EPIDEMIOLOGICAL EVIDENCE ON

ENVIRONMENTAL TOBACCO SMOKE AND STROKE -

A REVIEW WITH META-ANALYSES

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EXECUTIVE SUMMARY

15 publications have described the results of studies relating stroke (or related conditions) to ETS exposure in non-smokers. This document presents a comprehensive review of the evidence, with meta-analysis.

The studies varied considerably in design, ETS exposure indices used and definition of disease. Based on 23 sex-specific relative risk estimates from 14 studies, and using current spousal exposure (or nearest equivalent) as the index of exposure, random-effects meta-analysis gave an overall estimate of 1.26 (95% CI 1.13-1.40, $p<0.001$). Although only five of the individual estimates were significantly ($p<0.05$) increased, and seven were below 1.0, there was no significant heterogeneity between the estimates (chisquared = 28.16 on 22 d.f., $p>0.1$). However there was some indication that relative risks were less clearly elevated in prospective studies (than in case-control or cross-sectional studies) and in North American and European studies (than in Asian or Australasian studies). No elevation was seen in three studies of subarachnoid haemorrhage.

Results did not vary materially based on alternative exposure indices, preferring ever to current exposure, or total to spousal exposure, where available, but in fact few studies presented alternative estimates. No studies presented relative risks for workplace or for childhood ETS exposure. Adjustment for risk factors other than age had no obvious effect on the risk estimates.

Eight studies provided dose-response estimates. Meta-analysis of results for the highest level of exposure gave a relative risk of 1.65 (1.41-1.92) while for the lowest level of exposure the estimate was 1.17 (1.00-1.37).

Given the significant overall association, the lack of heterogeneity, and the evidence of a dose-response relationship, the possibility of a causal relationship demands serious attention. However some limitations of the evidence preclude a definite conclusion. The possibility of some bias due to uncontrolled confounding or to misclassification of smoking habits needs to be borne in mind. Perhaps more relevant is the likelihood of publication bias. There are a number of prospective studies (including the huge American Cancer Society CPS-I and CPS-II studies) for

which results have been reported relating ETS to lung cancer and to heart disease, but not relating ETS to stroke. It seems likely such findings would have been reported had an association been found. Furthermore, incomplete results from the Japanese Hirayama study that could not be included in our meta-analyses, suggested a much weaker association, based on more stroke cases, than seen in the 14 studies with detailed data.

Also relevant to the interpretation are the weaknesses evident in many of the studies. These include use of unvalidated diagnosis and ETS exposure assessment, incomplete follow-up, failure to re-assess smoking status and exposure at intervals in prospective studies, and use of inappropriate control groups in some studies. Also a number of the studies limit attention to either fatal or non-fatal stroke, with consequent potential bias.

Acknowledgment

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INTRODUCTION

Although we are currently aware of 15 publications[1-15] describing the results of studies relating stroke (or related conditions) to environmental tobacco smoke (ETS) exposure in non-smokers, no comprehensive review or meta-analysis has so far been reported. A recent estimate of deaths "attributable" to passive smoking[16] used a relative risk (RR) estimate for stroke of 1.45, based on the median from only seven studies,[2,4,7,8,12,13,17] one of which[17] did not actually report results restricted to non-smokers. This report attempts such a comprehensive review.

METHODS

In April 2005 publications describing the results of epidemiological studies relating the risk of stroke to ETS exposure in lifelong non-smokers (or exceptionally in those who had not smoked for a long period of time) were sought from MEDLINE searches, from the extensive files on smoking and health accumulated by P N Lee Statistics and Computing Ltd (PNLSC), and from reference lists of papers retrieved.

From these publications details were extracted onto a study database of the study location and design, the types of results available and the potential confounding variables considered. On an associated linked RR database details relating to a varying number of RRs per study were entered, including the type of stroke, the definition of exposure (and non-exposure), and the number of variables adjusted for, as well as the RR itself and its 95% confidence interval (CI). [Note that in this review the term "relative risk" is taken to include direct estimates of the RR from prospective studies, and indirect estimates (odds ratios) from case-control or cross-sectional studies.] For a given type of stroke and exposure, RRs and CIs were entered for the analysis which adjusted for age and the greatest number of additional variables, and also, if separately available, the analysis which adjusted for age only, or failing that, age and the smallest number of additional variables. Unless otherwise stated, the data presented and meta-analyses given in this review are always based on the "most adjusted" RRs. Where adjusted results were given only by level of exposure RRs and CIs for overall exposure were estimated as described by Fry and Lee.[18,19]

Fixed-effects and random-effects meta-analyses were conducted using standard methods[20] with the Egger test used to investigate publication bias.[21] As there was considerable variability between studies regarding the definitions of exposure and disease for which results were available, with some studies presenting multiple results, an order of preference was used to select RRs for a "principal" meta-analysis. This selection was based in turn on: type of exposure (spouse highest preference, then household, total, cotinine), time of exposure (current highest preference, then recent, during marriage, ever, in the past) and disease (prefer first named disease for those studies shown in Table 1 reporting results for more than one disease definition). Alternative preferences, as described in Table 5, were used in sensitivity analyses. Sex-specific estimates were included in the meta-analyses where available.

RESULTS

As shown in Table 1, five of the studies were published in the 1980s, with the next study not published until 1998. Six relevant publications have appeared since 2003, showing increasing recent interest in the subject.

Of the 15 studies, four have been conducted in the USA, four in Australia and/or New Zealand, three in Great Britain, two in Japan and two in China.

