A REVIEW OF THE EPIDEMIOLOGY OF ETS AND HEART DISEASE

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EXECUTIVE SUMMARY

It has been suggested that epidemiological studies of heart disease in nonsmokers support the hypothesis that environmental tobacco smoke (ETS) causes heart disease. This document examines this suggestion in detail, presenting an extensive review of the epidemiological evidence.

Data from 23 epidemiological studies of ETS and heart disease among lifelong nonsmokers have been considered. Nearly all the studies present results for females, with about half presenting results for males. A variety of indices of ETS exposure have been used in these studies. Most studies present results relating to smoking by the spouse, or other index of at-home ETS exposure, with workplace ETS exposure the other commonly used index. Spousal results relate sometimes to current and sometimes to ever smoking by the husband/wife.

The epidemiological evidence relating ETS and heart disease is most unconvincing. There is no significant association with ETS exposure in the workplace. While the overall data from the 23 studies do show a significant association with spousal smoking, whether ever smoking by the spouse (relative risk adjusted for covariates 1.07, 95% CI 1.03-1.10) or current smoking by the spouse (1.08, 95% CI 1.05-1.12) is used as the index, the association is quite weak and could well be a result of various forms of bias. These include:

(i) misclassification of smoking habits - there is evidence suggesting that smokers with non-fatal myocardial infarction, who are at high risk of subsequent death from heart disease, often ignore advice by their doctors to give up smoking but deny smoking on interview;

(ii) uncontrolled confounding - although adjustment for potential confounding factors was frequently found to modify spousal smoking relative risk estimates substantially, many studies had not controlled even for the major coronary risk factors;

(iii) recall bias - independent validation of reported ETS exposure was hardly ever carried out, and one study that did so provided strongly suggestive evidence that presence of disease may affect responses to questions on ETS exposure; and

(iv) publication bias - there was a clear tendency for spousal smoking relative risk estimates to be higher in smaller studies, consistent with publication bias.

There is also striking evidence of variation in spousal smoking relative risk estimates between three groups of studies:

(i) three recent studies without any apparent major weaknesses, each involving more than 1000 cases. In these there was no clear evidence of any increased risks (ever smoking by spouse 1.02, 95% CI 0.99-1.06; current smoking by spouse 1.04, 95% CI 1.00-1.08),

(ii) five other studies also without major weaknesses but generally involving less than 1000 cases. In these the relative risk estimates were lower but still indicative of a positive association (ever or current smoking by spouse 1.22, 95% CI 1.11-1.34), and

(iii) the remaining studies, which were reported only as abstracts or dissertations, involved less than 100 heart disease cases, and/or had identified major weaknesses. In such studies the spousal smoking relative risk estimates tended to be very high (ever smoking by spouse 1.50, 95% CI 1.30-1.72; current smoking by spouse 1.54, 95% CI 1.33-1.77).

It was also notable that, though there was some evidence of a dose-relationship in the last two groups of studies, there was no evidence of such a relationship in the first group, which included one study involving almost 15,000 heart disease deaths in nonsmokers.

When all the evidence is considered, the epidemiological data do not demonstrate that exposure to ETS increases the risk of heart disease.

This document also contains a briefer commentary dismissing claims by Glantz and Parmley that clinical and laboratory evidence demonstrates that ETS causes heart disease.

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1. Introduction

1.1 Objectives

The objective of this review is to provide a comprehensive compilation, analysis and interpretation of the epidemiological data on environmental tobacco smoke (ETS) and heart disease.

1.2 Need for a further review

This document concerns itself particularly with data from 23 studies [1-23]. While a number of previous reviews of the evidence have been published [e.g. 24-28], there are various reasons why a further review is felt necessary. First, further data have been rapidly accumulating, rendering earlier reviews out-of-date. Notably results of three very large studies [16,17,21], each involving over a thousand deaths, have been reported during 1995 and 1996. Second, the great majority of reviews have restricted their attention to a single index of ETS exposure, based on spousal smoking, ignoring the growing information about workplace ETS exposure and on other indices of exposure. Recently, also, it has been suggested [21] that it may be important to distinguish results for current and lifetime ETS exposure, and this review investigates this. Third, it is felt that some previous reviews have not always paid adequate attention to the various sources of bias that could affect the apparent association of ETS and heart disease or studied the way in which the association varies with differing factors, such as location, size and time of publication of the study. Finally, conclusions of earlier reviews have varied, with some reviews considering that a relationship has been established [24,25] and others that it has not been [26-28].

1.3 Structure of the review

Section 2 of this review concerns the materials and methods used, including the criteria used for selecting and rejecting studies and data, and the contents of the tables and meta-analyses used to summarize the data.

The main characteristics of the 23 studies selected are summarized in Section 3 and described in more detail in appendices.

The data relating heart disease in nonsmokers to smoking by the spouse, the most commonly used index of ETS exposure, are considered in detail in Section 4.

Data on smoking in the workplace are considered in Section 5, while Section 6 considers data for other indices of exposure, and Section 7 concerns some other aspects of the data.

The overall data are interpreted in Section 8, and conclusions are summarized in Section 9.

Following acknowledgements, in Section 10, and references, in Section 11, the tables presenting the results are given. Finally, a number of Appendices provide additional detail.

2. Methods

2.1 Selection of studies

Relevant studies were obtained from previous reviews updated by a literature search. All data identified by the end of 1996 are included in this review.

Following precedent, attention was restricted to studies of lifelong nonsmokers. There are three reasons for this. First, the great majority of the epidemiological evidence concerns never smokers. Second, there is little public concern about possible effects of ETS on the health of smokers. Third, in view of the association of active smoking with heart disease risk, it is likely to be extremely difficult reliably to detect any possible effects of ETS exposure in the presence of a history of smoking [28].

2.2 Exposure indices

Indices of ETS exposure, in all studies, have been based on questionnaire responses, with only one study [19] also attempting to estimate exposure by use of serum cotinine.

2.3 Extraction of relative risk data

An attempt has been made to extract all relevant relative risks and 95% confidence intervals (CIs) from the published sources, not only for spousal smoking, but also for workplace ETS exposure and all other indices for which data have been reported. Where studies present appropriate data on numbers of cases and controls for the various exposure categories, relative risks and 95% CIs are calculated, or checked, using the CIA program based on the methods described by Morris and Gardner [29] and made available by the British Medical Journal. For case-control studies, relative risks are estimated by the odds ratio $R = ad/bc$, where a is the number of exposed cases, b is the number of unexposed cases, c is the number of exposed controls and d is the number of unexposed controls, the variance of log R being estimated by $\text{var log } R = a^{-1} + b^{-1} + c^{-1} + d^{-1}$. For cross-sectional studies, the same formulae are used, but here a, b, c, d are defined by the 2x2 table dividing subjects according to exposure and to presence of heart disease. For prospective studies, the formula for the relative risk is the same, but here c and d are the numbers of exposed and unexposed subjects at risk. Here var log R is estimated by $a^{-1} + b^{-1} - c^{-1} - d^{-1}$. Appendix A gives details of how the cited data were extracted from

the source and other references [1-23,25,30]. All data extracted were independently checked.

2.4 Adjustment for covariates

In the tables presenting the results relating to the various indices of ETS exposure relative risks and CIs are usually presented both unadjusted and adjusted for covariates. In some tables, however, relative risks presented (and in some cases also CIs) are adjusted for covariates, if adjusted data are available, and otherwise are unadjusted. Where, in some studies, the source publication provides more than one adjusted estimate, the data that are adjusted for most covariates are normally presented. Appendix B gives details of the covariates taken into account in the analyses presented.

2.5 Meta-analysis

Combined estimates of relative risk from unadjusted and covariate adjusted results for the various indices of exposure are obtained by fixed effects meta-analysis [31]. In meta-analyses of covariate adjusted results, unadjusted results are used where covariate adjusted results are not available. Similarly covariate adjusted results are used in meta-analyses of unadjusted results where necessary. In the case of spousal smoking fixed effects meta-analysis is also applied to various subsets of results. Because the fixed effects method takes no account of other differences between studies, e.g. in study quality or the precise index of exposure used, these combined relative risk estimates should be interpreted with caution, particularly when there is significant heterogeneity in the individual risk estimates being combined. For those meta-analyses that show heterogeneity, the preferred method of approach is to look for the sources of the heterogeneity, as recommended in the recent guidelines of an expert working group [32]. However, on some occasions, results of random effects meta-analyses are also presented, based on the likelihood approach of Hardy and Thompson [33].

3. Study characteristics

3.1 Introduction

The review focuses on 23 studies of heart disease and ETS exposure for which results have been separately presented for lifelong never smokers [1-23]. Table 1 gives details for each study of the first author of the main publication describing the results of the study, its year of publication, the location of the study, the type of study design used, the endpoints considered, and the total number of heart disease cases studied in female and male lifelong nonsmokers. Appendix C gives a brief further description of the studies commenting on their strengths and weaknesses. Summarized below are some main impressions to be gained from this material.

3.2 Dates of publication

The first study to present data on ETS and heart disease was the interim report, in 1981, from the Hirayama study [41], which published updated results in 1984. Between 1985 and 1988 six further studies reported findings. Over the period 1989 to 1994 only eight additional studies were reported, but recently, in 1995 to 1996, a further eight studies have presented their findings.

3.3 Form of publication

Although the findings in most of the studies have been presented in published papers, some have been reported only in abstracts [4,7,18,23], in an abstract plus a review paper [22,40], theses [6,11], or as a letter [14].

3.4 Location

Thirteen studies have been conducted in the USA, four in Western Europe (two Scotland, one England, one Italy), three in Asia (two China, one Japan), two in Australasia (one Australia, one New Zealand), and one in South America (Argentina). No study has been reported from Eastern Europe or Africa.

3.5 Study type and endpoints

There were 10 studies of prospective, 10 of case-control and three of cross-sectional design.

In eight of the prospective studies [1,2,6,8,10,12,17,21] the endpoint was death from heart disease, but in two [5,22] onset of new non-fatal events was also included as an endpoint.

There were four hospital case-control studies [3,14,20,23] in which living heart disease cases were compared with appropriate control patients. In the two Chinese case-control studies [9,15], hospital patients were compared with a mixture of population and hospital controls. In one case-control study [7], the nature of the control group was not stated. In the two Australasian case-control studies [11,13], both living and dead cases were compared with population controls. In one case-control study [16], both cases and controls were decedents.

In the cross-sectional studies [4,18,19] subjects reported on presence or history of heart disease. In one of these [19], subjects also attended for clinical procedures, including ECG.

3.6 Cases

Two of the studies did not report on the total number of heart disease cases occurring in lifelong nonsmokers. Among those who did three involved less than 50 cases, five involved 50-100 cases, five involved 101-200 cases, four involved 201-500 cases and four more than 1000 cases. The largest study [17] involved substantially more cases, 14891, than all the remaining studies put together.

3.7 Sex

Results were reported for females in 19 studies and for males in 11 studies. Three studies only reported findings for sexes combined.

3.8 Interviews

In the prospective and cross-sectional studies subjects were interviewed directly. This was also true for many of the case-control studies. There were some exceptions, however:

(i) In the study by Jackson [11] , data for 43% of cases and 34% of controls came

from a study of coronary deaths and presumably would have been obtained from the next-of-kin.

(ii) In the study by Dobson [13], data were obtained by completely different methods for cases and controls, which could have led to bias. For cases, survivors were interviewed in hospital by study nurses, with information for decedents being collected from medical records, if available, or by questionnaires mailed to relatives. For controls, all information was obtained directly.

(iii) The study by Layard [16] involved interviewing next-of-kin of decedents from heart disease (cases) and from causes not generally considered to be smoking related (controls).

3.9 Confirmation of smoking status

The great majority of the studies involved the collection of data on the smoking habit of the subject from only one source, making no attempt to confirm from another source that the subject was indeed a lifelong nonsmoker, or to use biochemical measures to try to corroborate current nonsmoking status. Exceptionally, three prospective studies require comment:

(i) Svendsen [5] measured serum thiocyanate and carbon monoxide levels in their male subjects but did not attempt to use these data to question reported smoking status, only using them to compare levels according to the smoking status of the wife.

(ii) Tunstall-Pedoe [19] measured serum cotinine levels and excluded those with concentrations above 17.5 ng/ml from the self-reported never smokers which their analyses concerned.

(iii) Steenland [21] collected data from both husband and wife concerning both their own smoking habits and those of their spouse. In some analyses, attention was restricted to subjects where the data on ETS exposure obtained from both sources were the same. However no attempt was made to exclude subjects who reported never smoking themselves but whose spouse reported they had smoked.

It can be seen that only one of these, Tunstall-Pedoe [19], actually excluded subjects whose never smoking status was contradicted by other data.

3.10 Data on potential confounding variables

The studies involved the collection of variable amounts of information on potential confounding variables. See Appendix B for details of how these data were taken into account in the analyses. With some exceptions, virtually all studies adjusted or matched for age, and specifically restricted attention to married women and/or adjusted for marital status in the analysis of spousal smoking. The most commonly considered other risk factors were blood pressure (in 13 studies), cholesterol (ten studies), social class/education/income (nine studies) and obesity/weight (nine studies). No other risk factor was considered in more than five studies. It was notable that only one study [22] adjusted for any indices of dietary intake (other than cholesterol or obesity/weight).

3.11 Strengths and weaknesses of the studies

Appendix C describes strengths and weaknesses specific to a number of studies. Weaknesses include a small number of cases studied (eight of the 23 studies involved less than 100), a seriously incomplete follow-up of deaths in prospective studies [1,8], failure to confirm nonsmoking status or ETS exposure from an independent source (studies that do so are the exception rather than the rule), and limited control of confounding variables (see also Appendix B). It is also notable that in four studies [1,2,8,9] errors were made in presenting findings that were later corrected. Perhaps the most obvious major weakness in any of the studies was in the Dobson study [13] where data for cases and controls were collected in a completely different way. It is also important to note that the Tunstall-Pedoe study [19] used a subjective ETS exposure index which was shown, by use of cotinine data (see Section C20), to produce strongly biased results. Also, for a number of the studies reported in abstracts [4,7,18,23], it was not possible to identify their strengths and weaknesses clearly.

4. Smoking by the spouse

4.1 Introduction

Table 2 summarizes the exposure indices used. In 16 of the 23 studies the index is actually based on smoking by the spouse, but in seven studies it is based on the nearest equivalent index available. In five of these seven, the index is based on ETS exposure at home, but in two of them it is based either on overall ETS exposure [19] or on exposure at home or at work [22].

In eight studies, the index of exposure is based on comparison of ever/never smoking status by the spouse (or cohabitant). In one study [23], the comparison is between subjects whose spouse has ever smoked with subjects with no close contact relative (spouse and children) who has ever smoked. In seven further studies, the index is based on current/non-current ETS exposure. One study [12] bases the comparison on current/never spousal smoking. In six studies, the data allow calculation of both ever/never and current/never smoking by the spouse.

Table 3 summarizes the relative risks and 95% CIs reported in relation to smoking by the spouse for the 23 studies. Data are shown both unadjusted and adjusted for covariates, with significant ($p<0.05$) positive or negative relative risks indicated by a + or - sign respectively. Where the source gave data separately for fatal and non-fatal heart disease, relative risks and CIs based on the combined data are included in the main body of the table (and in all subsequent meta-analyses except where stated), with the data for fatal heart disease shown in the footnotes.

Results of various meta-analyses of these data are shown in Table 4, where *ever smoking* data are used if a choice is available, and in Table 5, where *current smoking* data are used if possible. Combined relative risk estimates are presented, based on all the relevant estimates available, and also for various subgroups of estimates. The covariate adjusted meta-analyses are based on covariate adjusted data, if available for a study, and on unadjusted data, if not. Similarly covariate adjusted data are used in the unadjusted meta-analyses, if unadjusted data are not available. Note that both relative risks and CIs must be available for the data to be used in the meta-analyses. Thus estimates from the

Palmer [7] and Mannino [18] studies, and the covariate-adjusted estimate from the Martin [4] study are not considered.

While Tables 3 to 5 concern simple exposed/unexposed comparisons, a number of studies present relative risks by extent of smoking by the spouse. These data are summarized in Table 6.

The conclusions to be drawn from the material presented in Tables 3 to 6 are described in the paragraphs that follow.

4.2 Overall association

Based on the overall data, which involve over 24,000 heart disease cases in lifelong nonsmoking men and women, the relative risk associated with ever smoking by the spouse is estimated using fixed-effects meta-analysis as 1.02 (95% CI 0.99-1.06) for the unadjusted data and 1.07 (95% CI 1.03-1.10) for the covariate adjusted data. The estimates associated with current smoking by the spouse are very similar, at 1.04 (95% CI 1.00-1.07) for the unadjusted data and 1.08 (95% CI 1.05-1.12) for the adjusted data. The differences between the adjusted and the unadjusted data can largely be explained by the female results for the Sandler study [8] where a crude relative risk of 0.70 which was significantly negative (95% CI 0.62-0.79) became significantly positive, at 1.19 (95% CI 1.04-1.36), after adjustment for age, housing quality, schooling and marital status.

Whether one considers data unadjusted or adjusted for covariates, and whether ever smoking or current smoking by the spouse is the index of exposure, there is evidence of highly significant heterogeneity ($p<0.01$ or $p<0.001$) between the individual study estimates. The heterogeneity is greatest for the unadjusted data, due to the contribution of the Sandler data for females. Even in the covariate adjusted data the heterogeneity is clear, the greatest contributors to it being the high relative risk estimates for Martin, Jackson (females), Dobson (females), and Tunstall-Pedoe, each of which is statistically significant, with the lower 95% CI above or close to the meta-analysis estimate, and the low relative risk for LeVois (males) which has an upper 95% CI below

the meta-analysis estimate.

One method of attempting to take account of this is to use random-effects meta-analysis which considers variation between study as well as within study. Using the Hardy and Thompson method [33] this gives somewhat higher estimates, both for ever smoking by the spouse (1.20, 95% CI 1.07-1.38 unadjusted, 1.18, 95% CI 1.08-1.32 covariate adjusted) and for current smoking by the spouse (1.20, 95% CI 1.08-1.38 unadjusted, 1.20, 95% CI 1.11-1.35 adjusted), all of which are highly significant ($p<0.001$). However, such random-effects estimates are open to question [32,42] and it is more helpful to look at variation in relative risk according to various study characteristics in order to try to explain the heterogeneity between the individual estimates. In the sections that follow, where results given in Tables 4 and 5 are summarized, attention, unless otherwise stated, is restricted to *fixed-effects* meta-analyses of *covariate adjusted* data for spouse *ever smoking*. Patterns seen are largely invariant of adjustment or the precise index of exposure used, reference being made to any exceptions.

4.3 Sex

Relative risk estimates are similar for females (1.07, 95% CI 1.02-1.11, based on 18 studies) and males (1.04, 95% CI 0.99-1.11, based on 11 studies). The relative risk estimate is also similar for the 12 studies which provide combined sex estimates (1.05, 95% CI 1.02-1.09).

4.4 Continent

Relative risk estimates vary significantly ($p<0.001$) by continent, being substantially higher in studies in Australasia and South America (1.59, 95% CI 1.22-2.08) and in Europe (1.34, 95% CI 1.11-1.61) than in Asia (1.18, 95% CI 0.97-1.44) or the USA (1.05, 95% CI 1.01-1.08). Note the much smaller confidence intervals for the US data, which include the four largest studies [8,16,17,21], involving over 21,000 of the heart disease cases.

4.5 Publication date

Relative risk estimates vary significantly ($p<0.001$) by publication date, being substantially higher for studies published in 1984-88 (1.22, 95% CI 1.04-1.44) and in 1989-94 (1.30, 95% CI 1.17-1.43) than in 1995-96 (1.03, 95% CI 1.00-1.07). The estimate for 1995-96 is contributed to by the three largest studies [16,17,21], none of which reported a significant association in either sex for ever smoking by the spouse, and only one of which [21] did so for current smoking by the spouse, and then only in males and not in females. (Note that the pattern is somewhat different for the data unadjusted for covariates, with less evidence of heterogeneity ($p<0.05$), and the relative risk estimates in 1989-94 notably lower than for the adjusted data.)

