META-ANALYSES OF THE EPIDEMIOLOGICAL EVIDENCE RELATING ETS TO LUNG CANCER AND HEART DISEASE

INTRODUCTION

In two separate documents, the epidemiological evidence relating to possible effects of ETS in never smokers is presented, on an individual study basis, from over 60 lung cancer studies[1] and from almost 30 heart disease studies.[2] In attempting to assess this overall evidence, the technique of meta-analysis is often used to combine the relative risk estimates from the individual studies. Results from a number of meta-analyses are presented in this document. However, before presenting these results, attention should be drawn to some features and limitations of the technique.

Meta-analysis was originally designed to combine evidence from randomised studies of similar design, to try to obtain a more accurate estimate of the possible effect of treatment. However, in recent years it has been increasingly used to combine evidence from epidemiological studies of quite widely varying design. It is important to realise that such a procedure may result in a combined relative risk estimate that has narrow confidence limits and therefore appears precise, but is in fact a quite inaccurate estimate of the true effect of treatment (if any).[3]

There are three major potential problems with meta-analysis.

The first, which also applies to the meta-analysis of randomised studies, lies in the possibility that the studies being analysed are unrepresentative of all those studies that actually exist. If, for example, editors are more likely to publish studies showing positive results than they are to publish studies showing negative results, and meta-analysis is based only on published evidence, such "publication bias" will lead to over-estimation of the true effect of treatment. Publication bias can result from various other sources also, and though various methods have been proposed for detecting and correcting for it, all have limitations.[4]

The second problem, specific to epidemiological studies, is that the results of the individual studies may be distorted by confounding and the other sources of bias that would be avoided in randomised studies. Some types of bias may be common to all (or most) of the studies. For example, it would be expected that studies would tend to find a higher risk of liver cirrhosis in heavy smokers than in nonsmokers, simply because heavy smokers are more likely to be heavy drinkers. Meta-analysis would not remove such a bias, and therefore may be misleading. A statistically significant result from a meta-analysis of epidemiological data does not necessarily establish that any underlying effect exists.[5,6]

The final problem, particularly important in epidemiological studies, arises because of differences between the studies being combined. Subjects classified as exposed may, for example, have higher average exposure to the agent of interest in some studies than others, so that, even in the absence of any bias, estimates of the true effect of exposure might not be expected to be the same in each study. Many other features of the study are also likely to add to the heterogeneity. These include aspects of study quality, such as the type of study design used and the accuracy of measurement of exposure and disease. They also include the nature of the population studied and where and when the study was conducted. If one is calculating a single combined estimate based on heterogeneous data - averaging apples and oranges in a sense - there is an obvious difficulty in interpreting the combined meta-analysis estimate.[7]

There are two main methods of conducting meta-analysis. One approach, **fixed-effects meta-analysis**, is to assume all the individual study estimates derive from a common mean, with their contribution to the overall estimate depending only on within-study variability, with large studies carrying more weight than do small studies. The alternative approach, **random-effects meta-analysis**, assumes that the individual study estimates derive from a distribution of effects, with the weighting of the individual estimates depending both on the within-study and the between-study variability. Both methods have their advantages and disadvantages.[8] While the fixed-effects method totally ignores the not at all unlikely possibility of systematic heterogeneity between studies, the attempt to take heterogeneity into account by the random-effects method depends on an assumption about the nature of the distribution of effects over studies that is difficult to justify. Where heterogeneity exists, it is often held[3,9] that more is to be gained by carefully examining its possible sources than by conducting random-effects meta-analysis.[10] If, for example, the true situation is that the effect is consistently X in one group of studies and Y in another, then it would seem better to report the results as such than to attempt to produce a combined estimate.

While meta-analysis has its problems, it nevertheless remains of some value. One might regard the resulting estimate as an indicator of the approximate magnitude of the association to be explained, to be compared with estimates of the approximate magnitude of the various biases that might exist. In the context of ETS and lung cancer, for example, Hackshaw *et al*[11] have claimed that the major sources of bias are insufficient to explain the magnitude of association, a view which has been hotly contested.[12]

Combined estimates of relative risk for the various indices of exposure, as estimated by both fixed- and random-effects meta-analysis[13] are set out below.

