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Environmental tobacco smoke exposure and heart disease: A systematic review

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Data sharing statement: Supplementary File 1 provides a description of the reasons for rejection of some papers. Supplementary File 2 gives full details of the meta-analyses conducted. Supplementary File 3 gives full details of the stepwise multiple regression analysis. Supplementary File 4 gives some results for less commonly used indices of ETS exposure. Copies of the database files are available on request from the corresponding author at peterLee@pnlee.co.uk.

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Abstract

AIM

To review evidence relating passive smoking to heart disease risk in never smokers.

METHODS

Epidemiological studies were identified providing estimates of relative risk (RR) of ischaemic heart disease and 95%CI for never smokers for various indices of exposure to environmental tobacco smoke (ETS). "Never smokers" could include those with a minimal smoking experience. The database set up included the RRs and other study details. Unadjusted and confounder-adjusted RRs were entered, derived where necessary using standard methods. The fixed-effect and random-effects meta-analyses conducted for each exposure index included tests for heterogeneity and publication bias. For the main index (ever smoking by the spouse or nearest equivalent, and preferring adjusted to unadjusted data), analyses investigated variation in the RR by sex, continent, period of publication, number of cases, study design, extent of confounder adjustment, availability of dose-response results and biomarker

data, use of proxy respondents, definitions of exposure and of never smoker, and aspects of disease definition. Sensitivity analyses were also run, preferring current to ever smoking, or unadjusted to adjusted estimates, or excluding certain studies.

RESULTS

Fifty-eight studies were identified, 20 in North America, 19 in Europe, 11 in Asia, seven in other countries, and one in 52 countries. Twenty-six were prospective, 22 case-control and 10 cross-sectional. Thirteen included 100 cases or fewer, and 11 more than 1000. For the main index, 75 heterogeneous ($P < 0.001$) RR estimates gave a combined random-effects RR of 1.18 (95%CI: 1.12-1.24), which was little affected by preferring unadjusted to adjusted RRs, or RRs for current ETS exposure to those for ever exposure. Estimates for each level of each factor considered consistently exceeded 1.00. However, univariate analyses revealed significant ($P < 0.001$) variation for some factors. Thus RRs were lower for males, and in North American, larger and prospective studies, and also where the RR was for spousal smoking, fatal cases, or specifically for IHD. For case-control studies RRs were lower if hospital/diseased controls were used. RRs were higher when diagnosis was based on medical data rather than death certificates or self-report, and where the never smoker definition allowed subjects to smoke products other than cigarettes or have a limited smoking history. The association with spousal smoking specifically (1.06, 1.01-1.12, $n = 34$) was less clear in analyses restricted to married subjects (1.03, 0.99-1.07, $n = 23$). In stepwise regression analyses only those associations with source of diagnosis, study size, and whether the spouse was the index, were independently predictive (at $P < 0.05$) of heart disease risk. A significant association was also evident with household exposure (1.19, 1.13-1.25, $n = 37$). For those 23 studies providing dose-response results for spouse or household exposure, 11 showed a significant ($P < 0.05$) positive trend including the unexposed group, and two excluding it. Based on fewer studies, a positive, but non-significant ($P > 0.05$) association was found for workplace exposure (RR = 1.08, 95%CI: 0.99-1.19), childhood exposure (1.12, 0.95-1.31), and biomarker based exposure indices (1.15, 0.94-1.40). However, there was a significant association with total exposure (1.23, 1.12-1.35). Some significant positive dose-response trends were also seen for these exposure indices, particularly total exposure, with no significant negative trends seen. The evidence suffers from various weaknesses and biases. Publication bias may explain the large RR (1.66, 1.30-2.11) for the main exposure index for smaller studies (1-99 cases), while recall bias may explain the higher RRs seen in case-control and cross-sectional than in prospective studies. Some bias may also derive from including occasional smokers among the "never smokers", and from misreporting smoking status. Errors in determining ETS exposure, and failing to update exposure data in long term prospective studies, also contribute to the uncertainty. The tendency for RRs to increase as more factors are adjusted for,

argues against the association being due to uncontrolled confounding.

CONCLUSION

The increased risk and dose-response for various exposure indices suggests ETS slightly increases heart disease risk. However heterogeneity, study limitations and possible biases preclude definitive conclusions.

Key words: Passive smoking; Heart disease; Dose-response; Meta-Analysis; Review

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Core tip: We present an up-to-date meta-analysis of the evidence relating environmental tobacco smoke (ETS) exposure to heart disease risk in never smokers. An association is evident for smoking by the spouse (or nearest equivalent) with the relative risk estimated as 1.18 (95%CI: 1.12-1.24), and also with some other indices of ETS exposure. Though the findings suggest a causal relationship, data limitations and bias limit interpretation.

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INTRODUCTION

This review concerns studies of environmental tobacco smoke (ETS) and heart disease in lifelong non-smokers ("never smokers"). In the 1990s some reviewers^[1-4] concluded that exposure of non-smokers to ETS increases risk of heart disease, based partly on meta-analyses of epidemiological data from between 12 and 19 studies which reported statistically significant overall increases of about 25%, and partly on evidence from experimental and clinical studies. Their conclusions were accepted by some major bodies^[5-8], and supported by some other reviewers^[9-13]. However, other reviewers^[14-18] disagreed, pointing to omission of relevant studies, inclusion of inappropriate estimates, heterogeneity of findings, study weaknesses and various sources of bias, as well as limitations in the experimental and clinical evidence.

Since then, the number of relevant epidemiological studies has increased, with over 50 now published. However, no recent comprehensive meta-analysis has been conducted, one published in 2015^[13] including fewer studies than in some earlier reviews.

Our main objective is to present an updated meta-analysis of the epidemiological data, although we also briefly discuss the experimental evidence, and studies

of smoking bans.

MATERIALS AND METHODS

Study inclusion and exclusion criteria

Attention is restricted to epidemiological prospective, case-control or cross-sectional studies providing relative risk (RR) estimates for never smokers for one or more of these ETS exposure indices: Spouse (including cohabiting partner), other at home exposure, at work, in adulthood, in childhood, in total, and biomarker based. We use the term "relative risk" to include estimates of it, such as the odds ratio or hazard ratio. Results must be available for a disease definition sufficiently close to ischaemic heart disease (IHD) as currently defined. Studies using a near equivalent definition of "never smokers" are accepted when results for stricter definitions are unavailable. Thus, never smokers may include occasional smokers, those with a minimal lifetime duration of smoking or number smoked, or those who quit at least 5 years ago.

Literature searches

At intervals until July 2016 potentially relevant papers were regularly sought from Medline searches, from extensive in-house files accumulated over many years and from references cited in papers obtained. At the end of the process no paper examined cited a possibly relevant paper not previously examined. The latest search used the terms ["tobacco smoke pollution" (MeSH terms)] AND [{"heart diseases"(MeSH Terms)] OR [{"cardiovascular diseases" (MeSH Terms)] OR [{"myocardial infarction" (MeSH Terms)}] AND ("2012/0101"[Date-MeSH]:"3000"[Date-MeSH]), restricted to humans, and published in the last 5 years.

Study identification

Relevant publications were separated into studies, noting multiple papers per study or multiple studies per paper, and any study overlaps.

Data recorded

Details were extracted on study author, publication year, study location and design, sexes included, number of cases, potential confounding variables considered, and definitions of disease and of never smoker. RR estimates, together with associated 95% CIs were obtained, where available, for ETS exposure at home, at work, in childhood, and in total, and using biomarker based estimates (cotinine or COHb). Separate estimates were extracted or calculated for fatal, non-fatal and overall outcomes and for both unadjusted (or for prospective studies, age-adjusted) and covariate-adjusted RRs. If a study provided more than one adjusted estimate, we used that adjusted for most covariates.

