The relationship between lung cancer and ETS exposure

Adjustment for the potential confounding effects of multiple risk factors and for misclassification of active smoking status

Updated analyses

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EXECUTIVE SUMMARY

In 1997 Hackshaw *et al* [1] published a paper in the BMJ concluding that neither adjustment for confounding by diet nor correction for misclassification bias materially affects the observed association between ETS exposure and risk of lung cancer in lifelong nonsmokers, and concluded that breathing other people's tobacco smoke is a cause of lung cancer. In a series of five papers [2-6] published in 2000-2002 we concluded that Hackshaw *et al* [1] had severely underestimated the importance of confounding and misclassification bias and had also overstated the evidence on the strength of the dose-response relationship of lung cancer risk with the number of cigarettes smoked. We also concluded that a causal effect of ETS on risk of lung cancer had not been demonstrated.

The updated analyses presented in this report are now based on a total of 67 epidemiological studies relating ETS exposure to risk of lung cancer in nonsmokers, and on currently available evidence on the relationship of potential confounding variables to nonsmoker lung cancer risk and to ETS exposure, and on the intercorrelations between the various potential confounding variables. Compared with our previous work we have generally based all our estimates on data for females and have used random-effects analyses to summarize all the main associations. We have also considered the effect of confounding and bias not only, as previously, on the estimated increase in lung cancer risk per 10 cigarettes per day smoked by the husband, but also on the more commonly cited increase in risk associated with the husband smoking regardless of amount. We attempted to extend the list of potential confounding variables for which data were extensive or reliable enough to include in our formal adjustment procedures, but were unsuccessful and our adjustments are based on the same four variables (fruit, vegetable and dietary fat consumption, and education) as used in 2001-2002. (The report does include some results adjusted for tea drinking, but these are tentative, being based on limited data).

As summarized in the table below, our updated analyses confirm that, in nonsmoking females, both lung cancer risk and ETS exposure are significantly reduced in relation to fruit consumption, vegetable consumption and education while being increased in relation to dietary fat consumption.

		Association with lung cancer risk		Association with ETS exposure at home	
Variable	Unit[a]	N[b]	RR (95% CI)[c]	N	δ (SE)[d]
Fruit consumption	SD	14	0.86 (0.78 to 0.96)	11	-0.073 (0.020)
Vegetable consumption	SD	16	0.88 (0.80 to 0.97)	16	-0.056 (0.021)
Dietary fat consumption	SD	6	1.22 (1.09 to 1.36)	12	+0.131 (0.032)
Education	Year	12	0.91 (0.88 to 0.95)	13	-0.534 (0.063)

[a] SD = standard deviation of the variable
[b] N = number of studies on which combined estimate of association is based
[c] RR (95% CI) = relative risk in nonsmoking females (95% confidence interval) per unit of the variable
[d] δ (SE) = difference in units (standard error) of the variable between nonsmoking females exposed and unexposed to ETS at home

Taking into account confounding by all these four factors (by a procedure which allowed for intercorrelations between them and whether or not the original ETS/lung cancer risk estimates for individual studies had already been adjusted for any of them) substantially reduced the estimated association between ETS exposure and lung cancer, and correction for misclassification, using techniques similar to those used in the 2000-2002 work, reduced the association further. The table overleaf summarizes the main results of the adjustments and corrections.

Studies	N[d]	Unadjusted and uncorrected[a] RR (95% CI)[e]	Adjusted for confounding[b] RR (95% CI)[e]	Also corrected for misclassification[c] RR (95% CI)[e]
Per 10 cigs/day smoked by the husband				
All	67	1.09 (1.06 to 1.14)	1.06 (1.02 to 1.10)	1.02 (0.98 to 1.06)
USA and Canada	21	1.06 (1.01 to 1.10)	1.03 (0.98 to 1.07)	0.98 (0.93 to 1.02)
Europe	16	1.07 (1.01 to 1.14)	1.03 (0.97 to 1.10)	1.02 (0.95 to 1.09)
Asia	30	1.15 (1.07 to 1.23)	1.10 (1.03 to 1.18)	1.07 (0.99 to 1.15)
Age adjustment	55	1.06 (1.03 to 1.10)	1.03 (0.99 to 1.06)	0.99 (0.95 to 1.03)
No age adjustment[f]	12	1.28 (1.15 to 1.42)	1.23 (1.11 to 1.37)	1.19 (1.06 to 1.34)
Husband smokes				
All	67	1.21 (1.12 to 1.31)	1.14 (1.05 to 1.23)	1.06 (0.97 to 1.16)
USA and Canada	21	1.11 (1.01 to 1.22)	1.04 (0.94 to 1.14)	0.93 (0.83 to 1.03)
Europe	16	1.23 (1.05 to 1.44)	1.15 (0.97 to 1.35)	1.12 (0.94 to 1.34)
Asia	30	1.30 (1.14 to 1.48)	1.21 (1.06 to 1.39)	1.14 (0.99 to 1.33)
Age adjustment	55	1.15 (1.07 to 1.24)	1.08 (1.00 to 1.17)	1.01 (0.92 to 1.10)
No age adjustment[f]	12	1.59 (1.29 to 1.95)	1.48 (1.20 to 1.83)	1.40 (1.11 to 1.78)

[a] Unadjusted for confounding and uncorrected for misclassification of smoking habits
[b] Adjusted for confounding by fruit, vegetables and dietary fat consumption and by education
[c] Assuming an additive model, a concordance ratio of 3 and misclassification rates of 2.5% for studies in North America and Europe and 10% for studies in Asia (see section 9.2.3 for interpretation of the misclassification rates)
[d] N = number of studies of ETS and lung cancer
[e] Relative risk of lung cancer (95% confidence intervals)
[f] 12 studies presented no analyses adjusted for age and did not match nonsmoking cases and controls on age

When adjustment for confounding and correction for misclassification is carried out the association between ETS and lung cancer is no longer statistically significant, whether results from all 67 studies are considered or whether results for North America, Europe or Asia are considered separately. When attention was further restricted to those studies that had presented age-adjusted results, generally considered extremely important in epidemiology, the association, whether with husband smoking (RR 1.01, 95% CI 0.92 to 1.10) or with each 10 cigarettes per day smoked by the husband (RR 0.99, 95% CI 0.95 to 1.03), was very close to 1.0. The lack of significance and closeness of the estimates to 1.0 would not have been affected by further adjustment for ETS exposure in the reference group ("background correction"), as carried out by Hackshaw *et al* [1].

While our estimates are subject to various uncertainties, as discussed in the report, the analyses have not shown an association. If an association did exist – and one cannot prove a negative – it is likely to be much weaker than that claimed by Hackshaw *et al* [1].

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1. Background – The series of five papers

In a series of papers published between 2000 and 2002 [2-6], entitled "Revisiting the association between environmental tobacco smoke exposure and lung cancer risk", we examined in detail arguments put forward to support the claim that exposure to environmental tobacco smoke (ETS) increases the risk of lung cancer in lifelong nonsmokers.* The series of papers were produced partly in response to an analysis by Hackshaw *et al* in 1997 [1] of 37 epidemiological studies of risk in nonsmoking females according to smoking by the husband. Hackshaw *et al* [1] had obtained a relative risk (RR) by meta-analysis of the results from the 37 studies of 1.24 (95% confidence interval [CI] 1.13 to 1.36). They had adjusted this for three types of bias – due to misclassification of active smoking by the subject, confounding by diet and exposure to ETS in the reference group – and had ended up with a RR estimate of 1.26 (95% CI 1.06 to 1.47) which they took to be their best estimate of the excess risk of lung cancer in nonsmokers from all sources of ETS exposure. Taking into account evidence of risk of lung cancer from active smoking and evidence of tobacco-specific carcinogens in the blood and urine of nonsmokers exposed to ETS, Hackshaw *et al* [1] argued that their estimate provided compelling evidence that breathing other people's tobacco smoke is a cause of lung cancer.

Hackshaw *et al* [1] had also estimated that (without adjustment for the three sources of bias) the risk of lung cancer in nonsmoking females rises by 23% (95% CI 14 to 32%)† for every 10 cigarettes smoked by the husband, and much of the work in our series of papers [2-6] concerned assessing the validity of this claim and calculating the extent to which the estimate was affected by correction for bias.

1.1 Paper I

The first paper "I. The dose-response relationship with amount and duration of smoking" [2] concluded that Hackshaw *et al* [1] had overestimated the association by restricting attention to those studies that had specifically

* Referred to henceforward as nonsmokers or on occasion never smokers.
† Alternatively expressed as an RR of 1.23 (95% CI 1.14 to 1.32).

reported results by level of exposure, since such studies reported markedly higher exposed/unexposed RRs than did those studies which only reported exposed/unexposed results. Using results from both types of study, including results from some additional studies published since 1997, and also correcting confidence limits from one study [11] that had been shown [12] to be clearly erroneous and had led to substantial overweighting of its results, resulted in a lower estimate of the risk increase in lung cancer per 10 cigarettes/day smoked by the husband of 10% (95% CI 5 to 15%). This was substantially lower than the original estimate of 23% (95% CI 14 to 32%) of Hackshaw *et al* [1]. Given that men typically smoke of the order of 20 cigarettes a day (and the data generally relate to total smoking by the husband and not smoking in the presence of the wife), a lower estimate seems appropriate anyway, since a 23% increase in relation to the husband smoking 10 cigarettes/day does not align well with a 24% increase in relation to overall smoking.

1.2 Paper II

The second paper "II. Adjustment for the potential confounding effects of fruit, vegetables, dietary fat and education" [3] described the extent to which adjustment for confounding by dietary variables and education might affect the estimated increase in risk per 10 cigarettes/day. Hackshaw *et al* [1] had adjusted for a single (unclearly defined) variable of fruit/vegetable consumption but our paper considered the separate and combined effects of adjustment for four specific sources of potential confounding – fruit consumption, vegetable consumption, dietary fat consumption and education. The correction process required three types of information:

(i) estimates of the association of each potential confounding variable with lung cancer in nonsmokers,
(ii) estimates of the association of each potential confounding variable with ETS exposure in nonsmokers, and
(iii) estimates of the correlation between each pair of potential confounding variables in nonsmokers.

This was obtained by combining evidence from available studies that provided such information. There were problems in combining the data for

the association of dietary fat and education with ETS exposure in that estimates weighted on sample size were dominated by one very large study (Cancer Prevention Study = CPS II) which provided results very different from those seen in multiple other studies. Accordingly, estimates were calculated based on both unweighted means and weighted means.

Paper II [3] described the methodology developed to account for confounding by multiple correlated variables. This methodology corrects the results of each of the ETS/lung cancer studies individually, taking account of whether the RRs had already been adjusted for any of the four confounding variables. After applying the methodology, we estimated that the increase in lung cancer risk per 10 cigarettes/day smoked reduced from 10% (95% CI 5 to 15%) to 6% (1 to 11%) using unweighted means or to 9% (5 to 14%) using weighted means.

1.3 Paper III

The third paper "III. Adjustment for the biasing effect of misclassification of smoking habits" considered the effects of bias due to some of the self-reported nonsmokers actually being true current or former smokers. We used a somewhat different method of correction [13] than did Hackshaw *et al* [1] but we showed, based on exposed/unexposed (rather than dose-response) data for smoking by the husband, that the two methods produced similar results. We also noted that the bias was increased if strong evidence of much higher misclassification rates in Asian females [14-17] was taken into account, and could then explain about half the observed association. We described an approach for misclassification correction of dose-response data and applied it to data relating risk to amount smoked by the husband. We showed that the estimate of risk increase per 10 cigarettes smoked by the husband adjusted for confounding using unweighted estimates reduced, following further adjustment for misclassification bias, from 6% (95% CI 1 to 11%) to 2% (-3 to 8%). Using weighted estimates reduced the estimate adjusted only for confounding from 9% (5 to 14%) to 5.5% (0 to 11%).

1.4 Paper IV

The fourth paper "IV. Investigating heterogeneity between studies" [5] noted that there is highly significant ($p<0.001$) heterogeneity between the lung cancer risk estimates from the 47 studies considered, whether in relation to the number of cigarettes/day smoked by the husband or the exposed/unexposed risk according to whether the husband smokes. Two major conclusions emerged from these analyses. First, there was a marked tendency for risk estimates to be higher in those studies that had not adjusted or matched for age, and there was a strong case for removing such studies from meta-analyses as being of unacceptable quality. Also, as noted above, studies which reported dose-response results for smoking by the husband also reported higher risks. There was also some evidence that risk estimates tended to be lower in larger studies, in studies published in the 1990s, in studies not requiring histological confirmation of all cases, and in studies where the proportion of proxy responders was no higher in cases than in controls, though these associations were not independent. We also concluded that variation in risk by study characteristics largely explained the apparently low RR in one large Chinese study [18], arguing against the view that it is an outlier which should be excluded from meta-analyses.

1.5 Paper V

The final paper in the series "V. Overall conclusions" [6] brought together all this material and added discussion on such issues as existence of a threshold, low-dose extrapolation, publication bias, systematic differences between cases and controls, diagnostic inaccuracy, errors in determining ETS exposure, bias due to exposure to ETS in the reference group, other indices of ETS exposure, histological type of lung cancer and expression of uncertainty. The abstract of the paper [6], repeated below for convenience, summarizes our main results and arguments:

"We examine in detail arguments put forward to support the claim that exposure to environmental tobacco smoke (ETS) increases risk of lung cancer in nonsmokers. Hackshaw et al. [1] have estimated that the risk

increases by 23% (95% CI 14% to 32%) per 10 cigarettes/day smoked by the husband. The estimated increase essentially disappears if proper adjustment is made for smoking misclassification bias, if correction is made for the joint effects of confounding by fruit, vegetables, dietary fat and education, if errors in published data in one study are corrected, and if results from all pertinent studies are included (and not just those which report risk by level of smoking by the husband). Taking account of all these factors and using unweighted estimates of the association between ETS exposure and the confounding variables (as one very large study reported results discrepant from those for numerous smaller studies), the risk increase per 10 cigarettes/day was found to be 2% (95% CI -3% to +7.5%), based on data from 47 ETS/lung cancer studies. Using weighted estimates, the risk increase was 5.5% (95% CI 0% to +11%). Restricting attention to the 36 studies that had adjusted for age, the increase reduced further to -2% (95% CI -6% to +3%) using unweighted estimates, or to +1% (95% CI -4% to +6%) using weighted estimates.

These estimates are not materially affected by bias due to the reference group (nonsmokers married to nonsmokers) having some ETS exposure from other sources. Other sources of potential upward and downward bias, not formally taken account of in the analysis, are discussed.

Based on extrapolation from the known lung cancer risk in smokers, Hackshaw et al. [1] estimate that environmental tobacco smoke exposure would be expected to increase the risk of lung cancer in nonsmokers by 19%. Using more appropriate assumptions (for the relative exposure to smoke constituents of passive and active smokers, for the lung cancer risk in those who have ever smoked and for the dose-response model) leads to a much lower estimate of about 0.5%. Even this estimate is open to question as a threshold might exist for the effects of tobacco smoke constituents on lung cancer risk.

Whether or not a true risk exists, it is clear that this is not demonstrated by the overall evidence. The true increase in risk per 10 cigarettes/day smoked by the husband is very unlikely to be as large as 23%. It might be as much as 5%, but it could well be 1% or less, or even zero."

2. Objectives and differences from our earlier work

The work published in our five papers [2-6] is now somewhat out of date, being based on publications up to about 1999. One objective of the updated analyses described in the present report is to produce more recent estimates including more current papers. To this end, we have extended the literature used on the association of lung cancer with ETS exposure and the four potential confounding variables considered previously (fruit, vegetables, fat, education) and on the association of the four potential confounders with ETS and with each other. Although we have updated our misclassification-corrected estimates, we have not attempted to search for additional literature on the extent of misclassification, partly because in any event the misclassification rates assumed are based already on a quite extensive literature [24].

Another objective is to improve our estimation in various ways. One is to use, where possible, estimates based on data for females. In our original work the ETS/lung cancer data related to risk in females associated with smoking by the husband. Although we included a limited number of estimates based on studies where only results for sexes combined had been presented (see Table 1 in section 4), these were typically studies where the great majority of the lung cancer cases in nonsmokers were females. However, our estimates of associations of potential confounders with lung cancer, ETS and with each other were often derived from data ignoring gender. Given there are sufficient data specifically for females, it seems more scientific to base all our calculations, as far as possible, on data for females.