4.6 Study size

A striking, and highly significant ($p<0.001$), tendency is seen for relative risk to vary by study size, with risks highest for the smallest studies (1.53, 95% CI 1.21-1.92 for <100 cases), intermediate for medium size studies (1.33, 95% CI 1.18-1.50 for 100-999 cases) and only slightly elevated for the largest studies (1.04, 95% CI 1.00-1.07 for 1000+ cases).

4.7 Study type

There was some evidence ($p<0.05$) of variation by study type, with relative risk estimates higher for the two cross-sectional studies (1.45, 95% CI 1.15-1.84) than for the case-control studies (1.11, 95% CI 0.99-1.24) or the prospective studies (1.05, 95% CI 1.02-1.09).

4.8 Fatal heart disease

Eleven studies provided estimates specific to fatal heart disease. The relative risk and 95% CI for these studies (1.05, 1.01-1.08) was similar to that given above for the prospective studies, since only one prospective study [22] did not provide fatal data separately and only two case-control studies [11,16] provided fatal data. The relative risk for the other studies was 1.42 (95% CI 1.23-1.63).

4.9 Consideration of confounding variables

There was no significant difference in relative risk between studies where at least

some confounders (other than age or marital status) had been considered (1.06, 95% CI 1.03-1.10) and studies where none had (1.19, 95% CI 1.01-1.40).

4.10 Spousal smoking the index

Relative risks were highly significantly ($p<0.001$) higher where spousal smoking was not the index (1.31, 95% CI 1.19-1.44) than where it was (1.04, 95% CI 1.00-1.07).

4.11 Dose-response data

Relative risks were highly significantly ($p<0.001$) lower for the 12 studies providing dose-response data in Table 6 (1.04, 95% CI 1.01-1.08) than for the other studies (1.27, 95% CI 1.15-1.40).

Based on the dose-response data shown in Table 6 for the 12 studies providing data, it can be seen that six studies showed trends (including the non-exposed group) which were significant at $p<0.05$. Examination of these data, however, shows that there is a striking contrast between the results of the three recently reported large US prospective studies [16,17,21], none of which show a significant trend (or even any real indication at all of a tendency for risk to rise with level of exposure, except perhaps for some of the Steenland results), and the results of the other nine, smaller studies [1,5,9,10,11,14,19,22,23]. These studies all show, with the single exception of Jackson (males) a tendency for risk to rise monotonically with dose, with eight of the 12 trends significant. In some of the studies, particularly He 1 [9], the reported relative risks for the most exposed groups seem remarkably large when viewed in the light of the relative risk for active smoking (see Section 8.3).

4.12 Study quality

Formal assessment of study quality is a difficult, and somewhat subjective, exercise. It is clear that some weaknesses, such as failure independently to confirm from other sources nonsmoking status or ETS exposure, apply to virtually all the studies. In addition, in a number of studies control for confounding variables has been rather inadequate. Study-specific weaknesses have been described in Appendix C and summarized in Section 3.11.

One possible way of attempting to obtain a database of improved quality is to exclude studies with obvious major weaknesses, or that have not demonstrated their scientific validity. Proceeding along these lines, one might reject the following studies:

(i) Studies only reported as abstracts or dissertations, which have not been subject to peer review (Martin [4], Butler [6], Palmer [7], Jackson [11], Mannino [18], Kawachi [22] and Ciruzzi [23]);

(ii) Studies involving less than 100 heart disease cases, which are not only likely to suffer from excessive variability in their results, but are also likely to be unrepresentative due to publication bias, which affects small studies much more than large studies (Garland [2], Svendsen [5], Butler [6], He I [9], Jackson [11], Humble [12], and He II [15]);

(iii) Studies where there was a clear non-comparability between the way the data were collected for cases and controls (Dobson [13]); and

(iv) (As regards spousal data) studies where the exposure index used seemed particularly susceptible to bias and was actually shown to be so (Tunstall-Pedoe [19]).

This leaves nine studies [1,3,8,10,14,16,17,20,21] which may be regarded as of better quality (though, as noted in Appendix C, a number still have weaknesses). The meta-analysis relative risk and 95% CI for these nine studies based on covariate adjusted data for spouse ever smoking is 1.05 (95% CI 1.01-1.08), based on 17 estimates, as compared with 1.50 (95% CI 1.30-1.72), based on 14 estimates, for the other studies providing data. These two estimates highly significantly differ ($p<0.001$). For spouse

current smoker the relative risks, 1.06 (95% CI 1.03-1.10) for the better quality studies, and 1.53 (95% CI 1.33-1.77) for the worse quality studies, similarly differ.

4.13 Sensitivity analyses

The meta-analyses of data for ever smoking by spouse (Table 4) and for current smoking by spouse (Table 5) showed significant heterogeneity of risks by continent, publication date, study size, and other factors. However, it seemed likely that much of this heterogeneity had arisen due to the fact that three recently published large US studies (16, 17, 21) had all reported relative risks that were quite close to unity, and with one exception (Steenland/males/current smoking) not statistically significant. Accordingly, it was decided, as a form of sensitivity analysis, to repeat the meta-analyses excluding data from these three studies. Overall, the relative risk, excluding these three studies, was estimated as 1.30 (95% CI 1.20-1.40) for ever smoking by the spouse and 1.31 (95% CI 1.21-1.41) for current smoking by the spouse.

Results of this sensitivity analysis (not presented in full) showed that, for the covariate-adjusted results, there was now no evidence of statistically significant heterogeneity by continent, publication date, study size, or any of the factors considered in Tables 4 and 5, except for study quality. For ever smoking by the spouse, estimates were 1.22 (95% CI 1.11-1.34) for the better quality studies and 1.50 (95% CI 1.30-1.72) for the worse quality studies, with the heterogeneity chi-squared 5.65 on 1 d.f. ($p<0.05$). For current smoking, corresponding estimates were 1.22 (95% CI 1.11-1.34) and 1.53 (95% CI 1.33-1.77), with the heterogeneity chi-squared 6.69 on 1. d.f. ($p<0.01$).

There also still remained some tendency for relative risks to decrease with increasing size. For ever smoking by the spouse, estimates were 1.53 (95% CI 1.21-1.92) for studies with <100 cases, 1.33 (95% CI 1.18-1.50) for 100-999 cases and 1.22 (95% CI 1.09-1.37) for 1000+ cases, with the heterogeneity chi-squared 3.15 on 2 d.f. ($p>0.1$). For current smoking, corresponding estimates were 1.65 (95% CI 1.28-2.12), 1.34 (95% CI 1.19-1.50) and 1.22 (95% CI 1.09-1.37), with the heterogeneity chi-squared 4.71 on 2 d.f. ($0.05<p<0.1$). It should, of course, be noted that total numbers of cases are substantially reduced when the three large US studies are excluded from consideration,

making it more difficult to detect heterogeneity. Nevertheless, the results of the sensitivity analyses confirmed the fact that much of the heterogeneity had arisen because of the low relative risks in the three US studies.

4.14 Summary of results regarding spousal smoking

The overall relative risk estimates, adjusted for covariates as far as the studies have done so, indicate a weak but significant association with both ever smoking by the spouse (1.07, 95% CI 1.03-1.10) and with current smoking by the spouse (1.08, 95% CI 1.05-1.12). After excluding small studies, studies reported as abstracts, and studies with patent major weakness in study design, these estimates reduce slightly, to 1.05 (95% CI 1.01-1.08) for ever smoking by the spouse and to 1.06 (95% CI 1.03-1.10) for current smoking by the spouse. Variation in relative risk estimates by factors such as continent, publication date and index of exposure used can be explained by the existence of three very large US studies, which together account for over 20,000 deaths from heart disease, and show little or no association with ETS (1.02, 95% CI 0.99-1.06 for ever smoking; 1.04, 95% CI 1.00-1.08 for current smoking). The risk in these three studies is much lower than that in the other studies (1.30, 95% CI 1.20-1.40 for ever smoking; 1.31, 95% CI 1.21-1.41 for current smoking). Interpretation of the results, in the light of this marked heterogeneity, and in the light of potential sources of bias, such as publication bias, misclassification bias, and failure fully to adjust for potential confounding variables, will be considered in Section 7.

5. Workplace ETS exposure

Table 7 presents relative risks and 95% CIs for those seven studies that have reported results for workplace ETS exposure. For the unadjusted data, one of the nine estimates presented is statistically significant ($p<0.05$) while, for the adjusted data, none of the 12 estimates is.

Results of meta-analyses shown in Table 8 provide an overall relative risk of 1.06 (95% CI 0.95-1.19) for unadjusted data and 1.07 (95% CI 0.96-1.19) for adjusted data. Neither estimate is statistically significant.

For the adjusted data, there is no statistically significant variation by sex (females 1.08, 95% CI 0.88-1.33; males 1.06, 95% CI 0.93-1.21) or by continent (USA 1.06, 95% CI 0.94-1.19; others 1.16, 95% CI 0.85-1.60). No such variation is seen for the unadjusted data either.

Table 9 reports results relating heart disease risk to extent of ETS exposure for the one study [15] that has reported such data. This shows a significant ($p<0.05$) positive trend (including the non-exposed group) for four of the five indices of exposure used. It should be noted that the relative risk estimates for the highest exposure groups are extremely high, bearing in mind the relative risk for active smoking (see Section 8.3), and have very large variability, based on small numbers of cases and controls. It should also be noted that the data were collected from a case-control study and may be subject to recall bias.

Overall, the data do not convincingly demonstrate the existence of an association between heart disease and workplace ETS exposure.

6. Other indices of ETS exposure

Table 10 collects together data from seven studies relating to various other indices of ETS exposure. The results do not form any consistent pattern. For many of the indices there is either no indication at all of a relationship (e.g. with pipe/cigar smoking by the spouse, with childhood exposure, or with exposure in transportation other than cars) or the relationship is not statistically significant (e.g. with serum cotinine group, with adult exposure or with exposure in cars). However significant findings were reported in two studies. In the study of He II [15], where a significant unadjusted but not adjusted association had been noted earlier, both with spousal and workplace exposure individually, a significant unadjusted association (4.18, 95% CI 1.63-10.92) was reported with joint exposure from both sources, but no adjusted results were presented. In the study by Ciruzzi [23], significant associations, adjusted for covariates, were noted with one or more relatives ever having smoked (1.66, 95% CI 1.2-2.3), and with one or more children ever having smoked (1.73, 95% CI 1.2-2.5).

In view of the fact that each of the various ETS exposure indices considered in Table 10 were generally only examined in one study, it is clear that more data are required before conclusions can be drawn about any of them. The interpretation of the overall epidemiological evidence concerning ETS and heart disease must depend mainly on the evidence relating to spousal and workplace ETS exposure.

7. Other aspects of the data

7.1 Variation in risk by age, sex, social class and race

Only the Hirayama study [1] has reported results relating ETS exposure to heart disease separately for different age groups. Relative risks of mortality in women associated with the husband ever smoking (1.36 1.24, 1.10 and 1.09 for, respectively, age-groups 40-49, 50-59, 60-69 and 70-79) did not vary significantly by the age of the *husband*. Note that Hirayama never adjusted heart disease relative risks for, or presented them by, the age of the women themselves.

The only other study to look for variation in risk for different subsets of their subjects was that by Humble [12]. They separated their overall adjusted estimates of 1.59 (95% CI 0.99-2.57) for spousal smoking into estimates of 1.78 (95% CI 0.86-3.71) for blacks, 1.97 (95% CI 0.72-5.34) for high social status whites, and 0.79 (95% CI 0.32-1.96) for low social status whites. They also noted that a trend in risk over level of husband's smoking was only seen among high social status whites.

Clearly, more data will be needed before one can conclude whether risk of heart disease associated with ETS varies by age, sex, social class or race.

7.2 ETS and symptoms of heart disease

The two studies conducted in Scotland both reported results relating ETS to symptoms of heart disease. In the study of Hole [10] smoking by cohabitants was not found to be associated with either angina (1.11, 95% CI 0.73-1.70) or major ECG abnormalities (1.27, 95% CI 0.48-3.35) after adjustment for covariates. In the study of Tunstall-Pedoe [19], an association was noted, after adjustment for covariates, between self-reported ETS exposure and angina, with relative risks of 1.0, 1.3 (95% CI 0.7-2.3), 1.6 (95% CI 0.9-2.8) and 2.1 (95% CI 1.1-3.9) for, respectively, "none", "little", "some" or "a lot". However, this association disappeared completely when the objective marker, serum cotinine, was used, with relative risks of 1.0, 0.9 (95% CI 0.5-1.4), 1.0 (95% CI 0.6-1.7) and 0.8 (95% CI 0.4-1.5) for, respectively, quartiles I, II, III and IV. In the Tunstall-Pedoe study, results were also presented separately for "undiagnosed CHD" (i.e. questionnaire angina or possible myocardial infarction, or ECG findings of myocardial

infarction or ischaemia in those without diagnosed coronary heart disease) or "diagnosed CHD" (i.e. the reporting of a medical diagnosis of angina, myocardial infarction, coronary thrombosis, or a heart attack). Here, there was no association between serum cotinine and "undiagnosed CHD" (relative risks 1.0, 0.9, 1.2 and 1.0 for the four quartiles), but there was with "diagnosed CHD" (relative risks 1.0, 1.5 (95% CI 0.8-3.0), 1.7 (95% CI 0.8-3.3), and 2.7 (95% CI 1.3-5.6) for the four quartiles.

8. Interpretation

8.1 Weakness of association between heart disease and indices of ETS exposure

As described in Section 5 there is no significant overall association between heart disease and ETS exposure in the *workplace*, with an overall covariate adjusted risk of 1.07 (95% CI 0.96-1.19). Nor does the rather limited evidence discussed in Section 6, relating to *indices other than spousal or workplace exposure*, provide anything more than an indication of a possible association with some, but not others, of the variety of indices studied.

As shown in Section 4, however, the overall covariate adjusted relative risk associated with *spousal smoking* (or in some studies with closely associated indicates, such as at home exposure) was statistically significant. Though significant, this association was very weak, whether *ever smoking* by the spouse (1.07, 95% CI 1.03-1.10) or *current smoking* by the spouse (1.08, 95% CI 1.05-1.12) was used as the index in those studies providing alternative estimates.

The question arises as to whether the weak, but statistically significant, association with spousal smoking indicates a causal relationship between heart disease and ETS exposure. Issues relating to this question are considered below.

8.2 Validity of spousal smoking as a marker of ETS exposure

A limitation of the studies considered in this review is that, with only one exception, indices of ETS exposure have been derived from questionnaire responses rather than from attempts to measure exposure using ambient air concentrations of tobacco smoke constituents or of uptake of constituents in body fluids. The exception was the cross-sectional study by Tunstall-Pedoe [19], which reported no significant association between prevalence of either CHD or questionnaire angina and level of serum cotinine, but in contrast reported a significant association of both CHD and questionnaire angina with answers to a question concerning extent of exposure to tobacco smoke from others in the last few days. The authors suggested the self-reported exposure data could be biased, with study participants with symptoms of disease exaggerating exposure. However, although the results of this study cast doubts on the validity of self-reported

exposure data they do not of themselves indicate that spousal smoking is an invalid marker, as answers to a question on self-reported extent of recent ETS exposure are clearly likely to be much more subjective than answers to a question concerning whether or not a specific person smokes.

There is evidence from a number of studies in US and Western European populations that cotinine levels in nonsmokers are increased in relation to smoking by the husband or self-reported indices of ETS exposure at home [43-48]. However, a recent study of 400 women in Japan [49], which reported nonsignificantly *lower* urinary cotinine in nonsmokers married to smokers than in nonsmokers married to nonsmokers suggests that one cannot necessarily assume that spousal smoking is a valid marker of increased ETS exposure in all populations. More evidence is needed to resolve the apparent conflict with the results of a study conducted in 13 centres in Asia, Europe and the USA [50] which reported that urinary cotinine was significantly positively associated with various indices of ETS exposure. Evidence from ETS biomarker studies is also needed for China and Argentina, countries where associations have been reported between heart disease and ETS exposure.

8.3 Plausibility

The increase in heart disease mortality relating to active smoking, though repeatedly demonstrated and associated with substantial numbers of deaths, is proportionately not large. Thus, in the huge American Cancer Society Prevention Study II, reported risks, relative to lifelong never smokers, were 1.94 (95% CI 1.80-2.08) in male current cigarette smokers, 1.78 (95% CI 1.62-1.97) in female current cigarette smokers, 1.41 (95% CI 1.33-1.50) in male former cigarette smokers and 1.31 (95% CI 1.19-1.44) in female former cigarette smokers, relative risks being somewhat higher in those aged 35-64 (up to about 3-fold for current smokers) than in those aged 65+ [51]. Also, in the British Doctors study, relative risks in males were 1.56 for current cigarette smokers and 1.19 for former cigarette smokers [52].

It is clear that marriage to a smoker is associated with a very much smaller exposure to smoke constituents than is the case for active smoking. For example, a

recent study in Yorkshire in which nonsmoking subjects wore a personal air sampler for 24 hours [53], estimated that having a smoking partner was associated with an increased median ETS exposure of 131 mg of particles and 19.4 mg of nicotine in a *year*. These annual exposures are, respectively, 0.15% and 0.27% of those of a typical 20 a *day* smoker of cigarettes delivering 12 mg of particles and 1 mg of nicotine per cigarette. In another study, a very large cross-sectional survey representative of the US population measuring serum cotinine by state-of-the-art analytical methods [54], the increase in cotinine associated with home ETS exposure was estimated as 0.665 mg/ml, representing only about 0.2% of the average cotinine level of about 300 mg/ml in active smokers. Though estimates of relative exposure of passive to active smokers depend on the smoke constituents measured, and in general will be higher for vapour phase components than for particulate phase components [55], it seems abundantly clear that average ETS exposure involves a substantially lower "dose" of any smoke constituent than obtained from average active smoking. This is underlined by recent reports [56,57] that heavy smokers receive considerably higher *ETS* exposure than is the case for passive smokers.

The relatively modest association of heart disease with active smoking, and the substantially lower exposure to smoke constituents for passive compared to active smokers, suggest strongly that if there is any true relationship of ETS to heart disease it will be very weak indeed. Assuming, as a very rough approximation, a doubling of risk associated with active smoking, and that exposure to spousal smoking involves 1% of the exposure from active smoking, one would expect (assuming a linear relationship) a relative risk of only 1.01 associated with spousal smoking in never smokers. While there are considerable uncertainties in this calculation, it would seem fairly implausible that a true relative risk as high as 1.07 or 1.08 might actually exist, and highly implausible that relative risks of 1.5 or higher (as were reported for a number of the studies - see Table 3) are actually unbiased estimates of actual risk from spousal smoking.

The apparent implausibility of the relative risks reported for ETS exposure in a number of the studies underlines the need to take potential biases very seriously into account. The various sources of possible bias are discussed below.

8.4 Misclassification bias

As clearly demonstrated in a recent literature review [58], there is abundant evidence that a proportion of current or former smokers deny ever having smoked (or are reported by proxy respondents as never having smoked) and are falsely categorized as lifelong nonsmokers. In the literature on ETS and *lung cancer* it has been widely recognized for a number of years [26,59] that inclusion of some misclassified smokers among the lifelong nonsmokers will, because of the tendency for husbands and wives to share smoking habits more often than expected by chance, lead to a higher risk of death in *reported* lifelong nonsmokers married to smokers, even in the absence of any true effect of ETS exposure. Elsewhere [60], I present a detailed analysis of the likely effect of misclassification bias on lung cancer meta-analysis relative risks, using methodology described and justified in detail [61]. Assuming, based on the literature review [58], that the bias is similar to that resulting from 2.5% of average risk ever smokers being misclassified as never smokers, I showed that a meta-analysis relative risk estimate of 1.12 (95% CI 1.01-1.24) for US data on spousal smoking and lung cancer would reduce to 1.00 (95% CI 0.90-1.12) after adjustment for misclassification. For Asian data, where there is evidence of very much higher rates of misclassification [49,62] an unadjusted meta-analysis relative risk estimate of 1.20 (95% CI 1.08-1.34) would reduce to 1.12 (95% CI 1.00-1.25) assuming a 10% misclassification rate or to 1.02 (95% CI 0.90-1.14) assuming a 20% misclassification rate.