Six of the studies were of prospective design, four of mortality and two included non-fatal events also. Three of the studies were of cross-sectional design, all of non-fatal events. Six of the studies were of case-control design, one[2] using hospital controls and the rest population controls. Two[2,8] of the case-control studies were of living cases, three[4,7,11] involved both living and dead cases, and one[14] only dead cases. Two of the studies[4,11] used proxy informants for patients who had died or were unable to communicate, using proxy informants also for their matched controls. One study[7] used proxy informants for the dead cases but not for the controls. In one study,[14] people reporting a death were asked questions about the lifestyle of the decedent and of a living person known to the informant.

The definition of the disease considered varied by study, with three of the studies presenting separate results for two differing endpoints. The most commonly considered endpoints were stroke (6 studies), cerebrovascular disease (3) and

subarachnoid haemorrhage (3), but results were also reported in one or two studies for ischaemic stroke, cerebral ischaemia, silent cerebral infarction, transient ischaemic attack and aneurysmal subarachnoid haemorrhage.

All the studies were of subjects who reported never smoking or only smoking for less than a defined short period (e.g. 3 months[4,8] or 6 months[15]) or never smoking regularly[11]. One study[13] confirmed current non-smoking by a serum cotinine <14.1 ng/ml. Exceptionally, one study[7] included exsmokers of cigarettes who had given up more than 10 years ago and two[6,7] included exsmokers of pipes or cigars.

Five studies[2-4,8,15] considered exposure from a smoking spouse (in one case[2] the first spouse); two of these studies[4,8] did not restrict analysis to married subjects. Nine studies considered exposure at home, either generally,[2,9,12] or from smoking by any other household member,[5,11,14] by other household members attending screening[1] or by parents.[4,8] Five studies considered exposure both inside and outside the home, which we refer to as total exposure in this report (home, work, travel or leisure,[2] home or work,[7] home, other small spaces or large indoor areas,[9] or unspecified exposure.[6,10]) Less commonly studied sources of exposure considered were work,[2] travel,[2] leisure,[2] small spaces other than home,[9] large indoor areas[9] and the combination of these two.[12]

The largest study[3] involved 2609 cases, with four other studies of between 500 and 1000 cases. The smallest study[1] involved only 12 cases, with four other studies of less than 100 cases.

Relative risk of stroke

Shown in bold in Table 2 are the 23 RR(CI) estimates used in the "principal" meta-analysis together with their CIs. These come from 14 studies, the largest study[3] reporting a non-significant ($p>0.05$) trend, but no estimates. Of the 23 estimates five were significantly above 1.00, and one was significantly below 1.00. The estimates ranged from 0.25 to 2.10. Table 2 also presents additional details of the RR including the source and timing of exposure and the disease definition. In 9 of the studies data were only available for one source of exposure (within those considered in the preference list) and one definition of exposure time and disease, so there was no

alternative RR that could be included in the meta-analysis. For three studies,[2,9,15] available alternative estimates are shown, which are used in the sensitivity meta-analyses. It should be noted that, although the intention had been to analyze, in the principal meta-analysis, estimates most nearly approximating to current spousal exposure, in fact only four studies presented RRs for spousal exposure and only five presented results for current exposure. For two studies[11,12] estimates for alternative disease definitions are also shown in Table 2.

Appendix Table A gives details of the potential confounding variables adjusted for in analysis. Age was always adjusted for, as too, with minor exceptions, was sex. Other factors adjusted for commonly were blood pressure (9 studies), diabetes (8), alcohol consumption (6), education (6), exercise (5) and obesity/weight (6). Six of the 15 studies adjusted for eight or more variables in at least some of the analyses.

Table 3 presents RR(CI)s for other rarer indices of ETS exposure and for dose-response analyses. These derive from nine studies, the other six providing no additional estimates. None of the studies give RRs specifically for childhood exposure though two[4,8] present findings for ETS from the parents, with the time of exposure unspecified. Very few of the RRs or trends are statistically significant. Those highlighted in bold type are those used in the dose-response meta-analyses.

Meta-analysis results

Table 4 presents results of the principal meta-analysis, together with subgroup analyses. Based on the 23 RR estimates highlighted in Table 2, fixed-effects meta-analysis shows a highly significant ($p<0.001$) increased risk associated with ETS exposure, with the overall RR estimated as 1.27 (95% CI 1.17-1.39). There is no significant heterogeneity between the estimates (chisquared 28.16 on 22 degrees of freedom [d.f.]) and the random-effects estimate is similar at 1.26 (1.13-1.40). Analysis by subgroup did not show any significant variation in the RR estimate by sex, year of publication, study size, study type, number of adjustment variables, exposure index and fatality, though the number of estimates by level was rather limited. There was, however, some indication that relative risks were higher in Asian and Australasian studies than in North American and European studies, higher in

case-control and cross-sectional than in prospective studies and higher in studies specifically of stroke or cerebrovascular disease. No elevated risk was seen in the studies of subarachnoid haemorrhage.

No significant evidence of publication bias was seen in this meta-analysis.

Table 5 presents results of various sensitivity meta-analyses. Estimates did not vary materially according to whether preferences were towards ever rather than current exposure, or towards total rather than spousal exposure or whether results for silent cerebral infarction, which may not be regarded as stroke, were excluded. Nor did estimates vary much according to whether we selected RRs adjusted for a minimal set of variables including age ("least adjusted") or RRs adjusted additionally for between 3 and 15 other variables ("most adjusted"). The pairs of RRs for those five studies for which separate "most adjusted" and "least adjusted" estimates were available are shown in Table 6, together with their ratio. No consistent effect of adjustment is seen.