Another possible method of improving our estimation is to add to the list of potential confounding variables. With that in mind, we have reviewed evidence relating lung cancer and ETS to various other potential confounders.

In our previous work, we had used random-effects analyses to summarize data relating lung cancer to ETS and to the potential confounders. However, we had summarized differences in potential confounding variables between ETS exposed and unexposed individuals by either weighted or

unweighted means. Here we use random-effects analysis for consistency and also to avoid problems of presenting multiple answers allowing selective citation of specific results, e.g. by IARC [8]. We do, however, include some results of analyses using weighted and unweighted means to illustrate the effect the different approaches make.

Previously, our analyses correcting for the effect of confounding and misclassification bias concerned the increase in risk per 10 cigarettes/day smoked by the husband. Though we again carry out analyses for this exposure index, we also carry out analyses for the simpler index of whether the spouse smokes or not. The latter analyses should be more readily explicable to ETS researchers who are used to this traditional index.

Our previous work included extensive analyses of heterogeneity [5]. We do not report such extensive analyses here, but we do present some results separated by region, year of publication, number of lung cancer cases in the study, whether the study actually provided dose-response results, whether adjustment had been made for age, and whether the study was of case-control or prospective design.

3. Structure of the rest of the report

We start by considering the dose-response results. Section 4 presents the ETS/lung cancer data uncorrected for confounding or misclassification bias, and gives meta-analysis results. Section 5 summarizes the data relating lung cancer risk to the various potential confounders considered and presents the combined estimates of the associations used in the adjustments. Similarly, section 6 summarizes the data relating ETS to the potential confounders. Section 7 then presents some additional information needed to carry out the confounder adjustments (including the intercorrelations between the potential confounders), after which section 8 then presents confounder-adjusted risk estimates. Section 9 summarizes the basis of the misclassification correction method used and presents the results of the risk estimates adjusted for both confounding and misclassification. Section 10 then turns to the exposed/unexposed index. Following a discussion of the findings in Section 11 the results are summarized in Section 12. The tables then follow, and then the references. Additional material is presented in a series of separate appendices, each with their own reference section where required.

4. The relationship between lung cancer risk and the number of cigarettes smoked by the husband

Table 1 shows for each study the data used in the dose-response analyses relating risk of lung cancer in lifelong nonsmoking females to the number of cigarettes smoked by the husband. Data relating risk in nonsmoking men to smoking by the wife are much sparser and are not considered. Sixty-seven studies [8,11,18,26-89] are included, as compared to forty-seven in our earlier analyses [2]. The 20 studies published from 1999 onwards are additional, as is one earlier study [88]. One study included earlier [90] has been superseded by updated results published in 2000 [61]. Appendix 1 explains why results from certain other publications, which might have been thought to cite relevant data, are not included. Reasons include the results already being given in another paper or being superseded by a later publication, the study being a single centre of a multicentre study published elsewhere, no results being presented separately for lifelong nonsmokers, the control group being inappropriate (typically patients with other smoking-related diseases), and the number of lung cancer cases considered being less than five.

Of the 67 studies, the first was published in 1981 [42], with a further 24 published in the 1980s, 27 in the 1990s and 15 in the 2000s. 21 studies were conducted in the USA or Canada, 16 in Europe, 18 in China (including Hong Kong) and 12 in other parts of Asia. Ten were prospective studies and 57 case-control. The studies varied in the number of lung cancer cases in lifelong nonsmokers, with 17 involving less than 50 cases (smallest 6 cases) and five over 400 cases (largest 653 cases).

Twenty-three of the studies provided data on risk of lung cancer by the number of cigarettes per day smoked by the husband while, for the remaining 44 studies, estimates were only available for overall exposure. For most of the studies, the index of exposure used was smoking by the husband, but in some the nearest equivalent index was used (typically smoking by other household members but sometimes ETS exposure at home and/or at work [79,81,82,87], general ETS exposure [29,73,76] or urinary cotinine >9.2 ng/mg creatinine

[37]. The term "relative risk" is taken to include direct estimates of the relative risks (RRs) from prospective studies and indirect estimates (odds ratios) from case-control studies.

RRs and 95% confidence limits in Table 1 are adjusted for covariates if adjusted data are available, and otherwise are unadjusted. In 12 studies [11,31,34-37,57,58,63,72,80,82], the RRs were not adjusted for age, either directly in analysis or by matching in design. (In some of these 12 studies, the whole set of cases and controls, regardless of smoking habits, were matched on age, but the lifelong nonsmoking cases and controls were not.)

Where studies present appropriate data on numbers of cases and controls (or populations at risk) unadjusted RRs and 95% CIs are calculated, or checked using standard software [91]. Some studies reported adjusted RRs and CIs only by a level of exposure other than cigarettes per day smoked by the husband. These adjusted RRs and CIs were used to estimate corresponding "effective numbers" of cases and controls (or subjects at risk) at each level, which could then be combined to allow estimation of RRs and CIs for overall exposure, as described elsewhere [2,92]. Note that the CIs for the Geng *et al* study [11] are not the erroneously narrow ones given in the source paper but have been corrected as described elsewhere [2,12].

For the 46 studies considered earlier [2], the RRs and CIs in Table 1 are identical to those presented in Table 1 of that paper, except for the CIs for the study by Gao *et al* [41], which were found to be slightly in error and were corrected from (0.89 to 1.91) to (0.87 to 1.94).

To each RR and CI given in Table 1, a cigarettes/day midpoint is attached, using the methods and rationale described in paper I of our series [2]. Note that the number of cigarettes per day smoked by husbands in US studies is about 5 more than that smoked by husbands in non-US studies.

The final column in Table 1 contains the estimate of β, the slope of the relationship of log RR to dose (in units of 10 cigarettes per day smoked by the

husband), together with its standard error (SE). For each study, β is derived from the available RRs using the model

$$RR\ (d_2,d_1) = (\exp\ (\beta(d_2-d_1))$$

where RR (d_2,d_1) is the RR for exposure to dose d_2 compared to d_1. Where d_1 is the unexposed group ($d_1 = 0$), the RR is given by

$$RR\ (d_2,0) = \exp\ (\beta d_2) \text{ or}$$
$$\log RR\ (d_2,0) = \beta d_2$$

The method for deriving β and SE(β) is as used previously [2,93]. It takes account of the fact that a set of RRs by number of cigarettes smoked for a given study is not independent, being based on a common control group. The method requires the data to be available in the form of counts of exposed and unexposed cases and controls (or populations at risk) at each level of exposure. For a set of RRs and CIs adjusted for age or other variables, corresponding hypothetical pseudo-numbers are estimated as described elsewhere [2,92]. The ratio, Z, of β to SE(β) can be taken to be an approximate normal deviate, and can be used to assess the significance of β in an individual study.

The individual study estimates of β and SE(β) can then be combined to give overall estimates using inverse-variance weighted random-effects or fixed-effects meta-analysis [94].

Appendix 2 contains the individual study estimates of β, SE(β) and Z, as well as the counts (or pseudo-numbers), and the results of the various meta-analyses conducted. It also contains listings and distributions of various other relevant variables.

The results of the meta-analyses are summarized in Table 2. Overall, the estimated increase in risk of lung cancer per 10 cigarettes/day smoked by

the husband is equal to 8% (95% CI 5 to 11%) using fixed-effects meta-analysis or 9% (6 to 14%) using random-effects meta-analysis. The heterogeneity chisquared is 101.62 on 66 degrees of freedom ($p<0.01$). Table 2 includes meta-analyses by region, year of publication, study size, availability of specific dose-response data by cigarettes/day smoked by the husband, adjustment (or matching) for age, and study design. The most notable difference seen was the tendency for the increases to be greater ($p<0.001$) by lack of age adjustment, with the 12 studies that did not adjust for age [11,31,34-37,57,58,63,72,80,82][*] having a very high estimate of 28% (15 to 42%, random-effects), and for the increases to vary by study size, with the five studies of over 400 cases [18,27,30,40,89] showing no increase (-1%, -11% to +9%, random-effects). In each analysis, the subset that contained the Wu-Williams study [18], the only study of the 67 that showed a significantly ($p<0.05$) reduced slope (as against 10 studies [11,40,43,57,58,61,63,80,82,88] that showed a significantly increased slope), always showed significant ($p<0.01$ or $p<0.001$) heterogeneity, but other subsets did not.

In the next section we will discuss the effect of adjustment for fruit, vegetable and dietary fat consumption and for education. It should be noted however that, as summarized below, there were a very limited number of estimates that were already adjusted for diet and rather more that were adjusted for education.

Thus, the RR was adjusted for fruit consumption in six studies [39,40,51,66,81,89], for vegetable consumption in six [33,40,50,51,66,81] and for dietary fat consumption in three [33,66,81]. This includes one study [89] that adjusted for vitamin C, taken as equivalent to adjusting for fruit; one study [81] that adjusted for energy intake, taken as equivalent to adjusting for dietary fat; and one study [66] that adjusted for meat, also taken as equivalent to adjusting for dietary fat. Some other studies, e.g. [54,70] had recorded data

[*] These were studies that did not present any age-adjusted analyses. In fact in three further studies [47,54,59], while the exposed/unexposed RR estimates used in section 10 were age-adjusted, the dose-response estimates used in sections 4 to 9 were not. These three studies have been included as having age-adjusted data for consistency with earlier work [5], and in order to make the analyses by age adjustment comparable for the dose-response and exposed/unexposed RRs.

on fruits, vegetables or dietary fat, but the RRs in Table 1 were not adjusted for these.

There were 23 studies that adjusted for education [18,29,33,39-41,44,50,51,53,55,56,61,63,65,75,77,78,81,84,86,87,89], or a variable related to it, such as income, socioeconomic status or, in the case of one study [84], ownership of a colour TV.

5. The relationship between lung cancer risk and potential confounding variables

5.1 Introduction

As described in our paper II [3], the correction for potential confounding of estimates of the relationship between lung cancer risk and the number of cigarettes smoked by the husband requires *inter alia* estimates of the relationship between lung cancer risk and the various potential confounding variables considered. Paper II [3] obtained estimates of the increase in risk per standard deviation of fruit, vegetable and dietary fat consumption and of the increase in risk per year of education. Data on social class and income and on occupational exposure to specific lung carcinogens were also studied, but were much sparser and more difficult to combine and no attempt was made to correct for these.

For this report we reviewed papers published since 2000 on fruit, vegetable and dietary fat consumption and on education and also on various other potential confounding variables – air pollution, alcohol, income, obesity, occupation, physical activity and socioeconomic status. The intent was to update our estimates for fruit, vegetable and dietary fat consumption and for education and to review our original decision not to adjust for additional potential confounding variables.

Appendix 3 gives details of each paper considered as potentially relevant from our literature search. For some of the papers, it explains why useful information could not be obtained and for the others it gives details of the relevant data from which the estimate was obtained.

While data were extracted from the relevant studies for males and for sexes combined, for never and exsmokers combined, and for certain other indices of exposure, it was decided to restrict attention to data for females, for never smokers (occasionally including long-term exsmokers) and for the specific indices for which results are given in Tables 3, 5 and 7.

5.2 Fruit and vegetable consumption

Table 3 presents data relating fruit and vegetable consumption to lung cancer risk in lifelong nonsmoking females. The table shows β, the logarithm of the estimated risk increase per SD of exposure, and Z, the ratio of β to its standard error. The table corresponds to Table 1 in our paper II [3] except that some earlier results are excluded due to the restrictions discussed in the previous paragraph. There are now 16 independent estimates of β for vegetable consumption (10 of which are the same as in paper II Table 1) and 14 independent estimates of β for fruit consumption (eight of which were included previously). Five of the 16 vegetable estimates are significantly below 0 ($Z < 1.96$), as are six of the 14 fruit estimates. None are significantly increased.

Table 3 also includes estimates from two studies relating to tea drinking. While these are not enough to give a very reliable picture, and it is possible that further literature search of older papers might provide additional data, they are shown in Table 3 as they are used later in the report to give an indication of what additional effect adjustment for tea drinking might have.

Appendix 4, similar in layout to Appendix 2, gives additional results including limited meta-analyses. Table 4 summarizes relevant results for random-effects meta-analyses. The combined RR estimate of 0.88 (95% CI 0.80 to 0.97) per SD of vegetable consumption is almost identical to that used in paper II (0.88, 0.81 to 0.95). The combined RR estimate of 0.86 (0.78 to 0.96) per SD of fruit consumption is also similar to the earlier estimate (0.84, 0.76 to 0.93). As found previously, the RRs for vegetable and for fruit consumption did not vary significantly by location, and were essentially unaffected if two studies which included long-term exsmokers were excluded. For tea consumption, the combined estimate was 0.73 (0.62 to 0.86 per SD), with the suggested reduction in risk quite similar in those two studies for which data were available.

5.3 Dietary fat consumption

Table 5 presents data relating dietary fat consumption to lung cancer risk and is laid out similarly to Table 3 of this report and to Table 2 of our 2001 paper [3]. Again we exclude results for males or for sexes combined, and restrict attention to results for never smokers or never smokers plus long term exsmokers. Of the six independent estimates of β in Table 5, two are significantly above one ($Z > 1.96$) and one almost so. None are significantly decreased.

For some of the studies considered in our paper II [3] results are available for alternative exposure indices (such as cholesterol rather than saturated fat [95,96], or animal fat or plant fat rather than total fat [97]), but we selected the one in Table 5 using the same order of preference we described earlier. For the first study in Table 5 [95,96] four sets of results were presented. Although we have calculated β for each set, our corrections will be based on the one given in Table 5, with adjustment for energy made using the "multivariate nutrient density" method, considered by the study authors [96] to be the most appropriate.

Appendix 5 gives additional results as well as meta-analyses, and Table 6 summarizes the meta-analyses. The combined RR estimate of 1.22 (95% CI 1.09 to 1.36) is slightly greater than that of 1.17 (1.08 to 1.26) used in our paper II [3]. There is no significant variation by region, but the data are rather limited. The estimate is little affected by excluding the two studies which included long-term exsmokers.

5.4 Education

Table 7 presents data (similar to Table 3 of our paper II [3]) relating education to lung cancer risk. Unlike for fruit, vegetable, and dietary fat where the results are expressed per SD, risks are quantified per year of education. Again we excluded results for males and for sexes combined. Results are generally for never smokers, but we include results for never plus occasional smokers in two studies. Of the 12 estimates of β in Table 7, seven

show a significant ($Z < -1.96$) decrease in risk with increasing education, and none a significant increase.

Appendix 6 gives additional results as well as meta-analyses, and Table 8 summarizes the meta-analyses. The combined estimate of 0.91 (95% CI 0.88 to 0.95) is similar to that of 0.92 (0.89 to 0.96) used in our paper II [3]. Estimates are very similar by region and are unaffected by omitting the two studies which included results for never plus occasional smokers.

5.5 Other factors

As noted earlier, Appendix 3 reviews papers relating to a larger number of factors considered than fruit, vegetable and dietary fat consumption and education. Although we considered the possibility of including air pollution, alcohol, income, obesity, occupation, physical activity and socioeconomic factors as additional potential confounding variables to adjust for, we decided in the end not to extend the list. Reasons for this decision are given in Appendix 3.

6. The relationship between at home ETS exposure and the potential confounding variables

6.1 Introduction

We now turn to some further information required to correct for confounding estimates of the relationship between lung cancer risk and the number of cigarettes smoked by the husband, namely estimates of the difference in levels of the confounders of interest between nonsmokers who were ETS exposed and those who were not.

We reviewed apparently relevant papers published since 2000 relating ETS exposure to fruit, vegetable and dietary fat consumption and to education. Appendix 7 gives details of each paper considered as potentially relevant from our literature search, explaining why useful information could not be obtained or presenting the relevant data where it could be.

In addition to the publications considered in Appendix 7, we also looked for additional publicly available databases that could provide useful data. In our previous work [3], we had used data from the UK Health and Lifestyle Study 2 (HALS2) [98], the 1993 Health Survey for England (HSE) [99] and the unpublished Hungarian Lifestyle Survey, all the estimates being provided by J Hamling as a personal communication. Here we investigated the possibility of additional databases and were successful in obtaining useful data from two.

