Subtotal (95%CI)	•	21.40	1.17 (0.93, 1.47)
Other			
HILL1		2.60	1.08 (0.56, 2.09)
ILCCO		28.39	1.20 (0.98, 1.46)
HILL2	<b></b>	2.59	1.45 (0.75, 2.81)
Subtotal (95%CI)		33.58	1.21 (1.01, 1.45)
Total (95%CI)	$\blacksquare$	100.00	1.14 (1.01, 1.29)
	0.10 0.20 1.00 10.00 IU.00		

Figure 2 Forest plots for smoking by wife, by region. Estimates of the random-effects RR and its 95%Cl are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%Cls and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1. In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RRs shown with a ~ are calculated using a 0.5 addition to each cell, due to a zero in the 2 x 2 table. RR: Relative risk.

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#### N America BROWN2 f 0.60 (0.30, 1.30) 2.84 IANERI C 22.16 1.12 (0.87, 1.47) FONTHA f 9.74 1.37 (0.92, 2.03) STOCKW f 1.55 2.20 (0.80, 2.80) GARFI2 f 5.40 5.00 (2.94, 8.51) Subtotal (95%CI) 41.69 1.58 (0.85, 2.92) Europe LEE m 0.34 0.60 (0.07, 4.86) ZATLOU f 1.27 0.66 (0.22, 1.96) BOFFET c 7.39 1.21 (0.77, 1.91) LEE f 0.35 1.70 (0.21, 13.40) ZARIDZ f 3.36 1.94 (0.99, 3.81) TRICHO f 5.07 2.08 (1.20, 3.59) KALAND f 1.32 2.58 (0.88, 7.57) PERSHA f 1.12 3.30 (1.10, 11.40) Subtotal (95%CI) 20.21 1.61 (1.17, 2.22) Asia MASJED c 0.18 0.19- (0.01, 3.44) TSE m 1.94 0.43 (0.18, 1.06) LAMT f 1.93 0.85 (0.35, 2.06) ZHENG f 0.27 1.04 (0.10, 11.14) ZHONG f 6.84 1.10 (0.70, 1.80) RAPITI c 1.82 1.20 (0.40, 2.50) KOO f 0.99 1.73 (0.50, 5.99) JIANG c 3.25 1.83 (0.92, 3.62) SUN f 3.14 2.06 (1.03, 4.15) SEKI f 0.88 2.24 (0.60, 8.38) Subtotal (95%CI) 21.23 1.21 (0.86, 1.70) Other ILCCO c 16.88 1.46 (1.08, 1.97) Subtotal (95%CI) 16.88 1.46 (1.08, 1.97) Total (95%CI) 100.00 1.44 (1.15, 1.80) 0.10 0.20 5.00 10.00 1.00

#### Lee PN et al. ETS and lung cancer

Weight (%)

Random RR 95%CI

Figure 3 Forest plots for squamous cell carcinoma and spousal smoking, by region. Estimates of the random-effects RR and its 95%Cl are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%Cls and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight RRs shown with a - are calculated using a 0.5 addition to each cell, due to a zero in the 2 x 2 table. RR: Relative risk.

#### Household ETS exposure

Ref. Sex

Random RR 95%CI

A total of 58 RR estimates were available for household ETS exposure from any source, as shown in Figure 7. Thirty-six RRs were above 1.00, statistically significant in six studies<sup>[35,43,45,60,70,71]</sup>. Twenty-one non-significantly negative RRs were also reported, while one study found no association. Overall RRs were 1.13 (1.07-1.19, fixed-effect) and 1.11 (1.05-1.18, random-effects). There was marked heterogeneity (P < 0.001) between the estimates, but no significant variation by study location,

or evidence of publication bias.

Restricting attention to sources of ETS other than the spouse, only 13 RRs were available, and the overall RR, although raised, was not significant (1.04, 0.89-1.21, fixed-effect) or (1.12, 0.87-1.44, random-effects).

#### ETS exposure during travel

Figure 8 shows the eight RRs for ETS exposure during travel. Six were above 1.00, and two were below 1.00. Only one estimate<sup>[61]</sup> was significant, and its high RR of

Ref. Sex	Random RR 95%CI	Weight (%)	Random RR 95%CI
N America			
JANERI c	-	13.27	0.97 (0.79, 1.16)
BROWN2 f		8.31	1.00 (0.80, 1.30)
WU f		0.55	1.20 (0.50, 3.30)
FONTHA f		8.77	1.28 (1.01, 1.62)
STOCKW f	<b>_</b>	0.87	1.30 (0.60, 2.70)
GARFI2 f		1.90	1.33 (0.80, 2.21)
BROWN1 f		0.24	1.68 (0.39, 6.90)
Subtotal (95%CI)	•	33.89	1.08 (0.96, 1.22)
Europe			
	<b>_</b>	0 34	0 36 (0 11 1 22)
LFF f	· · · · · · · · · · · · · · · · · · ·	0.16	0.30(0.11, 1.22) 0.41(0.07, 2.40)
PERSHA f		1 12	0.80(0.40, 1.50)
BOFFF2 c		1 19	1.00(0.50, 1.80)
BOFFET c		6 49	1.08 (0.82, 1.42)
ZARIDZ f		2 35	1.52 (0.96, 2.39)
		0.91	2.04(0.98, 4.24)
		0.08	2.04 (0.50, 4.24)
		0.00	2.70 (0.24, 30.37)
Subtotal (95%CI)		12.65	1.11 (0.82, 1.49)
Δsia		0.65	0 75 (0 31 1 78)
SHEN f		0.05	1 00 (0 30 3 20)
RAPITIC		4 95	1 10 (0.80, 1.50)
7HONG f		1.86	1 18 (0 71 1 98)
TSE m		0.20	1.10(0.71, 1.90) 1.30(0.27, 6.14)
SEKIm		5 27	1.30(0.27, 0.14) 1.44(1.06, 1.95)
SEKI f		0.51	1.11(1.00, 1.00) 1.61(0.61, 4.29)
KOO f		1 27	1.01(0.01, 4.25) 1.83(0.98, 3.40)
		1.27	2.01(1.00, 2.72)
		2.10	2.01(1.09, 3.72)
		2.19	2.12 (1.32, 3.39)
ZHENC f		1 1 2	2.32(0.03, 0.36)
		1.12	2.40(1.24, 4.03)
		1.77	2.00 (1.09, 4.04)
JIANG c		0.80	4.55 (1.96, 9.49)
Subtotal (95%CI)		22.71	1.70 (1.35, 2.15)
Other		30.75	1.22 (1.08, 1.39)
ILCCO c			(,)
Subtotal (05%CT)	、	20 75	1 22 (1 08 1 28)
565(0ta) (5570CI)		د ۱۰۷۰	1.22 (1.00, 1.30)
Total (95%CI)		100.00	1.33 (1.17, 1.51)
	0.10 0.20 1.00 5.00	10.00	

Figure 4 Forest plots for adenocarcinoma and spousal smoking, by region. Estimates of the random-effects RR and its 95%Cl are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%Cls and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.

5.20 was the major contributor to the significant (P < 0.05) heterogeneity. Fixed effect meta-analysis gave a RR which was just significant (1.24, 1.01-1.53), but the random-effects RR was not (1.34, 0.94-1.93).

#### ETS exposure in social situations

Analysis of the relationship of lung cancer to ETS exposure in social situations was based on 15 RR estimates, shown in Figure 9. One<sup>[33]</sup> study provided a significantly increased

Ref. Sex	Random RR 95%CI	Weight (%)	Random RR 95%CI
N America			
KABAT1 f	<b>B</b>	0.55	0.68 (0.32, 1.47)
JANERI c	<b>I</b>	2.04	0.91 (0.61, 1.35)
GARFI2 f		1.21	0.93 (0.55, 1.55)
BROWN2 f		3.95	0.98 (0.74, 1.31)
CARDEN f		1.73	1.00 (0.65, 1.54)
KABAT2 m		0.63	1.02 (0.50, 2.09)
CARDEN m		1.02	1.09 (0.62, 1.91)
KABAT2 f		0.84	1.15 (0.62, 2.13)
		2.13	1 21 (0.82, 1.78)
BRENNEC		2.13	1 26 (0.87, 1.82)
WILF		0.36	1 30 (0 50 3 30)
		1 15	1.36(0.80, 2.30)
SCHWAR c		2.07	1.50(0.00, 2.51)
		2.07	1.50(1.00, 2.20)
		0.05	1.51(0.75, 5.05)
		4.90	1.50 (1.21, 2.02)
GORLOV M		0.44	1.58 (0.67, 3.70)
GORLOV F		0.84	1.95 (1.05, 3.62)
KABAT1 m		0.23	3.27 (1.01, 10.62)
		27.00	
Subtotal (95%CI)		27.08	1.21 (1.08, 1.37)
_			
Europe			
IARCKR m	<b>_</b>	0.37	0.50 (0.20, 1.30)
LEE f		0.19	0.63 (0.17, 2.33)
ZARIDZ f		1.45	0.88 (0.55, 1.41)
BOFFET m		1.27	1.13 (0.68, 1.86)
BOFFET f	+ -	5.73	1.19 (0.94, 1.51)
EPICA c		0.79	1.28 (0.67, 2.40)
IARICKR f		1.26	1.40 (0.80, 2.20)
BOFFE2 c		0.74	1.50 (0.80, 3.00)
LEE m	<b>_</b>	0.16	1.61 (0.39, 6.60)
KALAND f		0.40	1.70 (0.69, 4.18)
RYLAND c	<b>B</b>	0.41	2.26 (0.93, 5.48)
Subtotal (95%CI)	$\bullet$	12.77	1.18 (1.01, 1.39)
Asia			
WANGT f		0.74	0.89 (0.46, 1.73)
LEECH f		1.00	0.91 (0.52, 1.62)
WU-WIL f		4.00	1.06 (0.80, 1.40)
RAPITI c		0.19	1.10 (0.30, 4.10)
TSE m	<b>_</b>	1.69	1.15 (0.74, 1.77)
GELAC m		2.83	1.16 (0.83, 1.63)
SHIMIZ f	— <b>——</b> —	1.14	1.18 (0.70, 2.01)
KOO f		0.39	1.19 (0.48, 2.95)
Kuraha f		1.68	1.32 (0.85, 2.04)
SUN f		2.15	1.38 (0.94, 2.04)
OHNO f	<b>_</b>	2 01	1 38 (0 92 2 05)
GELAC f		6.69	1 47 (1 18 1 83)
WANGLO		0.54	1 56 (0 70 3 30)
MASIED m		0.18	1 58 (0 42 2 95)
		2.06	1.30(0.42, 2.33)
		1.20	1.70(1.30, 2.30)
	<b>_</b>	1.52	1.79(1.09, 2.95)
MASJED I	· · · · · · · · · · · · · · · · · · ·	0.05	0.36- (0.20, 104.06)
Subtotal (95%CI)		30.64	1 33 (1 20 1 47)
		30.01	
Other			
ILCCO c		29.52	1.10 (0.99, 1.22)
Subtotal (95%CI)		29.52	1.10 (0.99, 1.22)
		100.00	1 22 (1 15 1 20)
		100.00	1.22 (1.15, 1.30)
	0.10 0.20 1.00 5.00 10.00		

Figure 5 Forest plots for workplace environmental tobacco smoke exposure by region. Estimates of the random-effects RR and its 95%Cl are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%Cls and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RRs shown with a - are calculated using a 0.5 addition to each cell, due to a zero in the 2 x 2 table. RR: Relative risk.



#### Table 3 Meta-analyses of smoking by the spouse (or nearest equivalent)

Estimates considered	No. of estimates	Relative risk (95	Relative risk (95% confidence limits)	
		Fixed-effects meta-analysis	Random-effects meta-analysis	
All	119	1.18 (1.14-1.23)	1.21 (1.14-1.29)	+++
N America	38	1.08 (1.00-1.17)	1.09 (0.95-1.26)	+++
Europe	22	1.15 (1.03-1.28)	1.16 (1.00-1.35)	(+)
Asia	54	1.24 (1.17-1.32)	1.31 (1.20-1.44)	+++
Asia - Japan	13	1.26 (1.11-1.45)	1.26 (1.11-1.45)	NS
Asia - Hong Kong	8	1.32 (1.12-1.57)	1.31 (1.06-1.63)	NS
Asia - China	23	1.16 (1.06-1.27)	1.29 (1.08-1.54)	+++
Asia - Other	10	1.34 (1.19-1.51)	1.37 (1.19-1.57)	NS
Heterogeneity between Asian countries				NS
Other continents	5	1.20 (1.09-1.33)	1.20 (1.09-1.33)	NS
Heterogeneity between continents				(+)
Published in 1981-1989	34	1.38 (1.24-1.54)	1.38 (1.24-1.54)	NS
Published in 1990-1999	33	1.09 (1.01-1.17)	1.15 (1.02-1.28)	++
Published in 2000-2009	34	1.22 (1.12-1.33)	1.21 (1.08-1.36)	+
Published in 2010 onwards	18	1.17 (1.10-1.26)	1.13 (0.94-1.36)	+++
Heterogeneity by publication date				++
1-49 cases	23	1.44 (1.14-1.81)	1.47 (1.15-1.88)	NS
50-99	31	1.30 (1.14-1.47)	1.27 (1.08-1.50)	+
100-199	29	1.09 (1.00-1.19)	1.10 (0.96-1.26)	+++
200-399	22	1.33 (1.21-1.46)	1.32 (1.16-1.50)	+
400+	14	1.14 (1.07-1.20)	1.13 (1.02-1.25)	++
Heterogeneity by study size		· · · ·	. ,	++
Case-control	97	1.18 (1.13-1.23)	1.22 (1.13-1.31)	+++
Prospective	22	1.18 (1.05-1.33)	1.18 (1.05-1.33)	NS
Heterogeneity by study type		, , , , , , , , , , , , , , , , , , ,	× ,	NS
Not age adjusted	21	1.34 (1.19-1.50)	1.42 (1.18-1.71)	+
Age adjusted	98	1.16 (1.11-1.21)	1.18 (1.10-1.26)	+++
Heterogeneity by age adjustment		, , , , , , , , , , , , , , , , , , ,	× ,	NS
Dose-response results not reported	46	1.13 (1.06-1.21)	1.18 (1.06-1.31)	++
Only no dose-response stated	2	0.95 (0.60-1.50)	0.95 (0.60-1.50)	NS
Dose-response results reported	71	1.21 (1.15-1.28)	1.24 (1.14-1.35)	+++
Heterogeneity by dose response reporting		, , , , , , , , , , , , , , , , , , ,	× ,	NS
Spouse the index	71	1.18 (1.11-1.24)	1.21 (1.12-1.31)	++
Spouse not the index	48	1.19 (1.12-1.27)	1.20 (1.07-1.35)	+++
Heterogeneity by index definition		· · · ·	× ,	NS
0 , ,				

<sup>1</sup>Significance levels indicated by +++ P < 0.001, ++ P < 0.05, (+) P < 0.1 for heterogeneity within level and for heterogeneity between level. NS: Not significant,  $P \ge 0.1$ .