RR derivation

Where studies report RRs/CIs only by level of exposure, those for the overall unexposed/exposed comparisons were estimated^[19,20]. These methods were also used to

estimate significance of dose-related trends, if not given in the source. Similar methods were used to estimate RRs and CIs excluding stroke from a broader circulatory disease definition.

Meta-analyses

Pre-planned fixed-effect and random-effects meta-analyses were conducted using standard methods^[21]. Heterogeneity between RR estimates was assessed by the heterogeneity χ^2 , the ratio of which to its degrees of freedom, H , relates to the I^2 statistic^[22] by $I^2 = 100 (H-1)/H$. Publication bias tests were also carried out^[23].

For our main analyses, we aimed to produce an exposure index most closely equivalent to "spouse ever smoked", since spousal smoking is the traditional index for studying ETS effects, women married to a smoker having a markedly higher ETS exposure, as measured by cotinine, than women married to a non-smoker^[24]. Thus, results (sex-specific if available, otherwise combined sex) were selected in the following order of preference for: Exposure (spouse, household, total), time of exposure (ever, during marriage, current, in the past, in the last 10 years, in adulthood), disease type (fatal or non-fatal, fatal only, non-fatal only), disease definition (circulatory disease minus stroke, overall circulatory disease), and definition of no ETS exposure (unexposed to the specific ETS exposure, unexposed to any ETS, low exposure to the specific ETS exposure, never exposed to the specific ETS exposure, unexposed to ETS at home and at work). In addition, results selected were those adjusted for the most confounders for which results were given. This approach of selecting the most relevant result allowed the meta-analyses to include results from each study. Apart from conducting meta-analyses based on all selected estimates, additional meta-analyses using the same set of estimates, investigated variation in RR by the factors sex, continent, publication period, number of cases, study type, number of confounders considered in the study, availability of dose-response results, whether the spouse was the index, and whether (where the spouse was the index), analyses excluded unmarried subjects. Variation was also studied by fatality of cases, definition of disease, whether biomarker data was used to exclude smokers, use of proxy respondents, type of control used, source of diagnosis, and never smoker definition.

Sensitivity analyses repeated the complete set of meta-analyses described above for the main index of exposure with the order of preference for time of exposure revised to favour current rather than ever exposure (current, during marriage, ever, in the past, in the last 10 years, in adulthood), and also preferring unadjusted (or least adjusted) estimates. Further sensitivity analyses were carried out omitting results from: (1) studies by Layard^[25] and LeVois *et al.*^[26]; (2) a study by Enstrom *et al.*^[27]; or (3) all three studies. These studies have been criticised (see discussion).

For the main exposure index stepwise regression analysis using forward selection^[28] was also used to

determine factors independently predicting risk of heart disease.

Similar meta-analyses were also conducted for other indices with sufficient data (household, workplace, childhood, total, biomarker based), though the meta-analyses by subset were more limited.

Results of meta-analyses are displayed in forest plots. Within each plot, study estimates are listed in increasing order of RR. For the main index, the estimates are grouped by location. The estimates are shown both as numbers and in graphical form logarithmically. In the latter representation an RR is shown as a square with area proportional to its inverse-variance weight. Arrows warn if a CI extends outside the range of the plot. Random-effects estimates are also presented, overall and by location, shown by a diamond whose width indicates the 95%CI.

RESULTS

Studies identified

Fifty-eight studies met the inclusion criteria. These come from 57 publications^[25-27,29-82], one publication^[66] describing results from two studies. Table 1 gives study details including author, reference(s), publication year, location, design, sexes included, disease definition and fatality, and numbers of cases in never smokers. The studies are listed in chronological order of publication and given consecutive study numbers. Minor overlap between cases in studies 16 and 30, was ignored. Table 2 gives variables adjusted for and never smoker definitions. Supplementary File 1 describes why other publications which might be thought possibly relevant are not included.

Of the 58 studies, 10 were published in the 1980s, 15 in the 1990s, 21 between 2000 and 2009 and 12 more recently. Twenty studies were in North America (19 United States, one Canada), 19 in Europe (10 United Kingdom, two Sweden, two Greece, one each in Albania, Germany, Italy and Norway and one in multiple countries), 11 in Asia (two Hong Kong, five in the rest of China, and one each in Iran, Japan, Pakistan and Singapore) and eight in other countries (three in each of Australia and New Zealand, one in Argentina, and one in 52 countries worldwide).

Twenty six studies were prospective, with lengths of follow-up from three to 39 years, while 22 were case-control, and 10 cross-sectional. Thirteen studies were of females, and four of males. The rest included both sexes, though some did not report sex-specific results. Twenty studies considered only fatal cases and 26 only non-fatal cases, the other 12 including both. As shown in Table 1, although IHD specifically was the disease definition used in almost half the studies, various other definitions were used. The studies varied considerably in size, with 13 of < 100 cases and 11 of > 1000 cases, the largest being of 14891, 6280 and 5932 cases.

As Table 2 shows, two studies only provided unadjusted results. While in a number of the mainly earlier

studies there was quite limited adjustment, many studies adjusted for numerous variables. Apart from sex and age, variables adjusted for in > 10 studies included marital status, blood pressure (or hypertension), cholesterol, social class (or similar variables based on education or income), obesity (or weight), alcohol consumption, diabetes, family history of heart disease (or hypertension), race and exercise.

Thirty-five studies were of never smokers, though only nine of these clarified that subjects never smoked cigarettes, pipes or cigars. Nine studies were of never cigarette smokers, 11 allowed a minimal smoking history, such as smoking less than one cigarette a day or fewer than 100 cigarettes in life, while three studies allowed those who quit smoking some time ago. Four studies excluded subjects with cotinine levels indicative of current smoking.

Main exposure index

Our main analyses use an index as close as possible to ever smoking by the spouse. Four studies were not included in the main index analyses, one (study 40) only reporting risk per 10 years living or working with a smoker, and three (studies 33, 36 and 48) providing results only for a biochemical index. Table 3, supported by Figure 1, presents RRs for the main index, and also gives details of ETS exposure, the definitions of the unexposed group being given in Supplementary File 2. RRs for the sensitivity analysis preferring current exposure are also in Table 3, nine studies providing RRs and 95%CIs for both ever and current exposure. RRs for the sensitivity analysis preferring unadjusted to adjusted results are given in Supplementary file 2. Studies 7, 17 and 25 only provided incomplete estimates that could not be included in meta-analyses. Similarly, the result for current exposure from study 4 could not be included in the sensitivity analysis. Otherwise, for each study/sex combination, the RR estimate listed first in Table 3 is that used in the main analysis. Exposure was based on spousal smoking for 24 studies, on at home exposure for 17, and on exposure from multiple sources, including outside the home, for 10. Table 4 presents results of meta-analyses, fuller details being given in Supplementary File 2. Table 5 presents dose-response data, separately for spousal and household exposure.

Table 3 demonstrates clear evidence of a positive association, about three-quarters of the main analysis RR estimates exceeding 1. Seventeen are significantly ($P < 0.05$) increased, and none significantly decreased. Study 16 contributed 31% of the total weight, with studies 20, 27, 30 and 38 each contributing about 10%.

The main meta-analysis (Table 4) shows a clear positive association, with the random-effects RR estimate 1.18 (95%CI: 1.12-1.24) based on 75 individual estimates. The RR is little changed in sensitivity analyses preferring unadjusted to adjusted estimates (1.16, 1.09-1.24), or preferring current to ever exposure estimates (1.19, 1.13-1.26). It is somewhat increased if studies 15, 16 and 30 are excluded (1.23, 1.17-1.29).