As shown in Table 7, based on the estimates highlighted in bold type in Table 3, there is evidence of a dose-response relationship based on the seven studies providing relevant data. For the highest level of exposure a clearly significant ($p<0.001$) increased risk of stroke associated with ETS exposure is seen (RR 1.65, 95% CI 1.41-1.92). For the lowest level of exposure (six studies) the increase is of marginal significance (1.17, 1.00-1.37, $p<0.05$).

DISCUSSION

Based on 23 estimates, from 14 studies, of the risk of stroke associated with current spousal ETS exposure, or the nearest equivalent available, random-effects meta-analysis gave a highly significant ($p<0.001$) increased RR estimate of 1.26 (1.13-1.40). For those seven studies providing dose-response data, the highest levels of exposure were associated with an even higher estimate of 1.65 (1.41-1.92). In assessing this association in terms of a causal relationship, various issues have to be taken into account, which are discussed in the sections that follow.

Consistency

Although there are considerable differences between studies in design, definition of exposure and definition of disease, there was no evidence of significant overall heterogeneity between estimates. Nor were the meta-analysis estimates materially affected by choice of individual RR estimates to be included based on time or type of exposure. Despite this apparent consistency, it should be noted that the limited number of RRs reported in many of the studies meant that only a few studies provided estimates for the sensitivity analyses that differed from those included in the principal analysis. Also, of the 23 estimates included in the principal analysis, only five were significantly ($p<0.05$) increased, with seven below 1.0, including one that was significantly negative (see Table 2). Subgroup analysis did suggest some possible sources of variability in the estimates, with the RR less clearly elevated in prospective studies and in North American and European studies, and not elevated in studies of subarachnoid haemorrhage.

Comparison with the estimate of Jamrozik

A previous estimate of 1.45,[16] based on the median from only seven studies, seems too high when the whole available data are considered. From the data used in our principal meta-analysis, the median of the 23 estimates is only 1.23, while combining sex-specific estimates the median of the estimates for the 14 studies is 1.16.

We now consider various potential sources of bias.

Misclassification of the subject's smoking status

It is well established that some smokers deny current or past smoking on interview, and that smokers are more likely than are non-smokers to be married to (or work with) smokers.[22,23] These two facts, taken in conjunction, imply that studies relating ETS exposure in self-reported never smokers to risk of a disease associated with smoking may observe an apparent increased risk even when no true risk of ETS exposure exists. This "misclassification bias" has been widely discussed for lung cancer, and we believe we have demonstrated it to be of material importance,[23,24] though other opinions differ.[25,26] As smoking is less associated with stroke than it is with lung cancer, this bias may be less important, but deserves some attention. We

note that none of the papers providing the data we review discuss this sort of bias at all. The only study to attempt to confirm nonsmoking status was that of Whincup *et al*[13] which used cotinine not only to quantify ETS exposure but also to exclude current smokers. However, even this study could not exclude the possibility that some of the subjects had failed to report past smoking.

Confounding

In principle, risk factors associated both with stroke and with ETS exposure could confound the association of interest. Although all the studies took into account age and sex, there was considerable variation between them in the extent to which other risk factors for stroke have been taken into account. While a number of the studies have considered no (or very few) additional adjustment variables in their analysis,[1-3,10,14] some have taken into account quite an extensive list,[6,9,11-13,15] at least in some of their analyses. While our analyses (see Tables 4, 5 and 6) do not indicate that such adjustment has any major effect on the RR estimate (with the possible exception of one study[13]), the data as presented do not allow separation of the effects of allowing for potential confounding by specific variables.

It is interesting to note that nine of the studies have adjusted for blood pressure, a very strong predictor of stroke. If in fact ETS exposure increases risk of hypertension, with strokes occurring as a result, then it would seem that such adjustment is unjustified ("overmatching"). We note that one of the studies[13] did report a significant positive association of blood pressure with cotinine level. However, see Appendix B, no such association was seen in large representative samples of the English population in 1996, 1998 and 2001.

Publication bias

While our principal and sensitivity analyses did not show statistically significant publication bias, this does not mean that failure to publish relevant findings has not materially affected our meta-analyses. It is clear that there are a number of prospective studies for which results have been reported concerning ETS and heart disease but not concerning ETS and stroke. It might reasonably be expected that results for stroke would have been reported had a significant association been found. The most notable omissions are the American Cancer Society Cancer Prevention

Studies I and II, where results have been reported based on as many heart disease cases as 14891 and 2819 respectively.[27,28] These studies could also have provided RR estimates based on many thousand cases of stroke, likely more than the 3611 cases considered in all the 14 studies combined in our meta-analyses.

It is also notable that the Hirayama study,[3] despite being based on as many as 2609 deaths from cerebrovascular disease, failed to report any RR, merely citing a Mantel-extension (trend) chi of 1.604 and a one-tail p value of 0.05436. Based on results for lung cancer, where the chi was 2.915 based on 200 deaths, and where data published in more detail elsewhere[29] give an RR(CI) for spousal smoking of 1.16 (0.94-1.43), we estimate that for stroke the corresponding RR(CI) values would be 1.06 (0.96-1.17). While we considered this estimate to be too tentative to be included in the meta-analyses shown in Tables 4 and 5, had we done so the fixed-effects estimate of 1.27 (1.17-1.39) would have reduced to 1.17 (1.10-1.25).