One was the National Health Interview Survey (NHIS) [100], a leading source of information on the civilian non-institutionalised population of the US. Although surveys have been conducted since 1960, individuals were not asked about smoking in the household in almost all of them, and since only one adult from each household was surveyed, household smoking information could not be obtained by linkage. In 2000, however, a direct question was asked which enabled one to distinguish those where someone smoked for 1-7 days per week inside the home and those where exposure was less than 1 day per week, rarely or not at all. Hence we could obtain estimates of differences between ETS exposed and non-exposed individuals for vegetable and fruit

consumption, for an estimate of dietary fat based on eating bacon, fried potatoes or chips, and for years of education.

The other publicly available source to provide useful data was the National Health and Nutrition Examination Survey III (NHANES III) [101], earlier surveys not having data on smoking within the household. NHANES III, however, included questions on cigarettes smoked in the home by household members. From this, we were able to derive estimates of differences between ETS exposed and non-exposed individuals for consumption of vegetables and fruit, for an estimate of dietary fat based on consumption of bacon, sausages, processed meats and eggs, for years of education and for regular tea drinking.

Using techniques developed for our earlier work [3], the new data from the publications and the publicly available databases were transformed to differences per SD for dietary variables or per year of education for education.

Although our initial review (Appendix 7) was more wide-ranging, the actual estimates of difference given in Tables 9, 11 and 13 are restricted to data for females and for never smokers, and to ETS exposure from the spouse or cohabitant.

In our earlier work [3], we had combined the meta-analysis estimates using either weighted or unweighted means. Here our main estimates, to be consistent with the estimates for lung cancer risk, are based on random-effects meta-analysis. However, we also present estimates based on unweighted and weighted means for comparison.

6.2 Fruit and vegetable consumption

Table 9 presents the available estimates for lifelong nonsmoking females of δ, the difference (in SDs) in fruit, vegetable or tea consumption associated with ETS exposure at home. Table 9 also presents the number of females exposed (N_e) or unexposed (N_u) to ETS at home. The table

corresponds to Table 4 in our paper II [3] except that results for males have been excluded. There are now 16 independent estimates of δ for vegetable consumption (12 of which were included previously) and 11 independent estimates of δ for fruit consumption (seven of which were included previously). Within the estimates for vegetable consumption 11 were negative and five were positive, while for fruit consumption only one estimate was positive, that from Italy [102], while the other 10 were negative. The study sizes on which the estimate were based varied considerably, especially between those of the very large prospective cohort studies of Cardenas and Hirayama and the small case control studies reported by Koo.

Table 9 also includes five independent estimates for tea drinking, used later in the report in our additional analyses to see what additional effect adjustment for tea drinking might have. All five of these estimates were negative, though the estimates for Europe were all greater than the one obtained from the US. Note that here all the data come from public databases, and the study sizes are reasonably comparable.

As shown in more detail in Appendix 8 and summarized in Table 10, various combined estimates were calculated:

(a) unweighted for study sizes,
(b) weighted on the combined sample size, $N_u + N_e$, or
(c) using random-effects analysis, using weights which were the inverse of the variance. The variance was estimated as $\sigma^2 ((1/N_u) + (1/N_e))$ where σ is 1 for the dietary variables and is estimated as 2.435 years for education (Appendix 9).

The estimates from the random-effects models of the differences for vegetables and for fruit are quite similar for the USA and Europe, with values of -0.0866 and -0.0892 for vegetables and -0.0862 and -0.0581 for fruit respectively. The estimates for the Asian studies of +0.0185 for vegetables and –0.1661 for fruit were less similar, but they have larger standard errors and are

not significantly different from the results for the USA and Europe. We will take the overall values of -0.0559, -0.0733 and -0.0655 for vegetables, fruit and tea respectively for our main analyses.

6.3 Dietary fat consumption

Table 11 presents estimates of δ for dietary fat consumption, together with the associated values of N_u and N_e. These estimates are all for lifelong nonsmoking females, and only those estimates for the most appropriate index of fat have been included. See Table 5 of our paper II [3] for estimates of δ using alternative indices (e.g. don't use low fat spread rather than fried foods for HALS2 and HSE93). One estimate previously included in Table 5 of our paper II [3] based on an analysis of NHANES III by Butler [103] is not now included as it is superseded by our own analysis.

There are now 12 estimates of δ for dietary fat. 10 of these are positive with only that based on the very large CPS II study [33] and the Italian study [102] being negative. Results of various combined analyses are given in Table 12, with further detail in Appendix 10. Because of the very large size of the CPS II study we get very different results depending on the type of model used. Thus when using all the studies we see estimates ranging from 0.2089 when using unweighted analysis to 0.0001 when using simple weighted analysis, with the random-effects model giving us an estimate lying between these of 0.1310. As the random-effects models are being used throughout our analyses this is the main value we will use in our subsequent work. The random-effects estimates are similar for USA (0.1188) and Europe (0.1302). The single estimate from Asia is rather higher (0.3532).

6.4 Education

Table 13 presents the estimates of δ for education (here expressed in years rather than SDs), together with the associated values of N_u and N_e. Again, the estimates are all for lifelong nonsmoking females. Table 6 of our paper II [3] previously included results from the Butler analysis of NHANES III [103] but we exclude that now to avoid overlap with our own analysis.

There are now 13 estimates of δ for education. All of them show less years of education in the ETS exposed females. This was also true for our previous analysis, though an association in the opposite direction was noted for men in the very large CPS II study [33]. Results of combined analyses are given in Table 14, with further detail in Appendix 11.

The overall random-effects estimate is –0.5337 and estimates for the USA (-0.6083), Europe (-0.4752) and Asia (-0.5000) are all consistent with this. Bearing in mind the quite small standard error of the random-effects estimate, the data are quite consistent in showing that nonsmokers with ETS exposure at home have about half a year less education on average than do unexposed nonsmokers.

(Note that the estimate given for the Thornton study [104] shown in Table 13 differs from that given in Table 6 of our paper II [3]. This was due to an error in presenting Table 6, and the correct estimate, as used in our analyses then and now, is that shown in Table 13.)

7. Additional information required to carry out the adjustment for confounding

7.1 The method for confounder adjustment

It is helpful to repeat the part of our earlier paper [3] which describes the method:

"Suppose that lung cancer risk, L, is related to n factors x_1, x_2 …x_n by the linear equation

$$\log L = \beta_0^* + \sum_i^n \beta_i^* x_i$$

where exp (β_0^*) is the expected background risk in someone with zero exposure to each factor and exp (β_i^*) is the expected multiplication in risk associated with a unit increase in exposure to factor i.

Suppose that, instead of having direct estimates of β_i^*, data relating lung cancer risk to the factors are only available on a univariate basis, i.e. assuming that the relationship can be described by the equation

$$\log L = \beta_0 + \beta_i x_i$$

Here, exp (β_i) is the observed relative risk associated with a unit increase in dose of the factor unadjusted for other risk factors.

Now it can be readily be demonstrated that, provided log L is normally distributed, the β_i and the β_i^* are related by the matrix equation

$$\underline{B}^* = S^{-1}C^{-1}S\underline{B}$$

where $\underline{B}^*$ and $\underline{B}$ are the n x 1 column vectors of, respectively, β_i^* and β_i, S is the diagonal n x n matrix of the standard deviations of the factors s_i and C is the n x n matrix of correlations of the risk factors c_{ij}.

Assuming data on $\underline{B}$, C and S can be obtained, this gives a method for estimating $\underline{B}^*$. In our principal context there would be n = 5 factors, with i = 1 representing the factor ETS exposure, and i = 2, 3, 4 and 5 representing, respectively, fruit, vegetables, dietary fat and education. Exp (β_1) would be the unadjusted increase in risk associated with unit increase in ETS exposure (e.g. per 10 cigarettes/day smoked by the husband) and exp (β_i^*) would be the increase adjusted for the other four factors, so that the joint confounding effect would be estimated as $\exp(\beta_1)/\exp(\beta_i^*)$."

7.2 Availability of the relevant data

7.2.1 *Relationships of lung cancer risk to the factors (β_i)*

Estimates for each study of β_1, which quantifies the relationship of lung cancer to the number of cigarettes smoked by the husband (in units of 10 cigarettes/day), are generally those given in table 1 (as β). However, the method assumes that β_1 is an estimate of the relationship unadjusted for any of the other risk factors of interest which, as discussed in section 4, and as is clear from pages A-3 and A-4 of Appendix 2, is not always so. Where the estimates were already adjusted for one or more of the risk factors, the β_1 values were first back-corrected to remove the effect of the adjustment (and avoid erroneous double-adjustment) as described earlier [3].

Based on the data (for all studies given in Appendices 4, 5 and 6), we used the following estimates of β_2 to β_5:

β_2	Fruit	-0.1452	(14 studies)
β_3	Vegetables	-0.1264	(16 studies)
β_4	Dietary fat	+0.1960	(6 studies)

	β_5	Education	-0.0917	(12 studies)
[Also	β_6	Tea	-0.3112	(2 studies)]

These correspond to relative risks, respectively, of 0.86, 0.88, 1.22 and 0.91 [and 0.73] as given in Tables 4, 6 and 8.

7.2.2 *Standard deviations (s_i)*

s_1, the SD for the ETS variable, can be estimated directly for each study (in units of 10 cigarettes/day smoked by the husband) from the data for controls by level of exposure given in Appendix 2, as discussed in our paper I [2].

The SDs for the dietary variables, s_2, s_3 and s_4 [and s_6] are equal to 1 as they are measured in SDs.

The SD for education is taken as 2.435 years (see section 6.2 and Appendix 9).

7.2.3 *Correlations (c_{ij})*

Clearly, when i = j, $c_{ij} = 1$.

When quantifying the association between ETS exposure and the other risk factors (c_{12} ... c_{16}) we have derived (see tables 10, 12 and 14) combined estimates of δ_j, the difference in exposure to risk factor j associated with living with a smoker:

	δ_2	Fruit	-0.0733	(11 studies)
	δ_3	Vegetables	-0.0559	(16 studies)
	δ_4	Dietary fat	+0.1310	(12 studies)
	δ_5	Education	-0.5337	(13 studies)
[Also	δ_6	Tea	-0.0655	(5 studies)]

The variables δ_j and c_{1j} are related by the formula

$$c_{1j} = \delta_j s_1/(\bar{d}_1 s_j)$$

where $\bar{d}_1$ is the mean ETS exposure for exposed never smokers (see section 7.3 below). c_{1j} was derived separately for each study using a common estimate of δ_j and study-specific estimates of $\bar{d}_1$ and s_1.

When quantifying the correlations between the potential confounding variables, we used the data described below (in section 7.4).

7.3 Mean ETS exposure for exposed never smokers

For each study, Table 1 gives the mean exposure in cigarettes/day by level of exposure. For studies with only one level of exposure, this is (when divided by 10) the estimate of $\bar{d}_1$. For studies with more than one level of exposure, $\bar{d}_1$ is estimated by weighting the exposures by level by the corresponding numbers of exposed controls.

7.4 Intercorrelations between the potential confounding factors

Appendix 12 presents data from seven studies, four conducted in the UK (HALS, HALS2, HSE93, HSE94), one in Hungary (HULS) and two in the USA (NHIS2000, NHANES III). Averaging the data over the seven studies for females, we have the following correlations:

	Fruit	Vegetables	Dietary fat	Education	Tea
Fruit	1 (c_{22})	+0.3136 (c_{23})	-0.1036 (c_{24})	+0.1428 (c_{25})	-0.0074 (c_{26})
Vegetables		1 (c_{33})	-0.0538 (c_{34})	+0.1303 (c_{35})	+0.0399 (c_{36})
Dietary fat			1 (c_{44})	-0.0393 (c_{45})	+0.0254 (c_{46})
Education				1 (c_{55})	-0.0521 (c_{56})
Tea					1 (c_{66})

8. Confounder-corrected estimates of the relationship between lung cancer risk and number of cigarettes smoked by the husband

8.1 Results

Table 15 shows the results of simultaneous adjustment for fruit, vegetables, dietary fat and education. When the study-specific estimates of δ given in Tables 9, 11 and 13 were combined by random-effects analysis into a single mean, the unadjusted estimate of the increase in lung cancer risk per 10 cigarettes/day smoked by the husband was reduced from 1.095 (95% CI 1.055 to 1.136) to 1.057 (1.018 to 1.097). This suggests that uncontrolled confounding by the four risk factors biased the estimated increase upward by 1.095/1.057 = 1.036, or equivalently that about 40% of the observed excess risk may be due to confounding by these four variables alone.

Using unweighted rather than random-effects means of δ increased the estimated bias from 1.036 to 1.095/1.048 = 1.044, while using weighted means decreased it to 1.095/1.076 = 1.018.

Table 15 also breaks down the analyses into subgroups of region, date published, numbers of cases used, whether or not dose response data was used, whether age adjustment was used and whether the studies were case-control or prospective. The results for USA and Canada and for Europe were quite similar and neither of these was significant after correcting for the confounding, giving a combined value of 1.03 (0.99 to 1.06). The results for Asia were higher both for China and for the rest of Asia, with the combined result being marginally significant at 1.10 (1.03 to 1.18). There was evidence that estimates were: larger in the studies published in the 1980s than in those published later; lower in studies with large numbers of cases; larger for studies with dose response data than for those without; and lower for studies where age adjustment had been carried out than for those with no age adjustment (1.03 versus 1.23). There seemed to be no difference between the case control and the prospective studies.

Fuller details of the data used and results summarized in Table 15, including the effects of adjustment in individual studies, are given in Appendix 13.

Table 16 gives more details of the analysis showing how the estimate of the increase in risk per 10 cigarettes/day smoked by the husband varied following adjustment for only one of the four factors (fruit, vegetables, dietary fat and education), for tea drinking on its own and for all five factors. Also shown are the bias estimates. Results are shown overall and also separately for USA, Canada and Europe combined and for Asia. All the estimates are based on the same common random-effects combined estimates of δ for all studies given in Tables 10, 12 and 14.

The biggest effects were seen when the effects of education were controlled for. It was responsible for a bias correction of 1.024 on its own. Dietary fat and tea could account for about half this amount of bias when taken on their own, with fruit and vegetables having only about a quarter of the effect of education, with fruit correcting for a bias of 1.005 and vegetables of 1.004. When the four main confounding variables were taken together, the combined bias corrected for was 1.038. Adding in the effect of tea increased the bias corrected for to 1.052, resulting in an overall estimate that was now only on the borderline of significance – 1.043 (1.004 to 1.083).

Fuller details of the results relating to the findings summarised in Table 16 are given in Appendix 14.

8.2 Discussion

There are a number of sources of uncertainty in our adjusted estimates of the relationship of lung cancer risk to the number of cigarettes/day smoked by the husband (β_1^*). These include:

(i) lack of data specific for each study to allow estimation of the required elements of B, S and C to correct the unadjusted relationship, β_1, so

that estimates combined from those (usually separate) studies which did have relevant data had to be used instead;

(ii) uncertainties in the method of obtaining the combined estimates from the individual studies, especially where the available study estimates vary markedly;

(iii) statistical variability in these combined estimates, not reflected in the 95% CI of the adjusted estimates which essentially reflect the variability of the unadjusted estimates of β_1; and

(iv) failure to take into account other possibly relevant sources of confounding (e.g. occupation).

These are discussed further in our 2001 paper [3]. Nevertheless, we feel that the restriction of data specifically to females, and the use of random-effects analysis to combine estimates of δ for the confounding variables, has improved our original work. Taking into account the fact that the associations of fruit, vegetables, dietary fat and education with both lung cancer risk and with ETS exposure are generally statistically significant and quite consistent, we feel that the results presented in Tables 15 and 16 are a reasonable indication of the extent of bias arising from failure to adjust for these factors.

As noted in our earlier paper [3], the direct evidence available from those epidemiological studies of ETS and lung cancer that have presented results by varying extent of adjustment for confounding is of very limited value, and does not rule out the possibility of relevant uncontrolled confounding existing by fruit, vegetables, dietary fat or education.

9. Adjustment for bias due to misclassification of smoking habits

9.1 Introduction

Studies of the potential effects of environmental tobacco smoke (ETS) on lung cancer risk usually compare risk in never smoking females according to whether or not the husband smokes. If in fact a proportion of the females are actually current or exsmokers, bias may result. While random errors in determining exposure typically tend to dilute any true relationships, random errors in misclassifying ever smokers as never smokers tend to increase the observed association between lung cancer risk and smoking by the spouse. This 'misclassification bias' arises because smokers tend to be more likely to marry smokers than would be expected by chance, so that misclassified smokers are likely to be more frequent among those with a spouse who smokes. The size of the misclassification bias depends mainly on the following parameters – the misclassification rate, the excess risk associated with active smoking, the degree of smoking concordance between husband and wife, and the true proportions of subjects and of spouses who smoke [13].