One major determinant of the misclassification bias is the excess risk associated with ever having smoked. It is clear that this is substantially higher for lung cancer than for heart disease, perhaps by a factor of 10 or so. All other things being equal, it might be expected, therefore, that misclassification adjustment, instead of reducing spousal smoking relative risks downward by 0.1 or 0.2 as estimated for lung cancer, would only reduce heart disease relative risks by about 0.01 or 0.02. However other things may not be at all equal. There is clear evidence in the literature that misclassification rates are particularly high in patients with diagnosed coronary heart disease advised by their doctor to give up smoking [63], so that misclassified nonsmokers may contain a proportion of subjects with a particularly high risk of subsequent death from heart disease.

This possibility is given some support by recent results from a Danish prospective study in which self-reported smoking habits were recorded and serum samples taken for cotinine determination, in a population then followed up for 8 years [64]. Cumulative heart disease incidence in self-reported nonsmokers found to have cotinine levels above 100 ng/ml, a level inconsistent with nonsmoking, was 17.9%, based on 5 cases. This was not only higher than that in self-reported nonsmokers with cotinine levels below 100 ng/ml, 3.1% based on 43 cases, but was higher than that in self-reported current smokers with cotinine levels above 100 ng/ml, 4.3% based on 72 cases.

Misclassification adjustments for lung cancer have taken account of the fact that the cotinine levels in misclassified current smokers tend to be lower than in properly classified current smokers [58], (though perhaps not in Japan [49]), and that, compared with properly classified ex-smokers, misclassified ex-smokers tend to have smoked less and given up longer ago [58,63]. They have not taken into account the possibility that having the disease diagnosed by a doctor, coupled with advice to give up smoking, may increase the likelihood of denying smoking. This possibility is clearly much more relevant to heart disease than it is to lung cancer and it implies that the tentative preliminary estimate of bias reached above of only 0.01 or 0.02 might be considerably too low. While it is very difficult to come up with any reliable actual estimate of bias, it would certainly seem to be wrong to conclude that misclassification bias is irrelevant, especially considering that the excess risk calculated in Tables 4 and 5 from meta-analyses ignoring misclassification is only 0.07 or 0.08.

8.5 Confounding

Confounding is likely to be particularly relevant in epidemiological studies in which:

(a) There is a weak association between the exposure and the disease of interest,

(b) The extent of apparent association varies between countries and across studies,

(c) There are numerous other risk factors for the disease that are correlated with exposure,

(d) Those risk factors for which data have been collected are subject to error, and

(e) There are risk factors for which data have not been collected.

All these points apply to the association between ETS exposure, as indexed by spousal smoking and heart disease. In particular, it should be noted that:

(a) There is an extremely large number of risk factors for heart disease. A study published 15 years ago identified as many as 246 such factors [65] and numerous others have been reported since. Though not all of these risk factors have an independent effect, it is widely accepted that heart disease is multifactorial.

(b) Detailed analyses based on data from the UK Health and Lifestyle Survey [66] have shown that a wide range of lifestyle factors commonly associated with adverse health are more common in smokers than in nonsmokers, and, in nonsmokers, are more common in those living with a smoker. These analyses led to the conclusion that the magnitude of bias from confounding by multiple risk factors may be important for weak associations. Other studies, too, have concluded that ETS exposure is associated with an increased exposure to other risk factors [e.g. 40,67-69].

(c) Recent analyses based on follow-up data from the UK Health and Lifestyle Survey and on data from the Health Survey for England 1993 [60] have shown that, within nonsmokers, prevalence of heart disease risk factors tends to be more strongly associated with salivary and serum cotinine than it is with questionnaire indices of ETS exposure, such as living with, or marriage to, a smoker.

(d) Many of the epidemiological studies of ETS and heart disease paid only limited attention to potential confounding variables. As is made clear in Appendix B, about half the studies did not appear to take the classical coronary risk factors of blood pressure, cholesterol and body mass index into account, while the proportion of studies taking such factors as exercise, race, alcohol, diabetes and family history of heart disease or hypertension into account was quite low. It was notable that, despite the evidence that dietary habits differ markedly between smokers and nonsmokers and in relation to ETS exposure [66-69], only one study considered any dietary variables as potential confounding factors (except indirectly via cholesterol and obesity). In the study of Hirayama [1], relative risk estimates were not even adjusted for the age of the subject, results only being presented adjusted for the age of the spouse.

The above considerations imply that there is very likely to be some tendency for uncontrolled confounding to have led to overestimation of the ETS/heart disease relative risk, and the theoretical calculations in Thornton and Lee [66] suggest that the magnitude of the potential confounding effect could well be of the same order as the magnitude of the association reported.

Estimating accurately the magnitude of the bias due to uncontrolled confounding from the data presented in the 23 epidemiological studies is extremely difficult, if not impossible. This is partly because studies that do present relative risks adjusted for covariates sometimes do not present unadjusted data for comparison, and, even when they do, only present results in a way which allows one to deduce the effect of adjustment for all the variables considered combined, and not individually. Furthermore, the variables considered as confounders, and the way specific variables are measured and taken into account in analysis, vary widely from study to study.

Nevertheless, it is worth looking at the extent to which adjustment for potential confounding variables has actually affected the reported relative risk estimates associated with spousal smoking in the epidemiological studies. Table 11 summarizes the effects of adjustment, expressing the results by the index $A = \log_e (RR_A / RR_U)$, where RR_A is the adjusted relative risk and RR_U is the unadjusted relative risk. Values of A shown in Table 11 are presented in rank order, being calculated from the relative risks shown in Table 3, with three exceptions:

(a) in the Humble study [12], an age-adjusted relative risk of 1.34, not included in Table 3, was also used;

(b) in the La Vecchia study [14], where sexes combined relative risks were available adjusted for sex, adjusted for sex and age, and adjusted for sex, age and multiple risk factors (respectively 1.17, 1.31 and 1.21); and

(c) in the Kawachi study [40], an age-adjusted relative risk of 1.97, not included in Table 3, was also used.

The 24 values of A included in Table 11 can be divided into four groups:

(i) Five values of A relate to the effect of simple age adjustment, where A has been calculated from the ratio of the *age-adjusted relative risk* to the *crude relative risk*. Of these five values of A, four are positive (Butler current +0.197, Hirayama +0.148, La Vecchia +0.113 and Garland current +0.074) and one is negative (Butler ever -0.278). This suggests that age adjustment tended to increase relative risk estimates, and also that this effect was often quite substantial. The actual effect of age adjustment will in practice vary markedly from one study to another, depending on a number of factors relating to the study (such as whether the subjects were selected to be in a small defined age range in the first place, and where and when the study was conducted - the relative frequency of smoking by age and sex varying regionally and by birth cohort).

(ii) Five values of A relate to the effect of adjusting for factors other than age, where A has been calculated from the ratio of the *relative risk adjusted for age and other factors* to the *relative risk adjusted for age only* (or in one study [4] from the ratio of the relative risk adjusted for other factors only to the crude relative risk). Of these four values of A, one is positive (Humble +0.171) and four are negative (La Vecchia -0.079, Kawachi -0.142, Martin -0.258 and He I -0.853). This suggests that adjustment for other risk factors tended to decrease relative risk estimates, and also that this effect could be quite substantial.

(iii) Eight values of A relate to the effect of adjusting for age and one other factor, where A has been calculated from the ratio of the *relative risk adjusted for age and the factor* to the *crude relative risk*. These eight estimates come from four studies, the other risk factor being "whether marriage ongoing or ended" in the Lee study, social class in the Jackson study, prior history of heart disease in the Dobson study, and race in the Layard study. Six of these estimates are negative and quite small (Layard females -0.010, Jackson males -0.037, Lee females -0.042, Jackson females -0.065, Dobson males -0.070 and Lee males -0.078), one is positive and quite small (Layard males +0.042), and one is positive and large (Dobson females +0.424). It is difficult to draw any overall conclusion from these eight results, inasmuch as they show no clear pattern and they relate to the combined effect of adjustment for age and other factors.

(iv) Six values of A relate to the effect of adjusting for age and multiple risk factors, where A has been calculated from the ratio of the *relative risk adjusted for age and the factors* to the *crude relative risk*. Here four A values are positive (Sandler females +0.531, Sandler males +0.130, Svendsen +0.091 and Tunstall-Pedoe +0.037) while two are negative (Garland -0.262 and He II -0.536). Effects of adjustment in these studies are highly variable and often very large. It should be noted that the risk factors selected in the Sandler study, marital status, education and quality of housing do not include any of the classical coronary risk factors.

Where it was possible to identify separately effects of confounding due to age and due to other risk factors, these analyses suggested that age adjustment tended to increase relative risk estimates and adjustment for other risk factors tended to decrease relative risk estimates. It also seemed from these data that where adjustment for the classical risk factors had been carried out the overall tendency was for the relative risk to be decreased. Thus there were nine studies where at least two of blood pressure, cholesterol and body mass index had been adjusted for (among other factors also taken into account in some cases). In six of these studies, such adjustment had reduced relative risk estimates, usually quite markedly (La Vecchia -0.079, Kawachi -0.142, Martin -0.258, Garland -0.262, He II -0.536, He I -0.853) while in three it had raised them, typically to a smaller extent (Humble +0.171, Svendsen +0.091, Tunstall-Pedoe +0.037). It must be noted, however, that some of the change in relative risk following adjustment in four of these studies (Garland, Svendsen, He II, Tunstall-Pedoe) might have been due to age adjustment as in these studies it was only possible to study the joint effect of adjustment for age and the risk factors.

One striking observation from the data in Table 11 is how large many of the effects of adjustment were. Of the 24 values, four were outside the range -0.4 to +0.4, thus having the effect of multiplying or dividing the relative risk by a factor exceeding 1.49. Seven were outside the range -0.2 to +0.2, equivalent to a factor exceeding 1.22, while 13 were outside the range -0.1 to +0.1, equivalent to a factor exceeding 1.105. When one considers that the meta-analysis relative risk estimate for exposure to current

smoking is only 1.08 (95% CI 1.05-1.12) after such adjustment for covariates as was conducted - frequently only minimal - it seems readily apparent that uncontrolled confounding could be an important contributor to the association.

8.6 Errors in determining ETS exposure/recall bias

Of the 23 epidemiological studies of heart disease and ETS, 10 were of prospective design, 10 were case-control studies and 3 were cross-sectional studies. In case-control and cross-sectional studies, the possibility of recall bias is an important one, in that reporting of ETS exposure may be affected by knowledge of the disease. While the difference may not necessarily have resulted from recall bias, inasmuch as there are other relevant differences between studies of different types, it was notable (see Tables 4 and 5) that there was significant evidence of variation by study type, with risk estimates lowest for prospective studies, the type least susceptible to such bias. Also, as noted in Section 8.2, the Tunstall-Pedoe study [19] has provided strongly suggestive evidence that presence of disease may affect responses to questions on ETS exposure.

In the study of Steenland [21] attempts were made to validate spousal smoking status by conducting an analysis based only on subjects for which data they had provided on their own and their spouse's smoking habits were concordant with those provided by their spouse. In these analyses, relative risks of heart disease, adjusted for multiple covariates, associated with current smoking by the spouse, were 1.23 (95% CI 1.03-1.47) for men and 1.19 (95% CI 0.97-1.45) for women based on, respectively, 1180 and 426 deaths. These relative risks differed somewhat (particularly for women) from those based on the subject's own reported data, of 1.22 (95% CI 1.07-1.40) for men and 1.10 (95% CI 0.96-1.27) for women based on, respectively, 2494 and 1325 deaths. Attempting to estimate the extent of recall bias from these data is difficult, as the numbers of subjects in the two sets of analyses were so very different, the excluded subjects and the included subjects differing in ways other than concordance of smoking data.

8.7 Diagnostic errors

Errors in diagnosis can affect the reported association of ETS and heart disease. Random errors in diagnosis, independent of exposure status, could bias the association in either direction. If heart disease is confused with a disease which is actually unrelated to ETS (or with a disease more weakly associated with ETS than is heart disease) random errors will tend to mask any true association of heart disease with ETS. If, on the other hand, heart disease is confused with a disease that is strongly related to ETS, random errors in diagnosis will tend to exaggerate the association. Non-random errors in diagnosis, with exposure status affecting the probability of a correct diagnosis, may also bias the association.

In the case of the epidemiological studies of ETS and heart disease, there is no doubt that there will be inaccuracies of diagnosis. Thus, the 10 prospective studies, and one of the case-control studies, used death certificate diagnoses, known to be inaccurate [70], with only the Garland [2] and Svendsen [5] studies attempting to validate the diagnosis by examination of hospital records, interviews with physicians and/or study of autopsy material. Also, in the prospective studies of Hirayama [1] and of Sandler [8], follow-up of mortality was seriously inadequate, being limited to subjects dying in the study area. In the case of the other case-control studies, diagnoses were typically made in hospital, with no subsequent confirmation from autopsy material. In the three cross-sectional surveys, the diagnosis was obtained wholly or partly from the subject, also leading to likelihood of error.

None of the studies, not even those which did attempt some validation, provided any information on accuracy of diagnosis. Therefore, attempting to estimate its seriousness or the magnitude and direction of bias due to it, is speculative at best. The only indirect information on the possibility of bias comes from the study of Tunstall-Pedoe [19] which presented relative risks associated with self-reported ETS exposure and with cotinine level separately for the endpoint “diagnosed CHD”, where the subject reported a medical diagnosis of angina, myocardial infarction, coronary thrombosis, or a heart attack, and “undiagnosed CHD”, based on tests carried out at the time of interview. It was notable that, whereas there was no association at all between serum cotinine and undiagnosed CHD, there was a strong association between serum cotinine

and diagnosed CHD. Inasmuch as one would expect the two associations to be similar, if heart disease is truly affected by ETS exposure, the possibility arises that some of the difference in the reported associations arose because ETS exposure was associated with the extent to which subjects report existing, medically diagnosed, disease.

8.8 Lack of comparability of cases and controls

A standard principle of good experimental design is to compare "like with like". It follows that, in case-control studies, care should be taken to avoid systematic differences in which the data are collected for cases and controls. In one study, Dobson [13], it was apparent that this principle had been severely violated, with data collected for cases and controls in a completely different way. Other case-control studies do not have such obvious flaws, and compared with the situation for ETS and lung cancer [60], lack of comparability of cases and controls seems very much less of a problem.

8.9 Publication bias

It is well documented that, in many situations, scientists tend to be less likely to submit for publication, or journals less likely to publish, results from studies that do not find a significant positive relationship between the risk factor and the disease studied [71-73]. In these situations, meta-analyses derived from results in the published literature will tend to overstate the magnitude and significance of the true relationship.

The question arises as to whether such publication bias could have affected the representativeness of the published evidence on ETS and heart disease. In fact, there are a number of reasons to justify concern that publication bias might have had quite a major effect:

(i) There is, as noted in Section 4.6, a striking tendency for heart disease relative risks to be higher in studies with small numbers of deaths than in studies with large numbers of deaths. It is recognized [72] that small null studies are particularly likely not to get published, and the observed tendency is consistent with this.

(ii) It is abundantly clear that failure to publish results from the huge American Cancer Society Cancer Prevention Study I had a massive effect on earlier meta-

analyses. Results from this study for ETS and lung cancer were published as long ago as 1981 [39] but results for ETS and heart disease did not appear until as late as 1995 [17]. There had been a number of attempts to persuade the American Cancer Society to publish these findings [28], but it was not until two independent US scientists obtained the data and reported that they showed no relationship at all between ETS and heart disease, that the results appeared [17]. These two scientists, LeVois and Layard, also published results from Cancer Prevention Study II. It was interesting to note that when the American Cancer Society subsequently presented later data from the second study [21], their paper made no reference at all to the existence of Cancer Prevention Study I in their literature review!

(iii) A number of findings were published in the form of abstracts or theses, some many years ago [4,6,7,11], with no proper paper ever appearing later in the literature.

(iv) Many prospective studies continue to collect mortality (and incidence) data on an ongoing basis, but a number of these studies last reported findings many years ago. Only two [1,10] have ever reported updated results.

(v) The total literature on ETS and heart disease is rather sparse when one considers that heart disease in a nonsmoker is perhaps 50 times or more commoner than is lung cancer in a nonsmoker, and the literature on ETS and lung cancer is so extensive.

8.10 Evidence of inconsistency

In Section 4 it was noted that the results for spousal smoking showed statistically significant variation by continent, publication date, study size, study type, the choice of exposure index used and study quality. Further analysis showed that these variations could to a great extent be explained by there being a striking difference in results from three groups of studies:

(A) Three recently published large studies, all of better quality (as defined in Section 4.11),

(B) Five other studies of better quality, and

(C) The remaining studies, which all have obvious major weaknesses or have not demonstrated their scientific validity.

Table 12 shows this striking difference clearly. After adjusting for covariates, the relative risk estimates for the three groups of studies are very highly significantly different ($\chi^2 = 36.4$ on 2 d.f., $p<0.001$ for ever smoking by the spouse; ($\chi^2 = 34.0$ on 2 d.f., $p<0.001$ for current smoking by the spouse), despite there being no significant evidence that, within group, risk estimates vary by study. Thus whether or not ever or current smoking by the spouse is used as the index of ETS exposure, the relative risk estimates in group B, around 1.2, are highly significantly *lower* than those in group C, which are around 1.5, and are highly significantly *higher* than those in group A, which are only slightly above 1.0.

The very high relative risk estimates in group C can clearly not be taken as showing an increase in heart disease risk due to ETS. Not only were these studies defined as being in group C because they had major weaknesses or because they had not demonstrated their scientific validity, but the magnitude of risk suggested seems totally implausible bearing in mind the magnitude of the relative risk associated with active smoking. One suspects that publication bias is an important cause of the high relative risks in this group.

Major contributors to the smaller relative risk estimates in group B are the Hirayama [1] and Sandler [8] studies. Although studies in group B did not have the problems that resulted in inclusion in group C, it should be noted that, as discussed in Appendix A, both these studies did in fact have a number of weaknesses. Notably, their follow-up was incomplete and they did not adjust for any of the classical heart disease risk factors.

Although the relative risk was elevated in group A, and was marginally significant ($p<0.05$) in the case of the current smoking meta-analysis shown in Table 12, the magnitude of the relative risk (1.02 for ever smoking, 1.04 for current smoking) is very weak, and it is clearly not at all implausible that the elevation may have resulted

from the various biases already discussed, such as due to misclassification of active smoking or to uncontrolled confounding.

8.11 Dose-response data

Twelve of the spousal studies have reported one or more kinds of dose-response data. As shown in Table 6, most data relate heart disease risk to numbers of cigarettes per day, but some relate it to years of exposure, some to a product of years and number per day, and some to a grouped classification of overall extent of ETS exposure. Overall 22 dose-response relationships have been reported.

Twelve of the dose-response relationships relate to studies in groups B and C as defined in Section 8.10. Of these, all but one show a strictly monotonic trend, with relative risks steadily increasing with increasing exposure group, with eight of the trends statistically significant. For six of the trends, the relative risk in the highest exposure category exceeds 2.0, i.e. is greater than the relative risk associated with active smoking, with it exceeding 5.0 for three of the four trends in the He I study [9].

