EPIDEMIOLOGICAL EVIDENCE ON

ENVIRONMENTAL TOBACCO SMOKE AND STROKE -

A REVIEW WITH META-ANALYSES

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EXECUTIVE SUMMARY

23 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-analyses.

The studies varied considerably in design, ETS exposure indices used and definition of disease. Based on 36 sex-specific relative risk estimates from 24 studies, and using current spousal exposure (or nearest equivalent) as the index of exposure, random-effects meta-analysis gave an overall estimate of 1.28 (95% CI 1.17-1.40, $p<0.001$). There was no significant heterogeneity between the estimates (chisquared = 48.14 on 35 d.f., $p<0.1$). Relative risks were less clearly elevated in prospective studies (than in case-control or cross-sectional studies), in studies of household ETS exposure (than in studies of spousal or total ETS exposure) and in North American and European studies (than in Asian or Australasian studies). No elevation was seen in four studies of haemorrhagic stroke.

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. Too few studies presented relative risks for workplace or for childhood ETS exposure for adequate assessment. Adjustment for risk factors other than age had no obvious effect on the risk estimates.

Eleven studies provided dose-response estimates. Meta-analysis of results for the highest level of exposure gave a relative risk of 1.59 (1.38-1.82) while for the lowest level of exposure the estimate was 1.20 (1.04-1.37).

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 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 all the studies presenting 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

This document summarizes the evidence from 23 publications[1-23] describing the results of studies relating stroke (or related conditions) to environmental tobacco smoke (ETS) exposure in non-smokers. This updates not only our earlier report[24] based on 22 publications[1-22] with one additional relevant publication[23] but also a review we published in the Journal of Stroke and Cerebrovascular Diseases.[25] Only one[26] other comprehensive review, including meta-analysis, has so far been reported. Based on 20 studies, all of which were included in our earlier review,[24] the authors reported an overall risk estimate of 1.25 (95% CI 1.12-1.38). An earlier estimate, in 2005, by Jamrozik *et al*[27] of deaths "attributable" to passive smoking used a relative risk (RR) estimate for stroke of 1.45, based on the median from only seven studies,[2,4,7,8,12,13,28] one of which[28] did not actually report results restricted to non-smokers.

METHODS

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 PUBMED (using search terms “tobacco smoke pollution” and “cardiovascular diseases”) and from the extensive files on smoking and health accumulated by P N Lee Statistics and Computing Ltd (PNLSC), and from reference lists of the papers retrieved. Appendix A explains why results from certain other publications, which might have been thought to cite relevant data, are not included.

For all the studies details were entered into a study database of the study location and design, the types of results available, and the potential confounding variables considered. Details relating to a varying number of RRs per study were also entered, including the type of stroke, the precise 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 that adjusted for age and the greatest number of additional variables, (most-adjusted RRs). In addition, if

separately available, those RRs that adjusted for age only, or failing that, age and the smallest number of additional variables (least-adjusted RRs) were also entered. Where adjusted results were given only by level of exposure RRs and CIs for overall exposure were estimated.[29-31] For each study, all aspects of data extraction were carried out by one of us and checked by another.

Fixed-effects and random-effects meta-analyses were conducted using standard methods[32] with the Egger test used to investigate publication bias.[33] Due to marked variability 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 preference was based in turn on: type of exposure (spouse the highest preference, then household, total, cotinine), time of exposure (current the highest preference, then in the last 5 years, in the last 10 years, during marriage, in the last 20 years, in the last 25 years, during adulthood, ever, in the past) and stroke definition (prefer the first named category for those studies shown in Table 1 reporting results for more than one category of stroke). Alternative preferences, as described in Table 5, were used in sensitivity analyses. Unless otherwise stated, the data presented and meta-analyses given in this review are always based on the most-adjusted RRs. Sex-specific estimates are included in the meta-analyses where available.

The detailed results of these meta-analyses are available.[34]

RESULTS

As shown in Table 1, one of the publications[18] provided results for two separate, prospective studies. Five of the studies were published in the 1980s, with the next study not published until 1998. Details of 14 of the 24 studies have been published since 2004, showing increasing recent interest in the subject.

Of the 24 studies, six were conducted in Australia and/or New Zealand, six in the USA, five in China, four in Great Britain and two in Japan, and one in seven European countries .

14 of the studies were of prospective design: nine of mortality and five considering non-fatal events also. Four 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 six of the studies presenting separate results for two or more differing endpoints. The most commonly considered endpoints were stroke (12 studies), cerebrovascular disease (6) and ischaemic stroke (5), but results were also reported in a few studies for subarachnoid haemorrhage, haemorrhagic 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[16]) or never smoking regularly.[11,18(both studies)] Two studies confirmed current non-smoking by serum cotinine concentration, of <14.1 ng/ml[13] or <15ng/ml[22]. Exceptionally, one study[7] included ex-smokers of cigarettes who had given up more than 10 years ago and two[6,7] included ex-smokers of pipes or cigars.