Table 1 Studies providing evidence on heart disease and environmental tobacco smoke exposure in never smokers

Study No.	Ref. ¹	Year ²	Location	Type ³	Sexes included ⁴	Disease fatality ⁵	Disease definition ⁶	No. of cases ⁷
1	Hirayama ^[29]	1984	Japan	P16	F	F	IHD	494
2	Garland <i>et al</i> ^[30]	1985	United States/California	P10	F	F	IHD	19
3	Lee <i>et al</i> ^[31]	1986	England	CC	M, F	NF	IHD	118
4	Martin <i>et al</i> ^[32]	1986	United States/Utah	CS	F	NF	PHA	23
5	Svendsen <i>et al</i> ^[33]	1987	United States	P9	M	F + NF	IHD	69
6	Butler ^[34]	1988	United States/California	P6	F	F	IHD	80 ⁸
7	Palmer <i>et al</i> ^[35]	1988	United States/Not known	CC	F	NF	MI	336
8	Hole <i>et al</i> ^[36]	1989	Scotland	P12	M, F	F, NF	IHD, A/E	120
9	Jackson ^[37]	1989	New Zealand	CC	M, F	F + NF	IHD + MI	303
10	Sandler <i>et al</i> ^[38]	1989	United States/Maryland	P12	M, F	F	AHD	1358
11	Humble <i>et al</i> ^[39]	1990	United States/Georgia	P20	F	F	CVD	76
12	Dobson <i>et al</i> ^[40]	1991	Australia	CC	M, F	F + NF	IHD + MI	343
13	Gardiner <i>et al</i> ^[41]	1992	Scotland	CC	M+F	F + NF	IHD	12
14	La Vecchia <i>et al</i> ^[42]	1993	Italy	CC	M, F	NF	FMI	113
15	Layard ^[25]	1995	United States	CC	M, F	F	IHD	1389
16 ⁹	Le Vois <i>et al</i> ^[26] (CPS I)	1995	United States	P13	M, F	F	AHD	14891
17	Mannino <i>et al</i> ^[43]	1995	United States	CS	M + F	NF	CVD	?
18	Muscat <i>et al</i> ^[44]	1995	United States/4 cities	CC	M, F	NF	NMI	114
19	Tunstall-Pedoe <i>et al</i> ^[45]	1995	Scotland	CS	M + F	NF	IHD	428
20	Steenland <i>et al</i> ^[46]	1996	United States	P7	M, F	F	IHD	3819
21	Janghorbani <i>et al</i> ^[47]	1997	Iran	CC	F	NF	IHD	200
22	Kawachi <i>et al</i> ^[48]	1997	United States	P10	F	F + NF	IHD + MI	152
23	Ciruzzi <i>et al</i> ^[49]	1998	Argentina	CC	M, F	NF	FMI	336
24	McElduff <i>et al</i> ^[50]	1998	Australia	CC	M, F	F + NF	MI	283
25	Spencer <i>et al</i> ^[51]	1999	Australia	CC	M	NF	FMIS	91
26	He <i>et al</i> ^[52]	2000	China/Xi'an	CC	F	NF	MI/CS	115
27	Iribarren <i>et al</i> ^[53]	2001	United States	CS	M, F	NF	IHD	4801
28	Rosenlund <i>et al</i> ^[54]	2001	Sweden	CC	M, F	NF	FMI	334
29	Pitsavos <i>et al</i> ^[55]	2002	Greece	CC	M + F	NF	FMI/UA	279
30 ⁹	Enstrom <i>et al</i> ^[27]	2003	United States/California	P39	M, F	F	IHD	5932
31	Chen <i>et al</i> ^[56]	2004	Scotland	CS	M + F	NF	IHD	385
32	Nishtar <i>et al</i> ^[57] ¹⁰	2004	Pakistan	CC	M + F	NF	CAD	?
33 ¹¹	Whincup <i>et al</i> ^[58]	2004	Great Britain	P21	M	F + NF	IHD	111
34	McGhee <i>et al</i> ^[59]	2005	Hong Kong	CC	M, F	F	IHD	584
35	Qureshi <i>et al</i> ^[60]	2005	United States	P11	F	F + NF	CVD	328
36	Hedblad <i>et al</i> ^[61]	2006	Sweden	P19	M	F + NF	CVD-Stroke IHD + MI, FMI	219 91
37	Stranges <i>et al</i> ^[62]	2006	United States	CC	M, F	NF	FMI	284
38	Teo <i>et al</i> ^[63]	2006	52 countries	CC	M + F	NF	FMI	6280
39	Wen <i>et al</i> ^[64]	2006	China/Not known	P6	F	F	CVD	272
40	Eisner <i>et al</i> ^[65]	2007	United States	P8	M, F	F	CVD-Stroke CVD	115 1057
41	Hill <i>et al</i> ^[66]	2007	New Zealand	P3	M, F	F	IHD	2571
42	Hill <i>et al</i> ^[66]	2007	New Zealand	P3	M, F	F	IHD	1680
43	He <i>et al</i> ^[67]	2008	China/Beijing	CS	F	NF	IHD	431
44	Sulo <i>et al</i> ^[68]	2008	Albania	CC	M + F	NF	ACS	169
45	Vozoris <i>et al</i> ^[69]	2008	Canada	CS	M + F	NF	IHD	1773
46	Ding <i>et al</i> ^[70]	2009	Hong Kong	CC	F	NF	IHD	314
47	Gallo <i>et al</i> ^[71]	2010	Europe	P?	M, F	F	CVD ¹² IHD	399 81
48	Hamer <i>et al</i> ^[72]	2010	England, Scotland	P7	M + F	F	CVD	96
49 ¹¹	Jefferis <i>et al</i> ^[73]	2010	Great Britain	P11	M + F	F + NF	FMI	74
50	Peineman <i>et al</i> ^[74]	2011	Germany	CS	M + F	NF	IHD	128
51	Chen ^[75]	2012	China/4 provinces	CS	M + F	NF	IHD MI	405 171
52	He <i>et al</i> ^[76]	2012	China/Xi'an	P26	M, F	F	IHD	41
53	Clark <i>et al</i> ^[77]	2013	Singapore	P16	M, F	F	IHD	311
54	Iversen <i>et al</i> ^[78]	2013	Norway	P11	M, F	F + NF	FMI	326
55	Kastorini <i>et al</i> ^[79]	2013	Greece	CC	M + F	NF	ACS	52
56	Rostron ^[80]	2013	United States	P11	M + F	F	IHD	?
57	Batty <i>et al</i> ^[81] ¹³	2014	United Kingdom	P17	M, F	F	CVD	98