Our paper [4] described in detail two methods for bias correction, the 'Hackshaw method' and the 'Lee and Forey method'. We showed that the choice of method was not crucial, but the choice of misclassification rates was, noting that the original analysis by Hackshaw *et al* [1] did not, but should have, taken into account strong evidence of much higher misclassification rates in Asian females. Our paper described an extension of the Lee and Forey method to apply the correction to data relating risk to the number of cigarettes/day smoked by the husband. It also presented a variety of results using differing misclassification rate estimates and values of other parameters required for the analysis. For the purpose of the current work, we have used the extended method and have restricted attention to what we regarded as the most appropriate model parameters, and have used the same methods as described earlier [4]. Apart from input of some data specific to the new studies (see section 9.2), and starting with different confounder-adjusted estimates of risk associated with smoking by the husband, there are no differences from what we did previously.

9.2 Assumptions

9.2.1 *Model*

We use an additive rather than a multiplicative model for the joint effects of active smoking and ETS exposure.

9.2.2 *Concordance ratio*

The concordance (or aggregation) ratio expresses the tendency for husbands and wives to have similar smoking habits. It is the ratio of the odds of the husband smoking given the wife ever smoked to the odds of the husband smoking given the wife never smoked. Here we use an estimate of 3.0 based on an earlier review [105].

9.2.3 *Misclassification rates*

Both the Hackshaw method and the Lee and Forey method take into account the fact that misclassified smokers tend to have lower lung cancer risks than do non-misclassified smokers [4]. In the Hackshaw method, this is achieved by inclusion of a parameter which represents the risk for *misclassified* ever smokers (relative to all reported never smokers), the value taken for it being substantially less than typically observed for the ever/never smoking relative risk. In the Lee and Forey method, the actual ever/never smoking relative risk is used, but a lower misclassification rate. The lower rate is than interpreted as the proportion of *average risk* ever smokers denying smoking that would produce equivalent bias. In other words, although the actual misclassification rate is higher than this, the below average risk of misclassified smokers is taken into account by assuming a lower misclassification rate.

Here we used a misclassification rate of 2.5% for North American and European studies and of 10.0% for Asian studies. The interested reader can refer to our paper III [4] and to various papers cited there [13,17,105,106] and to reasons why we believe that the claim of Hackshaw *et al* [107] that the misclassification rates for Asian females are “implausibly high” is based on a specious argument. In fact, 10.0% seems to be quite a conservative estimate given the available data [17].

9.2.4 *Study-specific data on active smoking RRs*

The Lee and Forey method requires an estimate of the ever smoking/never smoking RR for each of the studies included. Table 17 shows these estimates as well as giving information on the percentage of smokers among controls, required by the Hackshaw method. As explained in the table, which corresponds in part to Table 1 of our paper III [4], some of these data were not available directly from the source paper and had to be estimated by other means.

9.3 Results

Table 18 shows the results of the meta-analyses corrected for misclassification and confounding by fruit, vegetables, dietary fat and education, comparing them with the results (previously shown in Table 15) adjusted for confounding only, and showing the bias by failing to correct for misclassification.

The overall result is now non-significant, with the estimate being 1.020 (0.979 to 1.063). Although estimates are somewhat higher for Asia (1.067, 0.988 to 1.151) than for the US, Canada and Europe (0.989, 0.952 to 1.027), neither are significant. Studies published in the 1980s still show effects that are significant, as do studies that are without age adjustment, but the more up-to-date studies and studies which adjust for age show no significant effect, with the estimate for age adjusted studies at 0.990 (0.952 to 1.029).

Fuller details of the results (including those adjusted for specific confounding variables) are shown in Appendices 15 and 16 corresponding to Appendices 13 and 14 which are uncorrected for misclassification.

10. The effect of adjustment for confounding and correction for misclassification on the exposed/unexposed lung cancer relative risk

10.1 Introduction

So far, we have followed most of our previous work [2-4] in concentrating mainly on the effect of adjustment for confounding and correction for misclassification on the estimated relative risk per 10 cigarettes/day smoked by the husband. The same methodology can also be applied to the simple relative risk according to whether the husband smokes or not, as demonstrated in this section.

10.2 Relative risk estimates

The exposed/unexposed ETS risk estimates in Table 19 correspond to the dose-response ETS risk estimates in Table 1. The RR estimates are the same as in Table 1 for the studies which only have results by level of exposure and are only different for the other studies. We have entered a dose level of 1 to represent the effect of the exposure to ETS by a spouse for all studies. This compares to the value of around 2 which was used in the previous work as beta there referred to the increase in risk from 10 cigarettes and the average number of cigarettes smoked is around 20 cigarettes per day. The betas and their standard errors are therefore around twice the value we had in the dose response work, thus increasing the estimates of RR and the 95% confidence limits accordingly.

10.3 Results

Table 20 presents the results of various meta-analyses of the risk of lung cancer according to whether the spouse smokes. Three sets of analyses are shown:

(a) unadjusted for confounding and uncorrected for misclassification,

(b) adjusted for confounding only, and

(c) adjusted for confounding and corrected for misclassification. Fuller details of these analyses are shown in Appendices 17, 18 and 19.

The results are essentially the same as seen for the dose-response analysis, except that the estimates of beta and standard errors of beta are

approximately twice as large. Thus the estimates of RR across all 67 studies now starts at a quite significant value of 1.215 (1.124 to 1.313), the excess then decreases by 37% to 1.136 (1.050 to 1.230) when allowing for the confounding by fruit, vegetables, dietary fat and education, and then decreases by another 53% to a non-significant value of 1.064 (0.974 to 1.161) when misclassification is corrected for. Values for USA, Canada and Europe reduce from 1.149 (1.059 to 1.247) to a non-significant 1.074 (0.986 to 1.169) allowing for the multiple confounders and then to 0.998 (0.905 to 1.100) when misclassification is corrected for. The estimate for studies that had age adjustment had a much lower value than those that had no such adjustment, 1.152 compared to 1.585. Their estimate was also non-significant when the multiple confounders were allowed for and was almost exactly 1 (1.008) when misclassification was corrected for. There was still evidence that studies published early had larger estimates than the later studies, and that studies with very large numbers of cases had a very low estimate of risk – 0.848 (0.663 to 1.086) where more than 400 cases were seen.

11. Discussion

11.1 Background

In their 1997 paper, Hackshaw *et al* [1] found a significantly increased risk of lung cancer in nonsmokers who lived with a smoker, considered that neither adjustment for confounding nor correction for misclassification bias had a material effect, and noted a significant dose-response relationship of lung cancer risk with the number of cigarettes smoked by the spouse. Based on these findings, and the supporting evidence of tobacco specific carcinogens in the blood and urine of ETS-exposed nonsmokers, they regarded it as compellingly demonstrated that breathing other people's tobacco smoke is a cause of lung cancer.

In our series of five papers [2-6] published in 2000-2002, we concluded that Hackshaw *et al* [1]:

(i) overstated the strength of the dose-response relationship of lung cancer risk with the number of cigarettes smoked by the spouse because they failed to consider studies which reported results only as exposed/unexposed and because the results from one study [11] were considerably overweighted;

(ii) underestimated the misclassification bias, by failing to account for the demonstrated high misclassification rates in Asian women [11]; and

(iii) inadequately considered confounding, by limiting attention only to fruit and vegetable consumption as potential confounding variables.

The original work of Hackshaw *et al* [1] only considered the effects of bias from misclassification or confounding on the simple association between lung cancer and whether or not the spouse smoked. They did not consider the effects such biases might have on the dose-response relationship.

The work we published in 2000-2002 [2-6], on the other hand, was mainly concerned with the effect adjustment for bias had on the dose-response relationship. Hackshaw *et al* [1] had estimated that the risk increases by 23% (95% CI 14-32%) per 10 cigarettes/day smoked by the husband. The various estimates we calculated were substantially less than this (see section 1.1.5) and

we concluded that a true risk is not demonstrated by the overall evidence, stating that "the true increase in risk per 10 cigarettes/day smoked by the husband is very unlikely to be as large as 23%. It might be as much as 5%, but it could well be 1% or less, or even zero."

The work we present here had a number of objectives:

1) To update the evidence on the association of lung cancer with ETS exposure and with the four potential confounding variables considered previously (fruit, vegetables, fat and education) and on the association of the four potential confounders with ETS and with each other.

2) If possible, to add to the list of potential confounding variables considered previously (fruit, vegetables, fat and education).

3) Where possible, to base estimates of the associations investigated on data for females. In our earlier work [3], estimates of the associations of potential confounders with lung cancer, with ETS and with each other were often derived from data ignoring gender.

4) Use random-effects analyses to summarize data relating to all the main associations. Previously [3], though we had used random-effects analyses to summarise data relating lung cancer to ETS and to the potential confounding variables, we had summarized differences in potential confounding variables between ETS exposed and unexposed individuals by either weighted or unweighted means, which was inconsistent and led to selective citation of results (see section 1.2.2).

5) To carry out analyses adjusting for confounding and correcting for misclassification bias not only, as before, on the estimated increase in risk per 10 cigarettes/day smoked by the husband, but also on the estimated increase in risk associated with smoking by the husband.

These objectives have largely been achieved, though we were unable to find any additional potential confounding variables for which data were extensive or reliable enough to include in our formal adjustment procedures.

(We do present some results adjusted for tea drinking, but these should only be regarded as tentative, being based on very limited data.)

11.2 Findings

The results in section 5 (Tables 3-8) confirmed that, in nonsmoking females, lung cancer risk is reduced in relation to fruit consumption (by a factor of 0.86 per SD, 95% CI 0.78 to 0.96), vegetable consumption (0.88 per SD, 95% CI 0.80 to 0.97), education (0.91 per year, 95% CI 0.88 to 0.95), and increased in relation to dietary fat consumption (1.22 per SD, 95% CI 1.09 to 1.36). Lung cancer risk was also reduced in relation to tea consumption (0.73 per SD, 95% CI 0.62 to 0.86), though this was based on only two studies.

The results in section 6 (Tables 9-14) also confirmed that, in nonsmoking females, ETS exposure at home is associated with decreased fruit consumption (-0.073 SDs), vegetable consumption (-0.056 SDs), education (-0.534 years), and increased dietary fat consumption (+0.131 SDs). Tea drinking was associated with a decrease of -0.066 SDs.

Taking into account confounding by all these four factors (by a procedure which allowed for intercorrelations between them and whether or not the original ETS/lung cancer risk estimates for individual studies had already been adjusted for any of them) substantially reduced the estimated association between ETS exposure and lung cancer. Fuller details are given in tables 15 and 20 for subsets of the data, but for all 67 studies the main findings are as follows:

	Unadjusted	Adjusted*
	RR (95% CI)	RR (95% CI)
Husband smokes	**1.214 (1.123 to 1.313)**	**1.136 (1.049 to 1.229)**
Per 10 cigs/day	**1.095 (1.055 to 1.136)**	**1.057 (1.018 to 1.097)**

* For fruit, vegetable and dietary fat consumption, and for education

In both analyses, adjustment explained about 40% of the excess risk.

Further correction for misclassification (see Tables 18 and 20 for fuller details) reduced the confounder-adjusted estimates further to non-significant levels.

	Uncorrected	Corrected*
	RR (9% CI)	RR (95% CI)
Husband smokes	**1.136 (1.049 to 1.229)**	**1.064 (0.975 to 1.162)**
Per 10 cigs/day	**1.057 (1.018 to 1.097)**	**1.020 (0.979 to 1.063)**

* Assuming an additive model, a concordance ratio of 3 and misclassification rates of 2.5% for studies in North America and Europe and 10% for studies in Asia

The results for USA, Canada and Europe showed a non-significant estimate of risk when the multiple confounders were allowed for, 1.074 (0.986 to 1.168) for husband smoking and 1.026 (0.992 to 1.061) for 10 cigs/day. This turned into a risk estimate of almost exactly 1 when misclassification was also allowed for, with estimates of 0.998 (0.905 to 1.100) for husband smoking and 0.989 (0.952 to 1.027) for 10 cigs/day.

Similarly, the results restricted to those studies which allowed for age-adjustment showed a non-significant estimate of risk when the multiple confounders were allowed for, 1.077 (0.995 to 1.165) for husband smoking and 1.026 (0.991 to 1.063) for 10 cigs/day. This too turned into a risk estimate of almost exactly 1 when misclassification was also allowed for, with estimates of 1.008 (0.923 to 1.101) for husband smoking and 0.990 (0.952 to 1.029) for 10 cigs/day.

11.3 Interpretation

Uncertainties in relation to our adjustment for confounding have been discussed earlier in section 8.2, while issues relating to adjustment for misclassification bias are no different from before and were discussed earlier [4,6].

One important point to note is that, whereas Hackshaw *et al* [1] adjusted for ETS exposure in the reference group ("background correction"), we have not done so. There are good reasons for this. Firstly, background correction makes no sense in the context of estimation of risk per cigarette/day smoked by the spouse. Second, while it is possible to correct estimates of risk of a nonsmoker with a smoking spouse calculated relative to that of a nonsmoker with a nonsmoking spouse so that they are calculated relative to a nonsmoker completely unexposed to ETS, this only seems appropriate when the original estimate of risk is significant. Third, even if one were to make such a correction, the effect would only be small. Assuming, as did Hackshaw *et al* [1], that total ETS exposure is three times higher in a nonsmoking female if married to a smoker, background correction would only increase RRs in the range 1.01 to 1.05 by a factor of about 1.5 (to 1.015 to 1.075) and would not affect the interpretation.*

All our analyses have been based on the available published data, with no attempt to take into account the possibility that studies showing stronger relationships may be more likely to be published. A number of attempts have been made to adjust the ETS/lung cancer data for publication bias [108-112] which are generally consistent in suggesting that the published evidence may overstate the association somewhat. However, there is no consensus on what is an appropriate method for adjustment, and there is recognition that many strong and largely untestable assumptions are often made, and that many approaches have shortcomings [113-115]. In any event, it seems unlikely that failure to publish has led to any underestimation of the true association.

* If Z is the ratio of cotinine in nonsmokers married to smokers compared to nonsmokers married to nonsmokers, the background corrected RR is RR(Z-1) / (Z-RR) [6].

Other potential sources of bias include recall bias (with knowledge of disease by patients in cases and controls affecting their reported answers on ETS exposure), systematic differences between cases and controls (e.g. cases interviewed in hospital, controls interviewed at home, or data obtained from next-of-kin more for cases than controls) and diagnostic inaccuracy. These have been discussed earlier [6], and seem unlikely to alter the interpretation of a lack of association of ETS with lung cancer risk once confounding and misclassification of active smoking are taken account of.

We have also discussed earlier [6] the argument put forward by Hackshaw *et al* [1] that extrapolation from the known lung cancer risk in smokers would lead one to expect a 19% increased risk of lung cancer in ETS exposed nonsmokers. Using more appropriate assumptions (for the relative exposure to smoke constituents of passive and active smokers, for the lung cancer risk in those who have ever smoked, and for the dose-response model) leads to a much lower estimate of about 0.5%. Even this estimate, equivalent to a RR of 1.005, is open to question as a threshold might exist for the effects of tobacco smoke constituents on lung cancer risk [6].

While our analyses are clearly affected by considerable uncertainties, they do allow conclusions to be reached. We certainly do not share the views of Hackshaw *et al* [1] that the evidence "provides compelling confirmation that breathing other people's tobacco smoke is a cause of lung cancer." Our detailed assessment shows that an association has *not* been demonstrated. Such an association might exist, but if so is likely to be far weaker than that claimed by Hackshaw *et al* [1].

12. Summary

In 1997 Hackshaw *et al* [1] published a paper in the BMJ concluding that neither adjustment for confounding by diet nor correction for misclassification bias materially affects the observed association between ETS exposure and risk of lung cancer in lifelong nonsmokers, and concluded that breathing other people's tobacco smoke is a cause of lung cancer. In a series of five papers [2-6] published in 2000-2002 we concluded that Hackshaw *et al* [1] had severely underestimated the importance of confounding and misclassification bias and had also overstated the evidence on the strength of the dose-response relationship of lung cancer risk with the number of cigarettes smoked. We also concluded that a causal effect of ETS on risk of lung cancer had not been demonstrated.