Nine studies[2-4,8,15-17,19,22] considered exposure from a smoking spouse (in one case[2] the first spouse); four of these studies[4,8,17,22] did not restrict analysis to married subjects. Twelve studies considered exposure at home, either generally,[2,9,12] or from smoking by any other household member,[5,11,14,18(both studies)21,23] by other household members attending screening[1] or by parents.[4,8] Seven 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;[7,20,23] home, other small spaces or large indoor areas;[9] spouse, workplace or early life;[17] or unspecified exposure.[6,10]) Less commonly studied sources of exposure considered were work,[2,17,21,23] travel,[2] leisure,[2]

small spaces other than home,[9] large indoor areas[9] and the combination of these two.[12] Only two studies [17,21] considered exposure in childhood (before age 20, from family members in the study by Wen *et al*, and by parents during childhood in the study by Gallo *et al*).

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

Relative risk of stroke

Shown in bold in Table 2, and also in Figure 1, are the 36 RR(CI) estimates used in the "principal" meta-analysis together with their CIs. These come from 23 studies, the largest study[3] reporting a non-significant ($p>0.05$) trend, but no estimates. Of the 36 estimates ten are significantly above 1.00, and one is significantly below 1.00. The estimates range 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 13 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 five studies,[2,9,16,17,22] estimates are available for alternative sources or timings of exposure, 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 eight studies presented RRs for spousal exposure and only 11 presented results for current exposure. For five studies[11,12,15,20,23] estimates for alternative disease definitions are also shown in Table 2.

Appendix Table B gives details of the potential confounding variables adjusted for in analysis. Age was always adjusted for, as too, with one minor exception, was sex. Other factors adjusted for commonly were blood pressure (14 studies), education (13), obesity/weight (13), diabetes (12), alcohol consumption (11), exercise (9), race/ethnicity (8), marital status (8), cholesterol/lipids (8), socioeconomic status (7), occupation (7) and region (6). Thirteen of the 23 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 14 studies. Only two studies[17,21] give RRs specifically for exposure in childhood though two others[4,8] present findings for ETS from the parents, with the time of exposure unspecified. While the majority of the studies do not find any significant trends, three recent studies[16,20,23] report clear trends with some measures of exposure. RRs 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 36 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 1.29 (95% CI 1.20-1.38). Although there is some heterogeneity between the estimates, it is not statistically significant (chisquared 48.14 on 35 degrees of freedom [d.f.], $p<0.1$) and the random-effects estimate is similar at 1.28 (1.17-1.40). Analysis by subgroup did not show any significant variation in the RR estimates by sex, study size, number of adjustment variables, and fatality, though the number of estimates by level was rather limited. There was, however, some indication that relative risks were higher in studies of spousal or total ETS exposure than in studies of household exposure, higher in Asian and Australasian studies than in North American and European studies and higher in case-control and cross-sectional than in prospective studies. No elevated risk was seen in the studies of haemorrhagic stroke. There was some variation by year of publication.

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 16 other variables ("most adjusted"). The pairs of RRs for those nine 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 11 studies providing relevant data. For the highest level of exposure a clearly significantly increased risk of stroke associated with ETS exposure is seen (RR 1.59, 95% CI 1.38-1.82, $p<0.001$). For the lowest level of exposure the increase is also statistically significant (1.20, 1.04-1.37, $p<0.01$).

DISCUSSION

Based on 36 estimates, from 23 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 1.28 (1.17-1.40). For those 11 studies providing dose-response data, the highest levels of exposure were associated with an even higher estimate of 1.59 (1.38-1.82). 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

Given the considerable differences between the studies in design, definition of exposure and definition of disease, it was unsurprising that there was evidence of some heterogeneity between the estimates. However the meta-analysis estimates were not materially affected by choice of the individual RR estimates to be included based on time or type of exposure, though 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. Of the 36 estimates included in the principal analysis, ten were significantly ($p<0.05$) increased, and 11 were below 1.0, including one that was significantly decreased (see Table 2). Subgroup analysis did suggest some possible sources of variability in the estimates, with the RR less clearly elevated in prospective studies, studies of household ETS

exposure, and in North American and European studies, and not elevated in studies of haemorrhagic stroke.

Comparison with the estimates of Jamrozik and Oono

An early, 2005, estimate of 1.45,[27] based on the median from only seven studies, seems rather too high when the currently available data are considered. From the data used in our principal meta-analysis, the median of the 36 estimates is between 1.23 and 1.24.

A more recent, 2011, estimate of 1.25 (1.12-1.38),[26] based on 35 estimates from 20 studies, is quite similar to our estimate of 1.28 (1.17-1.40).