Study weaknesses

There are a number of weaknesses that are common to many or a number of the studies. These include the following:

(i) failure to validate the diagnosis of stroke by CT scan, with a number of the studies based on unconfirmed death certificate diagnosis[1,3,5,10,14] and some based on a diagnosis reported by the subject;[9,15]

(ii) small number of cases, with one study involving only 12 cases,[1] and four others of less than 100 cases;[2,6,10,13]

(iii) incomplete follow-up in prospective studies by only tracking deaths occurring in the study area (e.g. [3,5]);

(iv) in prospective studies of some years duration, determining ETS exposure and other risk factors only at baseline, so not allowing for possible changes;[3,5,10,12,13]

(v) with the exception of one study using cotinine,[13] reliance on unconfirmed subjective assessment of ETS exposure, sometimes determined from proxy respondents;[4,7,11,14]

(vi) failure to restrict attention to married subjects when analyzing spousal exposure[4,8] or to control for household size when analysing household exposure (no studies did) and

(vii) failure to restrict attention to ETS exposure before the occurrence of disease.[9,15]

It should also be noted that case-control studies of survivors from stroke[2,8] and prospective studies of fatal cases[1,3,5,10] need not necessarily provide an accurate assessment of the relationship of ETS exposure to onset of stroke. Hypothetically at least, if ETS exposure does not cause stroke, but increases the chances of survival in those who suffer one, one would expect to see a positive association in a study of survivors from stroke.

Some other issues related to specific studies also deserve comment.

(i) The large Japanese prospective study[3] not only failed to report its results in terms of RRs, but also adjusted for the age of the spouse rather than the age of the subject, as is usual,

(ii) It seems likely there may have been some overlap in the cases considered by the two Australian case-control studies,[4,8]

(iii) The New Zealand case-control study[7] had a poor design, using proxy interviews only for cases, and conducting interviews for controls two years after the interviews for cases, and

(iv) The Hong Kong case-control study[14] had a most unusual design which produced very implausible findings. In this study each person who reported a death in 1998 at four death registries was given a questionnaire which asked about the lifestyle 10 years earlier of the decedent and of a living control person about the same age who was well known to the informant, analyses being restricted to those never smoking cases and controls who had a living spouse in 1998. The representativeness of controls selected in this way is clearly open to question. It is interesting to note that the study reported similar large relative risks, of order 1.7, associated with two or more smokers in the home for essentially all causes of death, regardless of whether they were smoking associated. Thus, estimates were implausibly similar (and high) for lung cancer and for cancer other than the lung, and also for all cancer, all circulatory deaths and all other deaths. This suggests strongly that all the findings are biased by a common inappropriate control group.

SUMMARY AND CONCLUSIONS

15 publications have described the results of studies relating stroke (or related conditions) to ETS exposure in non-smokers. This document presents a comprehensive review of the evidence, with meta-analysis.

The studies varied considerably in design, ETS exposure indices used and definition of disease. Based on 23 sex-specific relative risk estimates from 14 studies, and using current spousal exposure (or nearest equivalent) as the index of exposure, random-effects meta-analysis gave an overall estimate of 1.26 (95% CI 1.13-1.40, $p<0.001$). Although only five of the individual estimates were significantly ($p<0.05$) increased, and seven were below 1.0, there was no significant heterogeneity between the estimates (chisquared = 28.16 on 22 d.f., $p>0.1$). However there was some indication that relative risks were less clearly elevated in prospective studies (than in case-control or cross-sectional studies) and in North American and European studies (than in Asian or Australasian studies). No elevation was seen in three studies of subarachnoid haemorrhage.

Results did not vary materially based on alternative exposure indices, preferring ever to current exposure, or total to spousal exposure, where available, but in fact few studies presented alternative estimates. No studies presented relative risks for workplace or for childhood ETS exposure. Adjustment for risk factors other than age had no obvious effect on the risk estimates.

Eight studies provided dose-response estimates. Meta-analysis of results for the highest level of exposure gave a relative risk of 1.65 (1.41-1.92) while for the lowest level of exposure the estimate was 1.17 (1.00-1.37).

Given the significant overall association, the lack of heterogeneity, and the evidence of a dose-response relationship, the possibility of a causal relationship demands serious attention. However some limitations of the evidence preclude a definite conclusion. The possibility of some bias due to uncontrolled confounding or to misclassification of smoking habits needs to be borne in mind. Perhaps more relevant is the likelihood of publication bias. There are a number of prospective studies (including the huge American Cancer Society CPS-I and CPS-II studies) for

which results have been reported relating ETS to lung cancer and to heart disease, but not relating ETS to stroke. It seems likely such findings would have been reported had an association been found. Furthermore, incomplete results from the Japanese Hirayama study that could not be included in our meta-analyses, suggested a much weaker association, based on more stroke cases, than seen in the 14 studies with detailed data.

Also relevant to the interpretation are the weaknesses evident in many of the studies. These include use of unvalidated diagnosis and ETS exposure assessment, incomplete follow-up, failure to re-assess smoking status and exposure at intervals in prospective studies, and use of inappropriate control groups in some studies. Also a number of the studies limit attention to either fatal or non-fatal stroke, with consequent potential bias.