Ten of the dose-response relationships relate to studies in group A. Here none shows a strictly monotonic dose-response relationship, and none of the trends is statistically significant. The only dose-response patterns even slightly suggestive of a trend are in the Steenland study [21] where the relative risk in the highest exposure category is 1.20 or greater in both sexes for duration of exposure and in females for pack-years of exposure. With regard to these trends, it should be noted that in the results presented in Table 3 Steenland only reported a significant association, and then only in males, in relation to *current* smoking and not to *ever* smoking by the spouse. It is hard to reconcile a true increase in risk in relation to duration of exposure, if current smoking only is relevant.

Although evidence of a dose-response relationship is one of the factors which is often cited as support for an inference of a causal relationship, there are a number of methodological problems that might result in artefactual evidence of a dose-response

relationship even in the absence of causality. Thus, the following non-causal explanations must be considered:

(a) Confounding Exposure to many lung cancer risk factors is increased in smokers in relation to the amount they smoke, and is also increased in nonsmokers in relation to living with a smoker, partly because people living together share many habits in common [66]. On this basis, it is only to be expected that exposure to these risk factors is also likely to be increased in nonsmokers in the household in relation to the amount smoked by the husband, and some support for this comes from analyses of two recent surveys showing a clear relationship of cotinine level in nonsmokers to their prevalence of many risk factors [60]. It is also to be expected that the longer a nonsmoker is exposed to the husband's smoking, the longer the nonsmoker will have to be exposed to these other lung cancer risk factors. Thus some dose-response relationship in heart disease risk in nonsmokers would perhaps be expected, both in relation to the amount and the duration of the spouse's smoking, as a result of confounding by these other risk factors.

(b) Misclassification of smoking habits Concordance of smoking habits between spouses increases with amount smoked [43]. For a given misclassification level, therefore, the magnitude of the misclassification bias will increase with amount smoked, also creating some apparent dose-response relationship.

(c) Recall bias In case-control or cross-sectional studies, subjects with heart disease (or their proxy respondents) may overstate spousal cigarette consumption, relative to controls, in an attempt to rationalize their disease state. This would have the effect of creating or exaggerating differences in cigarette consumption between the spouses of cases and controls. Recall bias could also affect reported duration of smoking, and particularly reported extent of ETS exposure when recorded on a subjective scale. Strong evidence of recall bias in this situation comes from the study of Tunstall-Pedoe [19] where presence of heart disease was found to be associated with self-reported extent of ETS exposure, but not with cotinine level.

(d) Publication bias The fact that dose-response data were only presented for 12 of the 23 studies gives some scope for bias, even among the studies that were

published. It is also possible that failure to find a significant dose-response relationship might have persuaded some researchers not to submit their results for publication.

Having made these points, it remains unclear why the evidence regarding dose-response relationships varies so markedly between studies in group A and those in groups B and C. Had misclassification of smoking habits, or confounding, caused a major bias to the dose-response relationship it is hard to see why no evidence of such a relationship appeared in the studies in group A. Recall bias seems a more plausible explanation, inasmuch as some of the studies showing a trend in Table 6 were of the case-control or cross-sectional design that might be susceptible to such a bias. However recall bias does not explain the significant trends seen in the Hirayama [1], Hole [10] and Kawachi [22] prospective studies, or the lack of trend in the Layard [16] case-control study. It would also seem implausible that so many significant trends could have appeared simply due to publication bias.

In any event, the lack of evidence of a trend in the three largest studies argues against the view that a dose-relationship has been clearly demonstrated.

8.12 Experimental data

Elsewhere (see Appendix D) my colleague Dr F J C Roe and I review and dismiss the claims of Glantz and Parmley [24] that experimental evidence has demonstrated that ETS is a cause of heart disease.

9. Conclusions

The epidemiological evidence relating ETS and heart disease, which has been examined in detail in this review, is most unconvincing. There is no significant association with ETS exposure in the workplace. While the overall data from the 23 studies do show a significant association with spousal smoking, whether ever smoking by the spouse (relative risk adjusted for covariates 1.07, 95% CI 1.03-1.10) or current smoking by the spouse (1.08, 95% CI 1.05-1.12) is used as the index, the association is quite weak and could well be a result of various forms of bias. These include:

(i) misclassification of smoking habits - there is evidence suggesting that smokers with non-fatal myocardial infarction, who are at high risk of subsequent death from heart disease, often ignore advice by their doctors to give up smoking but deny smoking on interview;

(ii) uncontrolled confounding - although adjustment for potential confounding factors was frequently found to modify spousal smoking relative risk estimates substantially, many studies had not controlled even for the major coronary risk factors;

(iii) recall bias - independent validation of reported ETS exposure was hardly ever carried out, and one study that did so provided strongly suggestive evidence that presence of disease may affect responses to questions on ETS exposure; and

(iv) publication bias - there was a clear tendency for spousal smoking relative risk estimates to be higher in smaller studies, consistent with publication bias.

There is also striking evidence of variation in spousal smoking relative risk estimates between three groups of studies:

(i) three recent studies without any apparent major weaknesses, each involving more than 1000 cases. In these there was no clear evidence of any increased risks (ever smoking by spouse 1.02, 95% CI 0.99-1.06; current smoking by spouse 1.04, 95% CI 1.00-1.08),

(ii) five other studies also without major weaknesses but generally involving less than 1000 cases. In these the relative risk estimates were lower but still indicative of a positive association (ever or current smoking by spouse 1.22, 95% CI 1.11-1.34), and

(iii) the remaining studies, which were reported only as abstracts or dissertations, involved less than 100 heart disease cases, and/or had identified major weaknesses. In such studies the spousal smoking relative risk estimates tended to be very high (ever smoking by spouse 1.50, 95% CI 1.30-1.72; current smoking by spouse 1.54, 95% CI 1.33-1.77).

It is also notable that, though there was some evidence of a dose-relationship in the last two groups of studies, there was no evidence of such a relationship in the first group, which included one study involving almost 15,000 heart disease deaths in nonsmokers.

When all the evidence is considered, the epidemiological data do not demonstrate that exposure to ETS increases the risk of heart disease.

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I alone bear responsibility for the views expressed.

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T1

TABLE 1

Studies providing information on risk of heart disease in relation to ETS exposure in lifelong nonsmokers

Study						Number of heart disease cases in lifelong nonsmokers		
Ref	Author	Year	Location	Type	Endpoints	Females		Males
1	Hirayama	1984	Japan	P	F	494		
2	Garland	1985	USA/California	P	F	19		
3	Lee	1986	England	CC	H	77		41
4	Martin	1986	USA/Utah	CS	NF	23		
5	Svendsen	1987	USA	P	F,NF			69
6	Butler	1988	USA/California	P	F	80		
7	Palmer	1988	USA/?	CC	H	*		
8	Sandler	1989	USA/Maryland	P	F	988		370
9	He I	1989	China	CC	H	34		
10	Hole	1989	Scotland	P	F(S)	55		65
11	Jackson	1989	New Zealand	CC	F,NF	20		49
12	Humble	1990	USA/Georgia	P	F	76		
13	Dobson	1991	Australia	CC	F+NF	160		183
14	La Vecchia	1993	Italy	CC	H	44		69
15	He II	1994	China	CC	H	59		
16	Layard	1995	USA	CC	F	914		475
17	LeVois (CPS-I)	1995	USA	P	F	7133		7758
18	Mannino	1995	USA	CS	NF	*		*
19	Tunstall-Pedoe	1995	Scotland	CS	NF(S)	←	428	→
20	Muscat	1995	USA/4 cities	CC	H	46		68
21	Steenland	1996	USA	P	F	1325		2494
22	Kawachi	1996	USA	P	F+NF	152		
23	Ciruzzi	1996	Argentina	CC	H	←	336	→

Footnotes

The study author is the name of the first author in the publication from which the data were extracted, see references

The study year is the year of that publication

The study types are CC=case control, CS=cross-sectional and P=prospective

The endpoints are F=fatal heart disease, H=hospitalized heart disease and NF=non-fatal heart disease. (S) implies data also available on prevalence of cardiovascular symptoms. + implies data only available for fatal and non-fatal heart disease combined

Numbers of heart disease cases in lifelong nonsmokers are totals in the study; for analyses relating to specific types of exposure numbers may be less than this. For studies 7 and 18 (indicated by *) data on numbers were not provided. For studies 19 and 23, data were only provided for sexes combined. For study 6, numbers relate to the spouse-pairs cohort only as the AHSMOG cohort included ex-smokers. For study 13, numbers also exclude ex-smokers

T2

TABLE 2

Smoking by the spouse
Actual index of exposure

Study Ref	Author		Exposed Group	Comparison Group
1	Hirayama		Spouse ever smoked	Spouse never smoked
2	Garland	A.	Spouse ever smoked	Spouse never smoked
		B.	Spouse current smoker	Spouse never smoked
3	Lee		Spouse ever smoked in marriage	Spouse never smoked in marriage
4	Martin	A.	Spouse ever smoked	Spouse never smoked
		B.	Spouse current smoker	Spouse never smoked
5	Svendsen		Spouse smoker at entry to study	Spouse nonsmoker at entry to study
6	Butler	A.	Spouse ever smoked in marriage	Spouse never smoked in marriage
		B.	Spouse current smoker in marriage	Spouse never smoked in marriage
7	Palmer		Spouse ever smoked*	Spouse never smoked*
8	Sandler		Household smoker at entry to study	No household smoker at entry to study
9	He I		Spouse smoked in marriage for >5 years	Spouse smoked in marriage for ≤5 years
10	Hole		Cohabitant ever smoked	Cohabitant never smoked
11	Jackson		Exposed to passive smoking at home	Not exposed to passive smoking at home
12	Humble		Spouse current smoker	Spouse never smoked
13	Dobson		Exposed to ETS at home	Not exposed to ETS at home
14	La Vecchia	A.	Spouse ever smoked	Spouse never smoked
		B.	Spouse current smoker	Spouse never smoked
15	He II		Spouse smoked in marriage for >5 years	Spouse smoked in marriage for ≤5 years
16	Layard		Any spouse ever smoked	No spouse ever smoked
17	LeVois (CPS-I)	A.	Spouse ever smoked	Spouse never smoked
		B.	Spouse current smoker	Spouse never smoked
18	Mannino		Exposed to ETS at home	Not exposed to ETS at home
19	Tunstall-Pedoe		Any ETS exposure in last 3 days	No ETS exposure in last 3 days
20	Muscat		Spouse ever smoked	Spouse never smoked
21	Steenland	A.	Spouse ever smoked in marriage	Spouse never smoked in marriage
		B.	Spouse current smoker	Spouse never smoked in marriage
22	Kawachi		Regular or occasional ETS exposure at home or work	No ETS
23	Ciruzzi		Spouse ever smoked*	Spouse and children never smoked

* For studies 7 and 23 it is probable that the exposed group was as stated, though the wording does not exclude the possibility that the exposed group was "spouse current smoker"

For studies 2,4,6,14,17 and 21 data were presented separately for never, ex- and current smokers so relative risks can be calculated for both indicated comparisons

T3

TABLE 3

Relative risk of heart disease among lifelong nonsmokers in relation to smoking by the spouse

Study				Unadjusted data		Covariate adjusted data	
Ref	Author	Sex	Exposure Index	Relative risk (95% CI)	Signi-ficance	Relative risk (95% CI)	Signi-ficance
1	Hirayama	F	E	1.00 (0.82-1.23)		1.16 (0.94-1.43)	
2	Garland	F	E	3.51 (0.82-15.04)		2.70 (0.70-10.50)	
		F	C(N)	2.09 (0.30-14.64)		2.25 (0.31-16.24)	
3	Lee	M	E	1.34 (0.64-2.80)		1.24 (0.59-2.59)	
		F	E	0.97 (0.56-1.69)		0.93 (0.54-1.62)	
4	Martin	F	E	2.60 (1.20-5.70)	+		
		F	C(N)	4.40	+	3.40	+
5	Svendsen	M	C	1.47 (0.89-2.41)		1.61 (0.96-2.71)	
6	Butler	F	E	1.36 (0.82-2.25)		1.03 (0.62-1.72)	
		F	C(N)	1.15 (0.42-3.17)		1.40 (0.51-3.84)	
7	Palmer	F	E			1.20	?
8	Sandler	M	C	1.15 (0.93-1.41)		1.31 (1.05-1.64)	+
		F	C	0.70 (0.62-0.79)	-	1.19 (1.04-1.36)	+
9	He I	F	E	3.52 (1.43-8.65)	+	1.50 (0.63-3.60)	
10	Hole	M	E			1.73 (1.01-2.96)	+
		F	E			1.65 (0.79-3.46)	
11	Jackson	M	C	1.10 (0.40-3.00)		1.06 (0.39-2.91)	
		F	C	4.00 (1.35-13.10)	+	3.75 (1.15-12.19)	+
12	Humble	F	C(N)			1.59 (0.99-2.57)	
13	Dobson	M	C	1.04 (0.59-1.84)		0.97 (0.50-1.86)	
		F	C	1.61 (1.06-2.43)	+	2.46 (1.47-4.13)	+
14	La Vecchia	M	E	1.09 (0.47-2.53)			
		F	E	1.27 (0.52-3.09)			
		M	C(N)	1.05 (0.41-2.67)		1.09 (0.39-3.01)	
		F	C(N)	1.31 (0.48-3.56)		1.36 (0.46-4.05)	
15	He II	F	E	2.12 (1.12-4.01)	+	1.24 (0.56-2.72)	
16	Layard	M	E	0.93 (0.71-1.22)		0.97 (0.73-1.28)	
		F	E	1.00 (0.85-1.17)		0.99 (0.84-1.16)	
17	LeVois (CPS-I)	M	E			0.97 (0.90-1.05)	
		F	E			1.03 (0.98-1.08)	
		M	C(N)			0.98 (0.91-1.06)	
		F	C(N)			1.04 (0.99-1.09)	

TABLE 3 (continued)

Relative risk of heart disease among lifelong nonsmokers in relation to smoking by the spouse

Study				Unadjusted data		Covariate adjusted data	
Ref	Author	Sex	Exposure Index	Relative risk (95% CI)	Signi-ficance	Relative risk (95% CI)	Signi-ficance
18	Mannino	M+F	C			1.12	?
19	Tunstall-Pedoe	M+F	C	1.32 (1.03-1.69)	+	1.37 (1.07-1.75)	+
20	Muscat	M	E	1.38 (0.70-2.75)			
		F	E	1.33 (0.59-2.99)			
21	Steenland	M	E			1.10 (0.99-1.22)	
		F	E			1.03 (0.91-1.18)	
		M	C(N)			1.22 (1.07-1.40)	+
		F	C(N)			1.10 (0.96-1.27)	
22	Kawachi	F	C			1.71 (1.03-2.84)	+
23	Ciruzzi	M+F	E(NR)			1.43 (0.90-2.00)	

Footnotes

In seven studies (8,10,11,13,18,19,22) the index of exposure is not actually based on spousal smoking but on the nearest equivalent index (see Table 2)

Exposure index E=ever smoked (compared to never smoked); E(NR)=ever smoked (compared to no relative ever smoked); C(N)=current smoker (compared to never smoked); C=current exposure (compared to non-current exposure)

The study author is the name of the first author in the publication from which the data were extracted; see references

For study 5 the relative risks and CIs given are for fatal or non-fatal heart disease; for fatal heart disease the corresponding data are 2.10 (0.69-6.36) unadjusted and 2.23 (0.72-6.92) adjusted for covariates. Similarly for study 11 data for fatal heart disease are, for males, 1.00 (0.20-4.50) unadjusted and 1.10 (0.23-5.22) adjusted for covariates and, for females, 7.80 (1.30-48.00) unadjusted and 5.80 (0.95-35.24) adjusted for covariates.

See Appendix A for details of how the data were extracted from the source publication

See Appendix B for the covariates considered in adjusted analyses

Significant ($p<0.05$) positive (negative) relative risks are indicated by + (or -)

TABLE 4

Meta-analyses of data for ever smoking by the spouse

	Number of estimates		Unadjusted data: Relative risk (95% CI)	Unadjusted data: Signi-ficance	Unadjusted data: Heterogeneity Within	Unadjusted data: Heterogeneity Between	Data adjusted for covariates: Relative Risk (95% CI)	Data adjusted for covariates: Signi-ficance	Data adjusted for covariates: Heterogeneity Within	Data adjusted for covariates: Heterogeneity Between
All 21 studies	31		1.02(0.99-1.06)	NS	***		1.07(1.03-1.10)	+++	**	
All 21 studies	31	R	1.20(1.07-1.38)	+++	***		1.18(1.08-1.32)	+++	**	
Sex										
Females	18		1.01(0.97-1.05)	NS	***	NS	1.07(1.02-1.11)	++	**	NS
Males	11		1.04(0.98-1.10)	NS	NS		1.04(0.99-1.11)	NS	NS	
Combined	12		1.01(0.98-1.05)	NS	***		1.05(1.02-1.09)	++	**	
Continent										
USA	16		1.01(0.97-1.04)	NS	***	***	1.05(1.01-1.08)	++	*	***
Europe	7		1.32(1.10-1.59)	++	NS		1.34(1.11-1.61)	++	NS	
Asia	3		1.13(0.94-1.37)	NS	**		1.18(0.97-1.44)	NS	NS	
Other	5		1.45(1.14-1.85)	++	NS		1.59(1.22-2.08)	+++	NS	
Publication date										
1984-88	7		1.15(0.98-1.35)	NS	NS	*	1.22(1.04-1.44)	+	NS	***
1989-94	13		0.93(0.85-1.02)	NS	***		1.30(1.17-1.43)	+++	NS	
1995-96	11		1.03(1.00-1.07)	NS	NS		1.03(1.00-1.07)	NS	NS	
Study size										
<100	9		1.78(1.42-2.23)	+++	NS	***	1.53(1.21-1.92)	+++	NS	***
100-999	14		1.25(1.11-1.40)	+++	NS		1.33(1.18-1.50)	+++	NS	
1000+	8		1.00(0.96-1.03)	NS	***		1.04(1.00-1.07)	+	NS	
Study type										
Case/control	15		1.13(1.02-1.26)	+	*	**	1.11(0.99-1.24)	NS	NS	*
Prospective	14		1.01(0.97-1.04)	NS	***		1.05(1.02-1.09)	++	**	
Cross-sectional	2		1.40(1.11-1.78)	++	NS		1.45(1.15-1.84)	++	NS	
Endpoint										
Fatal	17		1.00(0.97-1.04)	NS	***	***	1.05(1.01-1.08)	++	*	***
Other	14		1.43(1.25-1.64)	+++	NS		1.42(1.23-1.63)	+++	NS	
Confounders considered (other than age or marital status)										
No	7		1.12(0.95-1.32)	NS	NS	NS	1.19(1.01-1.40)	+	NS	NS
Yes	24		1.02(0.99-1.05)	NS	***		1.06(1.03-1.10)	+++	***	
Spousal smoking the index										
No	10		0.94(0.86-1.03)	NS	***	NS	1.31(1.19-1.44)	+++	NS	***
Yes	21		1.04(1.00-1.07)	+	*		1.04(1.00-1.07)	+	NS	
Dose-response data available										
No	12		0.91(0.83-1.00)	-	***	**	1.27(1.15-1.40)	+++	NS	***
Yes	19		1.04(1.01-1.08)	+	**		1.04(1.01-1.08)	+	*	
Study quality (see Section 4.12)										
Better	17		1.00(0.97-1.03)	NS	***	***	1.05(1.01-1.08)	++	NS	***
Worse	14		1.52(1.33-1.74)	+++	NS		1.50(1.30-1.72)	+++	NS	

Footnotes

All meta-analyses are fixed-effects [31] except where the relative risk is preceded by an R, when they are random-effects using the Hardy and Thompson method [33].

Significance codes are: +++, - - -, *** p<0.001; ++, - -, ** p<0.01; +, -, * p<0.05; and NS (not significant) p>0.05.

Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.

For the fatal endpoint analyses the data used for studies 5 and 11 are those shown in the footnotes of Table 3.