LUNG CANCER

Combining the overall incidence for each of the four most commonly used indices of ETS exposure, the meta-analysis results show no association with childhood or social exposure, but a possible weak association with smoking by the spouse and in the workplace.

Index of ETS exposure	Estimates combined	Meta-analysis relative risk (95% confidence limits) Fixed effects	Random-effects
Smoking by the husband	62	1.17 (1.11-1.24)	1.22 (1.13-1.33)
Smoking by the wife	21	1.13 (0.95-1.35)	1.13 (0.95-1.35)
Workplace exposure	30	1.21 (1.11-1.31)	1.21 (1.11-1.31)
Childhood exposure from any cohabitant	29	1.07 (0.99-1.16)	1.18 (1.00-1.40)*
Childhood exposure from the mother specifically	9	0.96 (0.77-1.20)	0.98 (0.77-1.25)
Social exposure	12	1.04 (0.92-1.17)	1.02 (0.80-1.28)

*Inflated by one study[14] reporting an extremely high estimate of 12.0 (4.30-32.0) for women.

Subdividing the data on smoking by the husband produces the following:

Studies	Estimates combined	Meta-analysis relative risk (95% confidence limits) Fixed effects	Random-effects
Estimates published in 1981-1989	25	1.38 (1.23-1.55)	1.38 (1.23-1.55)
Estimates published in 1990-2003	37	1.11 (1.04-1.18)	1.16 (1.04-1.28)

It is notable that studies published since 1989 show a statistically significantly lower relative risk than those published earlier.

The meta-analysis relative risks for smoking by the spouse and for workplace ETS exposure are statistically significant. However, the associations are weak and may be explained by various sources of bias, including:

- **Confounding**
  Many of the studies on ETS and lung cancer fail to consider diet, lifestyle, family medical history, socio-economic status and other factors known to differ between smoking and nonsmoking households.[15,16]

- **Misclassification**
  Some of the subjects classified as lifelong non-smokers will in fact be current or past smokers who have failed to report this.[17,18]

- **Recall bias**
  The studies rely on reported rather than objectively measured ETS exposure data, which may be affected by presence or knowledge of disease.[12]

- **Publication bias**
  Studies finding a negative relationship of ETS exposure with lung cancer may be less likely to report their findings than those that find a positive relationship.[4]

When all the results are considered, and even when meta-analysis is applied, claims that the epidemiological data for lung cancer support an inference of causality[11] cannot be convincingly justified.[12]

HEART DISEASE

The technique of meta-analysis has also been used to combine the results of epidemiological studies on ETS and ischaemic heart disease. The breakdown of results in relation to smoking by the spouse and to workplace ETS exposure can be summarised as follows:

Studies	Estimates combined	Meta-analysis relative risk (95% confidence limits) Fixed-effects	Random-effects
Spouse ever smoked*	42	1.07 (1.04-1.09)	1.14 (1.07-1.20)
Spouse current smoker†	42	1.08 (1.05-1.11)	1.16 (1.09-1.23)
Workplace ETS exposure	17	1.11 (1.01-1.23)	1.13 (1.01-1.27)

* Using estimates for "spouse ever smoked" where a study also provides data for "spouse current smoker".
† Using estimates for "spouse current smoker" where a study also provides data for "spouse ever smoked".

As for lung cancer, heart disease studies published in recent years show a weaker relationship of risk to smoking by the spouse than previously published studies. It is notable that the relative risks from the two largest US studies, published in 1995 and 2003, were very close to 1.00 in each sex, and not statistically significant. These studies provide data on a total of over 20,000 heart disease cases, greater than the total number in all the other studies combined.

While the overall adjusted relative risk estimates for spousal smoking are statistically significant, they are based on heterogeneous estimates which are substantially higher in small than in large studies. Many of the studies failed to control adequately for confounding or the various other sources of bias present in such epidemiological studies, with none adjusting for misclassification of smoking habits. Heart disease studies show no clearly significant relationship with workplace ETS exposure.