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TABLE 1: Studies providing information on risk of stroke in relation to ETS exposure in lifelong non-smokers

Study	Year	Location	Type	Endpoints		Number of cases in lifelong non-smokers		
				Fatality	Disease	Females	Combined	Males
Gillis[1]	1984	Scotland	P	F	CVD	6		6
Lee[2]	1986	England	CC	NF	STR	68		24
Hirayama[3]	1987	Japan	P	F	CVD,SAH	2609		0
Donnan[4]	1989	Australia	CC	B	CIS/I		142	
Sandler[5]	1989	USA	P	F	CVD	529		126
Howard[6]	1998	USA	CS	NF	SCI/I		77	
Bonita[7]	1999	New Zealand	CC	B	STR		265	
You[8]	1999	Australia	CC	NF	IST/I		154	
Iribarren[9]	2001	USA	CS	NF	STR	95		42
Yamada[10]	2003	Japan	P	F	SAH/I	67		5
Anderson[11]	2004	Australia/NZ	CC	B	SAH,ASH/I	105		30
Iribarren[12]	2004	USA	P	B	IST,TIA/I	447		259
Whincup[13]	2004	Gt.Britain	P	B	STR/I	0		41
McGhee[14]	2005	China (Hong Kong)	CC	F	STR	300		297
Zhang[15]	2005	China	CS	NF	STR	526		0

Footnotes

Under **study** is shown the first author of the publication cited

The **year** is the year of that publication

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

Fatality is indicated by F = fatal and NF = non fatal. B implies data only available for both fatal and non fatal occurrences combined

Disease, as named by the authors of the paper: ASH = aneurysmal subarachnoid haemorrhage, CIS = cerebral ischaemia, CVD = cerebrovascular disease, IST = ischaemic stroke, SAH = subarachnoid haemorrhage, SCI = silent cerebral infarction, STR = stroke, TIA = transient ischaemic attack, /I = incident indicates that the cases were restricted to those with first occurrence of the disease or excluded those with history of stroke

Numbers of cases in lifelong non-smokers are totals in the study; for analyses relating to specific types of disease or specific exposures, numbers may be less than this. Where studies report sex-specific results, sex-specific numbers are shown except for study 7 where only combined numbers are available. Where studies report results for combined sexes only, combined numbers are shown. For study 3, numbers are of CVD; there were 126 cases of SAH. For study 11, numbers are of SAH; numbers of ASH not available. For study 12, numbers are of IST; numbers of TIA were 99 in females and 52 in males

TABLE 2: RR of stroke among lifelong non-smokers in relation to current smoking by the spouse (or nearest equivalent)

Study	Exposure		Endpoint		Number of adjustment variables		Sex	RR (95% CI)	Signif-icance
	Source	Timing	Fatality	Disease					
Gillis[1]	H	R(5)	F	CVD	1		M	**0.33 (0.04-2.84)**	
							F	**1.88 (0.22-16.0)**	
Lee[2]	S	C	N	STR	2		M	Not significant	
	S	C			2		F	Not significant	
	S	M			2		M	**0.84 (0.31-2.27)**	
	S	M			2		F	**0.92 (0.51-1.65)**	
	T	C			1		M	1.35 (0.44-4.12)	
	T	C			1		F	1.19 (0.57-2.50)	
Hirayama[3]	S	E	F	CVD	1		F	No significant trend	
				SAH				No significant trend	
Donnan[4]	S	E	B	CIS	3	(+ sex)	C	**1.60 (0.60-3.90)**	
Sandler[5]	H	E	F	CVD	4		M	**0.97 (0.65-1.46)**	
							F	**1.24 (1.03-1.49)**	+
Howard[6]	T	C	N	SCI	10	(+ sex)	C	**1.06 (0.64-1.75)**	
Bonita[7]	T	R(10)	B	STR	4		M	**2.10 (1.33-3.32)**	+
							F	**1.66 (1.07-2.57)**	+
You[8]	S	E	N	IST	5	(+ sex)	C	**1.70 (0.98-2.92)**	
Iribarren[9]	H	C	N	STR	11		M	**0.25 (0.04-0.82)**	–
	H						F	**1.23 (0.75-1.96)**	
	T						M	0.27 (0.11-0.57)	–
	T						F	0.89 (0.57-1.38)	
Yamada[10]	T	E	F	SAH	1		M	**1.13 (0.19-6.85)**	
							F	**0.94 (0.57-1.55)**	
Anderson[11]	H	E	F	SAH	8		M	**0.50 (0.20-1.30)**	
				SAH			F	**1.30 (0.70-2.30)**	
				ASH			M	0.60 (0.20-1.70)	
				ASH			F	1.20 (0.60-2.40)	
Iribarren[12]	H	C	B	IST	10		M	**1.02 (0.71-1.48)**	
				IST			F	**1.17 (0.92-1.50)**	
				TIA			M	1.16 (0.49-2.71)	
				TIA			F	1.26 (0.76-2.08)	
Whincup[13]	C	C	B	STR	16		M	**1.54 (0.68-3.47)**	
McGhee[14]	H	P(10)	F	STR	2		M	**1.31 (0.87-1.99)**	
							F	**1.57 (1.11-2.24)**	+
Zhang[15]	S	C	N	STR	14		F	**1.44 (1.20-1.72)**	+
		E						1.27 (1.05-1.54)	+

Footnotes

Under **study** is shown the first author of the publication cited

Source of exposure is coded as C = cotinine (above lowest level), H = household, S = spouse, T = total. See text for detailed definition

Timing of exposure is coded as C = current, E = ever (or unspecified), M = during marriage, R(N) = recent, within last N Years, P(N) = past, N years ago. For study 2, current spousal exposure refers to last 12 months of first marriage

Fatality is indicated by F = fatal and NF = non fatal. B implies data only available for both fatal and non fatal occurrences combined

Disease, as named by the authors of the paper: ASH = aneurysmal subarachnoid haemorrhage, CIS = cerebral ischaemia, CVD = cerebrovascular disease, IST = ischaemic stroke, SAH = subarachnoid haemorrhage, SCI = silent cerebral infarction, STR = stroke and TIA = transient ischaemic attack