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.[35,36] 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,[36,37] though other opinions differ.[38,39] 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 (with the exception of Hill *et al*[18] who only considered misclassification of the subject's smoking status in relation to their overall mortality results, Jefferis *et al*[22] who discussed the possibility of genetic factors that affect cotinine level also being associated with stroke risk and He *et al*[23] who consider that collection of smoking data on two occasions 18 years apart is sufficient to minimise this source of bias) none of the publications providing the data we review discuss this sort of bias at all. The only studies to attempt to confirm nonsmoking status were those of Whincup *et al*[13] and Jefferis *et al*[22] which used cotinine not only to quantify ETS exposure but also to exclude current smokers. However, even these studies 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,[6,9,11-13,15-17,19,20,22,23] 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 14 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 and similar findings have been reported elsewhere[40]. However, no such association was seen in the study by Jefferis *et al,*[22] or in large representative samples of the English population in 1996, 1998 and 2001 (see Appendix C).

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.[41,42] These studies could also have provided RR estimates based on many thousand cases of stroke, possibly more than the 5863cases considered in all the 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[43] 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 1.29 (1.20-1.38) would have reduced to 1.21 (1.14-1.28).

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[1,3,5,10,14,17,18,21,22] and some based on a diagnosis reported by the subject;[9,16,19]

(ii) small number of cases, with one study involving only 12 cases,[1] and six others of less than 100 cases;[2,6,10,13,22,23]

(iii) incomplete follow-up in prospective studies by only tracking deaths occurring in the study area (e.g. [3,5]), or by failure of linkage;[18]

(iv) in prospective studies of some years duration, determining ETS exposure and other risk factors only at baseline, so not allowing for possible changes;[3,5,10,12,13,15,19,21-23]

(v) with the exception of two studies using cotinine,[13,22] reliance on unconfirmed subjective assessment of ETS exposure, sometimes determined from proxy respondents;[4,7,11,14] and

(vi) failure to restrict attention to married subjects when analyzing spousal exposure[4,8,17,22] or to control for household size when analysing household exposure (no studies did).

It should also be noted that case-control studies of survivors from stroke[2,8] and prospective studies of fatal cases[1,3,5,10,17,18,21,23] 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

23 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-analyses.

The studies varied considerably in design, ETS exposure indices used and definition of disease. Based on 36 sex-specific relative risk estimates from 24 studies, and using current spousal exposure (or nearest equivalent) as the index of exposure, random-effects meta-analysis gave an overall estimate of 1.28 (95% CI 1.17-1.40, $p<0.001$). There was some heterogeneity between the estimates, but it failed to reach statistical significance (chisquared = 48.14 on 35 d.f., $p<0.1$). Relative risks were less clearly elevated in prospective studies (than in case-control or cross-sectional studies), in studies of household ETS exposure (than in studies of spousal or total ETS exposure) and in North American and European studies (than in Asian or Australasian studies). No elevation was seen in four studies of haemorrhagic stroke.

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. Too few studies presented relative risk for workplace or for childhood ETS exposure for adequate assessment. Adjustment for risk factors other than age had no obvious effect on the risk estimates.

Eleven studies provided dose-response estimates. Meta-analysis of results for the highest level of exposure gave a relative risk of 1.59 (1.38-1.82) while for the lowest level of exposure the estimate was 1.20 (1.04-1.37).

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 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 all the studies presenting 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.

FIGURE 1: RR of stroke among lifelong non-smokers in relation to current smoking by the spouse (or nearest equivalent)