The updated analyses presented in this report are now based on a total of 67 epidemiological studies relating ETS exposure to risk of lung cancer in nonsmokers, and on currently available evidence on the relationship of potential confounding variables to nonsmoker lung cancer risk and to ETS exposure and on the intercorrelations between the various potential confounding variables. Compared with our previous work we have generally based all our estimates on data for females and have used random-effects analyses to summarize all the main associations. We have also considered the effect of confounding and bias not only, as previously, on the estimated increase in lung cancer risk per 10 cigarettes per day smoked by the husband, but also on the more commonly cited increase in risk associated with the husband smoking regardless of amount. We attempted to extend the list of potential confounding variables for which data were extensive or reliable enough to include in our formal adjustment procedures, but were unsuccessful and our adjustments are based on the same four variables (fruit, vegetable and dietary fat consumption, and education) as used in 2001-2002. (The report does include some results adjusted for tea drinking, but these are tentative, being based on limited data).

As summarized in the table below, our updated analyses confirm that, in nonsmoking females, both lung cancer risk and ETS exposure are

significantly reduced in relation to fruit consumption, vegetable consumption and education while being increased in relation to dietary fat consumption.

		Association with lung cancer risk		Association with ETS exposure at home	
Variable	Unit[a]	N[b]	RR (95% CI)[c]	N	δ (SE)[d]
Fruit consumption	SD	14	0.86 (0.78 to 0.96)	11	-0.073 (0.020)
Vegetable consumption	SD	16	0.88 (0.80 to 0.97)	16	-0.056 (0.021)
Dietary fat consumption	SD	6	1.22 (1.09 to 1.36)	12	+0.131 (0.032)
Education	Year	12	0.91 (0.88 to 0.95)	13	-0.534 (0.063)

[a] SD = standard deviation of the variable
[b] N = number of studies on which combined estimate of association is based
[c] RR (95% CI) = relative risk in nonsmoking females (95% confidence interval) per unit of the variable
[d] δ (SE) = difference in units (standard error) of the variable between nonsmoking females exposed and unexposed to ETS at home

Taking into account confounding by all these four factors (by a procedure which allowed for intercorrelations between them and whether or not the original ETS/lung cancer risk estimates for individual studies had already been adjusted for any of them) substantially reduced the estimated association between ETS exposure and lung cancer, and correction for misclassification, using techniques similar to those used in the 2000-2002 work, reduced the association further. The table overleaf summarizes the main results of the adjustments and corrections.

Studies	N[d]	Unadjusted and uncorrected[a] RR (95% CI)[e]	Adjusted for confounding[b] RR (95% CI)[e]	Also corrected for misclassification[c] RR (95% CI)[e]
Per 10 cigs/day smoked by the husband				
All	67	1.09 (1.06 to 1.14)	1.06 (1.02 to 1.10)	1.02 (0.98 to 1.06)
USA and Canada	21	1.06 (1.01 to 1.10)	1.03 (0.98 to 1.07)	0.98 (0.93 to 1.02)
Europe	16	1.07 (1.01 to 1.14)	1.03 (0.97 to 1.10)	1.02 (0.95 to 1.09)
Asia	30	1.15 (1.07 to 1.23)	1.10 (1.03 to 1.18)	1.07 (0.99 to 1.15)
Age adjustment	55	1.06 (1.03 to 1.10)	1.03 (0.99 to 1.06)	0.99 (0.95 to 1.03)
No age adjustment[f]	12	1.28 (1.15 to 1.42)	1.23 (1.11 to 1.37)	1.19 (1.06 to 1.34)
Husband smokes				
All	67	1.21 (1.12 to 1.31)	1.14 (1.05 to 1.23)	1.06 (0.97 to 1.16)
USA and Canada	21	1.11 (1.01 to 1.22)	1.04 (0.94 to 1.14)	0.93 (0.83 to 1.03)
Europe	16	1.23 (1.05 to 1.44)	1.15 (0.97 to 1.35)	1.12 (0.94 to 1.34)
Asia	30	1.30 (1.14 to 1.48)	1.21 (1.06 to 1.39)	1.14 (0.99 to 1.33)
Age adjustment	55	1.15 (1.07 to 1.24)	1.08 (1.00 to 1.17)	1.01 (0.92 to 1.10)
No age adjustment[f]	12	1.59 (1.29 to 1.95)	1.48 (1.20 to 1.83)	1.40 (1.11 to 1.78)

[a] Unadjusted for confounding and uncorrected for misclassification of smoking habits
[b] Adjusted for confounding by fruit, vegetables and dietary fat consumption and by education
[c] Assuming an additive model, a concordance ratio of 3 and misclassification rates of 2.5% for studies in North America and Europe and 10% for studies in Asia (see section 9.2.3 for interpretation of the misclassification rates)
[d] N = number of studies of ETS and lung cancer
[e] Relative risk of lung cancer (95% confidence intervals)
[f] 12 studies presented no analyses adjusted for age and did not match nonsmoking cases and controls on age

When adjustment for confounding and correction for misclassification is carried out the association between ETS and lung cancer is no longer statistically significant, whether results from all 67 studies are considered or whether results for North America, Europe or Asia are considered separately. When attention was further restricted to those studies that had presented age-adjusted results, generally considered extremely important in epidemiology, the association, whether with husband smoking (RR 1.01, 95% CI 0.92 to 1.10) or with each 10 cigarettes per day smoked by the husband (RR 0.99, 95% CI 0.95 to 1.03), was very close to 1.0. The lack of significance and closeness of the estimates to 1.0 would not have been affected by further adjustment for ETS exposure in the reference group ("background correction"), as carried out by Hackshaw *et al* [1].

While our estimates are subject to various uncertainties, as discussed in the report, the analyses have not shown an association. If an association did exist – and one cannot prove a negative – it is likely to be much weaker than that claimed by Hackshaw *et al* [1].

Table 1 Lung cancer risk in relation to the number of cigarettes smoked per day by the husband in lifelong nonsmokers

Study [ref]	Year	Location	Type[a]	Number of lung cancers[b]	Cigarettes/day Group	Midpoint	RR (95% CI)[c]	β (SE(β))[d]
Akiba *et al* [26]	1986	Japan	CC	94	1-19	10.00	1.30 (0.62 to 2.57)	0.19 (0.14)
					20-29	21.35	1.50 (0.71 to 3.16)	
					30+	38.39	2.10 (0.57 to 8.07)	
Boffetta *et al* [27]	1998	West Europe	CC	509	0.1-10.0[e]	13.38	1.00 (0.77 to 1.31)	0.01 (0.05)
					10.1-18.0[e]	25.88	0.57 (0.34 to 0.93)	
					18.1+[e]	43.06	1.34 (0.83 to 2.17)	
Boffetta *et al* [28]	1999	Europe	CC	66	Any	18.18	1.00 (0.50 to 1.90)	0.00 (0.19)
Brownson *et al* [29]	1987	USA	CC	19	Any	23.16	1.68 (0.39 to 6.90)	0.22 (0.32)
Brownson *et al* [30]	1992	USA	CC	432	Any	23.16	1.00 (0.80 to 1.20)	0.00 (0.04)
Buffler *et al* [31]	1984	USA	CC	41	Any	23.16	0.80 (0.34 to 1.90)	-0.10 (0.19)
Butler [32]	1988	USA	P	8	Any	23.16	2.02 (0.48 to 8.56)	0.30 (0.32)
Cardenas *et al* [33]	1997	USA	P	246	1-19	10.04	1.10 (0.50 to 2.20)	0.14 (0.07)
					20-39	22.67	1.20 (0.70 to 2.20)	
					40+	43.14	1.90 (1.00 to 3.60)	
Chan and Fung [34]	1982	Hong Kong	CC	84	Any	18.18	0.75 (0.43 to 1.30)	-0.16 (0.16)
Choi *et al* [35]	1989	Korea	CC	75	Any	18.18	1.63 (0.92 to 2.87)	0.27 (0.16)
Correa *et al* [36]	1983	USA	CC	25	Any	23.16	2.07 (0.81 to 5.25)	0.31 (0.21)
de Waard *et al* [37]	1995	Netherlands	CC	23	Any	18.18	2.57 (0.84 to 7.85)	0.52 (0.31)
Du *et al* [38]	1993	China	CC	75	1-19	10.00	0.67 (0.33 to 1.39)[f]	0.17 (0.12)
					20+	26.03	1.49 (0.82 to 2.70)[f]	
Enstrom and Kabat [39]	2003	USA	P	177	Any	23.16	0.94 (0.66 to 1.33)	-0.03 (0.08)
Fontham *et al* [40]	1994	USA	CC	653	Any	23.16	1.29 (1.04 to 1.60)	0.11 (0.05)
Gao *et al* [41]	1987	China	CC	246	Any	18.18	1.30 (0.87 to 1.94)	0.15 (0.11)
Garfinkel [42]	1981	USA	P	153	1-19	10.04	1.27 (0.86 to 1.89)	0.03 (0.07)
					20+	27.52	1.10 (0.76 to 1.59)	
Garfinkel *et al* [43]	1985	USA	CC	134	1-19	10.04	0.84 (0.40 to 1.77)	0.15 (0.06)
					20-39	22.67	1.08 (0.64 to 1.82)	
					40+	43.14	1.99 (1.13 to 3.49)	
Geng *et al* [11]	1988	China	CC	54	1-9	4.85	1.40 (0.49 to 4.02)	0.38 (0.15)
					10-19	12.73	1.95 (0.60 to 6.33)	
					20+	26.03	2.73 (1.23 to 6.08)	
Gorlova *et al* [44]	2006	USA	CC	130	Any	23.16	1.15 (0.63 to 2.10)	0.06 (0.13)
Hirayama [45]	1984	Japan	P	200	1-19[g]	8.60	1.35 (0.92 to 1.99)	0.15 (0.08)
					20+	26.03	1.59 (1.03 to 2.46)	
Hole *et al* [46]	1989	Scotland	P	6	1-14[g]	2.08	1.30 (0.12 to 14.3)	0.37 (0.36)
					15+	24.09	2.71 (0.28 to 26.0)	
Humble *et al* [47]	1987	USA	CC	20	1-20	15.82	1.80 (0.49 to 6.96)	0.11 (0.25)
					21+	33.92	1.20 (0.23 to 6.89)	
IARC (Kreuzer) [8]	2004	Germany	CC	100	Any	18.18	0.80 (0.50 to 1.30)	-0.12 (0.13)
Inoue and Hirayama [48]	1988	Japan	CC	28	1-19	10.00	2.58 (0.31 to 6.63)	0.35 (0.27)
					20+	26.03	3.09 (0.84 to 15.3)	
Janerich *et al* [49]	1990	USA	CC	146	Any	23.16	0.75 (0.47 to 1.20)[h]	-0.12 (0.10)
Jee *et al* [50]	1999	Korea	P	79	1-19	10.00	2.00 (1.10 to 3.90)	0.09 (0.15)
					20+	26.03	1.50 (0.70 to 3.30)	
Johnson *et al* [51]	2001	Canada	CC	71	Any	18.18	1.20 (0.62 to 3.30)	0.10 (0.18)
Kabat and Wynder [52]	1984	USA	CC	53	Any	23.16	0.79 (0.25 to 2.45)	-0.10 (0.25)
Kabat *et al* [53]	1995	USA	CC	69	1-10[j]	16.54	0.82 (0.42 to 1.61)	0.00 (0.11)
					11+[j]	36.38	1.06 (0.49 to 2.30)	
Kalandidi *et al* [54]	1990	Greece	CC	91	1-20	13.38	1.54 (0.79 to 3.00)	0.11 (0.09)
					21-40	29.02	1.77 (0.83 to 3.79)	
					41+	53.35	1.57 (0.54 to 4.57)	
Koo *et al* [55]	1987	Hong Kong	CC	88	1-10	7.08	2.33 (0.92 to 5.92)	0.09 (0.14)
					11-20	17.67	1.74 (0.81 to 3.75)	
					21+	31.83	1.19 (0.46 to 3.03)	
Lagarde *et al* [56]	2001	Sweden	CC	242	Any	18.18	1.15 (0.84 to 1.58)[h]	0.08 (0.09)
Lam [57]	1985	Hong Kong	CC	75	Any	18.18	2.01 (1.09 to 3.72)	0.38 (0.17)
Lam *et al* [58]	1987	Hong Kong	CC	202	1-10	7.08	2.18 (1.14 to 4.15)	0.27 (0.09)
					11-20	17.67	1.85 (1.19 to 2.87)	
					21+	31.83	2.07 (1.07 to 4.03)	
Layard [59]	1994	USA	CC	39	1-14	8.19	0.60 (0.23 to 1.59)	-0.18 (0.15)
					15+	26.64	0.63 (0.28 to 1.40)	
Lee *et al* [60]	1986	UK	CC	32	Any	18.18	1.00 (0.37 to 2.71)	0.00 (0.28)
Lee *et al* [61]	2000	Taiwan	CC	268	Any	18.18	1.87 (1.29 to 2.71)	0.34 (0.10)
Liu *et al* [62]	1991	China	CC	54	Any	18.18	0.77 (0.30 to 1.96)	-0.14 (0.26)
Liu *et al* [63]	1993	China	CC	38	1-19	10.00	0.70 (0.23 to 2.20)	0.44 (0.18)
					20+	26.03	2.90 (1.20 to 7.30)	
Malats *et al* [64]	2000	Europe/Brazil	CC	105	Any	18.18	1.50 (0.77 to 2.91)[h]	0.22 (0.19)

McGhee *et al* [65]	2005	Hong Kong	CC	179	Any	18.18	1.38 (0.94 to 2.04)	0.18 (0.11)
Nishino *et al* [66]	2001	Japan	P	24	Any	18.18	1.80 (0.67 to 4.60)	0.32 (0.27)
Ohno *et al* [67]	2002	Japan	CC	191	Any	18.18	1.00 (0.67 to 1.49)[k]	0.00 (0.11)
Pershagen *et al* [68]	1987	Sweden	CC	83	Any	18.18	1.20 (0.70 to 2.10)	0.10 (0.15)
Rapiti *et al* [69]	1999	India	CC	41	Any	18.18	1.20 (0.50 to 2.90)	0.10 (0.25)
Rylander and Axelsson [70]	2006	Sweden	CC	31	Any	18.18	1.37 (0.57 to 3.30)[h]	0.17 (0.25)
Schwartz *et al* [71]	1996	USA	CC	185	Any	23.16	1.10 (0.72 to 1.68)[h]	0.04 (0.09)
Seow *et al* [72]	2002	Singapore	CC	176	Any	18.18	1.29 (0.93 to 1.80)	0.14 (0.09)
Shen *et al* [73]	1998	China	CC	70	1-9	4.85	0.65 (0.21 to 2.07)	-0.09 (0.16)
					10-19	12.73	1.05 (0.32 to 3.38)	
					20+	26.03	0.70 (0.28 to 1.76)	
Shimizu *et al* [74]	1988	Japan	CC	90	Any	18.18	1.08 (0.64 to 1.82)	0.04 (0.15)
Sobue [75]	1990	Japan	CC	144	Any	18.18	1.13 (0.78 to 1.63)	0.07 (0.10)
Speizer *et al* [76]	1999	USA	P	35	Any	23.16	1.50 (0.30 to 6.30)	0.18 (0.34)
Stockwell *et al* [77]	1992	USA	CC	210	Any	23.16	1.60 (0.80 to 3.00)	0.20 (0.15)
Sun *et al* [78]	1996	China	CC	230	Any	18.18	1.16 (0.80 to 1.69)	0.08 (0.11)
Svensson *et al* [79]	1989	Sweden	CC	38	Any	18.18	1.36 (0.53 to 3.49)	0.17 (0.26)
Trichopoulos *et al* [80]	1983	Greece	CC	77	1-10	7.08	0.57 (0.12 to 2.63)	0.26 (0.11)
					11-20	17.67	2.50 (1.26 to 4.94)	
					21-30	25.88	3.97 (1.31 to 12.0)	
					31+	43.06	1.87 (0.70 to 5.01)	
Vineis *et al* [81]	2005	Western Europe	P	70	Any	18.18	1.05 (0.55 to 2.02)	0.03 (0.18)
Wang *et al* [82]	1996	China	CC	82	Any	18.18	2.53 (1.26 to 5.10)	0.51 (0.20)
Wang *et al* [83]	1996	China	CC	135	1-9	4.85	0.35 (0.11 to 1.16)	0.17 (0.12)
					10-19	12.73	1.35 (0.74 to 2.45)	
					20+	26.03	1.40 (0.76 to 2.57)	
Wang *et al* [84]	2000	China	CC	200	Any	18.18	1.03 (0.60 to 1.70)	0.02 (0.15)
Wu *et al* [85]	1985	USA	CC	31	Any	23.16	1.20 (0.50 to 3.30)	0.08 (0.21)
Wu-Williams *et al* [18]	1990	China	CC	417	Any	18.18	0.70 (0.60 to 0.90)	-0.20 (0.06)
Zaridze *et al* [86]	1998	Russia	CC	189	1-10	7.08	1.66 (1.09 to 2.52)	0.13 (0.11)
					11+	22.93	1.35 (0.84 to 2.18)	
Zatloukal *et al* [87]	2003	Czech Republic	CC	84	Any	18.18	0.48 (0.21 to 1.09)[f]	-0.40 (0.23)
Zheng *et al* [88]	1997	China	CC	69	Any	18.18	2.52 (1.09 to 5.85)	0.51 (0.24)
Zhong *et al* [89]	1999	China	CC	504	1-10	7.08	1.40 (0.90 to 2.20)	-0.01 (0.09)
					11-20	17.67	0.90 (0.60 to 1.40)	
					21+	31.83	1.40 (0.70 to 2.60)	