Number of adjustment variables. See Appendix A for details

Sex is coded as C = combined, F = females and M = males

The **RRs and CIs** used for the main meta-analysis are highlighted in bold type. Significant ($p<0.05$) positive (or negative) relative risks are indicated by + (or –)

TABLE 3: RR of stroke among lifelong non-smokers for rarer indices of ETS exposure and for dose-response analyses

Study	Sex	Exposure grouping	RR by level (95% CI)
Lee[2]		**ETS exposure at home**	
	M	Not at all Little Average/a lot	Not significant, no significant trend
	F	Not at all Little Average/a lot	Not significant, no significant trend
		ETS at work	
	M	Not at all Little Average/a lot	Not significant, no significant trend
	F	Not at all Little Average/a lot	Not significant, no significant trend
		ETS during travel	
	M	Not at all Little Average/a lot	Not significant, no significant trend
	F	Not at all Little Average/a lot	Not significant, no significant trend
		ETS during leisure	
	M	Not at all Little Average/a lot	Not significant, no significant trend
	F	Not at all Little Average/a lot	Not significant, no significant trend
		Total ETS exposure	
	M	Score 0-1 2-4 5-12	**1.24 (0.39-3.99) 1.77 (0.41-7.61)**
	F	Score 0-1 2-4 5-12	**0.86 (0.37-1.99) 2.44 (0.90-6.58)**
Donnan[4]		**Either parent smoked**	
	C	No Yes	1.00 (0.50-2.10)
Howard[6]		**Total ETS exposure**	
	C	Hours per week	No significant relationship
You[8]		**Mother smoked**	
	C	No Yes	0.98 (0.44-2.20)
		Father smoked	
	C	No Yes	0.69 (0.43-1.12)
	C	**Either parent smoked**	
		No Yes	0.78 (0.48-1.26)
	C	**Cigarettes smoked by spouse**	
		0 1-20 >20 per day	**1.55 (0.83-2.88) 1.91 (0.94-3.88)**
Iribarren[9]		**ETS exposure at home**	
	M	No 40+ hrs/wk	Not significant
	F	No 40+ hrs/wk	**1.40 (0.53-3.04)**
		ETS exposure in small spaces	
	M	No Yes	0.47 (0.17-1.10)
		No 40+ hrs/week	1.03 (0.16-3.62)
	F	No Yes	0.64 (0.36-1.08)
		No 40+ hrs/wk	0.58 (0.21-1.65)
		ETS exposure in large indoor areas	
	M	No Yes	0.35 (0.14-0.78)
		No 40+ hrs/wk	Not significant
	F	No Yes	0.68 (0.43-1.11)
		No 40+ hrs/wk	0.34 (0.02-1.62)
		Total ETS exposure	
	M	No 40+ hrs/wk	0.45 (0.10-1.32)
	F	No 40+ hrs/wk	0.52 (0.21-1.12)

TABLE 3 (continued)

Study	Sex	Exposure grouping	RR by level (95% CI)
Iribarren[12]		**ETS exposure at home**	
	M	0 1-19 20+ hrs/wk	**IST: 0.89 (0.56-1.42) 1.29 (0.75-2.20)** TIA: 1.20 (0.45-3.20) 1.06 (0.24-4.65)
	F	0 1-19 20+ hrs/wk	**IST: 0.99 (0.72-1.35) 1.50 (1.07-2.09)** TIA: 1.00 (0.52-1.93) 1.72 (0.88-3.35)
		Out-of-home exposure	
	M	No Yes	IST: 0.93 (0.70-1.25) TIA: 0.78 (0.41-1.51)
		0 1-19 20+ hrs/wk	IST: 0.99 (0.73-1.34) 0.75 (0.47-1.21) TIA 0.77 (0.38-1.54) 0.83 (0.30-2.30)
	F	No Yes	IST: 1.06 (0.85-1.33) TIA: 0.78 (0.49-1.26)
		0 1-19 20+ hrs/wk	IST: 1.08 (0.85-1.37) 1.00 (0.68-1.46) TIA: 0.81 (0.48-1.34) 0.70 (0.31-1.54)
Whincup[13]		**Serum cotinine concentration**	
	M	<0.8, 0.8-1.4, 1.5-2.7, 2.8+ ng/ml	**1.34 (0.53-3.40)** 1.39 (0.48-4.04) **2.16 (0.80-5.80)**
McGhee[14]		**Number of smokers in household**	
	C	0 1 2+	**1.34 (1.01-1.79) 2.08 (1.33-3.25)** [Trend p=0.001]
Zhang[15]		**Cigarettes smoked by husband**	
	F	0 1-9 10-19 20+ per day	**1.28 (0.92-1.77)** 1.32 (1.01-1.72) **1.62 (1.28-2.05)** [Trend p<0.001]
		Duration of smoking by husband	
	F	0 1-17 18+ years	1.13 (0.70-1.82) 1.47 (1.22-1.78) [Trend p=0.001]
		Pack-years of smoking by husband	
	F	0 1-13 14+	1.12 (0.82-1.54) 1.55 (1.27-1.90) [Trend p<0.001]

Footnotes

Under **study** is shown the first author of the publication cited

Sex is coded as C = combined, F = females and M = males

See text for definitions of total exposure

RRs are adjusted for covariates (see Appendix A) if adjusted data are available. The first exposure level is always the base for comparison (RR = 1.00). The disease is as defined in Table 1 except that for study 12 results are shown separately for IST = ischaemic stroke and TIA = transient ischaemic attack. Those highlighted in bold type are included in dose-response meta-analyses (see Table 7)