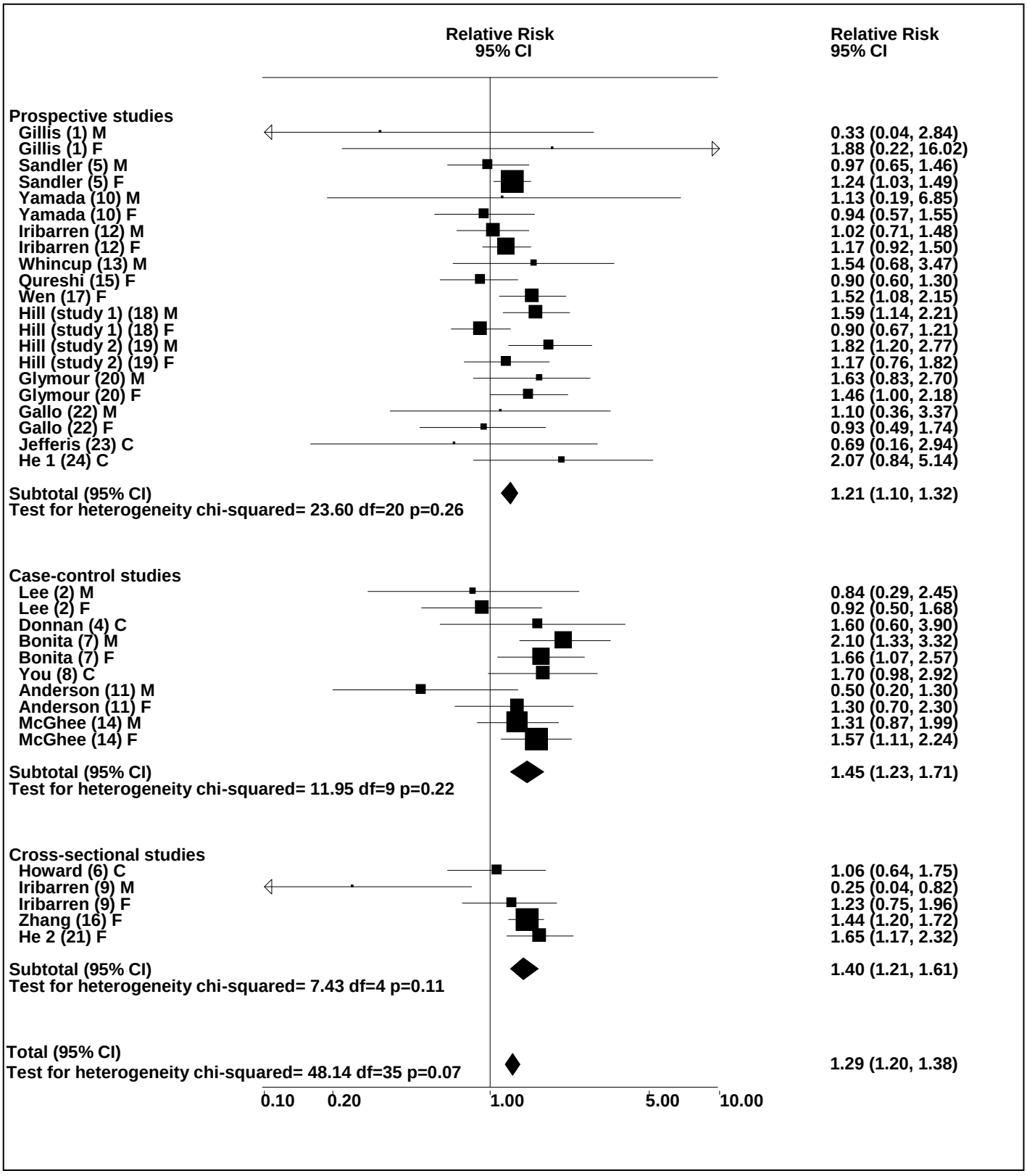

TABLE 1: Studies providing information on risk of stroke in relation to ETS exposure in lifelong non-smokers

Study		Year	Location	Type	Endpoints		Number of cases in lifelong non-smokers		
No.	Name				Fatality	Disease	Females	Combined	Males
1	Gillis[1]	1984	Scotland	P	F	CVD	6		6
2	Lee[2]	1986	England	CC	NF	STR	68		24
3	Hirayama[3]	1987	Japan	P	F	CVD, SAH	2609		0
4	Donnan[4]	1989	Australia	CC	B	CIS/I		142	
5	Sandler[5]	1989	USA	P	F	CVD	529		126
6	Howard[6]	1998	USA	CS	NF	SCI/I		77	
7	Bonita[7]	1999	New Zealand	CC	B	STR		265	
8	You[8]	1999	Australia	CC	NF	IS/I		154	
9	Iribarren[9]	2001	USA	CS	NF	STR	95		42
10	Yamada[10]	2003	Japan	P	F	SAH/I	67		5
11	Anderson[11]	2004	Australia/NZ	CC	B	SAH, ASH/I	105		30
12	Iribarren[12]	2004	USA	P	B	IS, TIA/I	447		259
13	Whincup[13]	2004	Gt.Britain	P	B	STR/I	0		41
14	McGhee[14]	2005	China (Hong Kong)	CC	F	STR	300		297
15	Qureshi[15]	2005	USA	P	B	STR/I ,IS/I	109		0
16	Zhang[16]	2005	China	CS	NF	STR	526		0
17	Wen[17]	2006	China	P	F	STR	157		0
18	Hill (study 1)[18]	2007	New Zealand	P	F	CVD	468		231
19	Hill (study 2)[18]	2007	New Zealand	P	F	CVD	249		204
20	Glymour[19]	2008	USA	P	B	STR/I		386	
21	He 1[20]	2008	China	CS	NF	STR, HS, IS	172		
22	Gallo[21]	2010	Europe (7 countries)	P	F	CVD	111		35
23	Jefferis[22]	2010	Gt.Britain	P	B	STR		70	
24	He 2[23]	2012	China	P	F	STR, HS, IS	19		41

Footnotes

Under **study** is shown the number used to identify the study and 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, HS = haemorrhagic stroke, IS = 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.