[a] P = prospective; CC = case-control
[b] Number of lung cancer cases in female lifelong nonsmokers; numbers with data by amount smoked may total less than this
[c] RR = Relative risk of lung cancer in nonsmoking females (baseline = husband nonsmoker); 95% CI = 95% confidence interval for RR
[d] β = Slope of relationship of log RR to dose (in units of 10 cigarettes/day by the husband); SE(β) = standard error of β
[e] Smoked in presence of the spouse
[f] Based on data for two control groups combined
[g] Lowest level includes exsmokers
[h] Relative risks were presented for sexes combined and assumed to apply to each sex separately, with confidence intervals weighted according to number of subjects by sex
[j] Smoked in marriage (including exsmokers)
[k] Based on data for hospital controls. Data for population controls not used as non-response rate very high
[ℓ] Based on data for two pathological groups of lung cancer combined

Table 2 Meta-analyses of the relationship of the number of cigarettes smoked per day by the husband to risk of lung cancer in lifelong nonsmoking females (without adjustment for confounding[a] or correction for misclassification of active smoking by the subject)

		Fixed-effects meta-analysis		Random-effects meta-analysis
Studies	N	RR (95% CI)[b]	Heterogeneity chisquared (d.f.)p[c]	RR (95% CI)[b]
All	67	1.08 (1.05 to 1.11)	101.62 (66) **	1.09 (1.06 to 1.14)
USA and Canada	21	1.06 (1.01 to 1.10)	18.08 (20) NS	1.06 (1.01 to 1.10)
Europe	16	1.07 (1.01 to 1.14)	15.32 (15) NS	1.07 (1.01 to 1.14)
China (including Hong Kong)	18	1.07 (1.01 to 1.13)	54.48 (17) ***	1.14 (1.03 to 1.27)
Rest of Asia	12	1.16 (1.08 to 1.25)	8.25 (11) NS	1.16 (1.08 to 1.25)
Heterogeneity between levels			5.49 (3) NS	
USA, Canada and Europe	37	1.06 (1.03 to 1.10)	33.53 (36) NS	1.06 (1.03 to 1.10)
Asia	30	1.10 (1.06 to 1.15)	66.02 (29) ***	1.15 (1.07 to 1.23)
Heterogeneity between levels			2.06 (1) NS	
Published in 1980s	25	1.16 (1.10 to 1.22)	20.33 (24) NS	1.16 (1.10 to 1.22)
Published in 1990s	27	1.04 (1.00 to 1.08)	51.27 (26) **	1.06 (1.00 to 1.12)
Published in 2000s	15	1.08 (1.02 to 1.15)	18.60 (14) NS	1.08 (1.00 to 1.17)
Heterogeneity between levels			11.42 (2) **	
<100 cases	39	1.14 (1.08 to 1.20)	42.50 (38) NS	1.14 (1.07 to 1.21)
100-199 cases	14	1.07 (1.01 to 1.12)	12.74 (13) NS	1.07 (1.01 to 1.12)
200-399 cases	9	1.17 (1.10 to 1.25)	7.16 (8) NS	1.17 (1.10 to 1.25)
400+ cases	5	1.00 (0.95 to 1.04)	17.26 (4) **	0.99 (0.89 to 1.09)
Heterogeneity between levels			21.96 (3) ***	
With dose-response data[d]	23	1.11 (1.07 to 1.16)	27.57 (22) NS	1.12 (1.07 to 1.18)
Without dose-response data	44	1.05 (1.01 to 1.09)	69.41 (43) **	1.08 (1.02 to 1.13)
Heterogeneity between levels			4.63 (1) *	
With age adjustment[e]	55	1.05 (1.03 to 1.08)	67.12 (54) NS	1.06 (1.03 to 1.10)
Without age adjustment	12	1.27 (1.17 to 1.37)	16.59 (11) NS	1.28 (1.15 to 1.42)
Heterogeneity between levels			17.90 (1) ***	
Case-control studies	57	1.07 (1.04 to 1.11)	95.59 (56) ***	1.10 (1.05 to 1.14)
Prospective studies	10	1.08 (1.01 to 1.16)	5.96 (9) NS	1.08 (1.01 to 1.16)
Heterogeneity between levels			0.06 (1) NS	

[a] Other than the adjustments made for confounding by the authors of the studies
[b] Relative risk per 10 cigarettes/day smoked by the husband
[c] d.f. = degrees of freedom; p is coded as *** p<0.001, ** p<0.01, * p<0.05, (*) p<0.1, NS p≥0.1
[d] Specifically for number of cigarettes smoked by the husband
[e] Or matching (within nonsmokers)

Table 3 Relationship of fruit, vegetable and tea consumption to lung cancer risk in lifelong nonsmoking females

Study [ref]	Location	Smoking habits	Exposure index	β[a]	Z[b]
Agudo *et al* [116]	Spain	never	vegetables	-0.1293	-0.7839
Alavanja *et al* [95]	USA	never/ex 15+y	vegetables	-0.0071	-0.1232
			fruit	+0.0124	+0.0607
Candelora *et al* [117]	USA	never	vegetables	-0.4937	-3.6284
			fruit	-0.2512	-1.9734
Feskanich *et al* [118]	USA	never	vegetables	-0.0284	-0.1704
			fruit	-0.4945	-2.8116
Hirayama [45]	Japan	never	vegetables	-0.1608	-1.7378
Hu *et al* [119]	Canada	never	vegetables	+0.1246	+0.8696
			fruit	+0.0417	+0.3536
			tea	-0.3620	-2.8490
Kalandidi *et al* [54]	Greece	never	vegetables	+0.1166	+0.7738
			fruit	-0.2598	-1.7132
Ko *et al* [90]	Taiwan	never	vegetables	-0.5116	-2.5910
			fruit	0.0000	0.0000[c]
Koo [120]	China	never	vegetables	-0.2189	-1.3982
			fruit	-0.4413	-2.7219
Kreuzer *et al* [121]	Germany	never	vegetables	-0.2398	-2.5065
			fruit	-0.0577	-0.5616
Mayne *et al* [122]	USA	never/ex 10+y	vegetables	-0.2712	-2.3748
			fruit	-0.2381	-2.2463
Ozasa *et al* [123]	Japan	never	vegetables	+0.1388	+1.0966
			fruit	+0.1051	+0.6633
Rachtan [124]	Poland	never	vegetables[d]	-1.3832	-2.0906
			fruit	-0.5812	-2.0208
Seow *et al* [72]	Singapore	never	vegetables	-0.1111	-1.1287
			fruit	-0.2357	-2.3706
Shimizu *et al* [74]	Japan	never	vegetables	-0.0630	-0.3154
			fruit	+0.0895	+0.4230
Steinmetz *et al* [125]	Japan	never	vegetables	+0.0848	+0.3146
			fruit	+0.0229	+0.0811
Zhong [89]	China	never	tea	-0.2759	-2.6079

[a] Slope of dose relationship; exp (β) is the increase in risk per SD of exposure

[b] $Z = \beta/SE(\beta)$ and is an approximate normal deviate

[c] $SE(\beta) = 0.1858$

[d] Data for other vegetables used rather than data for carrots ($\beta = -1.4429$, $Z = -3.6324$)

Table 4 Random-effects meta-analyses of the relationship of vegetable, fruit and tea consumption to risk of lung cancer in lifelong nonsmoking females[a]

Exposure	Studies	N	RR (95% CI)[b]
Vegetable consumption	All	16	0.88 (0.80 to 0.97)
	North America and Europe	10	0.88 (0.77 to 1.02)
	Asia	6	0.88 (0.76 to 1.01)
	Excluding studies of never smokers plus long-term exsmokers	14	0.88 (0.78 to 0.98)
Fruit consumption	All	14	0.86 (0.78 to 0.96)
	North America and Europe	9	0.86 (0.76 to 0.97)
	Asia	5	0.89 (0.73 to 1.08)
	Excluding studies of never smokers plus long-term exsmokers	12	0.85 (0.76 to 0.96)
Tea consumption	All[c]	2	0.73 (0.62 to 0.86)
	North America	1	0.70 (0.54 to 0.89)
	Asia	1	0.76 (0.62 to 0.93)

[a] Includes two studies of never smokers plus long-term exsmokers (see Table 3)
[b] Relative risk per standard deviation of exposure
[c] Both studies were of lifelong nonsmokers

Table 5 Relationship of dietary fat consumption to lung cancer risk in lifelong nonsmoking females

Study [ref]	Country	Smoking habits	Exposure index	β[a]	Z[b]
Alavanja *et al* [95], Swanson *et al* [96]	USA	never/ ex 15+ years	saturated fat	+0.2666	+2.9136
Hu *et al* [126]	Canada	never	French fries or fried potatoes	+0.2543	+2.0330
Kalandidi *et al* [54]	Greece	never	fats and oils	-0.0796	-0.4742
Ozasa *et al* [123]	Japan	never	fried foods	+0.2567	+1.8884
Swanson *et al* [127]	USA	never/ ex 15+ years	saturated fat	-0.0376	-0.1849
Wu *et al* [97]	USA	never	total fat	+0.1989	+1.1231

[a] Slope of dose-relationship; exp(β)
[b] $Z = \beta/SE(\beta)$ and is an approximate normal deviate

Table 6 Random-effects meta-analyses of the relationship of dietary fat consumption to risk of lung cancer in lifelong nonsmoking females[a]

Studies	N	RR (95% CI)[b]
All	6	1.22 (1.09 to 1.36)
USA and Canada	4	1.25 (1.10 to 1.42)
Other countries	2	1.11 (0.80 to 1.54)
Excluding studies of never smokers plus occasional smokers	4	1.20 (1.04 to 1.39)

[a] Includes two studies of never smokers plus long-term exsmokers (see Table 5)
[b] Relative risk per standard deviation of exposure

Table 7 Relationship of years of education to lung cancer risk in lifelong nonsmoking females

Study [ref]	Country	Smoking habits	β[a]	Z[b]
Boffetta *et al* [27]	West Europe	never	-0.2257	-5.0111
Fontham *et al* [40]	USA	never	-0.1390	-6.0108
Kabat and Wynder [52]	USA	never	-0.0227	-0.3781
Kabat *et al* [53]	USA	never	-0.0274	-0.4661
Kalandidi *et al* [54]	Greece	never	+0.0478	0.8327
Ko *et al* [90]	Taiwan	never	-0.0484	-1.1503
Mao *et al* [128]	Canada	never	-0.0653	-2.0365
Sobue *et al* [75]	Japan	never	-0.1172	-3.7846
Stockwell *et al* [77]	USA	never	-0.0902	-2.1399
Wichmann *et al* [129][c]	Germany	never/occasional	+0.0212	+0.1352
Wichmann *et al* [129][d]	Germany	never/occasional	-0.1280	-2.3385
Zaridze *et al* [86]	Russia	never	-0.1425	-2.3243

[a] Slope of dose-response relationship; exp(β) is the increase in risk per year of education
[b] $Z = \beta/SE(\beta)$ and is an approximate normal deviate
[c] Data for study BIPS
[d] Data for study GSF

Table 8 Random-effects meta-analysis of the relationship of education to risk of lung cancer in lifelong nonsmoking females[a]

Studies	N	RR (95% CI)[b]
All	12	0.91 (0.88 to 0.95)
USA and Canada	5	0.92 (0.88 to 0.96)
Europe	5	0.90 (0.81 to 1.00)
Asia	2	0.92 (0.86 to 0.98)
Excluding studies of never smokers plus occasional smokers	10	0.91 (0.88 to 0.95)

[a] Includes two studies of never smokers plus occasional smokers (see Table 7)
[b] Relative risk per additional year of education

Table 9 Differences in fruit, vegetable and tea consumption in SDs between lifelong nonsmoking females exposed or unexposed to ETS at home

Study [ref]	Location	ETS source	Fruit, tea or vegetables	δ[a]	N_u[b]	N_e[c]
Published papers						
Cardenas *et al* [33]	USA	spouse	vegetables	-0.0852	71,634	104,686
Forastiere *et al* [102]	Italy	spouse	vegetables[d]	-0.2022	725	1,208
			fruit	+0.1043	722	1,229
Hirayama [45]	Japan	spouse	vegetables	+0.0245	21,895	69,645
Hirayama [130]	Japan	spouse	vegetables	-0.0240	456	1,512
Koo *et al* [131]	Hong Kong	spouse	vegetables	+0.3532	419	111
			fruit	-0.3009	419	111
	Japan	spouse	vegetables	-0.0863	8,146	4,901
			fruit	-0.0818	8,146	4,901
	Sweden	spouse	vegetables	-0.9022	69	18
			fruit	-0.6795	69	18
	USA	spouse	vegetables	+0.2859	60	84
Matanoski *et al* [132]	USA	spouse	vegetables	-0.0449	1,214	2,124
Reynolds *et al* [133]	USA	cohabitant	vegetables	-0.0582	8,388[l]	20,413[l]
			fruit	-0.0871	9,665[l]	22,848[l]
Thornton *et al* [104][e]	UK	cohabitant	vegetables	+0.0527	1673	678
			fruit	-0.0561	1673	678
			tea	-0.0341	1671	678
Public databases						
HALS2[f]	UK	cohabitant	vegetables	+0.0447	974	291
			fruit	-0.1256	974	291
			tea	-0.1263	974	291
HSE93[g]	UK	cohabitant	vegetables	-0.0851	3007	657
			fruit	-0.0887	3007	657
			tea	-0.1069	3007	657
HULS[h]	Hungary	cohabitant	vegetables	-0.0718	643	305
			fruit	-0.0446	643	305
			tea	-0.0753	643	305
NHIS2000[j]	USA	cohabitant	vegetables	-0.1170	4564	532
			fruit	-0.0846	4567	533
NHANES III[k]	USA	cohabitant	vegetables	-0.2238	2555	616
			fruit	-0.0760	2555	616
			tea	-0.0194	2555	616

[a] δ = SD difference in fruit, vegetable or tea consumption associated with ETS exposure at home
[b] N_u = number of lifelong nonsmokers unexposed to ETS
[c] N_e = number of lifelong nonsmokers exposed to ETS
[d] Data for fresh vegetables rather than for cooked vegetables (δ = -0.1294)
[e] The source reference presented results for sexes combined; results for females were provided by J Hamling [personal communication]
[f] UK Health and Lifestyle Study 2 [98]. Estimates provided by J Hamling [personal communication]
[g] Health Survey for England 1993 [99]. Estimates provided by J Hamling [personal communication]
[h] Hungarian Lifestyle Survey. Estimates provided by J Hamling [personal communication]
[j] National Health Interview Survey 2000 [100]
[k] National Health and Nutrition Examination Survey III [101]
[l] Estimated

Table 10 Combined estimates of the differences, δ, in vegetable, fruit and tea consumption (in SDs) between lifelong nonsmoking females exposed or unexposed to ETS at home