T6

TABLE 5

Meta-analyses of data for current smoking by the spouse

	Number of estimates		Unadjusted data: Relative risk (95% CI)	Unadjusted data: Signi-ficance	Unadjusted data: Heterogeneity Within	Unadjusted data: Heterogeneity Between	Data adjusted for covariates: Relative Risk (95% CI)	Data adjusted for covariates: Signi-ficance	Data adjusted for covariates: Heterogeneity Within	Data adjusted for covariates: Heterogeneity Between
All 21 studies	31		1.04(1.00-1.07)	+	***		1.08(1.05-1.12)	+++	**	
All 21 studies	31	R	1.20(1.08-1.38)	+++	***		1.20(1.11-1.35)	+++	***	
Sex										
Females	18		1.02(0.98-1.06)	NS	***	NS	1.08(1.04-1.12)	+++	**	NS
Males	11		1.05(0.99-1.12)	NS	NS		1.07(1.00-1.13)	+	*	
Combined	12		1.03(0.99-1.06)	NS	***		1.07(1.03-1.11)	+++	***	
Continent										
USA	16		1.02(0.98-1.05)	NS	***	**	1.06(1.03-1.10)	+++	**	**
Europe	7		1.32(1.10-1.60)	++	NS		1.34(1.12-1.62)	++	NS	
Asia	3		1.13(0.94-1.37)	NS	**		1.18(0.97-1.44)	NS	NS	
Other	5		1.45(1.14-1.85)	++	NS		1.59(1.22-2.08)	+++	NS	
Publication date										
1984-88	7		1.12(0.95-1.32)	NS	NS	*	1.24(1.05-1.47)	+	NS	***
1989-94	13		0.93(0.85-1.02)	NS	***		1.30(1.17-1.44)	+++	NS	
1995-96	11		1.05(1.01-1.09)	++	*		1.05(1.01-1.09)	++	*	
Study size										
<100	9		1.82(1.43-2.32)	+++	NS	***	1.65(1.28-2.12)	+++	NS	***
100-999	14		1.25(1.11-1.40)	+++	NS		1.34(1.19-1.50)	+++	NS	
1000+	8		1.01(0.97-1.04)	NS	***		1.05(1.02-1.09)	++	*	
Study type										
Case/control	15		1.13(1.02-1.26)	+	*		1.11(0.99-1.24)	NS	NS	*
Prospective	14		1.02(0.99-1.06)	NS	***		1.07(1.03-1.11)	+++	**	
Cross-sectional	2		1.40(1.11-1.78)	++	NS	**	1.45(1.15-1.84)	++	NS	
Endpoint										
Fatal	17		1.02(0.98-1.05)	NS	***	***	1.06(1.03-1.10)	+++	*	***
Other	14		1.43(1.25-1.65)	+++	NS		1.42(1.23-1.64)	+++	NS	
Confounders considered (other than age or marital status)										
No	7		1.10(0.93-1.30)	NS	NS	NS	1.21(1.02-1.44)	+	NS	NS
Yes	24		1.03(1.00-1.07)	+	***		1.08(1.04-1.11)	+++	***	
Spousal smoking the index										
No	10		0.94(0.86-1.03)	NS	***	*	1.31(1.19-1.44)	+++	NS	***
Yes	21		1.05(1.02-1.09)	++	*		1.05(1.02-1.09)	++	NS	
Dose-response data available										
No	12		0.90(0.82-0.99)	-	***	**	1.28(1.15-1.41)	+++	NS	***
Yes	19		1.06(1.02-1.09)	++	***		1.06(1.02-1.10)	+++	*	
Study quality (see Section 4.12)										
Better	17		1.01(0.98-1.05)	NS	***	***	1.06(1.03-1.10)	+++	NS	***
Worse	14		1.52(1.32-1.74)	+++	NS		1.53(1.33-1.77)	+++	NS	

Footnotes

All meta-analyses are fixed-effects [31] except where the relative risk is preceded by an R, when they are random-effects using the Hardy and Thompson method [33].

Significance codes are: +++, - - -, *** p<0.001; ++, - -, ** p<0.01; +, -, * p<0.05; and NS (not significant) p>0.05.

Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.

For the fatal endpoint analyses the data used for studies 5 and 11 are those shown in the footnotes of Table 3.

TABLE 6

Relative risk of heart disease among lifelong nonsmokers in relation to extent of smoking by the spouse

Study Ref	Author	Sex	Exposure grouping	Relative risks by grouping	Signi-ficance (trend)
1	Hirayama	F	0 1-19 20+ (cigs/day)	1.00 1.10 1.31	+
5	Svendsen	M	0 1-19 20+ (cigs/day)	1.00 1.20 1.75	
9	He I	F	0 1-20 21+ (cigs/day)	1.00 2.30 6.86	+
			0 1-10 11-20 21+ (years)	1.00 1.88 3.07 5.49	+
			0 1-199 200-399 400-599 600+ (cigs/day x years)	1.00 1.54 2.30 5.07 12.67	+
10	Hole	F	No Low High (exposure)	1.00 2.09 4.12	+
11	Jackson	M	None Low High (exposure)	1.00 1.30 0.90	
		F	None Low High (exposure)	1.00 2.10 7.50	+
14	La Vecchia	M+F	0 1-14 15+ (cigs/day)	1.00 1.13 1.30	
16	Layard	M	0 1-14 15-34 35+ (cigs/day)	1.00 0.76 1.07 0.92	
		F	0 1-14 15-34 35+ (cigs/day)	1.00 0.85 1.15 1.06	
17	LeVois (CPS-I)	M	0 1-19 20-39 40+ (cigs/day)	1.00 0.99 0.98 0.72	
		F	0 1-19 20-39 40+ (cigs/day)	1.00 1.04 1.06 0.95	
19	Tunstall-Pedoe	M+F	None Little Some A lot (exposure)	1.00 1.2 1.5 1.6	+
21	Steenland	M	0 1-19 20 21+ (cigs/day)	1.00 1.33 1.17 1.09	
		F	0 1-19 20 21-39 40+ (cigs/day)	1.00 1.15 1.07 0.99 1.04	
		M	0 1-12 13-21 22-29 30+ (years)	1.00 1.14 1.13 1.14 1.25	
		F	0 1-14 15-25 26-33 34+ (years)	1.00 0.84 0.99 1.20 1.20	
		M	0 1-5 6-14 15-27 28+ (pack years)	1.00 1.25 1.33 1.13 1.10	
		F	0 1-12 13-25 26-33 34+ (pack years)	1.00 0.83 1.12 1.09 1.26	
22	Kawachi	F	None Occasional Regular	1.00 1.58 1.91	+
23	Ciruzzi	M+F	0 1-20 21+ (cigs/day)	1.00 1.27 2.41	

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references

For study 1 the 1-19 cigs/day group includes ex-smoking spouses

Relative risks presented are adjusted for covariates if adjusted data are available

Significant ($p<0.05$) positive (negative) trends are indicated by + (or -)

Study 15, He II, reported that the crude odds ratios showed significant trends with cigs/day, years and their product, but that they became non-significant after adjusting for ETS exposure at work and for five other risk factors. Actual data were not shown.

TABLE 7

Relative risk of heart disease among lifelong nonsmokers in relation to workplace ETS exposure

Study			Unadjusted data		Covariate adjusted data	
Ref	Author	Sex	Relative risk (95% CI)	Signi-ficance	Relative risk (95% CI)	Signi-ficance
3	Lee	M	0.53 (0.23-1.21)		0.66 (0.26-1.66)	
		F	0.50 (0.20-1.29)		0.69 (0.26-1.87)	
5	Svendsen	M			1.40 (0.80-2.50)	
11	Jackson	M	1.50 (0.80-3.00)		1.80 (0.94-3.46)	
		F	2.20 (0.70-7.40)		1.55 (0.48-5.03)	
13	Dobson	M	0.90 (0.52-1.55)		0.95 (0.51-1.78)	
		F	0.71 (0.24-2.09)		0.66 (0.17-2.62)	
15	He II	F	2.45 (1.30-4.61)	+	1.85 (0.86-4.00)	
20	Muscat	M	1.17 (0.62-2.19)		1.20 (0.60-2.20)	
		F	0.97 (0.38-2.46)		1.00 (0.40-2.50)	
21	Steenland	M			1.03 (0.89-1.19)	
		F			1.06 (0.84-1.34)	

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references

For study 5 the relative risk and CIs given are for fatal or non-fatal heart disease; for fatal heart disease the corresponding data are 2.60 (0.50-12.70) adjusted for covariates. Similarly for study 11 data for fatal heart disease are, for males, 1.30 (0.50-3.60) unadjusted and 1.80 (0.67-4.83) adjusted for covariates and, for females, 3.60 (0.70-20.10) unadjusted and 2.20 (0.41-11.79) adjusted for covariates.

See Appendix A for details of how the data were extracted from the source publication

See Appendix B for the covariates considered in adjusted analyses

Significant ($p<0.05$) positive (or negative) relative risks are indicated by + (or -)

T9

TABLE 8

Meta-analyses of data for workplace ETS exposure

		Unadjusted data				Data adjusted for covariates			
	Number of estimates	Relative risk (95% CI)	Signi-ficance	Heterogeneity		Relative Risk (95% CI)	Signi-ficance	Heterogeneity	
				Within	Between			Within	Between
All 7 studies	12	1.06(0.95-1.19)	NS	NS		1.07(0.96-1.19)	NS	NS	
Sex									
Females	6	1.12(0.91-1.37)	NS	NS	NS	1.08(0.88-1.33)	NS	NS	NS
Males	6	1.04(0.92-1.19)	NS	NS		1.06(0.93-1.21)	NS	NS	
Continent									
USA	5	1.05(0.94-1.19)	NS	NS	NS	1.06(0.94-1.19)	NS	NS	NS
Other	7	1.12(0.84-1.49)	NS	*		1.16(0.85-1.60)	NS	NS	

Footnotes
All meta-analyses are fixed-effects [31].
Significance codes are: +++, - - -, *** p<0.001; ++, - -, ** p<0.01; +, -, * p<0.05; and NS (not significant) p>0.05.
Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.

TABLE 9

Relative risk of heart disease among lifelong nonsmokers in relation to extent of workplace ETS exposure

Study					
Ref	Author	Sex	Exposure grouping	Relative risk by grouping	Signi-ficance (trend)
15	He II	F	0-5 6-10 11-20 21+ cigs/day	1.00 0.87 2.95 3.56	+
		F	0-5 6-15 16+ years	1.00 3.08 1.56	
		F	0 1-2 3 4+ smokers	1.00 1.16 5.06 4.11	+
		F	0 1-2 3-4 5+ hours/day	1.00 0.62 4.03 21.32	+
		F	0 1-2000 2001-4000 4000+ (cigs/day x years x smokers x hours)	1.00 1.00 2.05 9.23	+

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references

Relative risks presented are adjusted for covariates

Significant ($p<0.05$) positive (negative) trends are indicated by + (or -)

TABLE 10

Relative risk of heart disease among lifelong nonsmokers in relation to other indices of ETS exposure

Study Ref	Author	Sex	Exposure grouping	Relative risk by grouping (95% CI)	Signi-ficance
3	Lee		**Total ETS exposure**		
		M	Score 0-1 2-4 5-12	1.00 0.43 0.43	
		F	Score 0-1 2-4 5-12	1.00 0.59 0.81	
5	Svendsen		**Spousal and workplace ETS exposure**		
		M	Neither Work Spouse Both	1.0 1.0 1.2 1.7	
15	He II		**ETS from spouse and work**		
		F	Neither Home Work Both	1.00 2.07 2.53 4.18	+
17	LeVois (CPS-I)		**Spouse smoked pipe/cigar**		
		F	Never smoked at all Yes	1.06 (0.99-1.14)	
19	Tunstall-Pedoe		**Serum cotinine group**		
		M+F	I II III IV	1.00 1.00 1.30 1.20	
20	Muscat		**Childhood exposure**		
		M	None 1-17 >17 years	1.0 0.9 0.7	
		F	None 1-17 >17 years	1.0 0.6 0.8	
			Adult exposure		
		M	None 1-20 21-30 31+ years	1.0 1.7 1.5 1.1	
		F	None 1-20 21-30 31+ years	1.0 2.0 0.9 1.7	
			Cars		
		M	No Yes	1.0 1.07 (0.50-2.29)	
		F	No Yes	1.0 2.60 (0.9-8.0)	
			Other transportation		
		M	No Yes	1.0 0.95 (0.22-4.11)	
		F	No Yes	1.0 1.09 (0.15-8.08)	
23	Ciruzzi		**One or more relatives ever smoked**		
		M+F	No Yes	1.0 1.66 (1.2-2.3)	+
			One or more children ever smoked		
		M+F	No Yes	1.0 1.73 (1.2-2.5)	+
			Spouse and one or more children ever smoked		
		M+F	No Yes	1.0 1.6 (0.8-3.3)	

Footnotes

The study author is the name of the first author in the publication from which the data were extracted; see references

Relative risks presented are adjusted for covariates if adjusted data are available

When two groups only are being compared, the relative risk and 95% CI for the exposed group are shown: when more than two exposure groups are being compared, only the set of relative risks is shown

Significant ($p<0.05$) positive (or negative) differences or trends are indicated by + (or -)

TABLE 11

Effect of adjustment for covariates on relative risk of heart disease in relation to smoking by the spouse

Study					Covariates adjusted for	
Ref	Author	Sex	Exposure index	Effect of adjustment for covariates (A)	Age	Others
8	Sandler	F	C	+0.531	✓	2
13	Dobson	F	C	+0.424	✓	1
6	Butler	F	C(N)	+0.197	✓	
12	Humble	F	C(N)	+0.171		3
1	Hirayama	F	E	+0.148	✓	
8	Sandler	M	C	+0.130	✓	2
14	La Vecchia	M+F	C	+0.113	✓	
5	Svendsen	M	C	+0.091	✓	5
2	Garland	F	C(N)	+0.074	✓	
16	Layard	M	E	+0.042	✓	1
19	Tunstall-Pedoe	M+F	C	+0.037	✓	3
16	Layard	F	E	-0.010	✓	1
11	Jackson	M	C	-0.037	✓	1
3	Lee	F	E	-0.042	✓	1
11	Jackson	F	C	-0.065	✓	1
13	Dobson	M	C	-0.070	✓	1
3	Lee	M	E	-0.078	✓	1
14	La Vecchia	M+F	C	-0.079		7
22	Kawachi	F	C	-0.142		12
4	Martin	F	C(N)	-0.258		6
2	Garland	F	E	-0.262	✓	4
6	Butler	F	E	-0.278	✓	
15	He II	F	E	-0.536	✓	4
9	He I	F	E	-0.853		6

Footnotes

A = $\log_e(RR_A/RR_U)$ where RR_A is the relative risk adjusted for, and RR_U the relative risk unadjusted for, the covariates considered.

See Appendix B Table B1 for details of the actual other covariates adjusted for.

Exposure index E=ever smoked (compared to never smoked); E(NR)=ever smoked (compared to no relative ever smoked); C(N)=current smoker (compared to never smoked); C=current exposure (compared to non-current exposure)

The study author is the name of the first author in the publication from which the data were extracted; see references

TABLE 12

T13

Fixed-effects meta-analyses [31] of data in relation to smoking by the spouse

	Number of estimates	Unadjusted data: Relative risk (95% CI)	Unadjusted data: Signi-ficance	Unadjusted data: Heterogeneity Within	Unadjusted data: Heterogeneity Between	Data adjusted for covariates: Relative Risk (95% CI)	Data adjusted for covariates: Signi-ficance	Data adjusted for covariates: Heterogeneity Within	Data adjusted for covariates: Heterogeneity Between
Ever smoking by the spouse									
3 recent large studies of better quality	6	1.02(0.99-1.06)	NS	NS	***	1.02(0.99-1.06)	NS	NS	***
6 other studies of better quality	11	0.89(0.81-0.97)	- -	***		1.22(1.11-1.34)	+++	NS	
14 studies of poorer quality	14	1.52(1.33-1.74)	+++	NS		1.50(1.30-1.72)	+++	NS	
Current smoking by the spouse									
3 recent large studies of better quality	6	1.04(1.00-1.08)	+	NS	***	1.04(1.00-1.08)	+	NS	***
6 other studies of better quality	11	0.88(0.81-0.97)	- -	***		1.22(1.11-1.34)	+++	NS	
14 studies of poorer quality	14	1.52(1.32-1.74)	+++	NS		1.53(1.33-1.77)	+++	NS	

Footnotes

Significance codes are: +++, - - -, *** p<0.001; ++, - -, ** p<0.01; +, -, * p<0.05; and NS (not significant) p>0.05.
Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.
See Section 412 for definition of study quality.

T13

Fixed-effects meta-analyses [31] of data in relation to smoking by the spouse

	Number of estimates	Unadjusted data: Relative risk (95% CI)	Unadjusted data: Signi-ficance	Unadjusted data: Heterogeneity Within	Unadjusted data: Heterogeneity Between	Data adjusted for covariates: Relative Risk (95% CI)	Data adjusted for covariates: Signi-ficance	Data adjusted for covariates: Heterogeneity Within	Data adjusted for covariates: Heterogeneity Between
Ever smoking by the spouse									
3 recent large studies of better quality	6	1.02(0.99-1.06)	NS	NS	***	1.02(0.99-1.06)	NS	NS	***
6 other studies of better quality	11	0.89(0.81-0.97)	- -	***		1.22(1.11-1.34)	+++	NS	
14 studies of poorer quality	14	1.52(1.33-1.74)	+++	NS		1.50(1.30-1.72)	+++	NS	
Current smoking by the spouse									
3 recent large studies of better quality	6	1.04(1.00-1.08)	+	NS	***	1.04(1.00-1.08)	+	NS	***
6 other studies of better quality	11	0.88(0.81-0.97)	- -	***		1.22(1.11-1.34)	+++	NS	
14 studies of poorer quality	14	1.52(1.32-1.74)	+++	NS		1.53(1.33-1.77)	+++	NS	

Footnotes

Significance codes are: +++, - - -, *** p<0.001; ++, - -, ** p<0.01; +, -, * p<0.05; and NS (not significant) p>0.05.
Results of heterogeneity tests are shown both **within** the studies making up a subgroup and **between** the subgroups being compared.
See Section 412 for definition of study quality.

APPENDIX A

Extraction of data from source material

In extracting the relative risks and 95% CIs from the source material for each study several general rules were kept to:

1) Where studies presented appropriate data on numbers of cases and controls for the exposure categories of interest, unadjusted relative risks and 95% CIs were calculated using the CIA program based on the methods described by Morris and Gardner [29]. These calculated values were used in the tables in these reports whether or not they agreed with the data given by the author.
2) Adjusted relative risks and 95% CIs were also calculated using the Mantel-Haenszel stratified procedures available in the CIA program where (which was rarely the case) the source paper presented the data in sufficient detail to allow this.
3) Where data on numbers of cases and controls were not presented, unadjusted or adjusted relative risks and CIs were taken as given in the paper.
4) Where, for a particular exposure, more than one set of adjusted relative risks and CIs relating to differing adjustment variables were presented, the values used in the tables were those based on the most extensive set of adjustment variables.
5) Where data were given separately for fatal and nonfatal heart disease, relative risks and CIs based on the combined data have been used.

In some studies there was no problem in using these general rules to extract the data, and no more comment need be made. For a number, given below, some clarification is needed on how the data were extracted:

Hirayama [1] The relative risks and CIs were taken from the data in Table 5 of ref 1 by husband's age. The data in Table 6 of ref 1, by husband's age and 10 occupational groups, could not be used because of the large number of zero cells in that table.

Garland [2] Table 2 of ref 2 gives unadjusted data from which relative risks and 95% CIs can be calculated directly. That table gives age-adjusted rates for current and never smokers from which a relative risk can be calculated. A multiple adjusted ever/never relative risk is given in

the erratum to the paper. CIs for the adjusted relative risks were calculated, assuming the variance was the same as indicated by the unadjusted CIs.

Lee [3] Workplace data were calculated directly from the source data.

Martin [4] Unadjusted ever/never smoking relative risks are as cited by Wells [30].