TABLE 1 (continued)

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 studies 7 and 20 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 IS; numbers of TIA were 99 in females and 52 in males. For study 15, numbers are of STR; there were 100 cases of IS, For study 21, numbers are of STR; there were 109 cases of IS and 31 cases of HS. For study 24, numbers are of STR; there were 26 cases of HS and 14 cases of IS in men, and 6 cases of HS and 13 cases of IS in women.

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
No.	Name	Source	Timing	Fatality	Disease				
1	Gillis[1]	H	R(5)	F	CVD	1	M	**0.33 (0.04-2.84)**	
							F	**1.88 (0.22-16.0)**	
2	Lee[2]	S	C	N	STR	2	M	Not significant	
		S	C			2	F	Not significant	
		S	M			2	M	**0.84 (0.29-2.45)**	
		S	M			2	F	**0.92 (0.50-1.68)**	
		T	C			1	M	1.35 (0.44-4.12)	
		T	C			1	F	1.19 (0.57-2.50)	
3	Hirayama[3]	S	E	F	CVD	1	F	No significant trend	
					SAH			No significant trend	
4	Donnan[4]	S	E	B	CIS	3 (+ sex)	C	**1.60 (0.60-3.90)**	
5	Sandler[5]	H	E	F	CVD	4	M	**0.97 (0.65-1.46)**	
							F	**1.24 (1.03-1.49)**	+
6	Howard[6]	T	C	N	SCI	10 (+ sex)	C	**1.06 (0.64-1.75)**	
7	Bonita[7]	T	R(10)	B	STR	4	M	**2.10 (1.33-3.32)**	+
							F	**1.66 (1.07-2.57)**	+
8	You[8]	S	E	N	IS	5 (+ sex)	C	**1.70 (0.98-2.92)**	
9	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)	
10	Yamada[10]	T	E	F	SAH	1	M	**1.13 (0.19-6.85)**	
							F	**0.94 (0.57-1.55)**	
11	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)	
12	Iribarren[12]	H	C	B	IS	10	M	**1.02 (0.71-1.48)**	
					IS		F	**1.17 (0.92-1.50)**	
					TIA		M	1.16 (0.49-2.71)	
					TIA		F	1.26 (0.76-2.08)	
13	Whincup[13]	C	C	B	STR	16	M	**1.54 (0.68-3.47)**	
14	McGhee[14]	H	P(10)	F	STR	2	M	**1.31 (0.87-1.99)**	
							F	**1.57 (1.11-2.24)**	+
15	Qureshi[15]	S	E	B	STR	7	F	**0.90(0.60-1.30)**	
					IS			0.80(0.60-1.30)	
16	Zhang[16]	S	C	N	STR	14	F	**1.44 (1.20-1.72)**	+
			E					1.27 (1.05-1.54)	+
17	Wen[17]	S	C	F	STR	9	F	**1.52 (1.08-2.15)**	+
		S	M			9	F	1.33 (0.96-1.84)	
		T	E			9	F	1.64 (0.91-2.95)	

TABLE 2 (continued)

Study		Exposure		Endpoint		Number of adjustment variables	Sex	RR (95% CI)	Signif-icance
No.	Name	Source	Timing	Fatality	Disease				
18	Hill (study 1)[18]	H	C	F	CVD	2	M	**1.59 (1.14-2.21)**	+
						9	F	**0.90 (0.67-1.21)**	
19	Hill (study 2)[18]	H	C	F	CVD	9	M	**1.82 (1.20-2.77)**	+
						9	F	**1.17 (0.76-1.82)**	
20	Glymour[19]	S	C	B	STR	16	M	**1.63 (0.83-2.70)**	
							F	**1.46 (1.00-2.18)**	+
21	He 1[20]	T	R(10)	NF	STR	12	F	**1.65 (1.17-2.32)**	+
					IS	12	F	1.56 (1.03-2.35)	+
					HS	12	F	1.10 (0.52-2.34)	
22	Gallo[21]	H	E	F	CVD	5	M	**1.10 (0.36-3.37)**	
						5	F	**0.93 (0.49-1.74)**	
23	Jefferis[22]	S	C	B	STR	17	C	**0.69 (0.16-2.94)**	
		C						0.78 (0.48-1.26)	
24	He 2[23]	H	E	F	STR	10	C	**2.07 (0.84-5.14)**	
					HS	10	C	2.63 (0.83-8.39)	
					IS	10	C	1.71 (0.40-7.37)	

Footnotes

Under **study** is shown the number used to identify the study and 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, HS = haemorrhagic stroke, IS = ischaemic stroke, SAH = subarachnoid haemorrhage, SCI = silent cerebral infarction, STR = stroke and TIA = transient ischaemic attack.