TABLE 4: Results of principal meta-analysis, overall and by subgroup

Estimates included	Estimates	Analysis	RR (95% CI)	Significance
All	23	Fixed	1.27 (1.17-1.39)	p<0.001*
		Random	1.26 (1.13-1.40)	p<0.001
Sex : male	10	Fixed	1.15 (0.95-1.38)	NS
female	10	Fixed	1.30 (1.18-1.44)	
combined	3	Fixed	1.35 (0.96-1.91)	
Exposure index : Spouse	5	Fixed	1.40 (1.19-1.64)	NS
Total/cotinine	6	Fixed	1.41 (1.13-1.77)	
Household	12	Fixed	1.19 (1.06-1.33)	
Continent : N.America	7	Fixed	1.15 (1.02-1.30)	p<0.05
Europe	5	Fixed	1.02 (0.68-1.54)	
Asia	5	Fixed	1.39 (1.21-1.61)	
Australasia	6	Fixed	1.58 (1.25-2.00)	
Publication year : 1984-1989	7	Fixed	1.16 (0.99-1.36)	NS
1990-2001	6	Fixed	1.47 (1.19-1.82)	
2002-2005	10	Fixed	1.28 (1.15-1.44)	
Number of cases : 1-199	14	Fixed	1.10 (0.91-1.34)	NS
200+	9	Fixed	1.32 (1.20-1.45)	
Study type : prospective	9	Fixed	1.15 (1.02-1.30)	p<0.1
case-control	10	Fixed	1.44 (1.22-1.70)	
cross-sectional	4	Fixed	1.35 (1.15-1.58)	
Number of adjustment variables† :0-5	14	Fixed	1.30 (1.16-1.46)	NS
6+	9	Fixed	1.24 (1.10-1.40)	
Fatality : fatal	8	Fixed	1.23 (1.07-1.40)	NS
non-fatal	7	Fixed	1.32 (1.14-1.53)	
both	8	Fixed	1.28 (1.10-1.50)	
Disease : CVD or stroke	14	Fixed	1.34 (1.21-1.48)	NS
subarachnoid haemorrhage	4	Fixed	0.97 (0.68-1.37)	
other	5	Fixed	1.18 (0.99-1.40)	

Footnotes

Estimates indicates number of RR (CI) estimates included in meta-analysis

Analysis: Random-effects are shown only for the overall analysis and are generally the same as, or similar to, the fixed-effects estimates otherwise

Significance for the overall analysis relates to significance of the RR, otherwise it relates to the significance of the difference in RR between levels of the factors studied. NS = $p \geq 0.1$

*The heterogeneity chisquared was 28.16 on 22 d.f., NS

† Apart from sex

TABLE 5: Sensitivity meta-analyses

Analysis	Estimates	RR (95% CI) Fixed-effects	Random-effects	Heterogeneity χ^2	d.f.	p
Principal	23	1.27 (1.17-1.39)	1.26 (1.13-1.40)	28.16	22	NS
Preferring ever to current exposure*	23	1.24 (1.14-1.35)	1.23 (1.11-1.37)	25.95	22	NS
Preferring total to spousal exposure†	23	1.24 (1.15-1.35)	1.19 (1.05-1.36)	39.57	22	$p<0.05$
Excluding silent cerebral infarction	22	1.28 (1.18-1.39)	1.26 (1.13-1.41)	27.63	21	NS
Preferring "least adjusted" to "most adjusted" estimates	23	1.29 (1.18-1.39)	1.26 (1.13-1.40)	27.72	22	NS

Footnotes
* Using preference order for time of exposure: ever, during marriage, in the past, recent, current
† Using preference order for type of exposure: total, cotinine, spouse, household

TABLE 6: Effect of additional adjustment for variables other than age

Study	Sex	Adjustment variables	RR (95% CI)	Ratio
Howard[6]	C	Age, sex, race	1.03 (0.63-1.67)	
		Age, sex, race + 8	1.06 (0.64-1.75)	1.03
Bonita[7]	M	Age	2.06 (1.34-3.17)	
		Age + 3	2.10 (1.33-3.32)	1.02
	F	Age	1.50 (1.01-2.21)	
		Age + 3	1.66 (1.07-2.57)	1.11
Iribarren[12]	M	Age	1.12 (0.78-1.60)	
		Age + 9	1.02 (0.71-1.48)	0.91
	F	Age	1.23 (0.97-1.57)	
		Age + 9	1.17 (0.92-1.50)	0.95
Whincup[13]	M	Age, town	0.96 (0.49-1.89)	
		Age, town + 15	1.54 (0.68-3.47)	1.60
Zhang[15]	F	Age	1.46 (1.23-1.72)	
		Age + 13	1.44 (1.20-1.72)	0.99

Footnotes
See Appendix A for the additional adjustment factors
See Table 2 for extra information regarding exposure and disease
Under **study** is shown the first author of the publication cited
Sex is coded as C = combined, F = females and M = males

TABLE 7: Dose-response meta-analyses

Analysis	Estimates	RR (95% CI) Fixed-effects	Random-effects	Heterogeneity χ^2	d.f.	p
Low dose	8	1.17 (1.00-1.37)	1.17 (1.00-1.37)	4.96	7	NS
High dose	9	1.65 (1.41-1.92)	1.65 (1.41-1.92)	3.36	8	NS

Footnote
Based on estimates in Table 3 highlighted in bold type

APPENDIX TABLE A

Risk factors used as potential confounding factors to adjust relative risk analyses