58	Shiue ^{182]}	2014	Scotland	CS	M + F	NF	MI	255
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¹First author of paper, followed by a number to distinguish multiple studies with the same author; ²Year of publication; ³Study types are CC: Case-control, CS: Cross-sectional, P: Prospective. Number after P is estimated mean years of follow-up; ? : Indicates length of follow-up not stated; ⁴M + F indicates only results for combined sexes available; M, F indicates separate sex results available; ⁵F: Fatal; NF: Non-fatal; F + NF indicates only combined results available; F, NF indicates separate results available; ⁶A/E: Angina or ECG abnormality; ACS: Acute coronary syndrome; AHD: Arteriosclerotic heart disease; CAD: Coronary artery disease; CVD: Cardiovascular disease; FMI: First myocardial infarction; FMI/UA: First myocardial infarction or unstable angina; FMIS: First myocardial infarction surviving 28 d, HD: Heart disease; IHD: Ischaemic (coronary) heart disease; MI: Myocardial infarction; MI/CS: Myocardial infarction or coronary stenosis; NMI: Newly diagnosed myocardial infarction; PHA: Previous heart attack. “+” indicates inclusion of cases with either disease, indicates different outcome definitions for fatal and non-fatal analyses respectively; ⁷Number of heart disease cases in never smokers are totals in the study. For analyses relating to some exposure indices, numbers may be lower than this. ? indicates numbers not available; ⁸For study 6 numbers relate only to the spouse-pairs cohort, the AHSMOG cohort including ex-smokers; ⁹Studies 16 and 30 were both part of CPS I. Study 30 covered a smaller geographic area but a longer follow-up period; ¹⁰For study 32, although the source paper does not state that the analyses were restricted to never smokers, this has been confirmed to us by the authors; ¹¹Study 49 included the same male participants as study 33, but started at the end of the follow-up period of that study, so there was no overlap of cases between the two studies; ¹²For study 47, CVD was defined as any circulatory disease excluding cerebrovascular causes; ¹³For study 57, results in never smokers were taken from Supplementary tables supplied by the authors.

There is clear ($P < 0.001$) heterogeneity between estimates for all these analyses. Analyses by subset (based on the main analysis) show highly significant ($P < 0.001$) variation by various factors:

Sex: Estimates are lower for males than for females or sexes combined.

Continent: Estimates are lower for North America than for Europe, Asia or elsewhere.

Publication period: Estimates are higher for the oldest (1984-1991) and newest (2010-2016) studies than for studies in intermediate periods.

Number of cases: Studies with fewer cases give higher estimates, consistent with the significant ($P < 0.001$) publication bias for the overall analysis.

Study type: Estimates are lower for prospective than for case-control or cross-sectional studies.

Spouse the index: Estimates are lower where the spouse is the index, and where the analysis is limited to married subjects.

Fatality: Estimates are lower when based on fatal cases.

Heart disease definition: Estimates are lower for IHD specifically than for other definitions.

Type of control: In case-control studies, estimates are lower where hospital/diseased controls rather than healthy controls, are used.

Source of diagnosis: Estimates are lower when diagnosis derives from death certificates or self-report than from medical data.

Definition of never smoker: Estimates are higher where the definition allowed “never smoking” subjects to smoke products other than cigarettes, or to have a limited smoking history.

Despite the heterogeneity, each RR estimate in Table 4 for each data subset exceeds 1.00, generally significantly so. Our analyses demonstrated 11 factors with highly significant ($P < 0.001$) heterogeneity by level, when considered one at a time. However, many were inter-correlated. To isolate the important factors, stepwise regression analysis was conducted (see Supplementary File 3). Only three of the 11 factors independently predicted heart disease risk at $P < 0.05$, with source of diagnosis introduced first into the model, then spouse the index, and then number of cases. While, for the factors remaining in the model, the direction of effect remained, the magnitude of variation between levels was slightly reduced from that shown in Table 4.

Further results for exposure at home

Table 3 also shows RRs for household exposure for five studies where separate results are available for both spousal and household exposure. Overall, there are 37 household exposure estimates from 22 studies, 10 showing a significant increase in risk, and none a significant decrease. The combined random-effects estimate is 1.19 (95%CI: 1.13-1.25). There is no marked heterogeneity between the estimates overall, and little indication of variation between males and females, continents, periods of publication or numbers of cases. Estimates do vary by study design ($P < 0.01$), being higher for case-control studies than other designs.

As shown in Table 5, 13 studies reported dose-response results for smoking by the spouse, 11 for smoking by household members, and one (study 47) for both. While only two studies providing dose-response data for spousal smoking reported a significant ($P < 0.05$) positive trend, nine did so for exposure to household members. These trend tests included the unexposed group. Had they excluded the unexposed group, they would have been significant for only one (study 26). There were no significant negative trends.

Other exposure indices

Table 6 presents results for ETS exposure at work, in childhood, a combined index of total exposure, and a biochemical index of exposure. For these four indices,

Table 2 Potential confounding variables adjusted for and definition of never smoker

Study No.	Ref. ¹	Variables adjusted for ²	Definition of never smokers ³
1	Hirayama ^[29]	Sex, age, marital status	Never cigarettes
2	Garland <i>et al</i> ^[30]	Sex, age, marital status, blood pressure, cholesterol, obesity	Never cigarettes
3	Lee <i>et al</i> ^[31]	Sex, age, marital status	Never NOS
4	Martin <i>et al</i> ^[32]	Sex, marital status, blood pressure, obesity, alcohol, diabetes, family history of heart disease, exercise	Never NOS
5	Svensden <i>et al</i> ^[33]	Sex, age, marital status, blood pressure, cholesterol, social class, obesity, alcohol	Never any product
6	Butler ^[34]	Sex, age, marital status	Never cigarettes
7	Palmer <i>et al</i> ^[35]	Sex, marital status	Never NOS
8	Hole <i>et al</i> ^[36]	Sex, age, blood pressure, cholesterol, social class, obesity	Never NOS
9	Jackson ^[37]	Sex, age, social class, obesity, family history of heart disease	Never NOS
10	Sandler <i>et al</i> ^[38]	Sex, age, social class, personal history of heart disease	Never any product
11	Humble <i>et al</i> ^[39]	Sex, age, marital status, blood pressure, cholesterol, obesity	Never NOS
12	Dobson <i>et al</i> ^[40]	Sex, age, social class, obesity, personal history of heart disease	Never cigarettes
13	Gardiner <i>et al</i> ^[41]	Sex, age, hospital admission date	Never any product
14	La Vecchia <i>et al</i> ^[42]	Sex, age, marital status, blood pressure, cholesterol, social class, obesity, diabetes, family history of heart disease, coffee	Never NOS
15	Layard ^[25]	Sex, age, marital status, race	Never 100 cigarettes in lifetime
16	Le Vois <i>et al</i> ^[26] (CPS I)	Sex, age, marital status, race	Never NOS
17	Mannino <i>et al</i> ^[43]	Sex, age, social class, race, housing	Never NOS
18	Muscat <i>et al</i> ^[44]	Sex, age, blood pressure, social class, race	Never one cigarette, pipe or cigar per day for more than a year
19	Tunstall-Pedoe <i>et al</i> ^[45]	Age, blood pressure, cholesterol, housing	Never any product and cotinine < 17.5 mg/mL
20	Steenland <i>et al</i> ^[46]	Sex, age, marital status, blood pressure, social class, obesity, alcohol, diabetes, exercise, personal history of heart disease, occupation, oestrogen use, aspirin use, diuretic use and personal history of arthritis	Never any product daily for as long as a year (men), never cigarettes (women)
21	Janghorbani <i>et al</i> ^[47]	Sex, age, marital status	Never any product
22	Kawachi <i>et al</i> ^[48]	Sex, age, blood pressure, cholesterol, obesity, alcohol, diabetes, family history of heart disease, exercise, occupation, oestrogen use, oral contraceptive use, saturated fat intake, vitamin E intake, menopausal status and use of postmenopausal hormones	Never NOS
23	Ciruzzi <i>et al</i> ^[49]	Sex, age, blood pressure, cholesterol, social class, obesity, diabetes, family history of heart disease, exercise	Never NOS
24	McElduff <i>et al</i> ^[50]	Sex, age, social class, obesity, family history of heart disease	Never cigarettes or quit at least 10 yr ago, and not current other products
25	Spencer <i>et al</i> ^[51]	Sex, age	Never NOS
26	He <i>et al</i> ^[52]	Sex, age, blood pressure, cholesterol, family history of heart disease, personality type	Never NOS
27	Iribarren <i>et al</i> ^[53]	Sex, age, marital status, cholesterol, social class, obesity, alcohol, diabetes, race, exercise, personality type	Never any product
28	Rosenlund <i>et al</i> ^[54]	Sex, age, blood pressure, cholesterol, social class, obesity, diabetes, occupation	Never any product regularly for at least a year
29	Pitsavos <i>et al</i> ^[55]	Sex, age, blood pressure, cholesterol, obesity, alcohol, diabetes, exercise and family history of heart disease	Never cigarettes
30	Enstrom <i>et al</i> ^[27]	Sex, age, marital status, social class, obesity, race, exercise, housing, fruit or fruit juice intake and health status	Never any product ⁴
31	Chen <i>et al</i> ^[56]	Sex, age, blood pressure, cholesterol, social class, obesity, alcohol, family history of heart disease, employment status, dietary vitamin C and fibre	Never NOS and cotinine < 17.5 mg/mL
32	Nishtar <i>et al</i> ^[57]	Sex, age, matched pair (conditional logistic regression was used)	Never NOS
33	Whincup <i>et al</i> ^[58]	Sex, age, blood pressure, cholesterol, social class, obesity, alcohol, diabetes, exercise, personal history of heart disease, town of residence, FEV ₁ , height, triglycerides and white cell count	Never any product and cotinine < 14.1 mg/mL
34	McGhee <i>et al</i> ^[59]	Sex, age, marital status, social class	Never NOS
35	Qureshi <i>et al</i> ^[60]	Sex, age, marital status, blood pressure, cholesterol, obesity, alcohol, diabetes, race	Never NOS
36	Hedblad <i>et al</i> ^[61]	Sex, blood pressure, cholesterol, obesity, alcohol, diabetes, exercise, personal history of heart disease, triglycerides and FEV ₁	Never one cigarette per day
37	Stranges <i>et al</i> ^[62]	Sex, blood pressure, cholesterol, social class, obesity, alcohol, diabetes, race, exercise	Never 100 cigarettes in lifetime
38	Teo <i>et al</i> ^[63]	Sex, age, alcohol, exercise, region, consumption of fruits and vegetables	Never any product regularly
39	Wen <i>et al</i> ^[64]	Sex, age, social class, obesity, exercise, occupation, intake of meats, vegetables and fruit	Never NOS
40	Eisner <i>et al</i> ^[65]	Sex, age, marital status, social class	Never cigarettes or quit at least 20 yr ago, and < 10 pack-years
41, 42	Hill <i>et al</i> ^[66]	Sex, age, marital status, social class, race, occupation	Never NOS