Number of adjustment variables. See Appendix B 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 No.	Name	Sex	Exposure grouping	RR by level (95% CI)
2	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)**
4	Donnan[4]		**Either parent smoked**	
		C	No Yes	1.00 (0.50-2.10)
6	Howard[6]		**Total ETS exposure**	
		C	Hours per week	No significant relationship
8	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)**
9	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 No.	Name	Sex	Exposure grouping	RR by level (95% CI)
12	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)
13	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)**
14	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]
16	Zhang[16]		**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]
17	Wen[17]		**Pack-years of smoking by husband**	
		F	0 <8.8 8.8-17.9 18.0+	**1.35 (0.79-2.31)** 1.25 (0.76-2.07) **1.36 (0.94-1.96)** [Trend p=0.029]
			ETS at work	
		F	No Yes	0.73 (0.44-1.20)
			0 <10 10-24 25+ years	0.47 (0.17-1.29) 0.95 (0.47-1.90) 0.74 (0.35-1.56) [Trend p=0.520]
			ETS in early life	
		F	No Yes	1.10 (0.74-1.63)
		F	0 <20 20+ years [*sic*]	0.91 (0.56-1.47) 1.46 (0.86-2.45) [Trend p=0.342]
			Ever exposed by husband, at work or in early life	
		F	No Yes	1.64 (0.91-2.95)
21	He 1[20]		**Cigarettes exposed to at home or in the workplace**	
		F	0 1-9 10-19 20+ per day; stroke	**1.10 (0.62-1.96)** 1.72 (1.08-2.77) **1.83 (1.15-3.37)** [Trend p<0.001]
		F	As above, ischaemic stroke	1.31 (0.66-2.57) 1.45 (0.84-2.86) 1.72 (1.09-3.04) [Trend p=0.002]
		F	As above, haemorrhagic stroke	0.34 (0.05-2.60) 1.96 (0.82-4.73) 0.79 (0.22-2.75) [Trend p=0.25]
			Minutes of exposure per day	
		F	0 ≤20 ≤40 [*sic*] >40; stroke	1.68 (1.06-2.57) 1.56 (1.05-2.34) 1.74 (0.90-3.86) [Trend p=0.004]
		F	As above, ischaemic stroke	1.49 (0.75-2.96) 1.44 (0.88-2.35) 1.98 (0.96-4.36) [Trend p=0.02]
		F	As above, haemorrhagic stroke	0.65 (0.15-2.88) 1.18 (0.49-2.82) 1.98 (0.42-9.33) [Trend p=0.73]
22	Gallo[21]		**ETS at work**	
		M	No Yes	1.99 (0.25-15.70)
		F	No Yes	1.18 (0.58-2.39)
			ETS in childhood	
		M	No Yes	0.82 (0.38-1.78)
		F	No Yes	0.79 (0.53-1.20)
23	Jefferis[22]		**Serum cotinine concentration**	
		C	≤0.05 0.06-0.19 0.20-0.70 0.71-15 ng/ml	**0.91 (0.50-1.62)** 0.61 (0.30-1.26) **0.81 (0.33-1.99)** [Trend p=0.476]

TABLE 3 (continued)

Study No.	Name	Sex	Exposure grouping	RR by level (95% CI)			
24	He 2[23]		**ETS at work**				
		C	No Yes; stroke	2.34 (1.15-4.76)			
		C	As above, haemorrhagic stroke	1.74 (0.67-4.53)			
		C	As above, ischaemic stroke	3.05 (0.97-9.55)			
			ETS exposure at home or at work				
		C	Score 0 1-2 3-4 5-6; stroke	**2.47 (1.25-4.90)**	2.17 (1.09-4.33)	**1.30 (0.29-5.78)**	[Trend p=0.73]
		C	As above, haemorrhagic stroke	2.65 (1.11-6.34)	1.49 (0.57-3.90)	0.00	[Trend p=0.92]
		C	As above, ischaemic stroke	2.16 (0.68-6.81)	3.60 (1.28-10.10)	2.72 (0.53-13.89)	[Trend p=0.02]

Footnotes

Under **Study** is shown the number used to identify the study and 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 B) 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).