RR, with seven studies giving non-significantly raised estimates. Seven RRs were below 1.00, significantly so in two<sup>[72,73]</sup> studies. Overall, there was no evidence of an increased risk, for either fixed-effect (1.03, 0.92-1.16) or random-effects RRs (1.01, 0.82-1.24).

#### Total ETS exposure

The 48 RRs for total ETS exposure are shown, by region, in Figure 10. Thirty-eight were above 1.00, significantly so for 12 studies<sup>[29,34,37-39,41-43,45,51,55,60]</sup>. Eight non-significantly reduced RRs were also reported, while two studies reported RRs of 1.00. Although there was marked heterogeneity (P < 0.001), fixed-effect RRs (1.30, 1.22-1.38), and random-effects RRs were quite similar (1.31, 1.19-1.45). Heterogeneity between the continents was statistically significant (P < 0.01), with random-effects RRs higher for Asia (1.51, 1.31-1.74), than for North America (1.22, 0.96-1.55) or Europe (1.09, 0.91-1.31). There was no evidence (P > 0.1) of publication bias.

#### Smoking by the husband - detailed analyses

Smoking by the husband (or nearest equivalent) is now considered in more detail, with results presented both for overall exposure and per 10 cigarettes per day smoked by the husband. A fuller report which includes adjustment for confounding and for misclassification of exposure, is available in www.pnlee.co.uk/downloads/ etslc/23482-supplementary file 2.pdf, with only the main findings presented here.

For overall exposure, the RRs considered are those shown in Figure 1 and briefly referred to in the section "smoking by the spouse". As noted there, combining estimates from 93 studies gave (RR = 1.19, 95%CI: 1.14-1.24, fixed-effects) and (RR =1.22, 95%CI: 1.14-1.31, random-effects).

Of the 93 studies, 29 were in North America, 18 in Europe, 26 in China or Hong Kong, 18 in the rest of Asia, and two in New Zealand. One Asian study<sup>[74]</sup> was of Chinese women in Singapore, and has been included in the subset of China studies. As the studies in New

Ref. Sex	Random RR 95%CI	Weight (%)	Random RR 95%CI
N America			
WU F		0.38	0.60 (0.20, 1.70)
ALZOUG c		1.03	0.66 (0.35, 1.27)
BRENNE c		2.93	0.80 (0.54, 1.17)
BROWN2 f		4.68	0.80 (0.60, 1.10)
FONTHA f		9.57	0.89 (0.72, 1.10)
KABAT2 m		0.78	0.90 (0.43, 1.89)
GARFI2 f		2.14	0.91 (0.58, 1.42)
JANERI c		2.25	1.33 (0.86, 2.06)
JOHNSO f		1.53	1.38 (0.81, 2.34)
YANG c		2.93	1.47 (1.00, 2.15)
KABAT2 f	<b>_</b>	1.26	1.63 (0.91, 2.92)
STOCKW f		0.81	1.66 (0.80, 3.44)
OLIVOM c		0.72	2.25 (1.04, 4.90)
Subtotal (95%CI)	★	31.00	1.06 (0.89, 1.28)
Europe	_		
BOFFE2 c		0.89	0.60 (0.30, 1.20)
BOFFEI f		7.64	0.77 (0.61, 0.98)
BOFFEI M		2.41	0.79 (0.52, 1.21)
		1.62	0.90 (0.50, 1.40)
ZARIDZ f	<b>_</b>	3.28	0.92 (0.64, 1.32)
IARCKR m		0.56	0.97 (0.40, 2.30)
PERSHA T		0.56	1.00 (0.40, 2.30)
EPICC C		1.65	1.34 (0.80, 2.22)
ZAILOUT		1.97	1.61 (1.01, 2.57)
SVENSS f		0.13	3.30 (0.50, 18.80)
RACHIA		0.46	3.31 (1.26, 8.69)
Subtotal (95%CI)	$\bullet$	21.18	1.02 (0.81, 1.29)
Asia			
KOO f		0.44	0.56 (0.21, 1.50)
WEN f	—— <b>—</b> ——	1.88	0.88 (0.55, 1.43)
WANGT f		1.80	0.91 (0.56, 1.48)
Kuraha f		1.28	0.93 (0.52, 1.66)
ZHONG f		6.58	0.93 (0.72, 1.20)
OHNO f		0.93	1.00 (0.51, 1.98)
RAPITI m		0.38	1.09 (0.38, 3.18)
GAO f	<b></b>	2.18	1.10 (0.70, 1.70)
LIANG f		3.47	1.21 (0.85, 1.72)
SOBUE f	<b>_</b>	1.23	1.28 (0.71, 2.31)
WANGL m		0.52	1.46 (0.60, 3.70)
WANGL f	<b></b>	2.76	1.51 (1.00, 2.20)
LEECH f		2.63	2.10 (1.40, 3.14)
SUN f		2.90	2.29 (1.56, 3.37)
RAPITI f	<b>}</b> •	0.43	12.00 (4.30, 32.00)
Subtotal (95%CI)	$\blacklozenge$	29.43	1.31 (1.02, 1.67)
Other			
ILCCO c		17.37	1.08 (0.92, 1.26)
FERREC c		1.01	1.57 (0.82, 3.02)
		10	
Subtotal (95%CI)		18.38	1.13 (0.89, 1.45)
Total (95%CI)	$\blacklozenge$	100.00	1.15 (1.02, 1.29)
	0.10 0.20 1.00 5.00 10.00		

Figure 6 Forest plots for childhood environmental tobacco smoke exposure by region. Estimates of the random-effects RR and its 95%Cl are shown separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%Cls and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.

Zealand were principally of people of European descent, they have been included in the European subset of studies. One of the studies<sup>[45]</sup> was international, but due

to a high proportion of Asian subjects has been included in the Rest of Asia subset.

The first study appeared in 1981<sup>[75]</sup>, a further



Ref. Sex	Random RR 95%CI	Weight (%)	Random RR 95%CI
BUFFLE m		0.17	0.51 (0.14, 1.79)
CARDEN m		0.26	0.63 (0.23, 1.76)
ALZOUG c	<b>.</b>	0.57	0.63 (0.32, 1.25)
ZHENG m		0.21	0.67 (0.22, 2.04)
TORRES c	— <b>——</b> —	1.74	0.71 (0.48, 1.05)
LIUZ f	·	0.30	0.77 (0.30, 1.96)
WU-WIL f	— <b>———</b>	2.32	0.78 (0.56, 1.10)
BRENNE c	— <b>B</b> —	1.52	0.80 (0.53, 1.21)
BIFFLE f	<b>-</b>	0.36	0.80 (0.34, 1.90)
LEE f		0.46	0.80 (0.37, 1.71)
LEECH f	<b>B</b>	1.35	0.80 (0.51, 1.24)
CARDEN f	<b>B</b>	1.52	0.84 (0.55, 1.27)
EPICA c	<b>-</b>	0.41	0.84 (0.38, 1.90)
NISHIN f		0.37	0.87 (0.37, 2.01)
ASOMAN C		1.04	0.88 (0.53, 1.46)
GAO f		1 48	0.90(0.60, 1.40)
TSF m	<b>_</b>	1.30	0.90(0.57, 1.41)
7ARID7 f		1 33	0.91(0.58, 1.42)
KARAT1 f		0.39	0.92(0.40, 2.08)
GELAC m	— <b>B</b> —	2 31	0.94 (0.67, 1.32)
KABAT2 f		0.82	0.95(0.57, 1.52)
		0.52	1.00(0.49, 2.01)
		0.55	1.00(0.79, 2.01)
	<b>_</b>	4.42	1.01(0.79, 1.29) 1.05(0.62, 1.77)
		0.97	1.05(0.02, 1.77) 1.05(0.27, 4.12)
		3.62	1.05(0.27, 4.12) 1.08(0.82, 1.41)
	•	0.61	1.00(0.02, 1.41)
		0.01	1.06 (0.56, 2.09)
	<b>B</b>	4.51	1.10 (0.80, 1.50)
	<u>+</u>	2.21	1.10(0.80, 1.80) 1.11(0.54, 2.20)
		0.51	1.11 (0.54, 2.29)
	·	5.50	1.12 (0.52, 2.45)
		0.45	1.13 (0.53, 2.45)
	+∎	0.68	1.15 (0.60, 2.10)
		4.90	1.15 (0.91, 1.45)
GORLOV T	<b>₽</b>	0.73	1.15 (0.63, 2.10)
GARFIZ T		1.39	1.15 (0.74, 1.78)
JOHNSO F		0.62	1.20 (0.62, 2.30)
ILCCO c		22.85	1.20 (1.08, 1.34)
WANGL m	<b>⊢</b> ∎−-	0.30	1.22 (0.50, 3.30)
FONTHA f		4.39	1.23 (0.96, 1.57)
KABAT1 m	-₩-	0.15	1.26 (0.33, 4.84)
GELAC f		8.90	1.30 (1.09, 1.54)
MCGHEE m		1.12	1.34 (0.82, 2.17)
RYLAND c	<b>→---</b>	0.64	1.37 (0.72, 2.61)
MCGHEE f		1.77	1.38 (0.94, 2.04)
HILL2 f		0.84	1.38 (0.78, 2.41)
GORLOC m		0.37	1.41 (0.60, 3.30)
KALAND f		0.54	1.41 (0.70, 2.86)
HILL2 m		0.61	1.45 (0.75, 2.81)
BOFFET m		1.20	1.45 (0.91, 2.33)
KOO f		0.29	1.47 (0.56, 3.82)
STOCKW f	<b>→</b>	0.64	1.60 (0.84, 3.04)
FRANCO c	<b>_</b>	1.06	1.80 (1.10, 3.00)
SUN f		1.23	2.05 (1.29, 3.27)
MASJED m	·	0.33	2.12 (0.87, 5.16)
HOLE c	· · · · · · · · · · · · · · · · · · ·	0.09	2.41 (0.45, 12.83)
ZHENG f	│ ────	0.38	2.52 (1.09, 2.85)
SHIMIZ f		0.22	3.95 (1.31, 11.95)
Total (95%CI)		100.00	1.11 (1.05, 1.18)
	0.10 0.20 1.00 5.00 10.00		

Figure 7 Forest plot for household environmental tobacco smoke exposure. Estimates of the random-effects RR and its 95%Cl are shown, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Overall estimates of RRs, 95%Cls and weights are also shown. Studies are identified by the study reference code shown in Table 1. In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.

25, 27, 26 and 14 being published in, respectively,

1982-89, 1990-99, 2000-09 and 2010-2014. Sixteen

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Figure 8 Forest plot for exposure to environmental tobacco smoke during travel. Estimates of the random-effects RR and its 95%Cl are shown, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Overall estimates of RRs, 95%Cls and weights are also shown. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.



Figure 9 Forest plot for social environmental tobacco smoke exposure. Estimates of the random-effects RR and its 95%Cl are shown, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Overall estimates of RRs, 95%Cls and weights are also shown. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RRs shown with a - are calculated using a 0.5 addition to each cell, due to a zero in the 2 x 2 table. RR: Relative risk.

#### Table 4 Meta-analyses of childhood environmental tobacco smoke exposure

Estimates considered	No. of estimates	Relative risk (95	% confidence limits)	Heterogeneity <sup>1</sup>
		Fixed-effects meta-analysis	Random-effects meta-analysis	
From any cohabitant	41	1.08 (1.01-1.15)	1.15 (1.02-1.29)	+++
N America	13	1.00 (0.89-1.13)	1.06 (0.89-1.28)	+
Europe	11	0.94 (0.81-1.08)	1.02 (0.81-1.29)	+
Asia	15	1.26 (1.11-1.42)	1.31 (1.02-1.67)	+++
Other	2	1.10 (0.95-1.28)	1.13 (0.89-1.45)	NS
Heterogeneity between continents				+
From mother specifically	9	0.96 (0.77-1.20)	0.98 (0.77-1.25)	NS
From father specifically	11	0.90 (0.80-1.00)	1.00 (0.78-1.29)	+++
From parents specifically	8	0.78 (0.64-0.94)	0.78 (0.64-0.94)	NS

<sup>1</sup>Significance levels indicated by +++*P* < 0.001, ++*P* < 0.01, +*P* < 0.05, (+) *P* < 0.1 for heterogeneity within level and for heterogeneity between level. NS: Not significant,  $P \ge 0.1$ .

were prospective (cohort) studies and 77 case-control.

Twenty-two studies involved less than 50 cases in



Table 5         Estimates used when adjusting for potential confounding effects <sup>1</sup>												
	Statistic	Fruit consumption	Vegetable consumption	Dietary fat consumption	Education							
Lung cancer risk	N studies RR <sup>2</sup> (95%CI) per	14 0.86 (0.78-0.96) <sup>8</sup> SD	16 0.88 (0.80-0.97) <sup>8</sup> SD	6 1.22 (1.09-1.36) <sup>8</sup> SD	12 0.91 (0.88-0.95) <sup>6</sup> Year <sup>3</sup>							
ETS exposure at home	N studies Difference <sup>24</sup> (SE) unit	11 -0.073 <sup>7</sup> -0.02 SD	16 -0.056 <sup>8</sup> -0.021 SD	12 0.131 <sup>7</sup> -0.032 SD	13 -0.534 <sup>6</sup> -0.063 Year <sup>3</sup>							
Correlations <sup>5</sup>	Fruit consumption Vegetable consumption Dietary fat consumption Education	1	+0.314 <sup>7</sup> 1	-0.104 <sup>NS</sup> -0.054 <sup>NS</sup> 1	+0.143 <sup>NS</sup> -0.130 <sup>9</sup> -0.039 <sup>NS</sup> 1							

Note: *P* values are indicated by  ${}^{6}P < 0.001$ ,  ${}^{7}P < 0.01$ ,  ${}^{8}P < 0.05$ ,  ${}^{9}P < 0.1$ , or  ${}^{NS}P \ge 0.1$ .  ${}^{1}$ All data are for lifelong non-smoking females;  ${}^{2}$ Based on random-effects meta-analysis;  ${}^{3}$ The SD for education was taken as 2.435 years based on six studies;  ${}^{4}$ Difference in level of confounder between those exposed and unexposed to ETS at home;  ${}^{5}$ Based on seven studies, using unweighted means.