43	He <i>et al</i> ^[67]	Sex, age, marital status, blood pressure, cholesterol, social class, obesity, alcohol, diabetes, family history of heart disease, exercise, triglycerides, family history of stroke	Never 100 cigarettes in lifetime
44	Sulo <i>et al</i> ^[68]	Sex, age, blood pressure, social class, obesity, diabetes, family history of heart disease, race, exercise, occupation, financial loss in pyramid schemes, emigration of spouse and/or offspring, religious observance	Never cigarettes
45	Vozoris <i>et al</i> ^[69]	Sex, age, social class, province, immigration status, presence of children younger than 12 yr in household	Never cigarettes
46	Ding <i>et al</i> ^[70]	Sex, age, blood pressure, cholesterol, social class, alcohol, diabetes, family history of heart disease, exercise, oestrogen use, history of stroke, history of gout	Never NOS
47	Gallo <i>et al</i> ^[71]	Sex, age, social class, obesity, exercise, study centre	Never NOS
48	Hamer <i>et al</i> ^[72]	Sex, age, blood pressure, cholesterol, social class, exercise, personality type, survey location, log C-reactive protein, fibrinogen	Never NOS
49	Jefferis <i>et al</i> ^[73]	Sex, age, blood pressure, cholesterol, social class, obesity, alcohol, diabetes, exercise, region, triglycerides, FEV ₁ , C-reactive protein, interleukin 6, white cell count	Never any product or quit at least 5 yr ago, and cotinine < 15 mg/mL
50	Peinemann <i>et al</i> ^[74]	None	Never NOS
51	Chen ^[75]	None	Never cigarettes
52	He <i>et al</i> ^[76]	Sex, age, marital status, blood pressure, cholesterol, social class, obesity, alcohol, occupation, triglycerides	Never 100 cigarettes in lifetime
53	Clark <i>et al</i> ^[77]	Sex, age, social class, obesity, dialect, dietary fibre intake	Never NOS
54	Iversen <i>et al</i> ^[78]	Sex, age, blood pressure, cholesterol, obesity, exercise, living with a smoker (for analysis of hours spent in smoke-filled rooms), hours spent in smoke-filled rooms (for analysis of living with a smoker)	Never cigarettes
55	Kastorini <i>et al</i> ^[79]	Sex, age, blood pressure, cholesterol, obesity, diabetes, family history of heart disease, exercise, personality type, Mediterranean Diet Score	Never one cigarette a day
56	Rostron ^[80]	Sex, age, race, social class, alcohol, blood pressure, obesity, personal history of heart disease	Never 100 cigarettes in lifetime
57	Batty <i>et al</i> ^[81]	Sex, age, social class, alcohol, diabetes, exercise, personal history of heart disease, personal history of cancer	Never NOS
58	Shiue ^[82]	Sex, age, race, social class, alcohol, survey weighting, exercise, blood pressure, obesity	Never any product

¹First author of paper; ²In some cases similar adjustment variables have been considered under one name. Thus blood pressure includes hypertension; social class includes education and income; obesity includes weight; family history of heart disease includes family history of hypertension; and housing includes urban-rural; ³Never any product: Never smoked cigarettes, pipes or cigars; Never NOS: Never smoked, product unspecified; ⁴Questions on pipe and cigar smoking were asked at baseline, but not at the follow-up interviews.

results are available from, respectively, 14, 4, 24 and 8 studies. For some studies the estimates for total exposure are the same as those for the main exposure index. The RRs are supported by Figures 2-5, while Table 7 presents results of meta-analyses, and Table 8 the dose-response data. Again, fuller details of meta-analyses are given in Supplementary File 2. Supplementary File 2 also includes results for spousal smoking specifically.

For workplace exposure, there were 22 estimates, with only one showing a significant increase, the combined estimate of 1.08 (95%CI: 0.99-1.19) being almost significantly raised. There was no evidence of heterogeneity, and little evidence of variation by any factor considered.

For childhood exposure, one of the seven estimates showed a significant increase in risk. However, the combined estimate of 1.12 (95%CI: 0.95-1.31) was not significant.

For total exposure, the 33 estimates showed clear heterogeneity ($P < 0.001$), 11 estimates showing a significant ($P < 0.05$) positive association, and one a significant negative association. However, there was a clear preponderance of positive associations, with the random-effects estimate 1.23 (95%CI: 1.12-1.35). Subgroup analyses showed higher estimates for Asia;

for case-control studies, and for females and sexes-combined.