			δ (SE(δ))		
Dietary index	Studies	N	Random-effects	Unweighted	Weighted
Vegetable consumption	All	16	-0.0559 (0.0211)	-0.0712 (0.0672)	-0.0525 (0.0149)
	USA	6	-0.0866 (0.0191)	-0.0405 (0.0703)	-0.0835 (0.0101)
	Europe	6	-0.0892 (0.0596)	-0.1940 (0.1468)	-0.0653 (0.0535)
	USA+Europe	12	-0.0813 (0.0195)	-0.1173 (0.0810)	-0.0827 (0.0102)
	Asia	4	0.0185 (0.0471)	0.0669 (0.0981)	0.0117 (0.0252)
Fruit consumption	All	11	-0.0733 (0.0197)	-0.1382 (0.0610)	-0.0812 (0.0142)
	USA	3	-0.0862 (0.0113)	-0.0826 (0.0034)	-0.0859 (0.0021)
	Europe	6	-0.0581 (0.0481)	-0.1484 (0.1110)	-0.0503 (0.0427)
	USA+Europe	9	-0.0634 (0.0249)	-0.1264 (0.0725)	-0.0788 (0.0160)
	Asia	2	-0.1661 (0.1066)	-0.1913 (0.1096)	-0.0904 (0.0424)
Tea consumption	All	5	-0.0655 (0.0227)	-0.0724 (0.0205)	-0.0671 (0.0210)
	USA	1	-0.0194	-0.0194	-0.0194
	Europe	4	-0.0812 (0.0262)	-0.0856 (0.0202)	-0.0855 (0.0202)

Table 11 Differences in dietary fat consumption in SDs between lifelong nonsmoking females exposed or unexposed to ETS at home

Study [ref]	Location	ETS source	Index of fat consumption	δ[a]	N_u[b]	N_e[c]
Published papers						
Cardenas *et al* [33]	USA	spouse	dietary fat	-0.0307	71,634	104,686
Forastiere *et al* [102]	Italy	spouse	meat	-0.0837	722	1,210
Koo *et al* [131]	Hong Kong	spouse	fried food	+0.3532	419	111
	Sweden	spouse	fried potatoes, french fries	+0.8087	69	18
	USA	spouse	fat	+0.3578	60	84
Reynolds *et al* [133]	USA	cohabitant	meat	+0.0570	20,950[k]	21,287[k]
Thornton *et al* [104][d]	UK	cohabitant	fried foods	+0.1898	1,673	678
Public databases						
HALS2[e]	UK	cohabitant	fried foods	+0.0782	974	291
HSE93[f]	UK	cohabitant	fried foods	+0.0660	3007	657
HULS[g]	Hungary	cohabitant	fried foods	+0.2551	643	305
NHIS2000[h]	USA	cohabitant	bacon,fried potatoes,chips	+0.2218	4538	525
NHANESIII[j]	USA	cohabitant	bacon,sausages, processed meats and eggs	+0.2337	2555	616

[a] δ = SD difference in dietary fat consumption associated with ETS exposure at home
[b] N_u = number of lifelong nonsmokers unexposed to ETS
[c] N_e = number of lifelong nonsmokers exposed to ETS
[d] The source reference presented results for sexes combined; results for females were provided by J Hamling [personal communication]
[e] UK Health and Lifestyle Study 2 [98]. Estimates provided by J Hamling [personal communication]
[f] Health Survey for England 1993 [99]. Estimates provided by J Hamling [personal communication]
[g] Hungarian Lifestyle Survey. Estimates provided by J Hamling [personal communication]
[h] National Health Interview Survey 2000 [100]
[j] National Health and Nutrition Examination Survey III [101]
[k] Estimated

Table 12 Combined estimates of the differences, δ, in dietary fat consumption (in SDs) between lifelong nonsmoking females exposed or unexposed to ETS at home

Studies	N	δ (SE(δ)) Random-effects	Unweighted	Weighted
All	12	0.1310 (0.0317)	0.2089 (0.0680)	0.0001 (0.0200)
USA	5	0.1188 (0.0420)	0.1679 (0.0689)	-0.0048 (0.8745)
Europe	6	0.1302 (0.0633)	0.2190 (0.1271)	0.0917 (0.0549)
USA+Europe	11	0.1179 (0.0319)	0.1958 (0.0730)	-0.0006 (0.0204)
Asia	1	0.3532	0.3532	0.3532

Table 13 Differences in years of education between lifelong nonsmoking females exposed or unexposed to ETS at home

Study [ref]	Location	ETS source	δ[a]	N_u[b]	N_e[c]
Published papers					
Cardenas *et al* [134]	USA	cohabitant	-0.3160	71,892	141,262
Curtin *et al* [135]	Switzerland	cohabitant	-0.1920	698	81
Enstrom and Kabat [39]	USA	spouse	-0.3300	7,339	18,603
Forastiere *et al* [102]	Italy	spouse	-0.6422	724	1,209
Koo *et al* [131]	Hong Kong	spouse	-0.5000	419	111
	USA	spouse	-0.4000	60	84
Matanoski *et al* [132]	USA	spouse	-0.5032	1,380	2,411
Thornton *et al* [104][d]	UK	cohabitant	-0.3950	1,673	678
Public databases					
HALS2[e]	UK	cohabitant	-0.3200	974	291
HSE93[f]	UK	cohabitant	-0.5150	3007	657
HULS[g]	Hungary	cohabitant	-0.4600	643	305
NHIS2000[h]	USA	cohabitant	-0.9940	4515	523
NHANES III[j]	USA	cohabitant	-1.1239	2543	612

[a] δ = years difference in education associated with ETS exposure at home
[b] N_u = number of lifelong nonsmokers unexposed to ETS
[c] N_e = number of lifelong nonsmokers exposed to ETS
[d] The source reference presented results for sexes combined; results for females were provided by J Hamling [personal communication] – see also text in section 6.4
[e] UK Health and Lifestyle Study 2 [98]. Estimates provided by J Hamling [personal communication]
[f] Health Survey for England 1993 [99]. Estimates provided by J Hamling [personal communication]
[g] Hungarian Lifestyle Survey. Estimates provided by J Hamling [personal communication]
[h] National Health Interview Survey 2000 [100]
[j] National Health and Nutrition Examination Survey III [101]

Table 14 Combined estimates of the difference, δ, in years of education between lifelong nonsmoking females exposed or unexposed to ETS at home

		δ (SE(δ))		
Studies	N	Random-effects	Unweighted	Weighted
All	13	-0.5337 (0.0634)	-0.5147 (0.0744)	-0.3493 (0.0384)
USA	6	-0.6083 (0.0946)	-0.6112 (0.1451)	-0.3441 (0.0586)
Europe	6	-0.4752 (0.0548)	-0.4207 (0.0639)	-0.4614 (0.0551)
USA+Europe	12	-0.5331 (0.0651)	-0.5159 (0.0809)	-0.3490 (0.0401)
Asia	1	-0.5000	-0.5000	-0.5000

Table 15 Random-effects meta-analyses of the relationship of the number of cigarettes smoked per day by the husband to risk of lung cancer in lifelong nonsmoking females (with and without adjustment for confounding by fruit, vegetable and dietary fat consumption and by education, but with no correction for misclassification of active smoking by the subject)

Studies	N	Unadjusted for confounding RR (95% CI)[a]	Adjusted for confounding RR (95% CI)[a]	Bias[b]
All	67	**1.095 (1.055 to 1.136)**	**1.057 (1.018 to 1.097)**	1.036
USA and Canada	21	1.056 (1.014 to 1.099)	1.025 (0.985 to 1.067)	1.030
Europe	16	1.072 (1.008 to 1.140)	1.034 (0.968 to 1.104)	1.037
China (including Hong Kong)	18	1.143 (1.029 to 1.269)	1.102 (0.992 to 1.225)	1.037
Rest of Asia	12	1.162 (1.083 to 1.248)	1.112 (1.036 to 1.194)	1.045
USA, Canada and Europe	37	1.060 (1.025 to 1.096)	1.026 (0.992 to 1.061)	1.033
Asia	30	1.148 (1.070 to 1.231)	1.104 (1.029 to 1.185)	1.039
Published in 1980s	25	1.158 (1.099 to 1.219)	1.116 (1.060 to 1.176)	1.037
Published in 1990s	27	1.063 (1.004 to 1.125)	1.026 (0.968 to 1.088)	1.035
Published in 2000s	15	1.082 (1.002 to 1.168)	1.046 (0.969 to 1.129)	1.035
<100 cases	39	1.137 (1.072 to 1.206)	1.096 (1.032 to 1.164)	1.038
100-199 cases	14	1.065 (1.013 to 1.121)	1.028 (0.978 to 1.082)	1.036
200-399 cases	9	1.175 (1.102 to 1.252)	1.134 (1.065 to 1.209)	1.036
400+ cases	5	0.986 (0.892 to 1.090)	0.954 (0.857 to 1.061)	1.034
With dose-response data[c]	23	1.122 (1.069 to 1.177)	1.083 (1.031 to 1.137)	1.036
Without dose-response data	44	1.075 (1.022 to 1.132)	1.039 (0.986 to 1.094)	1.035
With age adjustment[d]	55	1.062 (1.027 to 1.099)	1.026 (0.991 to 1.063)	1.035
Without age adjustment	12	1.275 (1.149 to 1.415)	1.230 (1.108 to 1.367)	1.037
Case-control studies	57	1.097 (1.052 to 1.145)	1.059 (1.014 to 1.105)	1.036
Prospective studies	10	1.085 (1.014 to 1.160)	1.048 (0.980 to 1.121)	1.035

[a] Relative risk per 10 cigarettes/day smoked by the husband
[b] Bias = RR unadjusted for confounding/RR adjusted for confounding (RRs to 4 decimal places)
[c] Specifically for number of cigarettes smoked by the husband
[d] Or matching (within nonsmokers)

Table 16 Effect of adjustment for specific confounding variables on the relationship of the number of cigarettes smoked per day by the husband to risk of lung cancer in lifelong nonsmoking females

Studies	N	Adjustment	RR (95% CI)[a]	Bias[b]
All	67	None[c]	**1.097 (1.058 to 1.138)**	1
		Fruit	1.091 (1.052 to 1.132)	1.005
		Vegetables	1.093 (1.054 to 1.134)	1.004
		Dietary fat	1.083 (1.044 to 1.124)	1.013
		Education	1.071 (1.032 to 1.112)	1.024
		Fruit, vegetables, dietary fat and education	1.057 (1.018 to 1.097)	1.038
		Tea	1.086 (1.047 to 1.127)	1.010
		All five factors	1.043 (1.004 to 1.083)	1.052
USA, Canada and Europe	37	None[c]	1.063 (1.028 to 1.099)	1
		Fruit	1.057 (1.023 to 1.093)	1.005
		Vegetables	1.059 (1.024 to 1.095)	1.003
		Dietary fat	1.050 (1.016 to 1.086)	1.012
		Education	1.039 (1.005 to 1.075)	1.022
		Fruit, vegetables, dietary fat and education	1.026 (0.992 to 1.061)	1.035
		Tea	1.053 (1.018 to 1.088)	1.009
		All five factors	1.014 (0.980 to 1.048)	1.048
Asia	30	None[c]	1.150 (1.072 to 1.232)	1
		Fruit	1.143 (1.066 to 1.225)	1.006
		Vegetables	1.145 (1.068 to 1.227)	1.004
		Dietary fat	1.134 (1.058 to 1.216)	1.014
		Education	1.120 (1.045 to 1.202)	1.026
		Fruit, vegetables, dietary fat and education	1.104 (1.029 to 1.185)	1.041
		Tea	1.137 (1.060 to 1.218)	1.011
		All five factors	1.088 (1.014 to 1.168)	1.057

[a] Relative risk per 10 cigarettes/day smoked by the husband

[b] Bias = RR adjusted for no confounders/RR with adjustment shown

[c] 'Back-corrected' to remove effect of adjustment for those studies which reported estimates adjusted for fruit, vegetables, dietary fat and education (none reported estimates adjusted for tea drinking)

Table 17 Active smoking data used in misclassification analyses

Study [ref]	Year	Location	Type[a]	Smokers among controls (%)	RR active smoking	Source[b]
Akiba *et al* [26]	1986	Japan	CC	20.59	2.38	1
Boffetta *et al* [27]	1998	West Europe	CC	29	5	2
Boffetta *et al* [28]	1999	Europe	CC	29	5	2
Brownson *et al* [29]	1987	USA	CC	28.79	4.3	1
Brownson *et al* [30]	1992	USA	CC	43	8	4
Buffler *et al* [31]	1984	USA	CC	58.74	7.06	1
Butler [32]	1988	USA	P	14	4	3
Cardenas *et al* [33]	1997	USA	P	44.66	6.77	1
Chan and Fung [34]	1982	Hong Kong	CC	26.46	3.48	1
Choi *et al* [35]	1989	Korea	CC	13.68	1.68	1
Correa *et al* [36]	1983	USA	CC	47.22	12.40	1
de Waard *et al* [37]	1995	Netherlands	CC	25.68	5.79	1
Du *et al* [38]	1993	China	CC	32.10	3.01	1
Enstrom and Kabat [39]	2003	USA	P	22	6	5
Fontham *et al* [40]	1994	USA	CC	43	8	3
Gao *et al* [41]	1987	China	CC	25.74	2.77	1
Garfinkel [42]	1981	USA	P	22	3.58	3
Garfinkel *et al* [43]	1985	USA	CC	34	6	3
Geng *et al* [11]	1988	China	CC	40.76	2.77	1
Gorlova *et al* [44]	2006	USA	CC	36	8	4
Hirayama [45]	1984	Japan	P	15.95	3.19	1
Hole *et al* [46]	1989	Scotland	P	55.81	3.33	1
Humble *et al* [47]	1987	USA	CC	40.66	16.27	1
IARC (Kreuzer) [8]	2004	Germany	CC	35.31	3.62	1
Inoue and Hirayama [48]	1988	Japan	CC	12.96	2.14	1
Janerich *et al* [49]	1990	USA	CC	42	8	3
Jee *et al* [50]	1999	Korea	P	13.68	1.68	2
Johnson *et al* [51]	2001	Canada	CC	49.78	8.75	1
Kabat and Wynder [52]	1984	USA	CC	42	5.9	3
Kabat *et al* [53]	1995	USA	CC	42	8	4
Kalandidi *et al* [54]	1990	Greece	CC	17.73	3.25	1
Koo *et al* [55]	1987	Hong Kong	CC	31.50	2.77	1
Lagarde *et al* [56]	2001	Sweden	CC	39.79	5.15	2
Lam [57]	1985	Hong Kong	CC	22.16	4.12	1
Lam *et al* [58]	1987	Hong Kong	CC	24.04	3.84	1
Layard [59]	1994	USA	CC	34	6	4
Lee *et al* [60]	1986	UK	CC	60.42	4.63	1
Lee *et al* [61]	2000	Taiwan	CC	2.56	4.20	1
Liu *et al* [62]	1991	China	CC	32.01	3.01	2
Liu *et al* [63]	1993	China	CC	25	4.26	1
Malats *et al* [64]	2000	Europe/Brazil	CC	29	5	6
McGhee *et al* [65]	2005	Hong Kong	CC	26.04	3.55	2
Nishino *et al* [66]	2001	Japan	P	18.30	2.66	2
Ohno *et al* [67]	2002	Japan	CC	18.30	2.66	2
Pershagen *et al* [68]	1987	Sweden	CC	37	4.20	3
Rapiti *et al* [69]	1999	India	CC	21.55	3.01	2
Rylander and Axelsson [70]	2006	Sweden	CC	40.94	6.80	1
Schwartz *et al* [71]	1996	USA	CC	42	8	4
Seow *et al* [72]	2002	Singapore	CC	13.11	4.78	1
Shen *et al* [73]	1998	China	CC	32.1	3.01	2
Shimizu *et al* [74]	1988	Japan	CC	21	2.8	3
Sobue [75]	1990	Japan	CC	21	2.81	3
Speizer *et al* [76]	1999	USA	P	56.59	7.08	1
Stockwell *et al* [77]	1992	USA	CC	42	8	4
Sun *et al* [78]	1996	China	CC	32.10	3.01	2
Svensson *et al* [79]	1989	Sweden	CC	42.58	6.10	1
Trichopoulos *et al* [80]	1983	Greece	CC	10.36	2.81	1
Vineis *et al* [81]	2005	Western Europe	P	29	5	6
Wang *et al* [82]	1996	China	CC	5.05	3.90	1
Wang *et al* [83]	1996	China	CC	32.10	3.01	2
Wang *et al* [84]	2000	China	CC	10.55	1.27	1
Wu *et al* [85]	1985	USA	CC	61.27	2.71	1
Wu-Williams *et al* [18]	1990	China	CC	36.83	2.22	1
Zaridze *et al* [86]	1998	Russia	CC	10	3	2
Zatloukal *et al* [87]	2003	Czech Republic	CC	45.26	5.82	1
Zheng *et al* [88]	1997	China	CC	32.10	3.01	2
Zhong *et al* [89]	1999	China	CC	32.10	3.01	2