#### Table 6 Adjusted/corrected analyses: Husband smoking<sup>1</sup>

ncorrected for misclassification RR (95%CI)	Adjusted for confounding <sup>2</sup> Uncorrected for misclassification RR (95%CI)	Adjusted for confounding <sup>2</sup> Corrected for misclassification <sup>3</sup> RR (95%CI)
1.219 (1.138-1.305)	1.139 (1.062-1.221)	1.077 (0.999-1.162)
1.074 (0.937-1.232)	1.004 (0.873-1.154)	0.898 (0.775-1.039)
1.174 (1.007-1.369)	1.092 (0.934-1.277)	1.062 (0.899-1.254)
1.321 (1.144-1.524)	1.239 (1.071-1.433)	1.175 (1.005-1.374)
1.284 (1.187-1.389)	1.194 (1.103-1.291)	1.164 (1.072-1.262)
1.112 (1.004-1.231)	1.037 (0.935-1.150)	0.959 (0.858-1.072)
1.314 (1.199-1.439)	1.229 (1.121-1.348)	1.181 (1.070-1.304)
1.361 (1.216-1.522)	1.267 (1.132-1.417)	1.194 (1.059-1.347)
1.152 (1.016-1.305)	1.077 (0.948-1.225)	1.005 (0.871-1.160)
1.240 (1.105-1.392)	1.163 (1.034-1.308)	1.115 (0.987-1.260)
1.139 (0.945-1.372)	1.059 (0.877-1.277)	1.026 (0.844-1.247)
1.339 (1.178-1.521)	1.249 (1.098-1.422)	1.192 (1.038-1.370)
1.117 (0.973-1.284)	1.042 (0.904-1.200)	0.978 (0.846-1.131)
1.363 (1.190-1.561)	1.275 (1.114-1.460)	1.226 (1.051-1.429)
1.101 (0.973-1.247)	1.027 (0.905-1.166)	0.957 (0.826-1.108)
1.308 (1.181-1.449)	1.226 (1.105-1.359)	1.170 (1.052-1.302)
1.182 (1.088-1.286)	1.104 (1.014-1.201)	1.040 (0.948-1.141)
1.184 (1.100-1.274)	1.106 (1.027-1.191)	1.048 (0.966-1.136)
1.437 (1.194-1.728)	1.340 (1.110-1.618)	1.264 (1.026-1.556)
1.226 (1.133-1.326)	1.144 (1.057-1.239)	1.080 (0.990-1.177)
1.187 (1.043-1.350)	1.111 (0.977-1.264)	1.064 (0.928-1.220)
	Interpreted for misclassification RR (95%CI)           1.219 (1.138-1.305)           1.074 (0.937-1.232)           1.174 (1.007-1.369)           1.321 (1.144-1.524)           1.284 (1.187-1.389)           1.112 (1.004-1.231)           1.314 (1.199-1.439)           1.361 (1.216-1.522)           1.152 (1.016-1.305)           1.240 (1.105-1.392)           1.339 (0.945-1.372)           1.339 (1.178-1.521)           1.117 (0.973-1.284)           1.363 (1.190-1.561)           1.101 (0.973-1.247)           1.308 (1.181-1.449)           1.182 (1.088-1.286)           1.184 (1.100-1.274)           1.437 (1.194-1.728)           1.226 (1.133-1.326)           1.187 (1.043-1.350)	Interpreted for misclassification RR (95%CI)Projected for misclassification RR (95%CI)1.219 (1.138-1.305)1.139 (1.062-1.221)1.074 (0.937-1.232)1.004 (0.873-1.154)1.174 (1.007-1.369)1.092 (0.934-1.277)1.321 (1.144-1.524)1.239 (1.071-1.433)1.284 (1.187-1.389)1.194 (1.103-1.291)1.112 (1.004-1.231)1.037 (0.935-1.150)1.314 (1.199-1.439)1.229 (1.121-1.348)1.361 (1.216-1.522)1.267 (1.132-1.417)1.152 (1.016-1.305)1.077 (0.948-1.225)1.240 (1.105-1.392)1.163 (1.034-1.308)1.139 (0.945-1.372)1.059 (0.877-1.277)1.339 (1.178-1.521)1.249 (1.098-1.422)1.117 (0.973-1.284)1.042 (0.904-1.200)1.363 (1.190-1.561)1.275 (1.114-1.460)1.101 (0.973-1.247)1.027 (0.905-1.166)1.308 (1.181-1.449)1.226 (1.105-1.359)1.182 (1.088-1.286)1.104 (1.014-1.201)1.184 (1.100-1.274)1.066 (1.027-1.191)1.437 (1.194-1.728)1.340 (1.110-1.618)1.226 (1.133-1.326)1.114 (1.057-1.239)1.187 (1.043-1.350)1.111 (0.977-1.264)

<sup>1</sup>All analyses use random-effects models; <sup>2</sup>Adjusted for confounding by fruit, vegetables and dietary fat consumption and by education; <sup>3</sup>Using the Lee and Forey method<sup>[22]</sup> with an additive model and assuming a concordance ratio of 3 and misclassification rates of 2.5% for studies in North America and Europe and 10% for studies in Asia; <sup>4</sup>Specifically for smoking by the husband; <sup>5</sup>Or matching (within nonsmokers).

lifelong non-smokers, and nine over 400 cases.

Nine studies adjusted for fruit consumption, 11 for vegetables, and 4 for dietary fat. Less than half (32 studies) adjusted for an index of education.

Twenty-four of the studies provided data on lung cancer risk by amount smoked by the husband specifically, with the remainder only providing results for overall exposure. Table 1 of www.pnlee.co.uk/ downloads/etslc/23482-supplementary file 2.pdf gives the data used for each study and the fitted estimates of  $\beta$  and SE $\beta$ . Based on these data, it was estimated that each 10 cigarettes per day smoked by the husband multiplied risk by an estimated 1.09 (95%CI: 1.07-1.11) based on a fixed-effects analysis and 1.10 (1.07-1.14) using a random-effects analysis.

In order to adjust for the uncontrolled effects of confounding by diet (by fruit, vegetables and dietary fat) and education, summary estimates were required of the relationships of the four potential factors to both risk of lung cancer and ETS exposure, and of the correlations



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Ref. Sex	Random RR 95%CI	Weight (%)	Random RR 95%CI
N America			
CARDEN m	<b></b>	1.72	0.60 (0.40, 1.00)
WHIOS f	<b>_</b>	1.30	0.88 (0.52, 1.49)
CARDEN f		4 97	0.90(0.70, 1.20)
		0.85	1 00 (0.52 + 1.20)
		1 27	1.00 (0.60, 1.67)
		1.37	1.00 (0.00, 1.07)
GARFIZ T		2.05	1.12 (0.74, 1.70)
Fontha f		2.53	1.25 (0.86, 1.83)
Johnso f	<b></b>	0.69	1.44 (0.70, 2.98)
SPEIZE f	<b>_</b>	0.16	1.50 (0.30, 6.30)
GORLOV f		0.91	1.63 (0.87, 3.05)
BROWN1 f		0 17	1 68 (0 39 6 90)
VANG		2.06	2.00(1.30, 3.00)
		0.21	2.00 (1.00, 0.00)
GORLOV III		0.31	5.19 (1.08, 9.59)
GALLEG C	₽-≯	0.17	8.00 (1.83, 34.92)
Subtotal (95%CI)	◆	19.26	1.22 (0.96, 1.55)
-			
Europe		0.00	0 46 (0 15 1 40)
LEET	<b>_</b>	0.29	0.46 (0.15, 1.40)
ZATLOU f		0.53	0.48 (0.21, 1.09)
AUVINE m		0.43	0.69 (0.28, 1.74)
LOPEZC c		0.07	0.99 (0.11, 9.16)
EPICA c	<b></b>	1.17	1.05 (0.60, 1.82)
BOFFFT m		1 38	1 13 (0.68, 1.89)
BOFFET f		4 16	1 15 (0.86, 1.55)
		4.10	1.15 (0.60, 1.55)
MALAISC		0.80	1.20 (0.60, 2.30)
BOFFE2 c		0./1	1.20 (0.60, 2.50)
LAGARD c		0.44	1.38 (0.56, 3.39)
SVENSS f		0.24	1.51 (0.44, 5.17)
DEWAAR f		0.29	2.57 (0.84, 7.85)
LEE m	· · · · · · · · · · · · · · · · · · ·	0.08	3.47 (0.42, 28.72)
Subtotal (95%CI)	◆	10.60	1.09 (0.91, 1.31)
Acia			
ASId		0.40	0.75 (0.01, 1.70)
SHENT		0.48	0.75 (0.31, 1.78)
WENT	<b>_</b>	1.02	1.03 (0.57, 1.87)
GELAC m	<b></b>	2.78	1.04 (0.73, 1.50)
TSE m		1.71	1.06 (0.67, 1.68)
REN f		9.56	1.20 (0.99, 1.46)
LIANG f		2.15	1.34 (0.89, 2.02)
YIIf		0.82	1 35 (0 70 2 63)
		11.40	1.35(0.70, 2.03) 1.20(1.17, 1.67)
GLLAC I		11.40	1.39 (1.17, 1.07)
MASJED f		0./1	1.40 (0.70, 2.90)
MASJED m		0.44	1.70 (0.70, 4.30)
FANG f	<b></b>	1.43	1.77 (1.07, 2.92)
KOO f		0.60	1.78 (0.82, 3.87)
SUN f	│ <b>∎</b>	2.01	1.83 (1.20, 2.80)
HF m	<b>_</b>	0.18	1.86 (0.45, 773)
		2 30	1 03 (1 20 2 97)
		2.50	1,22 (1,20, 2,07)
		0.08	2.07 (0.23, 18.34)
JIANG C		0.97	2.27 (1.23, 4.18)
LIN f		2.14	2.50 (1.66, 3.77)
LAMW f	<b>_</b>	0.94	2.51 (1.35, 4.67)
WANGS f		0.74	2.53 (1.26, 5.10)
			· · ·
Subtotal (95%CI)	•	42.45	1.51 (1.31, 1.74)
Other			
ILCCO c		27.70	1.31 (1.17, 1.47)
Subtotal (95%CI)	◆	27.70	1.31 (1.17, 1.47)
Total (95%CI)		100.00	1 31 (1 19 1 45)
	0.10 0.20 1.00 5.00 10.00	100.00	1.51 (1.15, 1.75)

Figure 10 Forest plots for total environmental tobacco smoke exposure, by region. Estimates of the random-effects RR and its 95%Cl are shown, separately by region, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Weights (inverse-variance of log RR) are also shown, expressed as a percentage of the weight for all studies combined. Estimates of RRs, 95%Cls and weights are also shown for each region combined and overall. Studies are identified by the study reference code shown in Table 1, with sex identified by m (male), f (female) or c (sexes combined). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight. RR: Relative risk.



Table 7	Adjusted/corrected	analyses: Per 10 c	igs smoked by	'husband'

Studies	п	Unadjusted for confounding Uncorrected for misclassification RR (95%CI)	Adjusted for confounding <sup>2</sup> Uncorrected for misclassification RR (95%CI)	Adjusted for confounding <sup>2</sup> Corrected for misclassification <sup>3</sup> RR (95%CI)
All	93	1.102 (1.065-1.140)	1.062 (1.027-1.099)	1.032 (0.994-1.071)
North America	29	1.037 (0.977-1.101)	1.006 (0.946-1.070)	0.957 (0.896-1.022)
Europe and New Zealand	20	1.060 (0.995-1.128)	1.020 (0.956-1.088)	1.003 (0.938-1.073)
China (including Hong Kong and study LIM)	27	1.169 (1.082-1.263)	1.127 (1.041-1.219)	1.094 (1.006-1.191)
Rest of Asia (including study ILCCO)	17	1.142 (1.095-1.191)	1.094 (1.050-1.141)	1.079 (1.033-1.127)
North America, Europe and New Zealand	49	1.046 (1.001-1.094)	1.012 (0.967-1.059)	0.974 (0.928-1.023)
Asia	44	1.158 (1.104-1.216)	1.113 (1.060-1.170)	1.089 (1.033-1.147)
Published in 1980s	26	1.148 (1.092-1.207)	1.105 (1.052-1.162)	1.075 (1.019-1.134)
Published in 1990s	27	1.063 (1.004-1.125)	1.025 (0.967-1.087)	0.988 (0.926-1.053)
Published in 2000s	26	1.123 (1.056-1.194)	1.085 (1.020-1.155)	1.061 (0.995-1.132)
Published in 2010s	14	1.073 (0.970-1.188)	1.032 (0.932-1.143)	1.014 (0.912-1.128)
< 100 cases	49	1.143 (1.077-1.213)	1.101 (1.036-1.169)	1.072 (1.005-1.144)
100-199 cases	22	1.062 (0.993-1.137)	1.025 (0.957-1.098)	0.994 (0.926-1.066)
200-399 cases	13	1.176 (1.097-1.261)	1.134 (1.058-1.216)	1.111 (1.027-1.202)
400+ cases	9	1.041 (0.976-1.111)	1.002 (0.938-1.070)	0.966 (0.895-1.042)
With dose-response data <sup>4</sup>	24	1.123 (1.072-1.176)	1.082 (1.032-1.134)	1.053 (1.005-1.103)
Without dose-response data	69	1.091 (1.044-1.139)	1.053 (1.007-1.100)	1.021 (0.973-1.071)
With age adjustment <sup>5</sup>	75	1.084 (1.046-1.123)	1.044 (1.008-1.082)	1.015 (0.976-1.056)
Without age adjustment	18	1.211 (1.101-1.331)	1.168 (1.061-1.285)	1.131 (1.018-1.256)
Case-control studies	77	1.106 (1.064-1.150)	1.066 (1.025-1.109)	1.034 (0.991-1.080)
Prospective studies	16	1.081 (1.021-1.145)	1.043 (0.985-1.105)	1.018 (0.957-1.083)

<sup>1</sup>All analyses use random-effects models; <sup>2</sup>Adjusted for confounding by fruit, vegetables and dietary fat consumption and by education; <sup>3</sup>Using the Lee and Forey method<sup>[22]</sup> with an additive model and assuming a concordance ratio of 3 and misclassification rates of 2.5% for studies in North America and Europe and 10% for studies in Asia; <sup>4</sup>Specifically for smoking by the husband; <sup>5</sup>Or matching (within nonsmokers).

between the four factors. The estimates used are presented in Table 5, and show that, in non-smoking females, both risk of lung cancer and ETS exposure at home are associated with reduced fruit and vegetable consumption and education, and increased dietary fat consumption. All these associations are significant at least at P < 0.05, and for education at P < 0.001, with the data based on analysis of results from at least 10 studies (with one exception - dietary fat and lung cancer, based on 6 studies). Table 5 also shows the intercorrelations between the four confounding variables, based on combined estimates from seven studies. These show that fruit and vegetable consumption are strongly correlated with each other (P < 0.01). Other correlations are weaker and not significant at P < 0.05.