Butler [6] Butler's thesis describes results from two cohorts. For one, the AHSMOG cohort, the results presented do not relate to lifelong nonsmokers so are not considered. The spousal ever smoking relative risks and 95% CIs are calculated from Table 8.4 of the thesis, using age strata of 35-64, 65-74, 75-84 and 85-94 for the age-adjusted calculations. The spousal current smoking relative risks are taken directly from Table 8.5.

He I [9] The data in Table 2 of ref 9 provided the unadjusted relative risks overall and by level of exposure. Table 5 of ref 9 gives an adjusted relative risk of 1.50 stating it is statistically significant ($p<0.1$). Given the size of the study, with only 34 cases and 68 controls, it is impossible that the adjusted relative risk could be statistically significant, and the CIs given by Wells [25], which are consistent with the study size and the unadjusted CIs, but imply non-significance, are used in our Table 3.

Hole [10] The overall relative risks and CIs are as given by Wells [25] based on a personal communication of updated results provided by Hole. The relative risks by level of exposure are based on Table VI of ref 10 and are for females only. The significance of the trend can be calculated from these data.

Jackson [11] Unadjusted relative risks and CIs for home and for work exposure come directly from Table 6.5 of ref 11. Table 6.4 of ref 11 gives unadjusted relative risks and CIs and adjusted relative risks without CIs separately for home and for work exposure and for the fatal and nonfatal parts of the study. To obtain adjusted relative risks for CIs for fatal and nonfatal combined, it was first assumed that the width of the unadjusted limits applied to the adjusted data, the overall relative risks and CIs then being computed by meta-analysis.

La Vecchia [14] The table of results in ref 14 gives unadjusted numbers by sex and adjusted relative risks and CIs for the sexes combined. Data for spousal smoking "other or undefined" were omitted from all calculations. For both spousal ever smoking and spousal current smoking the crude data allow calculation of the sex-specific relative risks and 95% CIs and the combined relative risks and 95% CIs adjusted for sex. For spousal current smoking the sex-specific adjusted relative risks were estimated by assuming that the adjusted/unadjusted ratio of relative risks for the sexes combined data applied to the sex-specific data. The sex-specific adjusted CIs were estimated by assuming that the adjusted/unadjusted ratio of the variances of the log relative risk for the sexes combined data also applied to the sex-specific data. For spousal ever smoking it was not possible readily to estimate the adjusted relative risks from the estimates provided for current and former smoking separately.

LeVois [17] Only the results for the first American Cancer Society Cancer Prevention Study (CPS-I) are used, as Steenland [21] gives updated results for CPS-II. The results for spouse ever smoked come directly from Table 4 of ref 17. The relative risk and CIs for spouse current smoker are based on a meta-analysis of results given in that table for 1-19, 20-39 and 40+/day, adjusting the overall weight down (to compensate for non-independence of these estimates) by reducing it by a factor based on the Steenland study [21] where it is possible to compare the weight based on meta-analysis over level of smoking and the true weight based on the results actually presented for spouse current smoking.

Tunstall-Pedoe [19] The data presented are based on the results for all CHD in Table 3 of ref 19. The unadjusted relative risks and CIs can be estimated directly from the data in that table. The adjusted relative risks and CIs are given by level of exposure. The overall adjusted relative risk and CI is based on a meta-analysis of the data by level, adjusting the overall weight downward by a factor based on the unadjusted data, where it is possible to compare the weight based on meta-analysis over level and the true weight based on the combined data.

Steenland [21] The results for spouse current smoker come directly from Table 2 of ref 21. The relative risk and CIs for spouse ever smoker is based on a meta-analysis of results given in that table by level of current exposure and for former smoking, adjusting the overall weight by a factor based on the LeVois CPS-II analysis [17] where it is possible to compare the weights

based on meta-analysis over smoking category and the true weight based on the results actually presented for ever smoking.

Kawachi [22] Ref 22 gives adjusted relative risks and CIs separately for occasional and regular ETS exposure. The relative risk and CIs for overall exposure are given in ref 40.

APPENDIX B

Risk factors taken account of in relative risk estimation

Table B1 summarizes, for each of the 23 studies, the extent to which potential confounding factors have been taken into account in relative risk estimation.

1. Age The studies marked "yes" in Table B1 either explicitly adjusted for age in analysis or used age-matched lifelong nonsmoking cases and controls. Ignoring Palmer, where the abstract provided inadequate detail of what was done, the only studies with problems relating to age-adjustment are Martin, where confidence limits were only presented for the unadjusted data (see note below), and Hirayama, where the adjustment was for husband's age rather than wife's age.

2. Marital status Studies marked as "yes" in Table B1 specifically restricted attention to married women and/or adjusted for marital status in the analysis of spousal smoking. Studies marked "N/A" = not applicable used an index not based on spousal exposure (see Table 2). In the case of three studies (9, 20, 23) which reported risk for spousal smoking, it was not stated if the analyses were restricted to married subjects. Failure to exclude unmarried subjects in analyses using spousal smoking to index ETS exposure leads to a confounding of possible effects of ETS and marital status, as all the exposed subjects will be married, but some of the unexposed subjects will not.

3. Other risk factors The great majority of the studies adjusted for at least some risk factors other than age or marital status. The risk factors most commonly considered were as follows:

Blood pressure	(13 studies)
Cholesterol	(10 studies)
Obesity/weight	(9 studies)
Social class/education/income	(9 studies)
Alcohol	(5 studies)
Diabetes	(5 studies)
Family history of heart disease or hypertension	(5 studies)
Race	(5 studies)
Exercise	(4 studies)
Housing/urban-rural residence	(3 studies)

Other factors were only considered in at most two studies. It is notable that, with the exception of the Kawachi study, which adjusted for vitamin E and saturated fat intake, dietary variables were never considered as confounders (except indirectly via cholesterol and obesity).

For some studies, comments additional to those given in the tables should be made:

Hirayama [1] As noted in Appendix A, Hirayama presented data subdivided by age and ten levels of occupation, but these data could not be used because of the large number of zero cells in that table.

Martin [4] Although the abstract reported adjusted relative risks, no confidence limits were given for the adjusted data, so the unadjusted data are used in meta-analyses.

La Vecchia [14] Adjusted relative risks and 95% CIs could be obtained for spouse current smoking, but not for spouse ever smoking.

Layard [16] It was reported that "spousal smoking results were not appreciably affected by adjustment for history of hypertension, history of diabetes, family history of heart attack, relative weight, alcohol consumption, dietary factors, education and family income," but such adjusted risk estimates were not presented.

LeVois [17] It was reported that "relative risks were adjusted for age and race. Further adjustment using a weight index, exercise, highest level of education, dietary factors, alcohol consumption, history of hypertension, and history of diabetes had no appreciable effect on any of the reported associations." However, such further adjusted risk estimates were not presented.

Muscat [20] The nonsmoking cases and controls were matched on age and race. Adjustment for education and hypertension was only carried out in analyses of

workplace, adulthood and childhood ETS exposure, but not for other indices of ETS exposure, including spousal smoking.

TABLE B1

Risk factors taken account of in relative risk estimation

Study Ref	Author	Location	Age	Marital status	SES	Blood pressure	Chole-sterol	BMI	Alcohol	Housing	Exercise	Race	Diabetes	FH	Other
1	Hirayama	Japan	Yes	Yes											
2	Garland	USA	Yes	Yes		Yes	Yes	Yes							
3	Lee	England	Yes	Yes											
4	Martin	USA		Yes		Yes		Yes	Yes		Yes		Yes	Yes	
5	Svendsen	USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes						
6	Butler	USA	Yes	Yes											
7	Palmer	USA	(No reference in abstract to any adjustment for confounders)												
8	Sandler	USA	Yes	N/A	Yes					Yes					
9	He I	China	Yes			Yes	Yes		Yes		Yes			Yes	
10	Hole	Scotland	Yes	N/A	Yes	Yes	Yes	Yes							
11	Jackson	New Zealand	Yes	N/A	Yes										
12	Humble	USA	Yes	Yes		Yes	Yes	Yes							
13	Dobson	Australia	Yes	N/A											PH
14	LaVecchia	Italy	Yes	Yes	Yes	Yes	Yes	Yes					Yes	Yes	COF
15	He II	China	Yes	Yes		Yes	Yes								A
16	Layard	USA	Yes	Yes								Yes			
17	LeVois(CPS-I)	USA	Yes	Yes								Yes			
18	Mannino	USA	Yes	N/A	Yes					Yes		Yes			
19	Tunstall-Pedoe	Scotland	Yes	N/A		Yes	Yes			Yes					
20	Muscat	USA	Yes		Yes	Yes						Yes			
21	Steenland	USA	Yes	Yes	Yes	Yes		Yes	Yes		Yes		Yes		AR AS DI OCC OES PH
22	Kawachi	USA	Yes	N/A		Yes	Yes	Yes	Yes		Yes		Yes	Yes	FOCC OC OES SFAT VE
23	Ciruzzi	Argentina	Yes		Yes	Yes	Yes	Yes					Yes	Yes	

Key

A = Type A personality
AR = personal history of arthritis
AS = aspirin use
BMI = obesity/weight
COF = coffee consumption
DI = diuretic use
FH = family history of heart disease or hypertension
FOCC = occupation of father
OC = oral contraceptive use
OCC = occupation
OES = oestrogen use
PH = personal history of heart disease
SES = social class/education/income
SFAT = saturated fat intake
VE = vitamin E intake

APPENDIX C

Strengths and weaknesses of the 23 studies

C1 Introduction

In this Appendix, a brief description is given of each of the 23 studies, commenting particularly on their main strengths and weaknesses. The studies are considered in chronological order of publication.

C2 Hirayama [1]

In this prospective study somewhat over a quarter of a million adults aged 40+ and resident in six prefectures in Japan were interviewed at home during 1965 by trained public health nurses and midwives using a simple one page questionnaire. The population was followed up from census records and death certificates, but no further interviews were conducted, except in a small sample in 1971. Questions on ETS exposure were not asked, reliance being placed on data on smoking status collected for married subjects who were both in the study. Despite its prospective design and large size, the study has a number of problems including: (i) Data on smoking habits were collected only once in a 16-year follow up period; (ii) Subjects migrating out of the prefectures were not followed up for mortality; (iii) Only limited data on confounding variables were collected; (iv) Reliance was placed on death certificate diagnosis; (v) Hirayama, with one exception (certain results for lung cancer), always presented results for nonsmoking women adjusted for the age of the husband and not, as is appropriate, the age of the wife; (vi) Hirayama is known to have made a number of simple errors in statistical analysis; and (vii) Death rates in the study were much lower than expected, apparently because mortality tracing was incomplete, with deficits varying by demographic factors. It is also noteworthy that, based on follow-up to 1979, Hirayama (1981) reported relative risks for ischaemic heart disease of 1.00 (husband nonsmoker), 0.97 (husband ex-smoker or 1-19 per day) and 1.03 (husband 20+ per day) that indicated no association whatsoever with spousal smoking. In his later paper, [1], based on follow-up to 1981, he reported relative risks of 1.00, 1.10 and 1.31 which did indicate an association. Following correspondence in the New Zealand Medical Journal [34, 35] in which I pointed out that these risks implied an implausibly large positive trend for the

1980-81 period, Hirayama [36] produced revised figures for follow-up to 1979 of 1.00, 1.05 and 1.21, showing that the data published in 1981 were incorrect.

C3 Garland [2]

The paper describes results from a 10-year follow-up of men and women living in Rancho Bernardo, California, who participated between 1972 and 1974 in a survey of the prevalence of heart disease risk factors. The results concerned 695 women, aged 50-79, who were married, had never smoked, and were without a prior history of heart disease or stroke at the time of interview. Originally, the authors reported that the combined age and covariate adjusted ischaemic heart disease death rate for current and former smokers was higher ($p<0.10$) than for never smokers by a factor of 14.9. Later, in an erratum, they stated the relative risk was in fact 2.7, presumably due to a failure to take logarithms in analysis. The relative risk estimate is based on only 19 deaths from heart disease, 2 in never smokers, 15 in ex-smokers and 2 in current smokers. The very small number of deaths render their analyses adjusting for multiple risk factors extremely dubious.

C4 Lee [3]

A large hospital case-control study carried out in four hospital regions in England, including interviews with 507 patients with ischaemic heart disease and 1552 controls with diseases not associated with smoking. Among lifelong nonsmokers, the authors reported no significant association between risk of heart disease and any index of ETS exposure. No adjustment was made for any risk factors other than age or marital status. The analyses relating to lung cancer and ETS exposure in this study were criticized by the US Surgeon General [27]. However, as pointed out elsewhere [28], these criticisms were unfounded and based on a misunderstanding of the findings.

C5 Martin [4]

An abstract of a paper delivered at the 114th Annual Meeting of the American Public Health Association describes a cross-sectional study in which data were collected from parents of Utah high school students. The study was based on 23 heart attacks reported among 7115 never smoking women for which data were collected on the

husband's smoking status. No confidence limits for the findings were presented and, apart from the fact that data on a number of other risk factors were collected, no other details were provided.

C6 Svendsen [5]

The multiple risk factor intervention trial (MRFIT) was set up with the principal aim of testing whether a "special intervention" programme designed to reduce blood cholesterol, cigarette smoking and blood pressure also reduced risk of coronary heart disease. From over 350,000 original participants, 12,866 men aged 35-57 at high risk of coronary disease were selected and randomly allocated to receive special intervention or usual care. Among the high-risk men, 1,400 reported at entry into MRFIT that they had never smoked; 1,245 of these were married, 286 to women who smoked and 959 to women who did not.

The authors compared these two groups of men as a test of the relationship of ETS to coronary heart disease. Risks in nonsmokers married to smokers were generally higher than those of nonsmokers married to nonsmokers and there was some indication of a dose-response. However, numbers of deaths were small and the differences and trends seen were generally not statistically significant.

The major limitation of this study is the small number of deaths, which outweighs its strengths - there is quite good information on confounding variables and some objective information on smoking status. The authors calculated that among the self-reported nonsmokers the proportion with high (>100 μmol/l) thiocyanate levels was similar in the ETS-exposed (7.5%) and non-ETS exposed (7.3%) groups, concluding that "if some men were smoking they were equally divided among the two groups." While their conclusion may be correct, it would have been preferable to use cotinine as an objective marker of smoking status, since thiocyanate levels can be elevated by dietary and other sources.

One problem in interpreting results from this study which should be noted is that the subjects were selected to be at high risk of coronary disease. Given that they did not smoke, they would need to have had very high blood pressure and/or cholesterol levels to be included, so that any conclusions about the relationship of ETS to coronary disease for this group may not be relevant to normal healthy individuals.

C7 Butler [6]

In a dissertation, the author described the results from two subgroups of a study involving a total of 34,445 California Seventh-Day Adventists. For only one subgroup, the "spouse pairs cohort," were data presented for lifelong nonsmokers. The study is limited by the small number of heart disease cases and the fact that no confounding variables were taken into account.

C8 Palmer [7]

In an abstract, the authors reported results of an interim analysis based on a hospital case-control study of past oral contraceptive use and myocardial infarction, in which data were collected on the smoking habits of subjects' husbands. The relative risk reported was presented without confidence limits or any statement of significance, and no final analysis has ever been reported from this study. The authors reported there being a total of 336 married cases and 799 married controls, but did not state how many nonsmoking cases and controls there were.

C9 Sandler [8]

This study is based on 4,162 White men and 14,873 White women who reported in 1963, in a private census of 98% of households in Washington County, Maryland that they had never smoked. The census had provided data on demographic, smoking and other variables in 91,909 individuals. Death certificates of men and women who died up to mid-1975 in Washington County were coded. Death rates, adjusted for age, housing quality, schooling and marital status were calculated, based on estimated probabilities of still living in the County obtained from a follow-up study of a 5% sample of households in 1971.

There are a number of problems in interpreting results from this study, despite its advantages of being both prospective and based on a relatively large number of deaths:

(i) The ETS analysis is based on a comparison of people who lived with a smoker and those who did not, with no adjustment made for the number of people in a household.

(ii) The study is not a properly conducted prospective study in that death certificates were obtained only for those dying in Washington County.

(iii) The results for heart disease in females, although based on the same number of deaths and using the same confounding factors, were reported differently (1.24, 95% CI 1.1-1.4) in an earlier paper [37] and in the paper used in this review (1.19, 95% CI 1.04-1.36). The latter results have been used on the basis that the paper [8] was more recently published and therefore likely to have corrected an earlier error.

(iv) There are other problems, more relevant to other diseases, but still making it difficult to have much faith in the results of this study [28].

C10 He I [9]

The paper describes a case-control study carried out in Xijing, China, in 1985-87 of 34 female coronary heart disease cases (22 diagnosed by coronary arteriography and 12 myocardial infarction) and 68 controls. One group of 34 controls was selected randomly from the general population. The other group of 34 were hospital-based patients, either those admitted with suspect coronary heart disease but for whom the coronary arteries were confirmed as normal by arteriography, or heart, kidney, endocrine and certain surgical inpatients for whom coronary heart disease had been ruled out. Controls were matched to cases on race, occupation, place of residence and age.

One weakness of the study is the inclusion of single women with the group of wives of nonsmoking husbands, thus imparting a potential confounding between marital status and ETS exposure. Another weakness is that adjustment for the major coronary risk factors (blood pressure and cholesterol levels) seems to have been based on reported history rather than on actual measured levels.

It is noteworthy that the relative risk reduced substantially after adjustment for the risk factors as recorded. It seems possible that more accurate adjustment for these and taking account of other risk factors might have reduced the association still further. The possibility exists of inaccuracy of recording of smoking status of the women or their husbands. It is noted that "the husbands of some of the subjects were further interviewed in order to confirm accuracy," but no details are given in the paper as to the criteria for deciding when to carry out further interviews or the number of inaccuracies that were detected by this procedure. Some errors in presentation of the results (see Appendix A) have also been noted.

C11 Hole [10]

Results from this population cohort of men and women aged 45-64 years and resident in the towns of Renfrew and Paisley between 1972 and 1976 were reported originally by Gillis et al [38] and more recently by Hole et al [10]. The subjects attended a multiphasic health screening clinic and completed a questionnaire on smoking habits and symptoms of respiratory and cardiovascular disease. Mortality data were obtained from the National Health Service Central Register and the General Register Office for Scotland. Subjects living in households where another respondent had also attended for screening were classified into four groups according to whether they themselves and/or a cohabitee had ever smoked. It should be noted that information on smoking habits of the cohabitee was obtained directly from the cohabitee at screening, the questionnaire only including questions on the respondent's smoking habits. The analyses in 1989 differed from those in 1984 not only because of the longer follow-up but also because the later analyses excluded those who smoked only pipes and those who smoked cigarettes sporadically.

One limitation of the study is that only 80% of the identified population was screened and that the study was restricted to men and women aged 45-64, so that information on smoking by household members was incomplete. Results from a supplementary questionnaire sent to a subset of the population showed that 5% of all subjects and 21% of women classified in the analysis as "controls" (i.e. with no cohabitee in this study who had ever smoked) actually lived with a regular smoker who was not in the study.

Another limitation relates to the small number of deaths. It is also noteworthy that the adjusted relative risk of heart disease, for men and women combined, associated with ETS exposure, 2.01, was close to that associated with active smoking, 2.27.

C12 Jackson [11]

These comments are based on material sent to me by Dr K Brown relating to a thesis by Jackson on the Auckland Heart Survey (I was only sent Chapter 6 concerning passive smoking), together with copies of correspondence between Jackson, S Glantz and A J Wells which clarify some of the details. The ETS analyses are based on a case-control study involving the following numbers of never smokers:

		Men	Women
Cases	- non-fatal myocardial infarct	28	11
	- coronary deaths	21	9
Controls	- for myocardial infarct cases	123	112
	- for coronary deaths	61	62

No full details are given in Chapter 6 of how the various case and control groups were defined, but it seems that the subjects were aged 35-64 and that the controls for the myocardial infarct cases were population controls. It also seems probable that the controls for the coronary death cases were also decedents, Jackson pointing out that there is some overlap between the two sets of cases, as there was no restriction that decedent cases should not previously have been included in the living cases earlier when alive.