[a] P = prospective; CC = case-control

[b] Source of active smoking RR : 1 = Given in source paper or directly calculated from it; 2 = Estimated from other studies in the same country; 3 = As given by EPA Table B-11 [136]; 4 = Comparable to EPA estimates; 5 = Estimated from Garfinkel studies; 6 = Estimate from Boffetta studies

Table 18 Random-effects meta-analyses of the relationship of the number of cigarettes smoked per day by the husband to risk of lung cancer in lifelong nonsmoking females (adjusted for confounding by fruit, vegetables and dietary fat consumption and by education, with and without correction for misclassification of active smoking by the subject)

		Uncorrected for misclassification	Corrected for misclassification[a]	
Studies	N	RR (95% CI)[b]	RR (95% CI)[b]	Bias[c]
All	67	**1.057 (1.018 to 1.097)**	**1.020 (0.979 to 1.063)**	1.036
USA and Canada	21	1.025 (0.985 to 1.067)	0.976 (0.933 to 1.021)	1.050
Europe	16	1.034 (0.968 to 1.104)	1.018 (0.949 to 1.093)	1.015
China (including Hong Kong)	18	1.102 (0.992 to 1.225)	1.052 (0.939 to 1.179)	1.048
Rest of Asia	12	1.112 (1.036 to 1.194)	1.095 (1.016 to 1.180)	1.016
USA, Canada and Europe	37	1.026 (0.992 to 1.061)	0.989 (0.952 to 1.027)	1.038
Asia	30	1.104 (1.029 to 1.185)	1.067 (0.988 to 1.151)	1.035
Published in 1980s	25	1.116 (1.060 to 1.176)	1.088 (1.029 to 1.150)	1.025
Published in 1990s	27	1.026 (0.968 to 1.088)	0.980 (0.919 to 1.044)	1.047
Published in 2000s	15	1.046 (0.969 to 1.129)	1.021 (0.944 to 1.105)	1.024
<100 cases	39	1.096 (1.032 to 1.164)	1.062 (0.995 to 1.134)	1.032
100-199 cases	14	1.028 (0.978 to 1.082)	0.998 (0.946 to 1.053)	1.031
200-399 cases	9	1.134 (1.065 to 1.209)	1.102 (1.029 to 1.181)	1.029
400+ cases	5	0.954 (0.857 to 1.061)	0.901 (0.803 to 1.011)	1.059
With dose-response data[d]	23	1.083 (1.031 to 1.137)	1.048 (0.997 to 1.102)	1.033
Without dose-response data	44	1.039 (0.986 to 1.094)	1.000 (0.944 to 1.060)	1.038
With age adjustment[e]	55	1.026 (0.991 to 1.063)	0.990 (0.952 to 1.029)	1.037
Without age adjustment	12	1.230 (1.108 to 1.367)	1.194 (1.062 to 1.342)	1.030
Case-control studies	57	1.059 (1.014 to 1.105)	1.020 (0.972 to 1.069)	1.038
Prospective studies	10	1.048 (0.980 to 1.121)	1.022 (0.951 to 1.098)	1.026

[a] Using the Lee and Forey method [4] 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

[b] Relative risk per 10 cigarettes/day smoked by the husband

[c] Bias = uncorrected RR/corrected RR

[d] Specifically for number of cigarettes smoked by the husband

[e] Or matching (within nonsmokers)

Table 19 Lung cancer risk in lifelong nonsmoking females in relation to smoking by the husband

Study [ref]	Year	Location	Type[a]	Number of lung cancers[b]	RR (95% CI)[c]	β (SE(β))[d]
Akiba *et al* [26]	1986	Japan	CC	94	1.50 (0.93 to 2.76)	0.41 (0.28)
Boffetta *et al* [27]	1998	West Europe	CC	509	1.11 (0.88 to 1.39)	0.10 (0.12)
Boffetta *et al* [28]	1999	Europe	CC	66	1.00 (0.50 to 1.90)	0.00 (0.34)
Brownson *et al* [29]	1987	USA	CC	19	1.68 (0.39 to 6.90)	0.52 (0.73)
Brownson *et al* [30]	1992	USA	CC	432	1.00 (0.80 to 1.20)	0.00 (0.10)
Buffler *et al* [31]	1984	USA	CC	41	0.80 (0.34 to 1.90)	-0.22 (0.44)
Butler [32]	1988	USA	P	8	2.02 (0.48 to 8.56)	0.70 (0.74)
Cardenas *et al* [33]	1997	USA	P	246	1.20 (0.80 to 1.60)	0.18 (0.18)
Chan and Fung [34]	1982	Hong Kong	CC	84	0.75 (0.43 to 1.30)	-0.29 (0.28)
Choi *et al* [35]	1989	Korea	CC	75	1.63 (0.92 to 2.87)	0.49 (0.29)
Correa *et al* [36]	1983	USA	CC	25	2.07 (0.81 to 5.25)	0.73 (0.48)
de Waard *et al* [37]	1995	Netherlands	CC	23	2.57 (0.84 to 7.85)	0.94 (0.57)
Du *et al* [38]	1993	China	CC	75	1.09 (0.64 to 1.85)[e]	0.09 (0.27)
Enstrom and Kabat [39]	2003	USA	P	177	0.94 (0.66 to 1.33)	-0.06 (0.18)
Fontham *et al* [40]	1994	USA	CC	653	1.29 (1.04 to 1.60)	0.25 (0.11)
Gao *et al* [41]	1987	China	CC	246	1.30 (0.87 to 1.94)	0.26 (0.25)
Garfinkel [42]	1981	USA	P	153	1.17 (0.85 to 1.61)	0.16 (0.16)
Garfinkel *et al* [43]	1985	USA	CC	134	1.23 (0.81 to 1.87)	0.21 (0.21)
Geng *et al* [11]	1988	China	CC	54	2.16 (1.08 to 4.29)	0.77 (0.35)
Gorlova *et al* [44]	2006	USA	CC	130	1.15 (0.63 to 2.10)	0.14 (0.31)
Hirayama [45]	1984	Japan	P	200	1.45 (1.02 to 2.08)	0.37 (0.18)
Hole *et al* [46]	1989	Scotland	P	6	1.89 (0.22 to 16.12)	0.64 (1.10)
Humble *et al* [47]	1987	USA	CC	20	2.20 (0.76 to 6.56)	0.79 (0.55)
IARC (Kreuzer) [8]	2004	Germany	CC	100	0.80 (0.50 to 1.30)	-0.22 (0.24)
Inoue and Hirayama [48]	1988	Japan	CC	28	2.25 (0.77 to 8.85)	0.81 (0.62)
Janerich *et al* [49]	1990	USA	CC	146	0.75 (0.47 to 1.20)[f]	-0.29 (0.24)
Jee *et al* [50]	1999	Korea	P	79	1.72 (0.93 to 3.18)	0.54 (0.31)
Johnson *et al* [51]	2001	Canada	CC	71	1.20 (0.62 to 3.30)	0.18 (0.33)
Kabat and Wynder [52]	1984	USA	CC	53	0.79 (0.25 to 2.45)	-0.24 (0.58)
Kabat *et al* [53]	1995	USA	CC	69	1.08 (0.60 to 1.94)	0.08 (0.30)
Kalandidi *et al* [54]	1990	Greece	CC	91	2.11 (1.09 to 4.08)	0.75 (0.34)
Koo *et al* [55]	1987	Hong Kong	CC	88	1.64 (0.87 to 3.09)	0.49 (.032)
Lagarde *et al* [56]	2001	Sweden	CC	242	1.15 (0.84 to 1.58)[f]	0.14 (0.16)
Lam [57]	1985	Hong Kong	CC	75	2.01 (1.09 to 3.72)	0.50 (0.18)
Lam *et al* [58]	1987	Hong Kong	CC	202	1.65 (1.16 to 2.35)	0.70 (0.31)
Layard [59]	1994	USA	CC	39	0.58 (0.30 to 1.13)	-0.54 (0.34)
Lee *et al* [60]	1986	UK	CC	32	1.00 (0.37 to 2.71)	0.00 (0.51)
Lee *et al* [61]	2000	Taiwan	CC	268	1.87 (1.29 to 2.71)	0.63 (0.19)
Liu *et al* [62]	1991	China	CC	54	0.77 (0.30 to 1.96)	-0.26 (0.48)
Liu *et al* [63]	1993	China	CC	38	1.72 (0.77 to 3.87)	0.54 (0.41)
Malats *et al* [64]	2000	Europe/Brazil	CC	105	1.50 (0.77 to 2.91)[f]	0.41 (0.34)
McGhee *et al* [65]	2005	Hong Kong	CC	179	1.38 (0.94 to 2.04)	0.32 (0.20)
Nishino *et al* [66]	2001	Japan	P	24	1.80 (0.67 to 4.60)	0.59 (0.49)
Ohno *et al* [67]	2002	Japan	CC	191	1.00 (0.67 to 1.49)[g]	0.00 (0.20)
Pershagen *et al* [68]	1987	Sweden	CC	83	1.20 (0.70 to 2.10)	0.18 (0.28)
Rapiti *et al* [69]	1999	India	CC	41	1.20 (0.50 to 2.90)	0.18 (0.45)
Rylander and Axelsson [70]	2006	Sweden	CC	31	1.37 (0.57 to 3.30)[f]	0.31 (0.45)
Schwartz *et al* [71]	1996	USA	CC	185	1.10 (0.72 to 1.68)[f]	0.10 (0.22)
Seow *et al* [72]	2002	Singapore	CC	176	1.29 (0.93 to 1.80)	0.26 (0.17)
Shen *et al* [73]	1998	China	CC	70	0.75 (0.31 to 1.78)	-0.29 (0.45)
Shimizu *et al* [74]	1988	Japan	CC	90	1.08 (0.64 to 1.82)	0.08 (0.27)
Sobue [75]	1990	Japan	CC	144	1.13 (0.78 to 1.63)	0.12 (0.19)
Speizer *et al* [76]	1999	USA	P	35	1.50 (0.30 to 6.30)	0.41 (0.78)
Stockwell *et al* [77]	1992	USA	CC	210	1.60 (0.80 to 3.00)	0.47 (0.34)
Sun *et al* [78]	1996	China	CC	230	1.16 (0.80 to 1.69)	0.15 (0.19)
Svensson *et al* [79]	1989	Sweden	CC	38	1.36 (0.53 to 3.49)	0.31 (0.48)
Trichopoulos *et al* [80]	1983	Greece	CC	77	2.08 (1.20 to 3.59)	0.73 (0.28)
Vineis *et al* [81]	2005	Western Europe	P	70	1.05 (0.55 to 2.02)	0.05 (0.33)
Wang *et al* [82]	1996	China	CC	82	2.53 (1.26 to 5.10)	0.93 (0.36)
Wang *et al* [83]	1996	China	CC	135	1.11 (0.67 to 1.84)	0.10 (0.26)
Wang *et al* [84]	2000	China	CC	200	1.03 (0.60 to 1.70)	0.03 (0.27)
Wu *et al* [85]	1985	USA	CC	31	1.20 (0.50 to 3.30)	0.18 (0.48)
Wu-Williams *et al* [18]	1990	China	CC	417	0.70 (0.60 to 0.90)	-0.36 (0.10)
Zaridze *et al* [86]	1998	Russia	CC	189	1.53 (1.06 to 2.21)	0.43 (0.19)
Zatloukal *et al* [87]	2003	Czech Republic	CC	84	0.48 (0.21 to 1.09)[h]	-0.73 (0.42)
Zheng *et al* [88]	1997	China	CC	69	2.52 (1.09 to 5.85)	0.92 (0.43)
Zhong *et al* [89]	1999	China	CC	504	1.10 (0.80 to 1.50)	0.10 (0.16)

[a] P = prospective; CC = case-control
[b] Number of lung cancer cases in female lifelong nonsmokers
[c] RR = Relative risk of lung cancer in nonsmoking females (baseline = husband nonsmoker); 95% CI = 95% confidence interval for RR
[d] β = Slope of relationship of log RR to dose, with dose set as 1 for exposed and 0 for unexposed; SE(β) = standard error of β
[e] Based on data for two control groups combined
[f] Relative risks were presented for sexes combined and assumed to apply to each sex separately, with confidence intervals weighted according to number of subjects by sex
[g] Based on data for hospital controls. Data for population controls not used as non-response rate very high
[h] Based on data for two pathological groups of lung cancer combined

Table 20 Effect of adjustment for confounding and correction for misclassification on the estimated risk of lung cancer in lifelong nonsmoking females in relation to smoking by the husband (random-effects models)

Studies	N	Unadjusted for confounding Uncorrected for misclassification RR (95% CI)	Adjusted for confounding[a] Uncorrected for misclassification RR (95% CI)	Adjusted for confounding[a] Corrected for misclassification[b] RR (95% CI)
All	**67**	**1.215 (1.124 to 1.313)**	**1.136 (1.050 to 1.230)**	**1.064 (0.974 to 1.161)**
USA and Canada	21	1.111 (1.009 to 1.224)	1.039 (0.943 to 1.144)	0.928 (0.835 to 1.032)
Europe	16	1.229 (1.047 to 1.443)	1.145 (0.972 to 1.350)	1.120 (0.939 to 1.335)
China (including Hong Kong)	18	1.258 (1.034 to 1.529)	1.178 (0.966 to 1.437)	1.082 (0.873 to 1.341)
Rest of Asia	12	1.365 (1.191 to 1.565)	1.271 (1.109 to 1.457)	1.238 (1.073 to 1.427)
USA, Canada and Europe	37	1.149 (1.059 to 1.247)	1.074 (0.986 to 1.169)	0.998 (0.905 to 1.100)
Asia	30	1.299 (1.136 to 1.485)	1.215 (1.061 to 1.391)	1.144 (0.987 to 1.327)
Published in 1980s	25	1.385 (1.233 to 1.555)	1.289 (1.148 to 1.448)	1.223 (1.080 to 1.384)
Published in 1990s	27	1.152 (1.016 to 1.305)	1.077 (0.948 to 1.225)	0.992 (0.859 to 1.145)
Published in 2000s	15	1.163 (1.009 to 1.340)	1.089 (0.944 to 1.257)	1.043 (0.898 to 1.210)
<100 cases	39	1.334 (1.170 to 1.523)	1.246 (1.089 to 1.424)	1.181 (1.020 to 1.368)
100-199 cases	14	1.136 (1.018 to 1.267)	1.057 (0.947 to 1.179)	0.997 (0.887 to 1.120)
200-399 cases	9	1.351 (1.188 to 1.536)	1.266 (1.113 to 1.439)	1.198 (1.040 to 1.379)
400+ cases	5	1.014 (0.815 to 1.262)	0.951 (0.757 to 1.195)	0.848 (0.663 to 1.086)
With dose-response data[c]	23	1.314 (1.179 to 1.464)	1.231 (1.105 to 1.372)	1.170 (1.040 to 1.316)
Without dose-response data	44	1.155 (1.045 to 1.277)	1.079 (0.974 to 1.196)	1.002 (0.895 to 1.123)
With age adjustment[d]	55	1.152 (1.067 to 1.244)	1.078 (0.996 to 1.166)	1.008 (0.923 to 1.101)
Without age adjustment	12	1.585 (1.288 to 1.952)	1.481 (1.198 to 1.830)	1.402 (1.105 to 1.779)
Case-control studies	57	1.214 (1.111 to 1.326)	1.134 (1.036 to 1.240)	1.056 (0.955 to 1.166)
Prospective studies	10	1.223 (1.047 to 1.428)	1.149 (0.983 to 1.342)	1.101 (0.936 to 1.297)

[a] Adjusted for confounding by fruit, vegetables and dietary fat consumption and by education

[b] Using the Lee and Forey method [4] 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

[c] Specifically for smoking by the husband

[d] Or matching (within nonsmokers)

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