As described in the methods, we used misclassification rates of 10% for Asian studies and 2.5% elsewhere, these rates accounting for the lower rates of lung cancer seen among misclassified smokers than among nonmisclassified smokers.

Table 6 presents results of analyses adjusting for confounding and misclassification based on RRs for smoking by the husband, while Table 7 similarly presents results based on RRs per 10 cigarettes smoked by the husband. Each table presents three sets of results: (1) unadjusted; (2) adjusted for confounders; and (3) adjusted for confounders and corrected for smoking misclassification. They each give overall estimates and results subdivided by various aspects of the studies considered.

As shown in Table 6, adjustment for confounding variables reduces the overall RR for smoking by the husband

from 1.219 (1.138 to 1.305) to 1.139 (1.062-1.221), implying bias due to failure to control for the four variables is 1.219/1.139 = 1.070. Further correction for misclassification reduced the estimate to a marginally nonsignificant 1.077 (0.999-1.162), implying a further bias of 1.139/1.077 = 1.058. In the fully adjusted and corrected analyses, there is no evidence of an association in North America, Europe and New Zealand (RR 0.959, 0.858-1.072) but there is an association in Asia (1.181, 1.070-1.304).

RRs are higher for studies providing dose-response data (1.170, 1.052-1.302) than for other studies (1.040, 0.948-1.141), and higher for studies which did not adjust for age (1.264, 1.026-1.556) than for those which did (1.048, 0.966-1.136). However, neither difference is statistically significant (P = 0.10 and P = 0.08 respectively).

The pattern of results shown in Table 7, where RRs are per amount smoked by the husband, is similar, though the RRs themselves are lower. Thus, the unadjusted/ uncorrected overall RR of 1.102 (1.065-1.140) reduces to 1.062 (1.027-1.099) after adjustment for confounding (bias = 1.038), and to a nonsignificant 1.032 (0.994-1.071)after further correction for misclassification (additional bias = 1.030). Patterns of variation by study factors are very similar to those for overall smoking by the husband in Table 6.

Additional material presented in www.pnlee.co.uk/ downloads/etslc/23482-supplementary file 2.pdf shows that the effect of confounder adjustment was greatest for education, and least for fruit and vegetables. Thus, in the analysis of RRs per amount smoked by the husband, the biases due to uncontrolled confounding were estimated as 1.024 for education, 1.013 for dietary fat, 1.005 for fruit, and 1.004 for vegetables.

#### DISCUSSION

#### Introduction

We have demonstrated, as other reviews before  $us^{[6,76]}$ , a weak but significant (P < 0.05) association of ETS exposure with never smoker lung cancer risk. This can be seen for various indices of exposure, including spousal, household, workplace and total exposure. It is less clearly evident for exposure in travel and in social situations, where data are quite limited, and for childhood exposure where the results shown in Table 4 are rather conflicting. There is also clear heterogeneity between study-specific estimates for many of the indices of exposure. Meta-analyses for smoking by the spouse (or nearest equivalent) shown in Table 3 indicate that estimates are higher in early studies (published in 1981-89), in small studies (1-49 cases), and where estimates are not age-adjusted.

Do these quite weak associations provide good evidence of a causal relationship? To gain insight into this we carried out additional analyses for smoking by the husband investigating biases due to uncontrolled confounding by education and three aspects of diet (fruit, vegetables and dietary fat) and due to failure to adjust for misclassification of smoking by the subject. Based on 93 studies, confounder adjustment and misclassification correction substantially reduced the magnitude of the association with smoking by the husband, the RR (95%CI) estimate of 1.22 (1.14-1.31) reducing to 1.14 (1.06-1.22) after confounder adjustment, and further reducing to 1.08 (0.999-1.16) after additional correction for misclassification. The adjusted and corrected estimate is not quite significant, the same being true for analyses based on the RR per 10 cigs/day smoked by the spouse, where the overall RR reduced from 1.10 (1.07-1.14) to 1.06 (1.03-1.10) after adjustment for confounding and to 1.03 (0.994-1.07) after the further correction for misclassification.

Below we discuss some aspects of the evidence relevant to consideration of causality. Parts of the discussion are quite brief, the interested reader being referred to our publication<sup>[2]</sup> describing our earlier analyses.

#### Plausibility

Since active smoking causes lung cancer, and since ETS contains many of the carcinogens in tobacco smoke, it can be argued that some causal effect of ETS exposure is to be expected, though this argument depends on there being no threshold dose of exposure. If there is no threshold, what effect might one expect? Certainly, exposure from ETS is much less than that from active smoking, with studies based on cotinine indicating relative exposure factors of  $0.4\%^{[77]}$ ,  $0.2\%^{[78]}$  or  $0.06\%^{[79]}$  and studies based on particulate matter<sup>[80-88]</sup> suggesting a lower factor, of order 0.005%-0.02%. Given an RR for

current *vs* never smoking of 8.43, as reported in a recent meta-analysis<sup>[89]</sup> and assuming a linear dose-response relationship, even a relative exposure factor as high as 0.5% would only suggest that the RR for ETS exposure would be about 1.04, while a relative exposure factor of 0.1% would suggest a RR of about 1.008. These RRs are much less than the unadjusted/uncorrected RR of 1.22 for smoking by the husband (or nearest equivalent) shown in Table 6. Either the relationship between dose and risk is distinctly non-linear (and the evidence does not suggest this for active smoking<sup>[89]</sup>) or a substantial part, if not all, of the observed association is due to bias.

#### Confounding

Based on the evidence we collected, we have demonstrated a clear tendency for increased dietary fat consumption, reduced fruit and vegetable consumption and fewer years of education to be associated both with increased lung cancer risk and with increased at home ETS exposure. Given that relatively few of the studies adjusted for the dietary variables or education, it was to be expected that adjustment for these four factors would reduce the RR for smoking by the husband, and so it proved. While there is uncertainty in this adjustment, as discussed elsewhere<sup>[19]</sup>, it is clear that there is a considerable potential for bias. Among other things it should be noted that these are not the only potential sources of bias. We considered various other candidate confounding factors, including income, occupation, and socioeconomic factors, obesity, physical activity, air pollution, alcohol and tea drinking, but concluded that for none of these were there data adequate to provide any sort of reliable qualitative estimate of their relationship to lung cancer risk in non-smokers. That said, the general tendency for smoking and marriage to a smoker to be associated with lifestyle factors generally considered associated with adverse health<sup>[90-93]</sup>, suggests that our adjustments may well have been conservative.

#### Misclassification of active smoking

Some current or former smokers are known to deny having smoked, so being wrongly described as never smokers<sup>[26,94]</sup>. Also, marital partners' smoking habits are correlated, with smokers tending to marry smokers<sup>[3,23]</sup>. Taken together, these two tendencies, if ignored, will bias the observed association of smoking by the husband to never smoker lung cancer risk<sup>[3,21,95]</sup>. There are many difficulties in accurately estimating the extent of bias due to misclassification. These include the misclassification rates being dependent on the circumstances in which the questions were asked, as well as the fact that smokers who deny smoking are unrepresentative of all smokers, tending to be more often occasional smokers and longterm ex-smokers and so have lower lung cancer risks than non-misclassified smokers<sup>[23]</sup>. Here we have assumed, as earlier<sup>[22]</sup>, that misclassification correction can be carried out assuming that, among women, the percentage of average-risk ever-smokers who deny smoking is 10.0% in Asia and 2.5% elsewhere, these



misclassification rates taking account of the lower lung cancer rates in misclassified compared to nonmisclassified smokers.

While the misclassification correction is clearly open to question, and we have not formally updated the extensive work we did some years ago on estimating rates<sup>[23,26]</sup>, we still believe that the rates we have used are not unreasonable. Indeed given recent estimates of substantial denial of smoking in recent studies<sup>[94,96,97]</sup>, our correction may be somewhat conservative.

We now briefly comment on other sources of bias.

#### **Publication bias**

Publication bias occurs if the data that are published are not representative of all the data that exist on a topic. For many exposures, positive findings are published more often than negative findings<sup>[98-100]</sup>, so meta-analyses of data drawn from the literature overestimate true relationships. We have not attempted to quantify the extent of publication bias, though our detailed tables (www.pnlee.co.uk/downloads/etslc/23482-supplementary file 4.pdf) do include results of Egger tests<sup>[16]</sup>, a number showing some evidence that smaller studies are more likely to produce above average than below average RRs. This is consistent with the higher RRs reported in small studies seen in Table 3 for spousal smoking. We believe that some publication bias exists but given that the larger studies seem likely to publish regardless of the findings, and that these contribute most to the overall estimates, such bias is probably unimportant.

There is some evidence (P = 0.10) that RRs are higher for those studies which provide dose-response results than for those which do not so. If this represents a true effect, it is suggestive of a different form of publication bias, with authors tending to be more likely to report dose-response results where there is a strong association in the first place.

#### Diagnostic inaccuracy

Misdiagnosis of lung cancer certainly exists, especially when based on X-rays or sputum cytology<sup>[101-103]</sup>. The extent, and direction, to which it might have biased the RR estimate for ETS and lung cancer is difficult to determine. While randomly misdiagnosing as lung cancer diseases which are unassociated with ETS would tend to dilute any true RR, misdiagnosis might not be random and may be correlated with ETS exposure or factors associated with it. Since random-effects estimates for spousal smoking proved to be quite similar for studies that did or did not require full histological confirmation, this seems unlikely to be an important source of bias.

#### Errors in determining ETS exposure

Case-control studies collect exposure data after the disease has occurred, and the presence of the disease itself, or knowledge of it, may distort responses about past exposure. Such recall bias is not an issue for prospective studies. Given that our analyses for spousal smoking found little difference in RRs by study type, we

feel that recall bias is unlikely to be a major problem.

Random misclassification of smoking spouses as nonsmokers will not create a false effect if no true risk exists, but will underestimate a true relationship. It has been clearly shown<sup>[21]</sup> that such misclassification causes much less bias effect than does misclassification of the subject's smoking, so for practical purposes it can be ignored.

#### Bias from ETS exposure in the reference group

When considering the relationship of lung cancer risk to smoking by the husband, three categories of women are relevant: A - never smokers married to ever smokers; B - never smokers married to never smokers; and C - never smokers without any ETS exposure. Group C is a subset of group B. In the analysis of the effect of husband's smoking, the RR estimate is based on comparison of groups A and B, but it has been argued<sup>[3]</sup> that a better estimate RR\* is based on comparison of groups A and C. If a marker of ETS exposure, such as cotinine, is Z times higher in group A than group B, RR\* can be estimated by RR\* = RR(Z-1) / (Z-RR)<sup>[2,3]</sup>.

Some comments can be made on this revised estimate. First, and most noteworthy, to conduct background correction only makes sense when the original association, with marriage to a smoker, derives from a causal effect of ETS. Where adjustment for confounding and correction for smoker misclassification bias explains the whole of the observed association, background correction will have no effect. If such adjustment and correction explains most of the association, the correction will have a small effect. Thus, assuming Z =3, as estimated by Hackshaw *et a*<sup>[3]</sup>, this correction has quite a substantial effect on the unadjusted association for husband's smoking, increasing it from 1.22 to 1.37. However, applying it to the confounder adjusted and misclassification corrected estimate of 1.08 only increases it to 1.12. In any case, the validity of the backgroundcorrected estimate of 1.12 is dubious, given that the 1.08 was not statistically significant in the first place, and could itself be an overestimate due to the limitations in confounder adjustment and misclassification correction discussed above.

Second, background correction only applies to the simple comparison of risk in the exposed and comparison groups, and does not apply to estimates of the increase in risk for amount smoked by the husband. Also, background correction is only an indirect method for estimating lung cancer risk from sources of ETS exposure other than the spouse, using data only relating to spousal exposure. This method ignores existing data on risk from these other sources.

#### **Overall impression**

Coming to reliable conclusions regarding a weak association based on non-randomized epidemiological studies is difficult at the best of times. When, as here, there is evidence that adjustment for confounding and correction for misclassification substantially weakens the association most usually considered (smoking by



the husband) and renders it nonsignificant, and when these adjustments and corrections may themselves be somewhat limited, one cannot reliably conclude that a true effect of ETS exposure on lung cancer risk has been demonstrated. While one cannot prove a negative, and while the clear relationship of smoking to lung cancer suggests that some association might exist, the only conclusion that seems valid is that there may be a relationship of ETS to lung cancer risk (with the evidence stronger for Asian studies), but if it exists, it is certainly much weaker than suggested by meta-analyses that do not adjust for confounding and misclassification.

Most, if not all, of the weak association of ETS with risk of lung cancer is explicable by confounding and smoking misclassification. A causal relationship is not demonstrated.

#### ACKNOWLEDGMENTS

We thank Japan Tobacco International S.A. for supporting publication of this paper. The opinions and conclusions of the authors are their own, and do not necessarily reflect the position of Japan Tobacco International S.A. We also thank the United Kingdom Tobacco Manufacturers Association, Imperial Tobacco Ltd, British-American Tobacco Limited, and Philip Morris Products S.A. for earlier support in developing the databases used. Finally we also thank Pauline Wassell, Diana Morris and Yvonne Cooper for assistance in typing various drafts of the paper and obtaining relevant literature, and all the researchers who published the reports which formed the basis of our work.

#### COMMENTS

#### Background

The authors address the widely held claim that environmental tobacco smoke (ETS) exposure causes lung cancer by presenting an up-to-date comprehensive meta-analysis of the available evidence, considering exposure from various sources, and illustrating the potential magnitude of bias from confounding and misclassification of smoking.

#### **Research frontiers**

Based on all 102 studies providing relevant data, the authors demonstrate a significant (P < 0.05) increase in never smoker lung cancer risk for various exposure indices - from the spouse, at home, at work and overall, though the evidence for childhood exposure is less clear. Based on smoking by the husband, the most studied ETS exposure index, the RR is estimated as 1.22 (95%CI: 1.14-1.31). However, adjustment for confounding by education and by consumption of fruit, vegetables and dietary fat, and correction for misclassification of active smoking by the wife, markedly reduces this association, which becomes a nonsignificant 1.08 (95%CI: 0.999-1.16). Since these adjustments and corrections may not fully correct for the bias from these sources, and given the existence of other biases, one cannot conclude with any certainty that a true effect of ETS exposure on lung cancer risk exists.

#### Innovations and breakthroughs

The new feature of the paper is the extent of the evidence considered, and the adjustments and corrections made.

#### Applications

The authors analysis should engender caution in drawing inferences from weak associations seen in non-randomized epidemiological studies, particularly

where biases are known to exist.