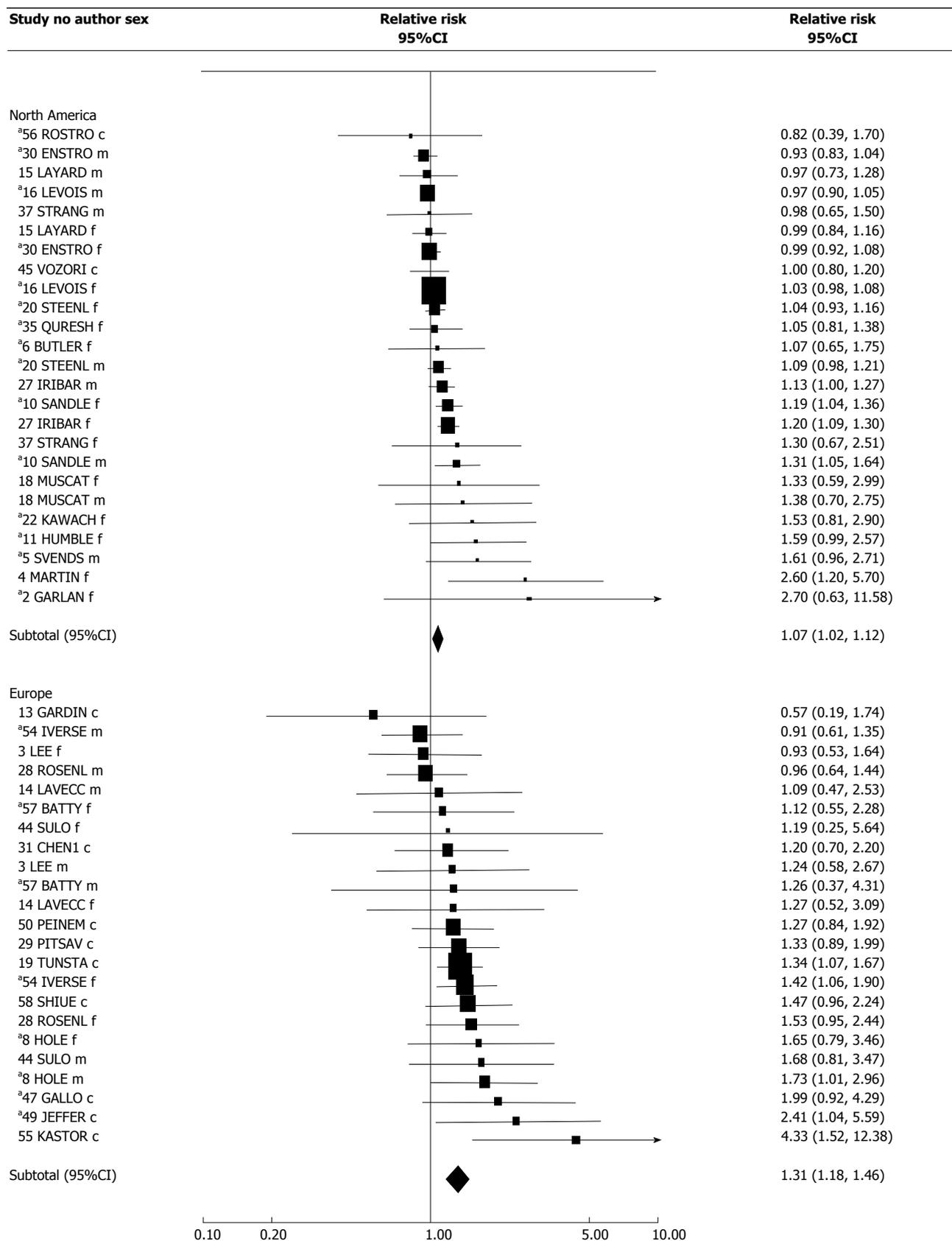
Of nine estimates for biomarker based exposure indices, all were cotinine-based apart from one based on COHb. There was some indication of heterogeneity ($P < 0.1$), the random-effects estimate of 1.15 (95%CI: 0.94-1.40) showing no clear association.

Table 8 presents dose-response data for these exposure indices. For studies reporting dose-response results, significant positive trends were seen (for at least one index) in 12 of 17 studies for total exposure, 3 of 8 studies for biomarker-based exposure, 1 of 5 studies for workplace exposure, and 1 of 2 studies for childhood exposure. No significant negative trends were seen.

Twelve studies presented RR estimates and/or dose-response results for one or more other exposure indices (Supplementary File 4). These results relate to many different indices, and are somewhat variable, with clear evidence of an increase being seen for studies 29 and 32, but a number of other studies showing no relationship with the indices studied.

DISCUSSION

Based on 58 studies, we present meta-analyses relating



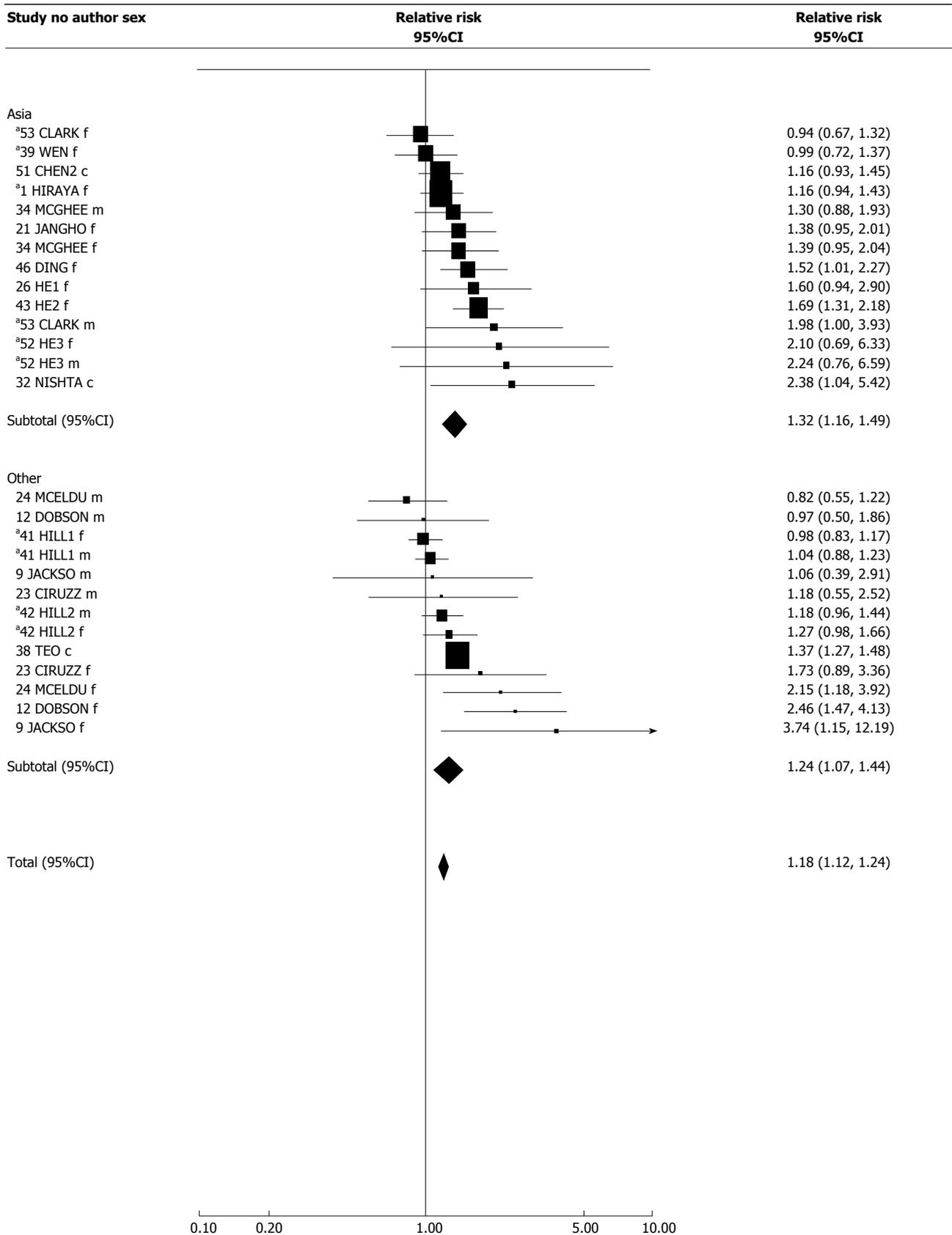


Figure 1 Forest plot for the main index, by continent. Estimates of the RR and its 95%CI are shown separately by continent, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). Arrows warn if the CI goes outside the range of the plot. Random-effects estimates (RRs and their 95%CIs) are shown for each continent and overall, represented graphically by a diamond whose width indicates the confidence interval. ^aProspective study.