Risk factor	Study 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Sex	-	-	-	x	-	x	-	x	-	-	-	-	-	x[a]	-
Age[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Race						x			x		x	x			
Socioeconomic status													x		x
Education					x			x	x			x		x	x
Marital status		x			x				x			x			
Occupation/employment									x						x
Diet						x									
Alcohol						x			x		x	x	x		x
Region of residence				x							x		x		
Housing quality					x										
Proxy respondent											x				
Exercise						x			x			x	x		x
Cholesterol						x			x			x	2		
Other blood tests						x							2		
Blood pressure				x		x	x	x	x		x	x	2		2
Diabetes						x	x	x	x		x	x	x		x
Hormone therapy[c]															3
Obesity/weight						x			x		x	x	x		x
History of heart disease							x	x					x		
Lung function													x		
Height													x		
Aspirin use															x

Key

x, 2, 3 Risk factor adjusted for by 1, 2, 3 … variables
- Not applicable as results given by sex
[a] Sex adjusted for except for first relative risk in Table 2
[b] Only age adjusted results were considered
[c] Includes menopause, oral contraception

APPENDIX B

Relationship between cotinine and blood pressure in nonsmokers in the Health Survey for England 1996, 1998 and 2001

In 1996, 1998 and 2001, data on cotinine, diastolic and systolic blood pressure and other relevant demographic and lifestyle characteristics were collected from large representative samples of the English population in the Health Survey for England (HSE).[1-3] Cotinine was determined in serum in 1996 and in saliva in 1998 and 2001. Based on these data the relationship of blood pressure to log cotinine was studied in men and women aged 35+, who had a cotinine level <20 ng/ml and who reported smoking no cigarettes or using nicotine products. Adjustment was made for age, sex, body mass index and units of alcohol per week. Results of the fitted models are shown in Appendix Table B.

For diastolic blood pressure, there was at each year a highly significant ($p<0.001$) positive association with age, body mass index and alcohol consumption and a negative association with female sex, but there was no consistent association of log cotinine. A marginally significant ($p=0.03$) positive association in the 1998 data was counterbalanced by nonsignificant negative associations in 1996 and 2001.

For systolic blood pressure, the associations with age, body mass index, alcohol consumption and sex were consistently seen, and again significant (at least $p<0.01$ in all analyses). However no consistent or significant association with log cotinine was seen.

These results do not suggest any meaningful relationship between ETS exposure and blood pressure.

References for Appendix B

1. Prescott-Clarke P, Primatesta P, editors. *Health survey for England '96. Volume 1: Findings. Volume 2: Methodology & documentation*. London: The Stationery Office; 1998. (Health Survey for England.) Series HS No. 6.

2. Erens B, Primatesta P, editors. *Health survey for England. Cardiovascular disease '98. Volume 1: Findings. Volume 2: Methodology & documentation*. London: The Stationery Office; 1999. (Health Survey for England.) Series HS No. 8.

3. Prior G, Deverill C, Malbut K, Primatesta P. Bajekal M, Primatesta P, Prior G, editors. *Health survey for England 2001. Methodology and documentation*. London: TSO (The Stationery Office); 2003. (Health Survey for England.) Series HS No. 11.

APPENDIX TABLE B

Results of regression analyses of blood pressure on log cotinine, age, sex, body mass index and alcohol consumption in nonsmokers aged 35+ with no reported use of nicotine products and a cotinine level <20 ng/ml

	Year of HSE Survey[a]		
	1996	1998	2001
Number of subjects			
- Male	2543	2147	2574
- Female	2989	2466	3066
- Total	5532	4613	5640
Diastolic BP			
Constant	56.4831	59.8164	62.2174
	Mean (SE)	Mean (SE)	Mean (SE)
Age[b]	+0.1604 (0.0111)	+0.1245 (0.0122)	+0.0968 (0.0111)
Sex (female v male)[b]	- 4.7047 (0.3229)	- 4.3386 (0.3548)	- 4.9135 (0.3180)
Body mass index[b]	+0.5315 (0.0357)	+0.4488 (0.0372)	+0.3893 (0.0319)
Units alcohol per week[b]	+0.0506 (0.0117)	+0.0550 (0.0122)	+0.0611 (0.0114)
Log cotinine	- 0.0069 (0.1281)	+0.2637 (0.1249)	- 0.0047 (0.1187)
	p = 0.957	p = 0.035	p = 0.969
Systolic BP			
Constant	71.8986	76.4112	77.1983
	Mean (SE)	Mean (SE)	Mean (SE)
Age[b]	+0.7477 (0.0174)	+0.6877 (0.0190)	+0.6592 (0.0172)
Sex (female v male)[c]	- 1.4173 (0.5053)	- 1.4963 (0.5498)	- 1.2651 (0.4906)
Body mass index[b]	+0.9762 (0.0558)	- 0.8757 (0.0577)	+0.8413 (0.0492)
Units alcohol per week[d]	+0.0709 (0.0183)	+0.0589 (0.0189)	+0.0822 (0.0176)
Log cotinine	- 0.2327 (0.2005)	+0.3021 (0.1936)	+0.0991 (0.1832)
	p = 0.246	p = 0.119	p = 0.589

[a] The data from the Health Survey for England are Crown Copyright and are made available through the ERSC Data Archive

[b] $p<0.001$ for each year

[c] $p = 0.005$, $p = 0.007$ and $p = 0.010$ for 1996, 1998, 2001 respectively

[d] $p<0.001$, $p = 0.002$ and $p<0.001$ for 1996, 1998 and 2001 respectively