#### Peer-review

It is an interesting paper.

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P-Reviewer: Kawai H, Pereira-Vega A S- Editor: Qiu S L- Editor: A E- Editor: Lu YJ







Submit a Manuscript: http://www.wjgnet.com/esps/ Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx DOI: 10.13105/wjma.v4.i2.44 World J Meta-Anal 2016 April 26; 4(2): 44-54 ISSN 2308-3840 (online) © 2016 Baishideng Publishing Group Inc. All rights reserved.

META-ANALYSIS

# Meta-analysis comparing differing methods of endoscopic therapy for colorectal lesions

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Author contributions: Patel N designed this paper; Patel N, Alexander J and Ashrafian H analysed and interpreted the data; Ashrafian H, Athanasiou T, Darzi A and Teare J criticised revision of the article for important intellectual content; all authors have approved the final draft submitted.

Conflict-of-interest statement: The authors deny any conflict of interest.

Data sharing statement: No additional data are available.

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Received: May 19, 2015 Peer-review started: May 20, 2015 First decision: June 19, 2015 Revised: July 18, 2015 Accepted: November 9, 2015 Article in press: January 4, 2016 Published online: April 26, 2016

#### Abstract

AIM: To compare the outcomes of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) of colorectal lesions.

**METHODS:** An electronic systematic literature search of four computerized databases was performed in July 2014 identifying studies reporting the outcomes of colorectal ESD and EMR. The primary outcome measures were *en-bloc* resection rate, endoscopic clearance rate and lesion recurrence rate of the patients followed up. The secondary outcome was the complication rate (including bleeding, perforation and surgery post EMR or ESD rate). Statistical pooling and random effects modelling of the studies calculating risk difference, heterogeneity and assessment of bias and quality were performed.

**RESULTS:** Six observational studies reporting the outcomes of 1324 procedures were included. The *en-bloc* resection rate was 50% higher in the ESD group than in the EMR group (95%CI: 0.17-0.83, P < 0.0001,  $I^2 = 99.7\%$ ). Endoscopic clearance rates were also significantly higher in the ESD group (95%CI: -0.06-0.02, P < 0.0001,  $I^2 = 92.5\%$ ). The perforation rate was 7% higher in the ESD group than the EMR group (95%CI: 0.05-0.09, P > 0.05,  $I^2 = 41.1\%$ ) and the rate of recurrence was 50% higher in the EMR group than in the ESD group (95%CI: 0.20-0.79, P < 0.001,  $I^2 = 99.5\%$ ). Heterogeneity remained consistent when subgroup analysis of high quality studies was performed (with the exception of piecemeal resection rate), and overall effect sizes remained unchanged for all outcomes.

**CONCLUSION:** ESD demonstrates higher *en-bloc* resection rates and lower recurrence rates compared to colorectal EMR. Differences in outcomes may benefit from increased assessment through well-designed comparative studies.

Key words: Colorectal; Colonic polyp; Endoscopic



mucosal resection; Endoscopic submucosal dissection; Colorectal cancer

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**Core tip:** Endoscopic mucosal resection (EMR) is the conventional resection method of colorectal polyps. However certain lesions such as large sessile polyps can be challenging. Piecemeal resection has been shown to result in a high recurrence rate requiring further endoscopic sessions or surgery. Colorectal endoscopic submucosal dissection (ESD) is still at a relatively early stage, there are very few studies directly comparing the two modalities, few randomised controlled trials and fewer still reporting longer-term outcomes. This meta-analysis reports mid-term follow-up outcomes of colorectal ESD and EMR. ESD demonstrates higher *en-bloc* resection rates and lower mid-term recurrence rates compared to colorectal EMR albeit with higher complication rates.

Patel N, Alexander J, Ashrafian H, Athanasiou T, Darzi A, Teare J. Meta-analysis comparing differing methods of endoscopic therapy for colorectal lesions. *World J Meta-Anal* 2016; 4(2): 44-54 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i2/44.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i2.44

#### INTRODUCTION

Colorectal cancer is the fourth most common cancer in the world with an incidence of 9.7% and a 8.5% mortality rate<sup>[1]</sup>. The introduction of colorectal cancer screening programmes, particularly in the western world, and advancements in endoscopic imaging are likely to result in a greater number of early cancers and polyps detected.

The conventional endoscopic treatment of colorectal polyps is polypectomy or endoscopic mucosal resection (EMR) which is performed worldwide<sup>[2,3]</sup>. Performing EMR on lesions such as laterally spreading tumours or complex sessile polyps can be challenging and may require a number of endoscopic sessions or surgery resulting in extra cost, potential in-patient hospital stays, increased complication rates and stress to the patient<sup>[4,5]</sup>. Furthermore, piecemeal resection makes histopathological assessment of whether the procedure was curative or not difficult and has also been shown to result in a high recurrence rate<sup>[6-8]</sup>.

As a result of the drive towards minimally invasive surgery, endoscopic submucosal dissection (ESD) has emerged as a viable endoscopic alternative for early colorectal cancers or polyps, which would otherwise have been treated surgically or endoscopically. The technique pioneered in Japan for early gastric cancer, has been used with great success particularly in East Asia<sup>(9-11)</sup> where it is now the standard of care. Given the success of the technique, the indications are now expanding and the technique is increasingly being used

to treat colorectal lesions<sup>[5,12,13]</sup>. ESD has improved *enbloc* resection rates for early gastric cancer compared to EMR<sup>[14-16]</sup>. However, the technique is also associated with long procedure times, greater complication rates as well as the need for a highly skilled endoscopist<sup>[5,17]</sup>.

The uptake of colorectal ESD has been slow for a number of reasons. It is a more challenging technique than EMR and gastric ESD due to the long colonic lumen which has a thin luminal wall and comprises of flexures and folds resulting in an already technically demanding and complex technique becoming even more so.

Whether ESD outcomes, which have been so successful for early gastric cancer, can translate to colorectal lesions is not yet  $clear^{[18]}$ . There are few studies directly comparing these techniques for colorectal lesions with insufficient information and varying short and mid-term outcomes<sup>[2,13,19-21]</sup>.

The objective of this meta-analysis is to compare the outcomes of colorectal EMR and ESD from the literature to date. The efficacy of the techniques was determined by establishing the following primary outcomes: *Enbloc* resection rate, endoscopic completeness rate and recurrence rate. Secondary outcome measures include the complication rate including perforation, bleeding and surgery after EMR or ESD.

#### MATERIALS AND METHODS

#### Search strategy

An electronic search was conducted from four computerized databases, MEDLINE (1946 to end July 2014), EMBASE (1974 to end July 2014), Cochrane Central Register of Controlled Trials and systematic reviews (1991 to end July 2014), CINAHL (1937 to end July 2014) using the following search strategy: (Endoscopic mucosal resection OR EMR) AND (Endoscopic submucosal dissection OR ESD) AND (exp colonic polyps OR Colon) AND (exp endoscopic polypectomy OR polypectomy). Additional studies identified through relevant reviews, references cited by included papers and PubMed "related articles" feature were also examined in full text for potential inclusion (Figure 1).

#### Inclusion criteria

Studies which analysed the outcomes of colonic lesions (early cancers or polyps) removed by EMR and ESD were considered for inclusion in this meta-analysis.

The primary outcome measures were *en-bloc* resection rate, endoscopic clearance rate and lesion recurrence rate of the patients followed up. The secondary outcome was the complication rate (including bleeding, perforation and surgery post EMR or ESD rate). Both full articles and abstracts were included.

#### Exclusion criteria

Published abstracts or articles which did not contain a primary outcome variable were excluded. In addition, reviews, editorials, letters, opinions, comments, case reports and surveys were not included. Data which



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## Figure 1 PRISMA flow diagram demonstrating search strategy.

Table 1 Study characteristics comparing outcomes of colorectal endoscopic mucosal resection vs endoscopic submucosal dissection

Ref.	Year	Study site	Publication type	Total sample size	e EMR			ESD				
				_	Sample size	Male (%)	Age [mean <u>+</u> SD (range)]	Sample size	Male (%)	Age [mean/median ± SD (range)]		
Tajika et al <sup>[22]</sup>	2011	Japan	Full paper	189	104	61	$59.9 \pm 10.6$	85	58	$64.3 \pm 9.2$		
Lee et al <sup>[23]</sup>	2012	South Korea	Full paper	454	140	64	63 (23-90)	314	55	61 (25-85)		
Kobayashi et al <sup>[24]</sup>	2012	Japan	Full paper	84	56	68	$65.9 \pm 9.9$	28	68	$65.1 \pm 9.7$		
Saito et al <sup>[25]</sup>	2010	Japan	Full paper	373	228	-	$64 \pm 4$	145	-	$64 \pm 11$		
Kim et al <sup>[26]</sup>	2009	South Korea	Abstract	121	76	-	-	45	-	-		
Tamegai et al <sup>[19]</sup>	2007	Japan	Full paper	103	32	-	-	71	54	63.4		

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

had been published by the same research group or published by the same author were not included; only the most recent data which included the previously published data were included.

Papers which reported data for patients who were treated with ESD or EMR in different time periods or in different sites in the gastrointestinal tract were included if the colorectal data could be easily extracted. Animal studies and endoscopic removal of inflammatory polyps or neuroendocrine tumours were excluded. Studies which reported outcomes from snare-assisted, hybrid ESD, laparoscopic ESD or which used new endoscopic tools were excluded.

#### Data extraction

Eligible articles were reviewed independently by two investigators (NP and JA); data was extracted into a standardized data extraction form<sup>[19,22-26]</sup>. Discrepancies were resolved by a third investigator (JT) who made the final decision for eligibility and data extraction.

The following data were extracted where available: Year of publication, study location, patient demographics, operating time, lesion size, *en-bloc* resection rate, piecemeal resection rate, complete resection rate, length of follow-up, lesion recurrence and treatment, endoscopic completeness rate and complication rate (bleeding, perforation and surgery post ESD) (Tables 1-4).

*En-bloc* resection rate was defined as the removal of a lesion in one piece as observed endoscopically. Piecemeal resection was defined as the removal of a lesion in more than one piece as observed endoscopically. Once removed, resected specimens are evaluated histologically. Specimens with clear lateral and basal margins of tumour were defined as an R0 resection, incomplete (R1) resection was defined as a positive lateral or basal margin for tumour and Rx resection where the margins of the specimen could not be evaluated due to piecemeal resection or as a result of thermal injury during resection.

Table 2 (	Colorecta	lesion ch	aracteristi	cs										
Ref.	Lesion size [mean Operating time [mean <u>+</u> SD (range) mm] or median <u>+</u> SD (range) min]			Lesion I	Lesion location (EMR: ESD cases)			Lesion type (EMR:ESD cases)						
	EMR	ESD	EMR	ESD	Left colon	Right colon	Rectum	Sessile	Depressed	Protruding	LST-G	LST- NG	LST-F	Recurrence
Tajika et al <sup>[22]</sup>	$25.5 \pm 6.8$ (20-55)	31.6 ± 9 (20-54)	29.4 ± 26.1 (3-115)	87.2 ± 49.7 (19-256)	41:13	35:41	28:31		0:1	68:10	28:33	7:38		1:3
Lee et al <sup>[23]</sup>	21.7 ± 3.5 (20-40)	28.9 ± 12.7 (20-145)	-	54.73 ± 40.9 (6-321)	41:82	82:172	0.75	36:73			49:129	55:112		
Kobayashi <i>et al</i> <sup>[24]</sup>	25 ± 9	27.1 ± 10.1	11 (2-280)	140 (45-400)	26:14	15:6	15:8			12:0	22:6	22:20		0:6
Saito et al <sup>[25]</sup>	28 ± 8 (20-95)	37 ± 14 (20-140)	29 ± 25 (3-120)	$108 \pm 7$ (15-360)	52:28	89:44	110:73	80:5	0:2		114:62	34:71		
Kim <i>et al</i> <sup>[26]</sup> Tamegai <i>et al</i> <sup>[19]</sup>	28.7 (20-60)	32.1 (13-75)	-	- 61.1 (7-164)	- -:28	- -:26	- -:17		0:2	12:19	28:48	6:16	22:2	

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LST-G: Laterally spreading tumour granular type; LST-NG: Laterally spreading tumour nodular granular type; LST-F: Laterally spreading tumour flat type.

#### Table 3 The outcomes of endoscopic mucosal resection and endoscopic submucosal dissection of colorectal lesions

Ref.	<i>En-bloc</i> resection rate (%)		Piecemeal resection rate (%)		RO lesion margins (%)		Endos completenes	Endoscopic completeness rate (%)		Perforation rate EMR:	Total complication	Surgery post EMR/ESD (EMR:ESD cases)	
	EMR	ESD	EMR	ESD	EMR	ESD	EMR	ESD	- F2D (%)	E2D (%)	rate (%)	Due to perfor-ation	Due to deep invasion
Tajika <i>et al</i> <sup>[22]</sup>	48.1	83.5	52.9	16.5	39.4	83.5	97	98.8	2.9:2.4	0:5.9	2.9:8.2	0:3	0
Lee et al <sup>[23]</sup>	42.9	92.7	57.1	7.3	32.9	87.6	99.1	90.8	0:0.6	0:8	5.7:11.5	0:2	9:26
Kobayashi <i>et</i> al <sup>[24]</sup>	37.5	92.9	62.5	7.1	-	-	98.2	100	1.8:7.1	0:10.7	1.8:17.9	0	0
Saito et al <sup>[25]</sup>	33	84	67	16	-	-	98.7	100	3.1:1.4	1.3:6.2	4.4:7.6	0	0
Kim et al <sup>[26]</sup>	72.4	80	27.6	20	-	-	100	100	-	-	3.9:6.7	-	-
Tamegai <i>et</i> al <sup>[19]</sup>	0	98.6	100	1.4	-	95.6	100	90.1	-:0	-:1.4	-:1.4	-	-:7

NB total complication rate includes coagulation syndrome. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

#### Table 4 Recurrent lesion characteristics

Ref.	Follow-up median <u>+</u> S	Recur rate	rence (%)	Piecemeal re of recurrent	Piecemeal resection rate of recurrent lesions (%)		t lesion hi ESD ca	istology ses)	Trea lesio	Treatment of recurrent lesion (EMR:ESD cases)			
	EMR	ESD	EMR	ESD	EMR	ESD	Adenoma	Non-inv cancer	Sm 1	Invasive cancer	APC	EMR	Surgery
Tajika <i>et al</i> <sup>[22]</sup>	53.8 ± 44.6 (3-191	14.3 ± 13.4 (3-53)	15.4	1.2	94	100	13/16:0	3/16:0	0:1/1	0:0	7/16:0	8/16:0	1/16:1/1
Lee <i>et al</i> <sup>[23]</sup>	26 (IQ range 13-41)	17 (IQ range 10-23)	25.7	0.8	90	50	-:2/2 (serrated)	-	-	-	0:0	28/29:2/2	1/29:0
Kobayashi et al <sup>[24]</sup>	38 (2.8-112.5)	19.9 (6.4-43.9)	21.4	0	92	n/a	8/12:0	3/12:0	0	1/12:0	0:0	11/12:0	1/12:0
Saito et al <sup>[25]</sup>	26 ± 17 (6-68)	20 ± 13 (6-61)	14	2	94	100	-:3/3	-	-	2/33:0	0:0	30/33: 3/33	3/33:0
Kim et al <sup>[26]</sup>	12 (6-12)	12 (6-12)	11.8	4.8	-	0	-	1/1:0	0	0:0	-	-	-
Tamegai et al <sup>[19]</sup>	19.2 (3-34)	12.2 (3-34)	6.3	0	100	-	-	-	-	-	-:0	2/2:0	0:0

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; APC: Argon photocoagulation.