Again, claims that the epidemiological data for heart disease support an inference of causality[19,20] cannot be convincingly justified.[21]

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Endpoint	Estimates included	Number of estimates	Relative risk (95% confidence limits) Fixed-effects	Random-effects
		LUNG CANCER		
Husband's smoking*	All	62	1.17 (1.11-1.24)	1.22 (1.13-1.33)
	USA†	20	1.11 (1.01-1.22)	1.11 (1.01-1.22)
	Europe	13	1.25 (1.10-1.44)	1.29 (1.08-1.54)
	Asia	29	1.19 (1.09-1.29)	1.30 (1.13-1.49)
	1981-86	12	1.30 (1.11-1.52)	1.30 (1.09-1.55)
	1987-89	13	1.49 (1.26-1.77)	1.49 (1.26-1.77)
	1990-94	11	0.99 (0.89-1.09)	1.04 (0.84-1.28)
	1995-98	11	1.23 (1.08-1.40)	1.25 (1.07-1.47)
	1999-2003	15	1.18 (1.05-1.34)	1.19 (1.03-1.36)
Wife's smoking*	All	21	1.13 (0.95-1.35)	1.13 (0.95-1.35)
	USA†	10	1.03 (0.79-1.35)	1.03 (0.79-1.35)
Husband or wife smoked*	All	78	1.17 (1.11-1.23)	1.22 (1.13-1.31)
	USA†	28	1.10 (1.01-1.21)	1.10 (1.01-1.21)
	Europe	16	1.24 (1.10-1.40)	1.27 (1.09-1.48)
	Asia	34	1.19 (1.09-1.29)	1.29 (1.13-1.48)
	1981-86	18	1.32 (1.14-1.53)	1.32 (1.13-1.54)
	1987-89	15	1.52 (1.28-1.80)	1.52 (1.28-1.80)
	1990-94	12	0.99 (0.89-1.10)	1.05 (0.85-1.29)
	1995-98	16	1.21 (1.08-1.37)	1.22 (1.07-1.39)
	1999-2003	17	1.15 (1.03-1.24)	1.14 (0.99-1.32)
Workplace ETS exposure	All	30	1.21 (1.11-1.31)	1.21 (1.11-1.31)
Childhood ETS exposure				
From any cohabitant	All	29	1.07 (0.99-1.16)	1.18 (1.00-1.40)
From the mother specifically	All	9	0.96 (0.77-1.20)	0.98 (0.77-1.25)
ETS exposure in social settings	All	12	1.04 (0.92-1.17)	1.02 (0.80-1.28)
		HEART DISEASE		
Spouse ever smoked*,‡	All	42	1.07 (1.04-1.09)	1.14 (1.07-1.20)
	1984-88	7	1.22 (1.04-1.44)	1.26 (1.02-1.55)
	1989-92	11	1.29 (1.17-1.43)	1.39 (1.18-1.64)
	1993-96	9	1.03 (0.99-1.07)	1.04 (0.99-1.08)
	1997-2003	15	1.08 (1.03-1.13)	1.14 (1.03-1.26)
	1-99 cases	5	1.53 (1.18-2.00)	1.55 (1.17-2.05)
	100-199	10	1.37 (1.11-1.69)	1.37 (1.11-1.69)
	200-999	14	1.28 (1.15-1.43)	1.32 (1.13-1.55)
	1000+	12	1.04 (1.02-1.07)	1.06 (1.00-1.11)
Spouse current smoker	All	42	1.08 (1.05-1.11)	1.16 (1.09-1.23)
Workplace ETS exposure	All	17	1.11 (1.01-1.23)	1.13 (1.01-1.27)

Note: The individual study data used for the meta-analyses and more detailed meta-analyses are given elsewhere for both lung cancer[22,23] and for heart disease.[24,25] The individual study estimates used in the table above are those adjusted for as many potential confounding variables as the authors have presented results for.

* Where spousal smoking data are not available, data for the nearest equivalent exposure index have been used.

† Includes one study in Canada.

‡ Studies by Palmer and Mannino omitted as confidence limits not available, and by Spence omitted as neither relative risk nor confidence limit available.

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