For analyses relating to ETS exposure, subjects were divided into four groups by home and/or work exposure. For home exposure, based on whether a cohabitant smoked or not, subjects were classified as having high exposure if more than one cohabitant smoked or there was exposure to more than seven cigarettes per day at home. Subjects were excluded if they had had a past admission to hospital for coronary heart disease or angina as diagnosed by the Rose questionnaire. The only potential confounding factors taken account of in analysis were age and social class.

C13 Humble [12]

The authors describe results from a 20-year follow-up of 328 White and 185 Black women who participated in 1960 in a cardiovascular disease study that included risk factor measurements, complete physical examination, and a demographic and medical history interview. The women studied were all never smokers who at the time of interview were married either to never smokers or to current smokers, in whom a total of 76 deaths from cardiovascular disease occurred. The authors state that there were no statistically significant differences according to husband's smoking for blood pressure, cholesterol or body mass index. It is difficult to understand, therefore, why adjustment for these risk factors should have had such a substantial effect on the risk estimates, increasing them from 1.34 (95% CI 0.84-2.21) to 1.59 (95% CI 0.99-2.57).

C14 Dobson [13]

The authors describe the results of a case-control study of myocardial infarction and sudden death conducted in New South Wales in 1988-89. Cases were all residents of the study area aged 35-69, with controls participants (of the same age group) in a risk factor prevalence survey conducted as part of the WHO MONICA project. Data on smoking habits were collected from 895 male and 387 female cases and from 1037 male and 1031 female controls. Data on ETS exposure at home and at work were collected for lifelong nonsmokers and for ex-smokers, with relative risks presented separately for the two groups adjusted for age and a prior history of myocardial infarction or other heart disease.

There are a considerable number of limitations of the study which seriously affect its conclusions:

(i) Data on smoking behaviour were collected by completely different methods for cases and controls. For cases, survivors were interviewed in hospital by study nurses, with information for decedents being collected from medical records, if available, or by questionnaires mailed to relatives. Controls either completed a self-administered questionnaire if they came to the study centre, completed a brief questionnaire if unable to attend, or were interviewed at home to obtain this information. The unreliability of medical records data is notorious, as is the potential for obtaining answers varying according to differing data collection techniques.

(ii) Response rates were far from 100%. Thus only 80% of the controls provided data, while for cases information on smoking habits was not obtainable for 34% of fatal cases and 4% of non-fatal cases, with data on ETS exposure missing for about 15% of all cases. The potential for bias is illustrated by the following data provided by the authors for women controls, which show smoking habits varying markedly according to source of response:

	Current Smokers	Ex-smokers	Never Smoked	Total
A. Interviewed at study centre	14%	19%	67%	100%
B. Brief questionnaire	21%	13%	66%	100%
C. Interviewed at home	31%	16%	53%	100%

(iii) Virtually no relevant confounding variables have been taken into account.

(iv) It is not explained why adjustment for age and prior history of heart disease generally had quite little effect on relative risk estimates, but for at home ETS exposure in female nonsmokers it had a large effect, pushing up an unadjusted relative risk of 1.61 (95% CI 1.04-2.47) to 2.46 (95% CI 1.47-4.13).

C15 La Vecchia [14]

A letter to the Lancet describes the results of analyses based on a case-control study of acute myocardial infarction conducted in 1988-89. From the original sample 113 cases aged 34-74 and 225 controls aged 29-74 were identified as currently married never smokers. Controls were from the same network of hospitals as the cases, suffering from acute diseases not related to any known or potential cardiovascular risk factor. Exposure to passive smoking at home was investigated through questions on the spouse's smoking status. The analyses took into account quite a wide range of potential confounding variables.

C16 He II [15]

The paper describes a case-control study involving 59 patients with coronary heart disease and 126 controls, all Chinese women with full time jobs, who had never smoked cigarettes. The cases were patients with non-fatal coronary heart disease from three large teaching hospitals in Xi'an between 1989 and 1992, with a final diagnosis of myocardial infarction according to WHO criteria or coronary stenosis confirmed by coronary arteriography. Controls were from three sources: patients admitted because of suspected or diagnosed coronary heart disease but confirmed to be normal after coronary arteriography, other medical outpatients attending cardiology departments, and a random sample of healthy subjects from a community screening programme for coronary heart disease. "Passive smoking from husband" was defined as living with a smoking husband for over five years, all subjects being married. "Passive smoking at work" was defined as working with smoking coworkers in the same office or factory unit for over five years, all subjects (somewhat remarkably) being found to be either not exposed or exposed for over five years. The characteristics of the controls from the three sources were stated not to be significantly different and results were only presented using the combined controls. Results were presented before and after adjustment for a wide range of risk factors included in a logistic regression model.

C17 Layard [16]

The National Mortality Followback Survey (NMFS), conducted in 1986 by the US National Center for Health Statistics, is based on a national probability sample of about 1% of all deaths in 1986 of US residents aged 25 or older. The NMFS sample includes data from 49 states and the District of Columbia. Next of kin decedents in the NMFS sample were asked to complete a questionnaire that included questions on demographic characteristics, dietary patterns, cigarette smoking (personal and spousal), alcohol consumption, education, income, and history of diseases. For the purposes of their analyses the authors restricted attention to those who had never smoked 100 or more cigarettes in their entire lives and excluded those who had never married, or whose marital or spousal smoking status was unknown. Cases were 475 male and 914 female ischaemic heart disease deaths, and controls were 998 male and 1930 female decedents from causes not generally considered to be smoking related. Spousal smoking status was

defined according to answers to the question "Did (any) spouse smoke at least 100 cigarettes?" Results were presented adjusted for age and race, but the author noted that the spousal smoking results were not appreciably affected by adjustment for the various risk factors recorded.

C18 LeVois [17]

In their well known prospective study, Cancer Prevention Study I (CPS-I), somewhat over a million men and women were enrolled by volunteer workers of the American Cancer Society (ACS) in 1959 and 1960. All members of the households involved aged over 30 completed a detailed questionnaire on a range of risk factors, with briefer repeat questionnaires completed in 1961, 1963, 1965 and 1972. Mortality status was determined at regular intervals and death certificates obtained. The study population is not fully representative of the USA, being mainly white and of higher social status and less exposed to occupational risk factors than average. The strengths of the study include its prospective design, its great size, the completeness of follow-up, and the large number of risk factors recorded.

These strengths have been widely recognized by the fact that it has been often cited as one of the major sources of data on the relationship between smoking and health. In 1981, Garfinkel [39] presented results relating smoking by the husband to risk of lung cancer in never smoking females. However, despite the increasing attention given to ETS and diseases other than lung cancer, the ACS has never published any results relating to heart disease or to any other cancer, despite attention being drawn to this omission in the scientific literature [28].

The paper by LeVois and Layard (not representatives of the ACS) describes results of analysis of data from CPS-I, based on a total of 88,458 male and 267,412 female nonsmokers with spouses having known smoking habits, among whom there were 7758 CHD deaths in males and 7133 CHD deaths in females during the follow-up period 1960-1972. Relative risks and 95% confidence limits are presented adjusted for age and race, it being noted that further adjustment using a weight index, exercise, highest level of education, dietary factors, alcohol consumption, history of hypertension, and history

of diabetes had no appreciable effect on any of the reported associations. The paper also includes results of analysis from the second ACS Cancer Prevention Study (CPS-II) based on follow-up from 1983 to 1988. These results are not included in this review, being superseded by the results reported by Steenland et al [21] for a longer follow-up period. The two sets of CPS-II results were in fact quite comparable.

C19 Mannino [18]

In an abstract, the authors describe analyses based on 20,265 non-institutionalized persons aged 18 and older who reported that they had never smoked, when interviewed in the National Health Interview Survey, conducted in 1991, by the Centers for Disease Control and Prevention. In this cross-sectional study, 1,895 adults who reported daily ETS exposure in their homes were compared with 16,764 adults who reported ETS exposure in their homes in respect of prevalence of cardiovascular disease (and also in respect of other health indices such as days of restricted activity). Analyses were adjusted for age, sex, race, socioeconomic status, and urban living. Relative risks only were reported, with no confidence limits or details on prevalence in the two groups.

C20 Tunstall-Pedoe [19]

In the Scottish Heart Health Study men and women aged 40-59 years were recruited by random sampling from general practitioner lists between 1984 and 1986. Each was sent a "personal health record" to complete and a clinic appointment. The former included the standard Rose questionnaire on angina and possible infarction, the MRC cough and phlegm questionnaire, questions on prior medical diagnoses, on current and former consumption of cigarette, pipe or cigar tobacco, and the question "Have you been exposed to tobacco smoke from someone else in the last three days?" with possible answers of "1 - yes, a lot; 2 - yes, some; 3 - yes, a little; 4 - none at all." Relevant clinic procedures included an ECG and venepuncture, with blood analysis for serum cholesterol and serum cotinine.

The paper concentrates on 786 men and 1492 women reporting never having smoked and with a cotinine level less than 17.5 ng/ml, a level intended to exclude deceivers about current smoking status. The paper presented the results of cross-

sectional analyses relating presence of chronic cough, chronic phlegm, questionnaire angina, undiagnosed CHD, diagnosed CHD and all CHD to (i) reported ETS exposure group and (ii) serum cotinine group. Adjustment was made for age and housing tenure and also, for the heart disease-related endpoints, for cholesterol and diastolic blood pressure. A striking feature of the results was that associations with reported ETS exposure were much stronger than with serum cotinine. Thus, comparing the risks for the highest and lowest exposure groups, one can see from the results summarized below that there were significant associations for 5 of the 6 endpoints as regards reported ETS exposure, but with only 1 of the 6 endpoints as regards serum cotinine, despite similarity of numbers of subjects in the groups being compared. The authors suggest that the self-reported data could be biased, participants with symptoms or disease exaggerating exposure, though they do note that this does not explain the results for diagnosed CHD.

	Relative risks (95% CI)	
	Self-reported ETS exposure	Serum cotinine
Endpoint	A lot vs none	IV vs I*
Chronic cough	2.3 (1.3-3.9)	1.1 (0.6-1.9)
Chronic phlegm	2.3 (1.4-3.9)	1.2 (0.7-2.0)
Questionnaire angina	2.1 (1.1-3.9)	0.8 (0.4-1.5)
Undiagnosed CHD	1.4 (0.9-2.0)	1.0 (0.7-1.4)
Diagnosed CHD	2.4 (1.1-4.8)	2.7 (1.3-5.6)
All CHD	1.6 (1.1-2.4)	1.2 (0.9-1.7)
Sample size	292 vs 618	295 vs 756

* Highest [IV] vs lowest [I] quartile

C21 Muscat and Wynder [20]

The paper describes results from a hospital case-control study of myocardial infarction conducted between 1980 and 1990. Newly diagnosed incident cases with myocardial infarction were interviewed directly in teaching hospitals in New York, Philadelphia, Chicago and Detroit. Controls were patients who did not have heart disease and were hospitalized for conditions unrelated to tobacco use, frequency matched to cases on the basis of age (± 5 years), race, and year of diagnosis. The analyses concerned only patients who reported never smoking cigarettes and involved 68 male and 46 female cases and 108 male and 50 female controls. The standardized questionnaire, administered to all subjects in hospital by trained interviewers, included an extensive series of questions on ETS exposure. Relative risks presented were adjusted, in some cases, for age, education and hypertension.

C22 Steenland [21]

The second American Cancer Society Cancer Prevention Study (CPS-II) was similar in many ways to CPS-I (see section C18). It involved almost 1.2 million men and women aged 30 or older enrolled nationwide by ACS volunteers. The participants completed, at the time of enrolment, a four-page questionnaire on a variety of risk factors. Unlike CPS-I, which only obtained data on spousal smoking from responses given by spouses, the questionnaire included a specific section on ETS exposure, with data collected on exposure at home, at work, and in other areas. For the purposes of analysis, participants who reported ever having smoked or who had unclassifiable data on smoking or marital status were excluded. Spousal exposure was calculated only for those married individuals with spouses also in CPS-II, with valid dates of marriage and with sufficient data on smoking association to indicate whether they had smoked during marriage. These restrictions led to "spousal ETS" cohorts of 101,227 men and 208,372 women, of which, respectively, 2,494 men and 1,325 women had died from coronary heart disease between 1982 and 1989. Some analyses were restricted to subjects who were concordant between self-report and spousal report for exposure or for non-exposure to current cigarette smoke at home. The study has the obvious strengths of being prospective and based on large numbers of deaths. Additionally, the relative risks and 95% CIs cited were adjusted for a very wide range of potential confounding variables.

C23 Kawachi [22]

An abstract reports results from the Nurses' Health Study, an ongoing cohort study of US female nurses. Self-reported exposures to passive smoking at home and at work were assessed among 32,046 women aged 36 to 61 who had never smoked and who were free of diagnosed coronary heart disease or stroke in 1982. During 10 years of follow-up, 152 incident cases or coronary heart disease occurred, 127 nonfatal and 25 fatal. A "broad range" of cardiovascular risk factors were taken into account in analysis. Some additional results are given separately in a review article by two of the authors [40].

C24 Ciruzzi [23]

An abstract briefly describes the results of analyses of data on lifelong nonsmokers from a case-control study conducted in 35 coronary care units in Argentina in 1991-1994, involving a total of 336 patients with acute myocardial infarction (AMI) and 446 patients in the same network of hospitals with acute disorders unrelated to smoking or to suspected risk factors for AMI. Data were collected by trained interviewers using a structured questionnaire and analyses adjusted for a moderately large number of risk factors for AMI.

C16

APPENDIX D

Experimental evidence on ETS and heart disease*

INTRODUCTION

Glantz and Parmley [24] concluded that "nonsmokers exposed to secondhand smoke in everyday life exhibit an increased risk of both fatal and nonfatal cardiac events." In their paper they cite clinical and laboratory evidence that they claim provides "a clearer understanding of the mechanisms by which passive smoking causes heart disease." In this appendix we consider the experimental evidence on ETS and heart disease, with particular reference to Glantz and Parmley's claims.

An insuperable problem in trying to assess the effects on humans of exposure to environmental tobacco smoke (ETS) is that it cannot be done 'blind'. In other words, people know whether and when they are exposed to it. Furthermore, if they are physically irritated and/or mentally annoyed by other people smoking in their presence, they may well experience stress effects secondary to the release of stress hormones. The spectrum of these effects include increased pulse rate, increased blood pressure, various changes in blood chemistry and reduced exercise tolerance in persons who already have compromising cardiovascular disease. In other words, effects of annoyance and of the chemical components of ETS can be indistinguishable.

Clearly, then, one of the most important questions relating to Glantz and Parmley's review [24] is: "Have the reviewers sufficiently taken into account the difficulties described above?" In fact, there appears to be no evidence at all that they are even aware of the problem, let alone that they have taken it into account.

It is not unreasonable to deduce that increased COHb levels can lead to reduced exercise tolerance and to other effects attributable to reduced oxygen delivery and availability to vital tissues. However, ETS is only one of many sources of CO, and by no means the most important in most situations. Vehicular exhaust fumes, and domestic heating systems are, overall, far more important sources of CO with many attributable deaths in the case of defective heating systems.

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*Prepared with the assistance of Dr F J C Roe

By comparison, rises in COHb levels in non-smokers resulting from exposure to ETS are for the most part trivial in extent and readily reversed following cessation of exposure.

Most of the animal experiments cited by Glantz and Parmley [24] are flawed in one or more ways. Most of them involve exposure to unrealistically high levels of ETS, entail the exposure to various types of stress, and/or consider endpoints that have no proven, or even likely, association with atherogenesis.

COMMENTS ON GLANTZ AND PARMLEY'S CLAIMS

Effects of ETS on oxygen delivery, processing, and exercise [27,74-91]

Glantz and Parmley [24] state that the CO in ETS competes with oxygen for binding sites on red blood cells. There is no reason to suspect that CO in ETS is any different from CO derived from any other source in this respect. The question which applies to all aspects of toxicology is: "Is the dose sufficient to have any measurable toxic consequences relevant to the development of heart disease?" The reduction in the amount of oxygen carried by the blood as a consequence of exposure to ETS is small compared with the effects of exposure to the lowered oxygen tension associated with climbing to moderately higher altitudes. Furthermore, the body fairly rapidly adapts to reduced oxygen delivery by the blood to tissues by increasing the red blood cell count and, hence, the concentration of haemoglobin per unit of blood. After this adaptation has occurred, exercise tolerance returns towards normal.

Glantz and Parmley [24] fail to take adaptation into account in their discussion of the potential effects of reduced oxygen-carrying capacity of blood in healthy subjects. Instead, they draw many of their conclusions from studies of effects of short-term exposure to CO in persons with existing heart disease symptoms under conditions in which no time is allowed for possible adaptation.

A second serious flaw in short-term studies of the effects of exposure to ETS is the fact that it is not possible to disguise from subjects the fact that they are being exposed to it as distinct from control air that is free of ETS. Consequently such studies cannot be undertaken blindly even though there is abundant evidence that some people react emotionally against exposure to tobacco smoke. Such emotional reaction can lead to the release of catecholamines

which have many of the same effects as exposure to nicotine, including increased blood pressure and heart rate.

There is, in fact, no evidence that exposure to realistic levels of CO-containing ETS has any measurable adverse effect on exercise tolerance, lactate production, cardiac function, ECG tracings, etc in healthy persons under conditions in which time is allowed for adaptation to very slightly raised COHb levels.

Effects on platelets [92-107]

A serious deficiency in relation to the data cited in this section is the failure of Glantz and Parmley [24] to justify their assumption that effects on platelets observed in ultra short term studies are relevant to the development of cardiovascular disease. Thus, the finding of Martin et al [98] that platelet volume was significantly higher in men who had suffered a myocardial infarction than in controls does not justify the assumption that increased platelet volume seen in response to non-blind exposure to ETS [95] has any relevance to the aetiology of atherosclerotic cardiovascular disease. Furthermore the explanation advanced by Glantz and Parmley of the failure of platelets to respond to ETS exposure in the same way in smokers as in nonsmokers is not backed up by any critical experimental investigation.

The reasons why data derived from animal studies generally have thrown no clear light on the possible effects of exposure to ETS or any of its constituents are discussed below. For these reasons the claim that data from animal studies support the conclusion that exposure to ETS increases the risk of thrombus formation because of an effect on platelet numbers or function is not sustainable.

Likewise, evidence of adverse effects on platelet activating factor derived from studies on smoke extracts [106] provide no direct support for the theory that ETS exposure is a risk factor for cardiovascular disease.

Finally, the claims that nicotine itself at the dose levels associated with exposure to ETS has any effect on platelets is not supported by any of the evidence cited. Nor does the comparison of smokers with the wearers of nicotine patches provide sound evidence that smoke components other than nicotine affect blood platelets or their functions.

Does exposure to ETS predispose to atherosclerosis?

There are several theories with regard to the pathogenesis of atherosclerosis. According to one theory, endothelial damage by toxins predisposes to the adherence of platelets to the vessel wall. In the absence of such damage prostacyclin produced by endothelial cells protects against the adherence of platelets. However once platelets become adherent they release mitogens, such as platelet-derived growth factor, which promote the proliferation of smooth muscle cells.

Glantz and Parmley [24] cite papers in which it is claimed that even just short term exposure to ETS increases the numbers of anuclear endothelial cell carcasses in the circulating blood [93,108]. In the experiment reported by Davis et al [93] the numbers of dead endothelial cells per counting chamber rose from 2.8±0.9 to 3.7±1.1 - a non-statistically significant difference. However, even if the rise had been significant, the interpretation would not have been straightforward. It is not possible to expose a nonsmoker to ETS without his/her knowledge and the knowledge of such exposure may itself have effects, particularly in an experimental situation. Stress can give rise to catecholamine release and numerous physiological changes secondary to such release. Davis et al [93] made no attempt to measure stress or to see if stress in the absence of exposure to ETS influences endothelial cell counts. It is theoretically possible that a quickening of the pulse and/or a rise in blood pressure and velocity would lead to a "sweeping out" of dead endothelial cells from blood vessels. In other words exposure to ETS did not damage their vascular endothelium; it simply led to the dislodgement of cells that died earlier, either as a result of natural apoptosis or as a consequence of prior exposure to a toxicant. Overall it is simply not plausible that sitting next to a smoker for 20 minutes in a hospital corridor could lead to a measurable increase in circulating dead anuclear endothelial cells as a direct consequence of exposure to tobacco-smoke constituents in the ambient air during that short period.