Trend tests given by original author

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

Estimates included	Estimates	Analysis	RR (95% CI)	Significance
All	36	Fixed	1.29 (1.20-1.38)	p<0.001*
		Random	1.28 (1.17-1.40)	p<0.001
Sex : male	14	Fixed	1.32 (1.14-1.53)	NS
Female	17	Fixed	1.27 (1.17-1.38)	
Combined	5	Fixed	1.38 (1.01-1.89)	
Exposure index : Spouse	10	Fixed	1.36 (1.20-1.54)	p<0.1
Total/cotinine	7	Fixed	1.48 (1.23-1.79)	
Household	19	Fixed	1.21 (1.10-1.32)	
Continent : N.America	10	Fixed	1.16 (1.04-1.29)	p<0.05
Europe	8	Fixed	0.99 (0.71-1.37)	
Asia	8	Fixed	1.45 (1.28-1.64)	
Australasia	10	Fixed	1.37 (1.19-1.58)	
Publication year : 1984-1989	7	Fixed	1.16 (1.00-1.36)	p<0.05
1990-1999	4	Fixed	1.61 (1.26-2.04)	
2000-2004	9	Fixed	1.09 (0.93-1.28)	
2005-2009	12	Fixed	1.37 (1.25-1.51)	
2010-2014	4	Fixed	1.13 (0.72-1.77)	
Number of cases : 1-199	21	Fixed	1.21 (1.06-1.38)	NS
200+	15	Fixed	1.32 (1.22-1.43)	
Study type : prospective	21	Fixed	1.21 (1.10-1.32)	p<0.1
case-control	10	Fixed	1.45 (1.23-1.71)	
cross-sectional	5	Fixed	1.40 (1.21-1.61)	
Number of adjustment variables† :0-5	16	Fixed	1.29 (1.15-1.44)	NS
6+	20	Fixed	1.29 (1.18-1.40)	
Fatality : fatal	16	Fixed	1.26 (1.14-1.39)	NS
non-fatal	8	Fixed	1.37 (1.20-1.57)	
Both	12	Fixed	1.26 (1.10-1.43)	
Disease : CVD or stroke	27	Fixed	1.33 (1.23-1.43)	NS
ischaemic stroke	4	Fixed	1.16 (0.97-1.39)	
haemorrhagic stroke	4	Fixed	0.97 (0.68-1.37)	
Other	1	Fixed	1.60 (0.63-4.08)	

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 = $p \geq 0.1$.

Disease categories: ischaemic stroke includes silent cerebral infarction; haemorrhagic stroke includes subarachnoid haemorrhage and aneurysmal subarachnoid haemorrhage. Where a study provides results for CVD or stoke and another disease definition, the results for CVD or stroke are selected.

*The heterogeneity chisquared was 48.14 on 35 d.f., p<0.1.

† Apart from sex.

TABLE 5: Sensitivity meta-analyses

Analysis	Estimates	RR (95% CI) Fixed-effects	RR (95% CI) Random-effects	Heterogeneity χ^2	d.f.	p
Principal	36	1.29 (1.20-1.38)	1.28 (1.17-1.40)	48.14	35	p<0.1
Preferring ever to current exposure*	36	1.23 (1.15-1.32)	1.23 (1.13-1.34)	45.42	35	NS
Preferring total to spousal exposure†	37	1.26 (1.18-1.35)	1.25 (1.12-1.38)	63.04	35	p<0.01
Excluding silent cerebral infarction	35	1.29 (1.20-1.38)	1.28 (1.17-1.41)	47.56	34	p<0.1
Preferring "least adjusted" to "most adjusted" estimates	35	1.29 (1.21-1.39)	1.28 (1.17-1.40)	48.21	34	p<0.1
Selecting by disease definition: stroke or CVD	27	1.33 (1.23-1.43)	1.32 (1.19-1.47)	38.17	26	p<0.1
Selecting by disease definition: ischaemic stroke[1]	7	1.15 (0.99-1.33)	1.16 (0.96-1.40)	8.27	6	NS
Selecting by disease definition: haemorrhagic stroke[2]	6	1.06 (0.78-1.44)	1.06 (0.77-1.48)	5.54	5	NS

Footnotes

* Using preference order for time of exposure: ever, in adulthood, in the last 25 years, in the last 20 years, during marriage, in the last 10 years, in the last 5 years, current, in the past.

† Using preference order for type of exposure: total, cotinine, spouse, household.

[1] Analysis of results for ischaemic stroke or silent cerebral infarction.

[2] Analysis of results for haemorrhagic stroke, subarachnoid haemorrhage or aneurysmal subarachnoid haemorrhage.

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

Study No.	Study Name	Sex	Adjustment variables	RR (95% CI)	Ratio
6	Howard[6]	C	Age, sex, race	1.03 (0.63-1.67)	
			Age, sex, race + 8	1.06 (0.64-1.75)	1.03
7	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
12	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
13	Whincup[13]	M	Age, town	0.96 (0.49-1.89)	
			Age, town + 15	1.54 (0.68-3.47)	1.60
15	Qureshi[15]	F	Age	0.90 (0.60-1.40)	
			Age + 6	0.90 (0.60-1.30)	1.00
16	Zhang[16]	F	Age	1.46 (1.23-1.72)	
			Age + 13	1.44 (1.20-1.72)	0.99
18	Hill (Study 1)[18]	F	Age, ethnicity	0.88 (0.66-1.17)	
			Age, ethnicity + 7	0.90 (0.67-1.21)	1.02
19	Hill (Study 2)[18]	M	Age, ethnicity	1.91 (1.23-2.96)	
			Age, ethnicity + 7	1.82 (1.20-2.77)	0.95
		F	Age, ethnicity	1.16 (0.75-1.79)	
			Age, ethnicity + 7	1.17 (0.76-1.82)	1.01
22	Gallo[21]	C	Age, sex, study centre	1.04 (0.60-1.80)	
			Age, sex, study centre + 3	1.02 (0.60-1.76)	0.98