Endoscopic clearance rates were defined as complete endoscopic removal of a lesion *en-bloc* or piecemeal and at one or more procedures.

#### Risk of bias assessment

The studies were assessed using the risk of bias tool from the Cochrane Collaboration<sup>[27]</sup> (Figure 2). The risk of

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Figure 2 Risk of bias graph (A) and risk of bias summary (judgments of each risk criteria presented as percentages across all included studies) and quality score results (B).

bias assessment domains examined were: (1) adequate sequence generation, determining if the allocation sequence generated by a computer or random numbers was adequate; (2) allocation concealment, determining if the participants and investigators enrolling the patients could foresee the study treatment arms during allocation; (3) blinding, which assessed if the study personnel, participants and assessors had knowledge of the allocation interventions during the study; (4) data reporting, determining if incomplete outcome data were adequately addressed; (5) selective outcome reporting, which is if the study protocols, primary outcomes and analysis methods are reported; and (6) other potential risks to study validity such as a potential source of bias related to the study design, or that the study was prematurely stopped due to a data-dependent process or fraudulent claims.

The quality of included studies was assessed using a modified Newcastle-Ottawa scale (Table 5). The quality domains examined were (1) patient selection; (2) intergroup comparability; and (3) outcome assessment using a star based system (maximum 3, 10 and 2 stars, respectively, total /15). The scoring was independently assessed by two authors (Patel N and Alexander J), with 100% inter-rater agreement (Figure 2).

#### Statistical analysis

Proportion difference between EMR and ESD outcomes

and calculated risk differences were calculated and pooled through DerSimonian and Laird random-effects modelling<sup>[27]</sup>. This considered both between-study and within-study variances which contributed to study weighting. Pooled values and 95%CIs were computed and represented on funnel plots. Statistical heterogeneity was determined by the  $I^2$  statistic; where < 30% is low, 30%-60% is moderate and > 60% is high. Analyses were performed using Stata version 12 (StataCorp LP, College Station, TX, United States).

#### RESULTS

The literature search identified 677 potential studies (Figure 1). The majority of these were excluded as they reported outcomes from animal studies, the use of new tools or a hybrid technique. Of the 57 studies that were assessed in full text for eligibility, 51 were excluded for the following reasons: No data on all primary outcome measures, no clearly defined follow up period, repeated published data and upper gastrointestinal endoscopic therapy. The final analysis included six studies published from 2007 to 2012 reporting 1324 lesions subjected to analysis, of which 688 were in the ESD group and 636 in the EMR group. Adequate demographic data was reported in three studies<sup>[22-24]</sup>, 59% of patients were men and 41% were women. The mean age was 62.5 years in the EMR group, and 61.9 years in the ESD

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Table 5 Citcella for i	
Quality Checklist	
Selection	
1	Assignment for treatment-any criteria reported (if yes, 1-star)?
2	How representative was the reference group (EMR group) in comparison to the general population for colorectal lesions? (If
	yes, 1-star, no stars if the patients were selected or selection of group was not described)
3	How representative was the treatment group (ESD group) in comparison to the general population for colorectal lesions?
	(If drawn from the same community as the reference group, 1-star, no stars if drawn from a different source or selection of
	group was not described)
Comparability	
Comparability variables	(1) Age; (2) gender; (3) lesion size; (4) LST; (5) lesion location; (6) LGD; (7) HGD; (8) submucosal tumor; (9)non-invasive
	cancer; (10) cancer
4	Groups comparable for 1, 2, 3, 4, 5 (If yes, 1-star was assigned for each of these. No star was assigned if the two groups
	differed)
5	Groups comparable for 6, 7, 8, 9, 10 (If yes, 1-star was assigned for each of these. No star was assigned if the two groups
	differed)
Outcome assessment	
6	Clearly defined outcome of interest (if yes, 1-star)
7	Follow-up (1-star if described)

#### Table 5 Criteria for modified newcastle ottawa scoring system

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LST: Lateral spreading tumor; LGD: Low grade dysplasia; HGD: High grade dysplasia.



Figure 3 Colorectal lesion histopathology. LGD: Low grade dysplasia; HGD: High grade dysplasia; SM1: Submucosal tumour < 1000  $\mu$ m invasion depth; SM2: Submucosal tumour > 1000  $\mu$ m invasion depth.

group (Table 1).

Mean procedure times were reported in four studies<sup>[19,22,23,25]</sup> (Table 2). The overall mean time was 29 min (range 2-280) for EMR<sup>[22,25]</sup> and 73 min (range 6-400) for ESD<sup>[19,22,23,25]</sup>. The mean follow up period was 29.7 mo in the EMR group and 15.9 in the ESD group, as reported in 4 studies<sup>[19,22,25,26]</sup> (Table 4).

Five studies reported data on the size of lesions<sup>[19,22-25]</sup> (Table 2). The mean size of lesion was 25.7 mm (range 20-95 mm) in the EMR group and 31.4 mm (range 13-145 mm) in the ESD group. The location of lesions was reported in three studies<sup>[22-24]</sup> shown in Table 2. In the EMR group, 44% lesions were in the right colon, 36% lesions were in the left colon and 20% were in the rectum. In the ESD group, 51% lesions were in the right colon, 26% were in the left colon and 23% in the rectum. Data on lesion type was available for 93% of all lesion outcomes reported (Table 2). The majority of procedures were carried out on lateral spreading tumour (LST) (365/574 treated by EMR and 535/656 by ESD). In the EMR group, 66% were the granular type (LST-G) and

23% were non-granular (LST-NG). In the ESD group, 52% were LST-G and 48% LST-NG. EMR was performed in a greater number of sessile lesions (20% EMR, 12% ESD) and protruding lesions (16% EMR, 4% ESD). ESD was performed in a greater number of patients with depressed or recurrent lesions (0.2% EMR, 2% ESD).

Histologically, 52% of lesions were adenomas (including low grade and high grade dysplasia). Eleven percent of lesions were described as non-invasive mucosal cancers and 4% as cancers. Submucosal tumours (SM1 and SM2+) made up 31% of the lesions resected (Figure 3).

#### Outcomes

The *en-bloc* resection rate was reported in all studies (Table 3). This demonstrated a 50% higher *en-bloc* resection rate in the ESD than the EMR group (95%CI: 0.17-0.83, P < 0.0001,  $I^2 = 99.7$ %) (Figure 4).

The piecemeal resection rate was also reported in all six studies (Table 3). The rate of piecemeal resection was 48% higher in the EMR group than in the ESD group (95%CI: -0.70-0.26, P < 0.0001,  $I^2 = 96.7\%$ ) (Figure 5).

The endoscopic clearance rate was reported in all studies (Table 3). This demonstrated a marginal but significant, 2% higher rate in the ESD group compared to the EMR group (95%CI: -0.06-0.02, P < 0.0001,  $I^2 = 92.5\%$ ) (Figure 6).

The R0 rates were reported in both groups in two studies<sup>[22,23]</sup> and only the ESD group from Tamegai *et*  $al^{(19)}$ . The average R0 rate for the EMR group was 36.2% and 88.9% in the ESD group.

#### Complications

The total reported complication rate, including perforation, bleeding and coagulation syndrome, was 3.9% in the EMR group and 9.2% in the ESD group. The perforation rate for both EMR and ESD was reported in four of the six studies (Tamegai *et al*<sup>[19]</sup> only reported perforation rate for ESD). The perforation rate was 7% higher in the ESD



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Study						%
ID					RD (95%CI)	Weight
lajika <i>et al<sup>22</sup></i>					0.35 (0.29, 0.42)	16.65
Lee <i>et al</i> <sup>[23]</sup>			- <b>*</b> -		0.50 (0.45, 0.54)	16.71
Kobayashi <i>et al<sup>[24]</sup></i>					0.55 (0.45, 0.66)	16.48
Saito <i>et al<sup>25</sup></i>					0.51 (0.46, 0.56)	16.70
Kim <i>et al</i> <sup>26]</sup>					0.08 (0.03, 0.12)	16.71
Tamegai <i>et al<sup>i19]</sup></i>				-	0.99 (0.96, 1.01)	16.75
Overall ( $I^2 = 99.7\%$ , $P = 0.000$ )					0.50 (0.17, 0.83)	100.00
with estimated predictive interval					(-0.74, 1.73)	
Note: Weight are from random effects ar	alysis					
i						
-1	-0.5	0	0.5	1		
	Favours EMR		Favours ESD			
	Pro	portion differen	ce			





Figure 5 Piecemeal resection proportion difference endoscopic mucosal resection vs endoscopic submucosal dissection. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.



Proportion difference

Figure 6 Endoscopic completeness rates proportion difference endoscopic mucosal resection vs endoscopic submucosal dissection. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

group than the EMR group (95%CI: 0.05-0.09, P > 0.05,  $I^2 = 41.1\%$ ) (Figure 7). Five patients required surgery due to perforation in the ESD group, compared to none in the EMR group (Table 3).

#### Recurrence rate

The recurrence rate was reported in all studies (Table 4). In cases that were followed up, the rate of recurrence was 50% higher in the EMR group than in the ESD

group (95%CI: 0.20-0.79, P < 0.001,  $I^2 = 99.5\%$ ) (Figure 8). The resected margins were reported in Tajika *et al*<sup>[22]</sup>. In the EMR group 7/16 cases had R1 margins and 9/16 Rx margins. In the ESD group, 41/56 cases were R0, 6/56 R1 and 9/56 cases Rx. All studies except Kim *et al*<sup>[26]</sup> reported the piecemeal rate in the recurrence groups. 92% (85/92) of cases in the EMR group and 71% (5/7) of cases in the ESD group had been removed by piecemeal. The recurrent lesions in



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Study						%
ID					RD (95%CI)	Weight
Tajika <i>et al<sup>j22]</sup></i>					0.06 (0.03, 0.09)	23.14
Lee <i>et al</i> <sup>23]</sup>		i 👘			0.08 (0.06, 0.10)	32.29
Kobayashi <i>et al<sup>[24]</sup></i>					0.11 (0.04, 0.17)	8.21
Saito <i>et al</i> <sup>25]</sup>					0.05 (0.03, 0.07)	36.36
Kim <i>et al<sup>[26]</sup></i>					(Excluded)	0.00
Tamegai <i>et al<sup>19]</sup></i>					(Excluded)	0.00
Overall ( $I^2 = 41.1\%$ , $P = 0.000$ )		-∲-			0.07 (0.05, 0.09)	100.00
with estimated predictive interval					(-0.01, 0.14)	
Note: Weight are from random effect	s analysis					
-1	-0.5	0	0.5	1		
	ESD		EMR			
		Proportion differ	ence			

Figure 7 Perforation proportion difference endoscopic mucosal resection vs endoscopic submucosal dissection. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.



Figure 8 Recurrence proportion difference endoscopic mucosal resection vs endoscopic submucosal dissection. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Table 6         Sub-group analysis of the four highest quality studies <sup>[22-25]</sup>									
I <sup>2</sup> (%) P value 95%CI Effect size									
En-bloc resection rate	82.3	< 0.0001	0.14-0.81	0.476					
Piecemeal resection rate	51.7	0.102	-0.76-0.19	-0.472					
Endoscopic completeness rate	93.1	< 0.0001	0.19-0.17	-0.008					
Recurrence rate	82.1	< 0.0001	0.13-0.82	0.476					

both groups were mainly adenomas (21/32 recurrent EMR cases and 5/6 ESD cases (data not available from Kim *et al*<sup>(26)</sup> in the ESD group). There were three invasive cancers reported as recurrent lesions in the EMR group and none in the ESD group. Seventy nine of the recurrent EMR cases were successfully treated with repeat EMR procedures, seven cases with argon photocoagulation and six required surgery (a portion of this group had multiple previous attempts at EMR before technical difficulties or invasive carcinoma were found at a later date) (data not available from Kim *et al*<sup>(26)</sup>). In the ESD group, 5 recurrent cases were successfully treated with EMR and one with surgery<sup>[22]</sup> (Table 4).

#### Risk of bias and quality scoring

All of the included trials had a high risk or unclear risk of

bias in one or more of the assessed domains (Figure 2). Random sequence generation, allocation concealment and blinding were the main potential risks of bias in studies included in this meta-analysis. The overall quality scores are shown in Figure 2. Four studies received score of  $\geq$  10 and were hence deemed to be of relative high quality. These studies were analysed as a sub-group to determine the source of heterogeneity (Table 6). There was no substantial change in heterogeneity when enbloc resection rate, endoscopic completeness rate and recurrence rates were re-analysed. Piecemeal resection rates however demonstrated a reduction from significant to moderate heterogeneity though effect sizes remained similar throughout. All studies adequately matched both EMR and ESD groups for comparability and outcome assessment.

#### DISCUSSION

This is one of the first meta-analyses comparing the outcomes of colorectal ESD and EMR. The pooled outcome results of this meta-analysis (from non-comparative studies) suggest that there may be a perceptible difference in the clinical outcomes colorectal of ESD and EMR. The results for ESD demonstrated higher *en-bloc* resection rates, endoscopic clearance rates and lower recurrence rates, albeit with higher pooled outcome complication



rates. However, any inferences regarding clinical superiority should be taken with caution, as these results do not derive from comparative studies and demonstrate high heterogeneity throughout.

Although EMR is an established technique, it is usually performed for smaller lesions or larger lesions in piecemeal (associated with higher recurrence rates). Piecemeal resection involving multiple smaller resections often makes the endoscopic field difficult to detect residual tissue due to electrocautery burns, blood and local trauma. Further therapeutic procedures may therefore be required with cost, time and increased complication rate implications. In comparison, creating a mucosal incision around the lesion during ESD means that the endoscopic resection margins have already been delineated minimising disruption of the endoscopic field during submucosal dissection.