The reports by Moskowitz et al [76] and by Feldman et al [81] of associations between exposure of children to ETS as a consequence of parental smoking and blood lipid parameters [e.g. red blood cell 2,3 diphosphoglycerate (2,3-DPG); serum cholesterol; and HDL cholesterol] are unconvincing because the apparent effects were different in boys and girls. Apart from this it is well documented [65-67] that the diets consumed by smoking families tend to differ from those consumed by nonsmoking families, particularly in respect of the consumption of fruit and

green vegetables. Such differences in lipid parameters as were seen by these investigators, if real, are more likely to relate to diet than exposure to ETS.

The evidence from animal experiments that exposure to ETS speeds the atherosclerotic process [103,104,109-115]

The suitability of the animal model used by Zhu et al [103], which involves the exposure of rabbits fed on a high cholesterol diet to high levels of second-hand smoke daily (on 5 days/week) for 10 weeks, can be criticized on several grounds. Firstly there is the doubt whether arterial plaque formation in the aorta and pulmonary artery of rabbits fed for just 10 weeks on an atherogenic diet is an appropriate model for coronary artery atherogenesis in humans. It is well known that fatty plaques arise in the intima of the aorta in milk-fed human babies and that these disappear after weaning on to a more varied diet. In other words, intimal fatty plaques do not necessarily progress to atherosclerotic plaques which involve the media as well as the intima. Zhu et al [103] made no attempt to study the effects of exposure to ETS on the coronary arteries. Secondly the levels of ETS exposure studied by these investigators greatly exceeded levels of human exposure that occur in everyday life. Thus even the so-called "low-dose" with its 18.8 ppm content of CO and 30 $\mu g/m^3$ of nicotine was much higher than nonsmokers exposed to ETS normally encounter. Thirdly, it is well known that rabbits experience severe stress when confined to exposure chambers, especially if there is noise from fans. In the experiments reported by Zhu et al [103] the high dose and low dose ETS-exposed rabbits were confined in cages of unstated size within chambers (eight rabbits per 3.58 m^3 chamber) equipped with three fans per chamber. No attempt was made to assess the potential contribution of confinement/noise stress to the effects seen. Although there were significant increases in the percentage of the aortic and pulmonary artery surface areas that were covered by what were termed "atherosclerotic lesions," differences in percentages between the low-dose and control groups were not statistically significant. Furthermore there were no significant between group differences in serum triglycerides, serum cholesterol or serum high density lipoprotein cholesterol.

In a thoughtful review, Benowitz [116] opined that cholesterol-fed rabbits "are of questionable relevance to human atherosclerosis."

The experiments involving the clamping of the coronary vessels in ETS exposed and control rats are difficult to relate to possible effects of ETS exposure on the incidence of coronary artery disease in humans. The fact that the bleeding time was shorter in ETS-exposed than in control rats is not directly indicative of increased risk of development of atherosclerosis.

Evidence that certain carcinogens of the polycyclic aromatic hydrocarbon (PAH) class predispose to atherosclerosis relies on the results of studies by Benditt and Benditt [117], Albert et al [118], Albert et al [119] and Revis et al [120]. In these studies chickens or White Carneau pigeons, given repeated huge doses of PAH carcinogens such as benzo(a)pyrene [B(a)P], dimethylbenz(a,h)anthracene, or 3-methylcholanthrene by intra muscular injection showed increased aortic plaque formation (i.e. increased number and size of plaques) compared with solvent-only injected controls. According to Albert et al [118] exposure to X-irradiation or to injections of chemical carcinogens of other types [e.g. 2-acetylaminofluorene (2-AAF), N-methyl-N-nitro-N-nitrosoguanidine (NNG)] did not affect plaque formation. Nor, according to Revis et al [120], did exposure to benzo(e)pyrene [B(e)P], a non-carcinogenic analogue of B(a)P.

Morphologically the plaques occurring in higher incidence in birds exposed to carcinogenic PAH were indistinguishable from plaques which occur spontaneously in untreated older birds and studies using tritiated thymidine indicated that plaque growth in carcinogen treated birds is a function of cell proliferation [119].

The mechanism by which the carcinogenic PAH in question increases aortic plaque growth is uncertain. The fact that birds given repeated very high doses of B(a)P or DMBA showed greatly reduced body weight gain [e.g. only 62% of untreated controls after 10 weeks in the case of DMBA and only 77% in the case of B(a)P] indicates a profound effect on the overall nutritional status of birds [119].

The fact that abdominal aortic plaques taken from women who are heterozygous with respect to glucose-6-phosphate dehydrogenase isoenzymes [117,121] is consistent with the possibility that individual plaques are derived from single cells. However to hypothesize further that plaques are in reality benign smooth muscle tumours of the aortic wall is not supported by the histopathological appearances of plaques.

The possibility that plaque formation in birds exposed to DMBA was attributable to an effect on serum cholesterol levels seems unlikely in view of the fact that the increase in plaque formation was confined to the abdominal aorta.

Citing the data of Penn et al [114], Glantz and Parmley [24] appear to contradict themselves when they write "The carcinogens appear to be acting as a promoter to facilitate the development of plaques rather than as initiator of plaques." This implies that they do not think that mutation due to carcinogens in ETS initiates the formation of plaques which they earlier suggested might be smooth muscle tumours.

Clearly, there is not enough information on which to base a conclusion that carcinogens per se or carcinogens specifically of the PAH-type predispose to atherosclerosis in birds as a consequence of their genotoxicity. Furthermore, insofar as atherosclerosis has not been described as a consequence of exposure to PAH in numerous studies in rodents and non-avian species makes it very unlikely that humans are put at risk of developing coronary heart disease as a consequence of exposure to very low concentrations of PAH carcinogens in ambient air.

A more recent claim [122] that exposure of cockerels to environmentally relevant concentrations of 1,3-butadiene, which is present in the vapour phase of ETS, also fails to provide any substantial evidence of risk of heart disease in humans from exposure to ETS. Occupational exposure to butadiene is associated with an SMR of 1.41 to coronary heart disease in black male production workers in the styrene-butadiene industry in the USA but with an SMR of only 0.91 in white production workers. Such ratios, in the absence of any attempt to control for dietary and other important potential confounding factors, including active smoking, render it ridiculous to assert that any risk of heart disease in humans has been demonstrated.

Finally, there remains the objection that enhancement of plaque size in the abdominal aorta of cockerels has not been validated as a model for coronary atherogenesis in humans.

Glantz and Parmley [24] rule out the possibility that exposure to ETS increases the risk of development of arterial atherosclerosis by increasing catecholamine release. Their basis for doing so is that dosing rabbits with the β-blocking agent metoprolol had no effect on

atherosclerotic plaque development in smoke-exposed cholesterol-fed rabbits as compared with control cholesterol-fed rabbits [104].

Glantz and Parmley [24] sought to address the criticism that enhancement of atherogenesis in rabbits by exposure to ETS requires the animals to be fed on an unnatural high cholesterol diet. According to them, their demonstrations [112,113] that cockerels fed on a normal low-cholesterol diet show enhanced atherogenesis when exposed to ETS overcomes this objection. However, there is clearly an error in their calculations [112] which imply that in the absence of exposure the lifespan of cockerels is 77 years (i.e. 16 weeks is only 0.4% of the projected lifespan). It should also be noted that, during their studies, no attempt was made to control for the likely effects of stress on male birds crowded many to a smallish cage, and that exposure to ETS was not, as claimed, truly "moderate" but was (in terms of total suspended particulates) some 300-fold higher than that to which humans are exposed [123]. In fact, exposure of cockerels for 13 weeks to just 10mg/m^3 total suspended particulates, which is still unrealistically very high, produced no adverse histopathologically detected effects in Glantz and Parmley's study.

In a paper published in 1994 Glantz and Parmley [113] claim to have produced evidence of enhanced atherogenesis in cockerels exposed to more realistic levels of ETS smoke constituents. However, the investigators made no attempt to control for stress due to multi-housing, e.g. by conducting studies in free-range birds or by including a group exposed to a non-ETS irritant. Nor did they monitor levels of stress hormones or examine adrenal glands histologically.

A major underlying weakness of Glantz and Parmley's studies on the effects of exposure of cockerels to ETS is that there is no clear basis for assuming that enhancement of aortic plaque formation which occurs naturally in birds as they get older has any relevance to coronary artery atherosclerosis in humans.

<u>Does the presence of free radicals in ETS predispose to ischaemic heart disease? [116,124-130]</u>

The results of studies of the effect of exposure to ETS or its constituents on the recovery of animals subjected to surgical occlusion of coronary arteries are of very doubtful relevance to this question [116,126-128]. At best such studies might be relevant to the investigation of the

effects of exposure to smoke constituents in patients who have experienced a heart attack due to coronary artery occlusion. They throw no clear light on the possible importance of free radicals in coronary artery atherogenesis. In the case of the experiment reported by van Jaarsveld et al [127] the extent of exposure of rats to any particular smoke constituent was not measured and no attempt was made to study the effects of exposure to chemicals that are not present in tobacco smoke. Thus the possibility that the effects seen were attributable to exposure to simple irritants cannot be excluded.

Similarly, the finding of van Jaarsveld et al [128] that antioxidant vitamin supplementation partially protected smoke-exposed rats from myocardial change following a 10 minute period of ischaemia followed by reperfusion is uninterpretable, not least because rats of most strains do not suffer from atherosclerosis of coronary vessels.

According to McCusker and Hordal [129] the exposure of hamsters to ETS led to enhancement of the activity of antioxidant enzymes (superoxide dismutase and catalase) in their pulmonary macrophages. The fact that the activities of these enzymes in nonsmokers is lower in the lung macrophages than that in smokers is interpreted by Glantz and Parmley as implying that nonsmokers exposed to ETS are at higher risk than smokers from free-radical damage. This speculation fails to consider questions of dose, frequency of exposure and the probability that extra protection from free-radical damage is not needed under conditions of realistic exposure to ETS in which the extent of increased free-radical damage is immeasurably small.

Apart from this, free-radical damage associated with the inhalation of tobacco smoke is more likely to influence the incidence of lung disease than that of heart disease.

The report by Anderson et al [130] describes a study of the effect of exposure of 16 nonsmokers (11 women and 5 men) for three hours to a smoky atmosphere in which the CO concentration averaged 17.5 ppm and the level of respirable particles was 2500 $\mu g\ m^3$. During the exposure period total mean leucocyte counts rose significantly in both nonsmokers not exposed to ETS and in nonsmokers exposed to ETS but only to a non-significant degree in smokers. There were also effects on phorbol myristate acetate-activated luminol-enhanced chemiluminescence and neutrophil-chemotactic responses in nonsmokers during exposure to ETS. The authors fail to provide a clear explanation of how their findings relate to enhancement

of risk of atherosclerosis. Furthermore, the interpretation of their study is seriously hampered by the lack of information on the diurnal variation in the parameters measured, by the fact that only small numbers of subjects were studied and by the absence of adequate information or control of potential confounding variables (e.g. dietary factors, infections, contraceptive pill, medication, etc.). Arguably chemiluminescence is a measure of smoke exposure rather than of a health consequence of such exposure.

All in all, the relevance of this study to the determination of risk of coronary artery disease as a consequence of exposure to ETS is extremely tenuous.

The relationship between exposure to ETS and myocardial infarction [131-134]

Evidence from studies in dogs which have been subjected to surgically induced coronary artery occlusion are said to have pointed to there being an adverse effect on the extent of myocardial damage as a consequence of ETS exposure prior to the surgical procedure. The first of the reports cited [131] involved two groups of five dogs and is the subject of a brief abstract. The mean size of infarcts (determined by triphenyl tetrazoluene chloride staining) was significantly ($p<0.025$) higher in the smoke-exposed dogs than in the controls. The findings in this small study are surprising and validation of the techniques involved as well as the results of a larger study are needed. In any case the findings do not concern the possible effect of exposure to ETS on atherogenesis.

Coronary artery flow was studied [132] in 16 men and 8 women during cardiac catheterization. Smoking a cigarette led to immediate constriction of coronary arteries as indicated by measurement of coronary artery flow using Doppler techniques. Coronary artery flow decreased (by 5%) and coronary vascular resistance increased by 21% five minutes after smoking. However these effects were no longer apparent 30 minutes after smoking.

This study in humans does not address the question of whether exposure to ETS predisposes to atherogenesis. On the contrary it is more relevant to the understanding of the pharmacodynamic effects of nicotine.

The study in the perfused hearts of rats reported by Fenton and Dobson [133] concerns the physiological effects of nicotine on the heart. It has no immediate relevance to whether or not exposure to ETS predisposes to atherosclerosis or consequential heart disease.

Kool et al [134] compared the distensibility and compliance coefficients of the common carotid and branchial arteries in habitual smokers and nonsmokers matched for age, height, body weight and gender. The average age of the subjects was 37 years. They found no difference between the two groups in haemodynamic variables or arterial stiffness but speculated that increased risk of plaque rupture secondary to immediate effects of nicotine (i.e. increased blood pressure and heart rate) might be a more important risk than the long-term effects of smoking.

Clearly the results of this study throw little light on whether or not realistic exposure to ETS predisposes to coronary heart disease.

DISCUSSION

By what mechanisms might exposure to Environmental Tobacco Smoke (ETS) increase the morbidity and/or mortality from coronary heart disease?

Introduction

Those who have sought answers to this question have focused on two components of ETS, namely, nicotine and carbon monoxide. In the case of each of these components of tobacco smoke, a variety of mechanisms have been suggested to explain increased risk of coronary heart disease (CHD) in active smokers. The problem is complicated by many factors and variables. In particular, CHD is not a single disease entity either in terms of the immediate manifestation of symptoms or in terms of prognosis. Secondly, it is clear that genetic constitution has a major impact on whether or not an individual might develop symptoms of any form of CHD and/or die from CHD. Thirdly, dietary factors constitute major determinants of development of and/or death from CHD. Fourthly, numerous other factors are known to be risk factors for cardiovascular disease generally. Important amongst these is the taking of oral contraceptives. Fifthly, the presence of lung disease of a kind that reduces lung function must be taken into account in any assessment of exercise tolerance.

Inhaling smokers receive not only a gradual build up of plasma nicotine levels but also pulse doses of nicotine. These have neuro-pharmacological effects which contribute to the pleasure of smoking. By contrast non-inhalers, nicotine gum suckers, tobacco chewers and wearers of nicotine patches who absorb the alkaloid transdermally only experience the slow steady rises of plasma nicotine. This difference in the mode of exposure to nicotine between inhalers and non-inhalers needs to be taken into account in any consideration of the possible association between exposure to nicotine and risk of CHD. In the case of exposure to nicotine present in ETS, although the route of exposure is inhalation, the doses are too small to have any measurable neuro-pharmacological effects. Certainly none have been recorded.

The affinity of carbon monoxide (CO) for haemoglobin with resultant reduced capacity of the blood to transport oxygen provide a plausible explanation of the reduction in exercise tolerance that has been reported after exposure to the gas. However, the position is complicated in so far as (i) CO is generated within the body, (ii) there are many environmental sources of CO other than tobacco smoke, (iii) exercise increases the rate of elimination of CO from the body provided that it is taken under conditions of only low ambient CO, while (iv) rest decreases the rate of elimination of CO.

Under conditions of a heavy level of smoking in a poorly ventilated indoor space, ambient levels of both CO and nicotine can rise. However, blood levels of neither of these smoke components rise nearly as much in non-smokers as they can do in smokers, even when the latter are smoking outdoors. In particular, the uptake of nicotine by non-smokers, even in very unpleasantly smoky rooms, is very low compared with that in smokers. Moreover, as pointed out above, the non-smoker is not pulse-dosed with nicotine.

These considerations indicate that it would be very unsafe to try to predict risk of CHD in non-smokers consequent on their passive exposure to ETS on the basis of epidemiological studies of the association between active smoking and CHD morbidity/mortality. The fact that pipe-smokers are far less apt to develop CHD than cigarette smokers despite having comparable exposure to nicotine, signals a particular warning to anyone minded to make glib assumptions in this area.

Benowitz [116] reviewed the possible ways in which nicotine may predispose to CHD. In his view a causal link between cigarette smoking and CHD is well established but the pathophysiology underlying the association is not. An important effect of nicotine is to stimulate the release of catecholamines (e.g. adrenalin and nor-adrenalin) from the adrenal medulla. Catecholamines are known to increase heart rate and raise blood pressure. These effects would be expected to put an increased strain on the heart. A healthy heart has plenty of functional reserve to deal with such increased strain. But an already diseased heart may not be able to do so with a consequent increased risk of cardiac dysfunction and sudden death. However, the more important question concerns whether nicotine is a cause of the underlying disease, which diminishes its ability to cope with a sudden release of catecholamines. After all, such a release is a normal physiological reaction which enables a wild animal to escape from a predator.

If nicotine predisposed (i) to increased circulating levels of blood lipids, (ii) to damage to the endothelial cells that line blood vessels, or (iii) to increased risk of thrombosis by activating blood platelets, it would be plausible that exposure to nicotine per se could lead to damage of the coronary vessels that supply the heart muscle both with nutrients and with oxygen. In fact, according to Benowitz [116], there is no clear or unequivocal evidence that nicotine has any of these effects and there is no persuasive evidence from studies on laboratory animals of any such effects of nicotine.

Wald et al [135] reported a lower incidence of CHD in pipe-smokers than in cigarette smokers. However, according to Carstensen et al [136] pipe-smoking does constitute a risk factor for CHD. Benowitz (1991) speculates that the higher risk in cigarette smokers relates to the neuropharmacological effects of the pulse doses of nicotine which inhaling cigarette smokers get but non-inhaling pipe smokers do not.

An overview of the available evidence combined with a consideration of plausibility leads one to the following conclusions.

(i) There is no persuasive evidence that passive exposure to nicotine causes atherosclerosis.

(ii) There is no persuasive evidence that passive exposure to carbon monoxide causes atherosclerosis.

(iii) Claims based on the result of short-term studies in humans or laboratory animals to the effect that exposure to CO, nicotine or ETS increases the risk of development of

atherosclerosis are not supported by data from long term studies in which atherosclerosis of the coronary arteries constitutes the end point.

(iv) It is plausible that a reduction in the oxygen-carrying capacity of the blood because of the reversible formation of carboxyhaemoglobin during and after exposure to CO would reduce exercise tolerance in persons with existing evidence of cardiac ischaemia; and it is also plausible that cardiac performance would be impaired by the formation of carboxymyoglobin in heart muscle. In so far as these effects are reversible it seems somewhat unlikely that exposure to CO contributes to any progressive disease of the heart.

(v) Similarly it is plausible that the pharmacodynamic effects of nicotine might temporarily increase the work-load of the heart and that this might show up as reduced exercise tolerance in persons with existing heart disease.

(vi) From the viewpoint of the toxicologist, plausibility of toxicity is heavily dependent on dose and in real life circumstances exposure to either CO or nicotine as a consequence of exposure to ETS is rarely high enough for it to be expected to exhibit a measurable effect.

(vii) From the viewpoint of the epidemiologist, no calculation of risk from exposure to either CO or nicotine based on comparisons of ETS-exposed and ETS non-exposed populations can be regarded as sound unless the possibility of serious confounding by variables known to affect the same endpoints are rigorously controlled. Given this stricture, there is no reliable evidence that exposure to ETS is a risk factor for CHD.