Footnotes
See Appendix B for the additional adjustment factors.
See Table 2 for extra information regarding exposure and disease.
Under **Study** is shown the number used to identify the study and 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	RR (95% CI) Random-effects	Heterogeneity χ^2	Heterogeneity d.f.	Heterogeneity p
Low dose	12	1.20 (1.04-1.37)	1.20 (1.04-1.37)	10.47	11	NS
High dose	13	1.59 (1.38-1.82)	1.59 (1.38-1.82)	6.74	12	NS

Footnote
Based on estimates in Table 3 highlighted in bold type

APPENDIX A

STUDIES/ANALYSES NOT INCLUDED IN TABLES AND FIGURES

In preparing the tables and figures in this document certain papers which might be thought to cite relevant data have not been referred to. For each of these papers, this appendix notes the authors, date of publication and country and the reasons for not referring to them.

- Molgaard *et al* 1986,[28] USA: Finding presented only for smokers and non-smokers combined.
- Howard *et al* 1994,[44] USA: Study of carotid artery disease.
- Lin *et al* 1994,[45] China: Unclear if non-smokers includes ex-smokers as well as never smokers.
- Wang *et al* 1994,[46] China: Unclear whether ETS results were based on never smokers, or on both smokers and non-smokers.
- Diez-Roux *et al* 1995,[47] USA: Study of carotid artery disease.
- Kiechl *et al* 2002,[48] Italy: Study of carotid artery disease.
- Ying *et al* 2003,[49] China: Data taken from [45] and [46].
- Ivan 2004,[50] Romania: Study of cases only with no controls.
- Miura *et al*,[51] 2004 Japan: No analysis in never smokers.
- Eisner *et al*,[52] 2007 USA: No analysis with stroke as separate endpoint.
- García-Núñez *et al*,[53] 2007 Spain: No analysis in never smokers.
- Heuschmann et al,[54] 2007 Germany: No analysis in never smokers. Paper reports theoretical model of stroke incidence rather than actual study.
- Efstratiadis *et al*,[55] 2008 USA: No analysis in never smokers, all participants had pre-existing angina.
- Seki *et al*,[40] 2010 Japan: Although based on a population of 579 and 6 cases, ETS exposure information was only available for a total of 474 subjects and 2 cases. In addition, the main purpose of this paper was to investigate the relationship between ETS and blood pressure.
- Hamer *et al*,[56] 2010 England and Scotland: No analysis with stroke as a separate endpoint.

- Firdaus *et al*,[57] 2011 India: No analysis with stroke as a separate endpoint.
- McClure *et al*, [58] 2011 USA: Ecological study.
- Pope *et al*,[59] 2011 USA: No analysis with stroke as a separate endpoint.
- Kent *et al*,[60] 2012 Ireland: Ecological study.

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

	Study number																							
Risk factor	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Sex	-	-	-	x	-	x	-	x	-	-	-	-	-	x[a]	-	-	-	-	-	-	-	-	x	x
Age[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	2	x	x	x	x
Race/ethnicity						x			x		x	x			x			x	x	2				
Socioeconomic status													x			x	x	3	3	x			x	
Education					x			x	x			x		x		x	x	x	x	3	x	x		x
Marital status		x			x				x			x						x	x		x			x
Occupation/employment									x							x	x	x	x	x				x
Diet						x											3							
Alcohol						x			x		x	x	x		x	x				x	x		x	x
Region of residence				x							x		x							x		x	x	
Housing quality					x													x	x					
Proxy respondent											x													
Exercise						x			x			x	x			x	x				x	x	x	
Cholesterol/lipids						x			x			x	2		x						x		3	x
Other blood tests						x							2								x		3	x
Blood pressure				x		x	x	x	x		x	x	2		x	2				x	x		2	x
Diabetes						x	x	x	x		x	x	x		x	x				x	x		x	
Hormone therapy[c]																3								
Obesity/weight						x			x		x	x	x		x	x	x			2	x	x	x	x
History of heart disease							x	x					x							x	x			
Family medical history																					x			
Lung function													x										x	
Height													x											
Aspirin use																x								

APPENDIX B (continued)

Key

x, 2, 3	Risk factor adjusted for by 1, 2, 3 … variables
-	Not applicable because the results are 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 C

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).[61-63] 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 C.

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.

APPENDIX TABLE C

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

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