ESD appears advantageous as it allows accurate histopathological assessment of the resected lesion and resected margins, associated with fewer reported recurrences or residual disease. However, colorectal ESD is technically complex requiring more highly skilled endoscopists compared to upper gastrointestinal ESD. Compared to EMR, the procedure times are longer, more demanding and have higher complication rates.

There are endoscopic tools which have been developed or are in development designed to facilitate ESD and further improve clinical effectiveness, long-term outcomes and safety. For example, hydrodissection in the submucosal plane can be performed using the HybridKnife (ERBE)<sup>[28]</sup> and a hybrid ESD approach using a snare has also been introduced.

ESD has been shown to result in significantly lower recurrence rates compared to EMR. This may result from greater *en-bloc* resection rates, lower piecemeal rates and, in the studies that reported the resected margins, a higher R0 rate. However, ESD is more time consuming and associated with significantly greater complication rates. Safety of the technique is an important consideration, particularly if the uptake of ESD is to increase. There are technical difficulties of performing ESD in the colonic environment which is thin-walled containing flexures and folds. However, it will be interesting to monitor the uptake and outcomes in countries other than East Asia such as the Western world where, although the incidence of colorectal cancer is higher, upper gastrointestinal ESD is an infrequent occurrence. In these countries the learning curve is likely to be greater as a result of difficulties with training opportunities resulting from a lack of clinical cases, experience and skilled tutors.

Trans-anal endomicroscopy allows full-thickness resection of rectal lesions with accurate staging albeit with a higher complication rate compared to endoscopic therapy. In addition, conventional rectal surgery is more invasive with the risk of stoma formation and problems with incontinence resulting in a drive for a favourable minimally invasive endoscopic approach. However, differences between rectal and colonic lesion endotherapy outcomes have been reported<sup>[29]</sup>. This is multifactorial with anatomical and vascular differences between the two sites. The rectum is the first place to start training endoscopists in ESD because it is easily accessible compared to other parts of the colon<sup>[30]</sup>. Furthermore, rectal insufflation creates a neat and stable workspace to perform ESD compared to a mobile, narrow colon with folds or flexures to consider. Significantly higher recurrence rates have been reported in patients with high-risk submucosal rectal cancers treated with endoscopic therapy compared to colonic lesions<sup>[29]</sup>. Further analysis of endoscopic therapy comparing these two lesion locations is required to determine whether or not definite surgical measures with lymph node dissection rather than ESD for these higher risk patients is a better longer-term treatment plan. To improve the quality of analysis of colorectal ESD outcomes, prospective randomised controlled trials with appropriate follow-up periods which also accommodate for learning curve effects and include quality of life data are required to validate the technique in the lower gastrointestinal tract.

#### Limitations

There are a number of limitations to this analysis which derive from significant clinical and statistical heterogeneity throughout. The significant statistical heterogeneity demonstrated suggests there is a risk the included studies were clinically heterogenous. This may result in the effect size difference being a secondary finding or a high risk for bias finding. The four high quality studies were also studied as a subgroup to determine if the heterogeneity decreases<sup>[22-25]</sup>. This only decreased from significant to moderate for piecemeal resection and effect sizes remained similar throughout. The quality scores of many of the included studies was moderate, there are few studies directly comparing the outcomes of colorectal ESD and EMR and no randomised controlled trials in the literature to date. The eligibility criteria are often unclear for both techniques, lesions had differing characteristics and size and all of the included studies were retrospective case-control studies or observational studies.

In addition, all the included studies originated from East Asia (Japan and South Korea) where there are a larger number of endoscopists familiar with the technique and hence this may cause bias. In a number of studies the time periods during which EMR and ESD were carried out were different reflecting a change in practice with the introduction of  $\text{ESD}^{[19,22,23]}$ . The outcomes of the studies may have hence been subject to bias with improvements in endoscopy technique and introduction of ESD tools and devices to facilitate the procedure reflected in the significant heterogeneity of the resulting outcomes. The effect size may also have been affected by the learning curve effect. Five out of the six studies scored poorly for the quality of patient selection, particularly how representative the groups were. The selection of the groups was not described

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adequately in these studies and may be reflected by the significant heterogeneity of the results.

Follow-up periods also differed in these studies and as a result lead-time and selection biases may have also occurred. Follow-up in some studies was difficult as the procedures were often carried out at tertiary referral centres with follow-up at local hospitals where the outcome data were not reported<sup>[24,25]</sup>.

In conclusion, Whilst ESD for early non-metastatic gastric cancer is now the treatment of choice in East Asia and is gaining popularity worldwide, colorectal ESD is still at a relatively early stage. The adoption of the technique in the West is particularly important given the significantly higher incidence and is another step towards the scarless surgery goal. The colonic environment is more challenging than the upper gastrointestinal tract and there is a learning curve to the technique. However, *en-bloc* resection has significantly more favourable mid-term outcomes compared to EMR. This is in addition to the benefits of not performing a surgical procedure in terms of recovery, cost and complications.

This meta-analysis reports on mid-term follow-up outcomes. In order to better identify the differences in outcome between these two modalities, case-matched prospective and randomised studies should be carried out with protracted follow-up periods to ascertain longer-term outcomes. The trade-off between safety and risk of perforation also needs to be established, patient selection and analysis of ESD and EMR colorectal registry data will be useful to establish this through more robust data in the future.

#### ACKNOWLEDGMENTS

The authors are grateful to the Departments of Surgery and Cancer and Gastroenterology at Imperial College London for their discussion regarding this meta-analysis and support during the data collection and writing of this article.

#### COMMENTS

#### Background

Minimally invasive endosurgical techniques such as endoscopic submucosal dissection (ESD) are gaining popularity worldwide as an alternative to conventional surgery. Whilst ESD for early non-metastatic gastric cancer is the treatment modality of choice in East Asia, the uptake of the technique in the Western world has been slow. This is in part due to the appropriate case load and also due to the high complexity of the technique. Colorectal cancer and polyps are highly prevalent in the Western world and hence endoscopic submucosal dissection should be explored and compared to current endoscopic therapy.

#### **Research frontiers**

A meta-analysis was used to evaluate the mid-term outcomes of colorectal ESD and endoscopic mucosal resection (EMR).

#### Innovations and breakthroughs

This is one of the first detailed meta-analysis evaluating immediate and midterm outcomes for colorectal ESD and EMR. Most of the literature to date report immediate outcomes after endoscopic therapy, there is no longer-term outcome data and little mid-term outcome data reported.

#### Applications

This meta-analysis showed that colorectal ESD demonstrates higher *en-bloc* resection rates and lower recurrence rates compared to colorectal EMR. Although the complication rates are higher with a significantly increased perforation rate, ESD obviates the need for surgery and reduces the need for further endoscopic procedures. Differences in outcomes may benefit from increased assessment through well-designed comparative studies.

#### Peer-review

This is a good meta-analysis, suitable for publication. This meta-analyses study reports the comparison between EMR and ESD for colorectal lesions. Although this kind of meta-analyses is not the first report, this is still useful to compare both methods for colorectal tumours.

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P- Reviewer: Kiriyama S, Kopacova M, Shibata T S- Editor: Gong ZM L- Editor: A E- Editor: Lu YJ







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META-ANALYSIS

### Computed tomography fluoroscopy guided percutaneous lung biopsy for ground-glass opacity pulmonary lesions: A meta-analysis

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**Conflict-of-interest statement:** The authors declare that there is no conflict of interest related to this study.

Data sharing statement: No additional data are available.

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Received: November 30, 2015

Peer-review started: December 1, 2015 First decision: December 28, 2015 Revised: February 2, 2016 Accepted: February 23, 2016 Article in press: February 24, 2016 Published online: April 26, 2016

#### Abstract

**AIM:** To obtain the diagnostic performance of percutaneous transthoracic needle biopsy (PTNB) under Computed tomography (CT) fluoroscopy guidance for lung ground-glass opacity (GGO).

**METHODS:** We searched for English- and Chineselanguage studies in PubMed, EMBASE, EBSCO, OVID, and CNKI (China National Knowledge Infrastructure) database. Data were calculated with Meta-Disc version 1.4 and Rev Man version 5.2 software. From the pooled data, we calculated sensitivity (Sen), specificity (Spe), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR). Summary receiver operating characteristic (SROC) curves were constructed and incidence of complications was recorded.

**RESULTS:** Four documents included in this present meta-analysis met the criteria for analysis. The pooled Sen, Spe, +LR, -LR and DOR with 95%CI were 0.91 (0.86-0.95), 1.0 (0.91-1.0), 18.64 (4.83-71.93), 0.11 (0.05-0.26) and 153.17 (30.78-762.33), respectively. The area under the SROC curve was 0.98. The incidence of pneumothorax and hemoptysis was 17.86%-51.80% and 10.50%-19.40%, respectively.

CONCLUSION: CT fluoroscopy-guided PTNB, which has an acceptable incidence of complications, can be used



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as a primary examination method for lung GGO, with moderate sensitivity and specificity.

Key words: Lung biopsy; Meta-analysis; Ground-glass opacity; Computed tomography fluoroscopy

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**Core tip:** There is no consensus in the literature about the diagnostic performance of percutaneous transthoracic needle biopsy (PTNB) under Computed tomography (CT) fluoroscopy guidance for lung ground-glass opacity (GGO). We performed a meta-analysis to obtain the diagnostic performance of CT fluoroscopy-guided PTNB of lung GGO in terms of pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio and incidence of complications. We also generated a summary receiver operating characteristic curve as a way of summarizing the global test performance of CT fluoroscopy-guided PTNB.

Yan GW, Yan GW, Sun QQ, Niu XK, Li B, Bhetuwal A, Xu XX, Du Y, Yang HF. Computed tomography fluoroscopy guided percutaneous lung biopsy for ground-glass opacity pulmonary lesions: A meta-analysis. *World J Meta-Anal* 2016; 4(2): 55-62 Available from: URL: http://www.wjgnet.com/2308-3840/full/v4/i2/55.htm DOI: http://dx.doi.org/10.13105/wjma.v4.i2.55

#### INTRODUCTION

Ground-glass opacity (GGO) in lung parenchyma is a image manifestation on thin-section Computed tomography (CT) that is defined as "hazy increased attenuation of the lung with preservation of bronchial and vascular margins"<sup>[1]</sup>. As prevalence of lung cancer screening with low-dose CT rises, so has the detection of pulmonary lesions that manifest as GGO nodules<sup>[2,3]</sup>. Since, GGO, not being a specific imaging finding, many differential diagnoses such as bronchoalveolar carcinoma, adenocarcinoma, atypical adenomatous hyperplasia, focal fibrosis and inflammatory diseases must be taken into consideration<sup>[4,5]</sup>. As a result, the importance of diagnosing lung GGO cannot be ignored once observation, clinical follow-up or chemotherapeutic therapy has ruled out the benign or inflammatory nature of the lesion. However, controversy does exist on whether PTNB should be attempted for the persistent presence of lung GGO or not.

Recent efforts<sup>[6-9]</sup> utilizing PTNB under the guidance of CT fluoroscopy have been attempted to increase the diagnostic accuracy of lung GGO but contain only few enrolled subjects. The objective of this article was to obtain the diagnostic performance of CT fluoroscopy guided PTNB for lung GGO with a meta-analysis, which, as far as the authors' understanding, has not been reported previously. #1 ("CT" or "computed tomography" or "CT fluoroscopy" or "CTF") [Title/ Abstract] #2 ("ground-glass opacity" or "GGO") [Title/Abstract] #3 ("lung" or "pulmonary") [Title/Abstract] #4 #1 and #2 and #3

Figure 1 Search strategy for PubMed. GGO: Ground-glass opacity.

#### MATERIALS AND METHODS

#### Literature search

We searched PubMed, EMBASE, OVID, EBSCO, and CNKI (China National Knowledge Infrastructure) databases without publication date or language restrictions, from inception to August 2015, using the search terms "CT", "computed tomography", "CT fluoroscopy", "CTF", "ground-glass opacity", "GGO", "lung", and "pulmonary". Search terms were present in the title or abstract of the articles. The detailed search strategy of PubMed is shown in Figure 1.

#### Study selection

A system documentation retrieval of human articles was accomplished by two independent observers to find out studies about the diagnostic value of CT fluoroscopyguided PTNB in patients with GGO. All case reports, letters, comments, and review articles were eliminated. Subsequently, studies, on the basis of their title and abstract, was either included or discarded.

Studies that complied with the following criteria were also included in this study: (1) Adequate data to calculate the number of true positive (tp), false positive (fp), false negative (fn), and true negative (tn) results; (2) definite criteria to define a positive imaging result were documented; and (3) clinical follow-up or clinical observation for at least one year and/or surgery.

Other potentially eligible studies were identified by manually searching the reference lists of the articles enrolled in this meta-analysis. Any differences of opinion in selecting the studies between the two reviewers were resolved through discussion. If there was any unresolved studies advices were sought from another two reviewers experienced in study selection and data extraction in more than six meta-analyses or systematic reviews.

#### Data extraction

A 2  $\times$  2 table was created to input following data extracted from each study included in the present metaanalysis: (1) true positive results (subjects with disease diagnosed correctly from the standard test); (2) false positive results (subjects without disease diagnosed as diseased from the standard test); (3) false negative results (subjects with disease diagnosed as without disease from the standard test); (4) true negative results (subjects without disease diagnosed correctly as without disease from the standard test); and (5) other clinical characteristics of the studies (including author, year of

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Figure 2 Flow chart of study selection.

publication, lesion size, and complications).

#### Quality assessment

Methodological quality was evaluated on the basis of the Quality Assessment of Studies of Diagnostic Accuracy included on Systematic Reviews (QUADAS-2) guidelines independently by the same two reviewers who had performed the literature search. The quality of studies of diagnostic accuracy was specifically evaluated by the evidence-based tool above. Any dispute was resolved through discussion among the reviewers. A more detailed description of each item and a guideline on how to use the QUADAS-2 tool are provided by Whiting *et al*<sup>[10]</sup>.

#### Statistical analysis

The data integration for the accuracy of CT fluoroscopyguided PTNB for lung GGO lesions was made by calculating pooled estimates of sensitivity (Sen), specificity (Spe), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic odds ratio (DOR) at a patient level. We also generated a summary receiver operating characteristic (SROC) curve as a way of summarizing the global test performance from different diagnostic studies. The pooled Sen, Spe, +LR, -LR, DOR, and SROC across studies were calculated by using a random or fixed effect model according to the heterogeneity. Heterogeneity across studies was evaluated by using the  $\chi^2$  and Fisher's exact tests. Threshold effect was assessed by using the Spearman rank correlation test. Subgroup analysis was also performed if necessary. Statistical analyses in this present meta-analysis were all carried out with Meta-disc software (version 1.4). P < 0.05 was considered statistically significant.