Table 3 Heart disease relative risk estimates used in the main analysis for spouse ever smoked (or nearest equivalent) and in sensitivity analyses for spouse a current smoker, as well as additional results for household exposure

Study No. ¹	Author ²	Sex	Exposure index		Fatality ⁵	Relative risk (95%CI) ⁶
			Source ³	Timing ⁴		
Results used in the main analysis ⁷						
1	Hirayama ^[29]	F	S	E	F	1.16 (0.94-1.43) ⁸
2	Garland <i>et al</i> ^[30]	F	S	E	F	2.70 (0.63-11.58)
3	Lee <i>et al</i> ^[31]	M	S	M	NF	1.24 (0.58-2.67)
		F	S	M	NF	0.93 (0.53-1.64)
4	Martin <i>et al</i> ^[32]	F	S	E	NF	2.60 (1.20-5.70) ⁹
5	Svendsen <i>et al</i> ^[33]	M	S	C	F + NF	1.61 (0.96-2.71)
6	Butler ^[34]	F	S	E	F	1.07 (0.65-1.75)
7	Palmer <i>et al</i> ^[35]	F	S	E	NF	1.20
8	Hole <i>et al</i> ^[36]	M	H ¹⁰	E	F	1.73 (1.01-2.96) ¹¹
		F	H ¹⁰	E	F	1.65 (0.79-3.46) ¹¹
9	Jackson ^[37]	M	H	C	F + NF	1.06 (0.39-2.91)
		F	H	C	F + NF	3.74 (1.15-12.19)
10	Sandler <i>et al</i> ^[38]	M	H	C	F	1.31 (1.05-1.64)
		F	H	C	F	1.19 (1.04-1.36)
11	Humble <i>et al</i> ^[39]	F	S	C(N)	F	1.59 (0.99-2.57)
12	Dobson <i>et al</i> ^[40]	M	H	C	F + NF	0.97 (0.50-1.86)
		F	H	C	F + NF	2.46 (1.47-4.13)
13	Gardiner <i>et al</i> ^[41]	M + F	S	M	F + NF	0.57 (0.19-1.74)
14	La Vecchia <i>et al</i> ^[42]	M	S	E	NF	1.09 (0.47-2.53)
		F	S	E	NF	1.27 (0.52-3.09)
15	Layard ^[25]	M	S	E	F	0.97 (0.73-1.28)
		F	S	E	F	0.99 (0.84-1.16)
16	Le Vois <i>et al</i> ^[26] (CPS I)	M	S	E	F	0.97 (0.90-1.05)
		F	S	E	F	1.03 (0.98-1.08)
17	Mannino <i>et al</i> ^[43]	M + F	H	C	NF	1.12
18	Muscat <i>et al</i> ^[44]	M	S	E	NF	1.38 (0.70-2.75)
		F	S	E	NF	1.33 (0.59-2.99)
19	Tunstall-Pedoe <i>et al</i> ^[45]	M + F	T	C	NF	1.34 (1.07-1.67)
20	Steenland <i>et al</i> ^[46]	M	S	E	F	1.09 (0.98-1.21)
		F	S	E	F	1.04 (0.93-1.16)
21	Janghorbani <i>et al</i> ^[47]	F	S	E	NF	1.38 (0.95-2.01)
22	Kawachi <i>et al</i> ^[48]	F	H	C	F + NF	1.53 (0.81-2.90) ⁹
23	Ciruzzi <i>et al</i> ^[49]	M	S	C	NF	1.18 (0.55-2.52)
		F	S	C	NF	1.73 (0.89-3.36)
24	McElduff <i>et al</i> ^[50]	M	T	C	F + NF	0.82 (0.55-1.22)
		F	T	C	F + NF	2.15 (1.18-3.92)
25	Spencer <i>et al</i> ^[51]	M	H	E	NF	No significant association
26	He <i>et al</i> ^[52]	F	S	E	NF	1.60 (0.94-2.90)
27	Iribarren <i>et al</i> ^[53]	M	H	C	NF	1.13 (1.00-1.27)
		F	H	C	NF	1.20 (1.09-1.30)
28	Rosenlund <i>et al</i> ^[54]	M	S	E	NF	0.96 (0.64-1.44)
		F	S	E	NF	1.53 (0.95-2.44)
29	Pitsavos <i>et al</i> ^[55]	M + F	H	C	NF	1.33 (0.89-1.99)
30	Enstrom <i>et al</i> ^[27]	M	S	E	F	0.93 (0.83-1.04)
		F	S	E	F	0.99 (0.92-1.08)
31	Chen <i>et al</i> ^[56]	M + F	H	C	NF	1.20 (0.70-2.20)
32	Nishtar <i>et al</i> ^[57]	M + F	S	E	NF	2.38 (1.04-5.42)
34	McGhee <i>et al</i> ^[59]	M	H	P	F	1.30 (0.88-1.93)
		F	H	P	F	1.39 (0.95-2.04)
35	Qureshi <i>et al</i> ^[60]	F	S	E	F + NF	1.05 (0.81-1.38) ¹²
37	Stranges <i>et al</i> ^[62]	M	H	E	NF	0.98 (0.65-1.50)
		F	H	E	NF	1.30 (0.67-2.51)
38	Teo <i>et al</i> ^[63]	M + F	T	C	NF	1.37 (1.27-1.48)
39	Wen <i>et al</i> ^[64]	F	S	M	F	0.99 (0.72-1.37) ¹³
41	Hill <i>et al</i> ^[66]	M	H	C	F	1.04 (0.88-1.23)
		F	H	C	F	0.98 (0.83-1.17)
42	Hill <i>et al</i> ^[66]	M	H	C	F	1.18 (0.96-1.44)
		F	H	C	F	1.27 (0.98-1.66)
43	He <i>et al</i> ^[67]	F	T	T	NF	1.69 (1.31-2.18)
44	Sulo <i>et al</i> ^[68]	M	S	C	NF	1.68 (0.81-3.47)
		F	S	C	NF	1.19 (0.25-5.64)
45	Vozoris <i>et al</i> ^[69]	M + F	T	C	NF	1.00 (0.80-1.20)
46	Ding <i>et al</i> ^[70]	F	H	E	NF	1.52 (1.01-2.27)
47	Gallo <i>et al</i> ^[71]	M + F	S	C	F	1.99 (0.92-4.29) ¹⁴
49	Jefferis <i>et al</i> ^[73]	M + F	S	C	F + NF	2.41 (1.04-5.59)