#### RESULTS

**Study selection** Literature search revealed 82 articles which, after



Figure 3 Quality assessment of diagnostic accuracy studies and criteria for included studies.

reading the titles and abstracts of the searched articles, 76 documents were discarded as they did not meet the inclusion criteria. After closer inspection of full text, 2 out of six were again discarded for the causes provided in Figure 2. Finally, the remaining four studies which fulfilled the inclusion criteria were included in this metaanalysis<sup>[6-9]</sup>. All 4 studies were published in English. Table 1 shows the basic characteristics of the included four studies. Methodological quality of the four studies, as evaluated by the QUADAS-2 tool, is shown in Figure 3.

#### **Diagnostic accuracy**

The pooled sensitivity with 95%CI was 0.91 (0.86-0.95), ranging from 0.71 to 0.88. However, the pooled specificity with 95%CI was 1.00 (0.91-1.00), and the specificities in the four studies were all reported as 1.00. The +LR, -LR and DOR with 95%CI was 18.64 (4.83-71.93), 0.11 (0.05-0.26), and 153.17 (30.78-762.33), respectively.  $\chi^2$  values of Sen, Spe, +LR, -LR, and DOR were 11.07 (P = 0.01), 0.0 (P = 1.0), 0.40 (P = 0.94), 11.14 (P = 0.01), and 0.84 (P = 0.84), respectively, indicating that there are some degree of heterogeneity among the four documents.

Forest plots (Figure 4) reveals the detailed sensitivity and specificity with 95%CI of each individual study. The detailed +LR and -LR with 95%CI for each individual study are shown in Forest plots (Figure 5). Figure 6 is the Forest plot of the DOR. The SROC curve showed a good overall diagnostic performance for CT fluoroscopyguided PTNB for all studies combined (Figure 7). In this meta-analysis, Q-value of the maximum joint sensitivity and specificity was 0.94. The area under the SROC curve (AUC) was 0.98, which indicated a relatively high level of overall accuracy.

#### Subgroup analysis

Subgroup analysis was performed according to the size of the lesions and pooled indexes (Sen, Spe, +LR, -LR,



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Table 1 Characteristics of the included four studies										
Ref.	Year	Lesion size (mm)	tp	fp	fn	tn	All	Complications		
Hur et al <sup>[6]</sup>	2009	$\leq 10$	4	0	2	4	10	Pneumothorax (5);		
		11-20	5	0	2	3	10	Hemoptysis (3); Thoracostomy tube insertion (2)		
		> 20	3	0	1	4	8			
		All	12	0	5	11	28			
Yamauchi et al <sup>[7]</sup>	2011	$\leq 10$	6	0	1	1	8	Pneumothorax (14); Hemoptysis (13); Thoracostomy tube		
		11-20	36	0	1	5	42	insertion (0)		
		> 20	17	0	0	0	17			
		All	59	0	2	6	67			
Inoue <i>et al</i> <sup>[8]</sup>	2012	$\leq 10$	21	0	1	2	24	Pneumothorax (30); Hemoptysis (7); Thoracostomy tube		
		11-20	36	0	2	3	41	insertion (1);		
		> 20	1	0	0	0	1	Air embolism (1)		
		All	58	0	3	5	66			
Yamagami et al <sup>[9]</sup>	2013	$\leq 10$	16	0	4	11	31	Pneumothorax (44); Hemoptysis (9); Thoracostomy tube		
		11-20	30	0	4	6	40	insertion (3)		
		> 20	12	0	0	2	14			
		All	58	0	8	19	85			

fn: False negative; fp: False positive; tn: True negative; tp: True positive.



Figure 4 Forest plot shows sensitivity and specificity from individual studies and pooled estimates. Summary sensitivity and specificity were 0.91 (95%CI: 0.86-0.95) and 1.0 (95%CI: 0.91-1.00), respectively.

DOR and SROC) with 95%CI are summarized in Table 2.

#### Complications

The incidence of pneumothorax ranged from 17.86% to 51.80%, and was reported in all four studies, with six patients requiring chest tube drainage. The incidence of hemoptysis ranged from 10.50% to 19.40% without any patients requiring treatment for it. Systemic air embolism occurred in one case as reported in the study by Inoue *et al*<sup>[8]</sup>. Apart from these, there were no other complications or adverse effects reported in the four studies included in the meta-analysis.

#### DISCUSSION

Bronchoscopy is one option for examination of patients with suspected lung masses. It can be used for tissue sampling, evaluating the nature and extent of a lung mass or a lesion and guiding therapy. However, in the case of a non-diagnostic bronchoscopy (*i.e.*, failure to obtain a histopathological diagnosis from lung lesion), image-guided PTNB is usually performed. Among these interventional techniques, lung biopsy under CT guidance has widespread acceptance as a preferred modality for the diagnosis of pulmonary masses. Its diagnostic



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Figure 5 Forest plot shows positive likelihood ratio and negative likelihood ratio from individual studies and pooled estimates. Summary positive likelihood ratio (LR) and negative LR were 18.64 (95%CI: 4.83-71.93) and 0.11 (95%CI: 0.05-0.26), respectively.

Tau-squared = 0.5068



Negative LR

	Diagnostic OR (95%CI)					
Hur <i>et al</i> <sup>[6]</sup>	52.27 (2.59-1053.92)					
Yamaauchi <i>et al</i> <sup>[7]</sup>	309.40 (13.36-7166.01)					
Inoue <i>et al</i> <sup>[8]</sup>	183.86 (8.37-4038.39)					
Yamagami <i>et al</i> <sup>(9]</sup>	268.41 (14.80-4867.71)					
Fixed effects model						
Pooled diagnostic OR = 153.17	(30.78 to 762.33)					
Cochran-Q = $0.84$ ; df = $3(P = 0.8395)$						
Inconsistency $(I^2) = 0.0\%$						

Diagnostic OR

Figure 6 Forest plot shows diagnostic odds ratio from individual studies and pooled estimates. Diagnostic odds ratio (OR) was 153.17 (95% CI: 30.78-762.33).

Table 2 Subgroup analysis of the included four studies									
Size	Sen	Spe	+ LR	-LR	DOR	SROC			
All	0.91 (0.86-0.95)	1.0 (0.91-1.0)	18.64 (4.83-71.93)	0.11 (0.05-0.26)	153.17 (30.78-762.33)	0.98			
$\leq 10 \text{ mm}$	0.85 (0.73-0.94)	1.0 (0.81-1.0)	8.03 (2.21-29.18)	0.24 (0.14-0.41)	37.94 (7.48-192.37)	0.92			
11-20 mm	0.92 (0.86-0.96)	1.0 (0.80-1.0)	9.35 (2.45-35.71)	0.13 (0.08-0.22)	67.98 (13.06-353.87)	0.96			
> 20 mm	0.94 (0.70-1.0)	1.0 (0.54-1.0)	6.24 (0.97-40.0)	$0.20 (0.07-0.60)^{a}$	38.93 (2.80-541.16) <sup>b</sup>	_ <sup>c</sup>			

<sup>ab</sup>Only studies 6 and 9 were calculated; SROC for GGO > 20 mm could not be calculated in this meta-analysis because of only two data points. Sen: Sensitivity; Spe: Specificity; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; DOR: Diagnostic odds ratio; SROC: Summary receiver operating characteristic; GGO: Ground-glass opacity.

accuracy is 92.9%-95% and the incidence of adverse effects is within an acceptable range<sup>[11-13]</sup>. Compared with techniques under conventional CT guidance, as it was reported, "CT fluoroscopy-guided PTNB allows continuous monitoring of the needle as it progresses toward the target lesion, enabling manipulation in response to respiratory movements"<sup>[14,15]</sup>.

Nevertheless, diagnostic performance of PTNB under

CT fluoroscopy quidance for the diagnosis of pulmonary GGO nodules is not well established. This meta-analysis investigated the overall diagnostic performance of CT fluoroscopy-guided PTNB in the differential diagnosis of GGO lesions with a high Sen and Spe, 0.91 (95%CI: 0.86-0.95) and 1.00 (95%CI: 0.91-1.00), respectively. The SROC curve stands for a global summary of test efficacy and indicates the trade-off between Sen and



Figure 7 Summary receiver operating characteristic curve. SROC: Summary receiver operating characteristic.

Spe<sup>[16]</sup>. Our meta-analysis, according to the SROC curve, indicated that the maximum joint Sen and Spe was 0.94 and the AUC was 0.98, suggesting a high level of overall diagnostic efficacy. We conclude that CT fluoroscopy-guided PTNB plays an important role in the diagnosis of GGO lesions. DOR which, combines the data from Sen and Spe into a single value, is another reference of test accuracy<sup>[17]</sup>. In our meta-analysis, the DOR with 95%CI was 153.17 (30.78-762.33), indicating that CT fluoroscopy-guided PTNB was valuable in the diagnosis of GGO lesions. Subgroup analysis was performed according to the size of the lesions, and the pooled parameters were still good, indicating that CT fluoroscopy-guided PTNB was valuable in the diagnosis of GGO lesions regardless of their size.

The rate of complications was thought to be within an acceptable range. Pneumothorax, with an incidence of 17.86%-51.8%, was the most frequently encountered complication of CT fluoroscopy-guided PTNB<sup>[6-9]</sup>. Out of the 246 patients, only six required chest tube drainage. The incidence of hemoptysis ranged from 10.5% to 19.4%, without any of the patients requiring treatment. Yamagami et al<sup>[9]</sup>, in the largest study, reported that the incidence of pneumothorax and hemoptysis was 51.8% and 10.6%, respectively. Inoue et al<sup>[8]</sup> reported one case of systemic air embolism. Even though an exact reason behind it could not be determined, there is a possibility of creating needle-induced fistula between the bronchus and the pulmonary vein in GGO lesion biopsy more than during solid lesion biopsy since GGO lesions preserve the bronchus and pulmonary vessels located inside them<sup>[8]</sup>. Hence, taking the results of Sen, Spe, DOR, +LR, and -LR into account, it is reasonable to think that CT fluoroscopy-guided PTNB can be used as one of the primary examination procedures for lung GGO lesions.

With respect to influencing factors for pneumothorax, there were significant differences reported, including patient age, sex, lesion location, number of pleural passages, and emphysema along the needle pathway<sup>[6-9,18]</sup>. Influencing

factors for hemoptysis included patient age and sex, lesion location, nodule type, and distance from the pleura to the target lesion. Ground-glass nodules and deeper-located lesions were significant independent risk factors for hemoptysis<sup>[6-9,18]</sup>. In addition, the needle–pleural angle is another predictor of pneumothorax as reported by Li *et al*<sup>[19]</sup> and Niu *et al*<sup>[20]</sup>. De Filippo *et al*<sup>[21]</sup> reported that non-calcified density (the higher the density, the better the accuracy) was a positive predictive factor for diagnostic accuracy. The diagnostic performance of PTNB under CT guidance can be elevated by the use of multiplanar reformatting imaging, which is useful for planning the path of the needle while performing needle aspiration.

The diagnostic outcomes of conventional CT-guided lung biopsy have been studied previously. Kim *et al*<sup>[22]</sup> reported the outcomes of 50 patients (< 2.0 cm vs  $\geq$ 2.0 cm and GGO component > 90% vs 50%-90%) who had been investigated with coaxial 18-gauge or 20-gauge core needles. The overall Sen, Spe, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were 92.0%, 90.0%, 97.0%, 75.0% and 91.0%, respectively. Sensitivity and accuracy were not significantly different between the two groups of lesion size and GGO components. Lu et al<sup>[23]</sup> reported the outcomes of 49 patients investigated with coaxial 20-gauge core needles. The overall Sen, Spe, PPV, NPV, and diagnostic accuracy were 93.62%, 100%, 100%, 40.0% and 93.88%, respectively. Compared to these results<sup>[22,23]</sup>, we assume that the methodologies used in the included studies[6-9] (i.e., the CT fluoroscopy and coaxial needle system) contributed to the high diagnostic accuracy observed.

This study is in accordance of the recommendation based upon the reporting of meta-analysis on diagnostic test<sup>[24]</sup>. We based this study on thorough literature searches and careful data extraction. Nevertheless, some limitations may be considered when interpreting the results. First, study includes only four articles. The limited number of patients (n = 246) may have an effect on our study. Second, the four studies did not compare directly the diagnostic accuracy of CT fluoroscopyguided PTNB with other methods. Thus, we cannot definitively state which method is better at this time. However, studies by Rotolo et al<sup>[25]</sup> and Prosch et al<sup>[26]</sup> concluded that CT fluoroscopy systems for lung nodule biopsy are similar in terms of diagnostic performance and effective dose as cone-beam CT-guided and multislice CT systems. Finally, the publication format of four studies was English, which might resort to the so called "Tower of Babel" bias. In a word, further, larger prospective studies may be needed.

In conclusion, in spite of the difficulties mentioned above, considering the high diagnostic performance of CT fluoroscopy-guided PTNB in our study, along with the acceptable number of complications, we still have the reason to believe that this method can be recommended in clinical practice. In the end, update of systematic review and meta-analysis is possible only when further



research and data is available on this topic.

#### COMMENTS

#### Background

In recent years, as prevalence of lung cancer screening with low-dose computed tomography (CT) rises, so has the detection of pulmonary lesions that manifest as ground-glass opacity (GGO) nodules. Recently, several efforts utilizing percutaneous transthoracic needle biopsy (PTNB) under the guidance of CT fluoroscopy have been attempted to increase the diagnostic accuracy of lung GGO. Despite this, no consensus is available in the literature about whether it is beneficial to the patient.

#### **Research frontiers**

Because lung GGO is a nonspecific finding, it occurs in both malignant and benign lung lesions. Thus, the diagnosis of GGO lesions has become an important issue. Global research is directed towards an accurate and minimally invasive method for the diagnosis of lung GGO.

#### Innovations and breakthroughs

In this study, the authors investigated the value of CT fluoroscopy-guided PTNB for diagnosis of lung GGO. It is believed to be the first meta-analysis evaluating the value of CT fluoroscopy-guided PTNB for lung GGO.

#### Applications

The present study helps the authors understanding of the role of a minimally invasive technique for the diagnosis of lung GGO.

#### Peer-review

The aim of manuscript was to evaluate the value of CT fluoroscopy guided PTNB for the diagnosis of lung GGO with the use of meta-analysis method. The authors used the restrictive inclusion criteria, so only 4 manuscripts were included into analysis. Based on this they made some useful conclusions.

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  - P- Reviewer: Chiang TA, Hsu WH, Roller J, Tabarkiewicz J S- Editor: Song XX L- Editor: A E- Editor: Lu YJ







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