50	Peinemann <i>et al</i> ^[74]	M + F	T	C	NF	1.27 (0.84-1.92)
51	Chen ^[75]	M + F	T	E	NF	1.16 (0.93-1.45) ¹⁵
52	He <i>et al</i> ^[76]	M	T	E	F	2.24 (0.76-6.59)
		F	T	E	F	2.10 (0.69-6.33)
53	Clark <i>et al</i> ^[77]	M	H	C	F	1.98 (1.00-3.93)
		F	H	C	F	0.94 (0.67-1.32)
54	Iversen <i>et al</i> ^[78]	M	H	A	F + NF	0.91 (0.61-1.35)
		F	H	A	F + NF	1.42 (1.06-1.90)
55	Kastorini <i>et al</i> ^[79]	M + F	T	E	NF	4.33 (1.52-12.38)
56	Rostron ^[80]	M + F	H	C	F	0.82 (0.39-1.70)
57	Batty <i>et al</i> ^[81]	M	H	C	F	1.26 (0.37-4.31)
		F	H	C	F	1.12 (0.55-2.28)
58	Shiue ^[82]	M + F	T	C	NF	1.47 (0.96-2.24)
Alternative result used in the analysis of spouse a current smoker						
2	Garland <i>et al</i> ^[30]	F	S	C(N)	F	2.25 (0.32-15.74)
4	Martin <i>et al</i> ^[32]	F	S	C	NF	3.40
6	Butler ^[34]	F	S	C(N)	F	1.40 (0.51-3.84)
14	La Vecchia <i>et al</i> ^[42]	M	S	C(N)	NF	1.09 (0.39-3.01)
		F	S	C(N)	NF	1.36 (0.46-4.05)
16	Le Vois <i>et al</i> ^[26] (CPS I)	M	S	C(N)	F	0.98 (0.91-1.06)
		F	S	C(N)	F	1.04 (0.99-1.09)
20	Steenland <i>et al</i> ^[46]	M	S	C(N)	F	1.22 (1.07-1.40)
		F	S	C(N)	F	1.10 (0.96-1.27)
28	Rosenlund <i>et al</i> ^[54]	M	S	C(N)	NF	0.98 (0.57-1.69)
		F	S	C(N)	NF	2.59 (1.27-5.29)
30	Enstrom <i>et al</i> ^[27]	M	S	C(N)	F	0.92 (0.80-1.05)
		F	S	C(N)	F	0.97 (0.89-1.06)
37	Stranges <i>et al</i> ^[62]	M	H	C	NF	0.71 (0.40-1.23)
		F	H	C	NF	0.94 (0.48-1.82)
39	Wen <i>et al</i> ^[64]	F	S	C	F	1.19 (0.84-1.67) ¹⁶
Additional household exposure results						
18	Muscat <i>et al</i> ^[44]	M	H	E	NF	1.40 (0.70-2.81)
		F	H	E	NF	1.55 (0.55-4.37)
20	Steenland <i>et al</i> ^[46]	M	H	C(N)	F	1.15 (1.01-1.32)
		F	H	C(N)	F	1.07 (0.98-1.17)
21	Janghorbani <i>et al</i> ^[47]	F	H	E	NF	1.34 (0.94-1.91)
23	Ciruzzi <i>et al</i> ^[49]	M	H ¹⁷	C	NF	1.89 (1.13-3.18)
		F	H ¹⁷	C	NF	1.54 (0.95-2.51)
47	Gallo <i>et al</i> ^[71]	M + F	H	C	F	1.31 (0.83-2.08) ¹⁸

¹Study 40 omitted as results only available per 10 years of living with a smoker. Studies 33, 36 and 48 omitted as they only provide results for a biochemical index of ETS exposure; ²First author of paper; ³S: Spouse (or partner), H: Household member (or exposure at home), T: Total; ⁴E: Ever exposed (compared to never exposed) or unspecified; M: During marriage; C(N): Current exposure (compared to never exposed); C: Current exposure (compared to non-current exposure), P: In the past, T: In the last 10 years, A: In adulthood; ⁵F: Fatal; NF: Non-fatal; F + NF indicates combined results were analysed; ⁶Relative risks are adjusted for covariates if adjusted data are available. Those without 95%CI are not used in the meta-analyses; ⁷Except where lacking a 95%CI, as in studies 7, 17 and 25; ⁸Adjusted for the age of the husband. Alternative estimates^[115] were very similar; ⁹Estimates given by Wells^[11]; ¹⁰Cohabitant(s) age 45-64 also attending screening; ¹¹Estimates given by Wells^[116]; ¹²Result for CVD - Stroke. Result also available for CVD: 1.00 (0.81-1.24); ¹³Result for CVD - Stroke. Result also available for CVD: 1.18 (0.92-1.51); ¹⁴Result for CVD. Result for IHD shown in the "household" section of this table; ¹⁵Result for IHD. Result also available for myocardial infarction: 0.93 (0.66-1.31); ¹⁶Result for CVD - Stroke. Results also available for CVD: 1.37 (1.06-1.78); ¹⁷Smoking by close relatives (although not necessarily living in same home); ¹⁸Result for IHD. Result also available for CVD: 1.82 (1.06-3.12). ETS: Environmental tobacco smoke; CVD: Cardiovascular disease; IHD: Ischaemic heart disease; CPS: Cancer Prevention Studies.

ETS exposure to heart disease risk in never smokers. Using an exposure index as equivalent as possible to having a spouse who ever smoked, a random-effects meta-analysis gave a significantly increased RR of 1.18 (95%CI: 1.12-1.24) based on 75 RR estimates. Positive associations, not all significant at $P < 0.05$, were also noted with spousal exposure specifically (1.10, 1.04-1.17, $n = 34$), household exposure (1.19, 1.13-1.25, $n = 37$), workplace exposure (1.08, 0.99-1.19, $n = 22$), childhood exposure (1.12, 0.95-1.31, $n = 22$), and total exposure (1.23, 1.12-1.35, $n = 33$). The overall estimate was also elevated for a biomarker-based index (1.15, 0.94-1.40, $n = 9$). There was also evidence of dose-response.

While the relationship of smoking with heart

disease^[83] suggests some effect may be evident for ETS, exposure to smoke constituents from ETS is much less than from active smoking. For example, studies of cotinine indicate relative exposure of ETS compared to smoking of 0.6% to 0.4%^[84-86], while studies of particulate matter suggest a lower factor, $< 0.02\%$ ^[87-95]. In interpreting our meta-analyses, one must note the clear heterogeneity between the RR estimates. Thus, for the main exposure index, estimates were higher for females, United States studies, and small studies, and smaller for prospective studies and for fatal cases, and varied by definition of exposure and source of diagnosis. Although these factors are not independent, and the variations may reflect characteristics of studies

Table 4 Meta-analyses of heart disease¹ risk among never smokers in relation to ever smoking by the spouse (or nearest equivalent)

Subgroup	n ³	Fixed-effect	Random-effects	Publication bias	Heterogeneity ²		
		Relative risk (95%CI)	Relative risk (95%CI)	P ⁴ value	χ ²	DF ⁵	P ⁶ value
Main analyses ⁷							
All	75	1.10 (1.08-1.13)	1.18 (1.12-1.24)	< 0.001	176.45	74	< 0.001
By sex							
Combined	14	1.32 (1.24-1.40)	1.30 (1.14-1.47)	NS	23.54	13	< 0.05
Males	25	1.04 (1.00-1.09)	1.07 (1.01-1.15)	< 0.05	32.90	24	NS
Females	36	1.09 (1.06-1.12)	1.20 (1.12-1.29)	< 0.001	81.04	35	< 0.001
			Between sexes		38.98	2	< 0.001
By continent							
North America	25	1.05 (1.02-1.08)	1.07 (1.02-1.12)	< 0.05	45.67	24	< 0.01
Europe	23	1.31 (1.18-1.46)	1.31 (1.18-1.46)	NS	20.63	22	NS
Asia	14	1.29 (1.17-1.42)	1.32 (1.16-1.49)	< 0.05	18.94	13	NS
Other	13	1.26 (1.19-1.33)	1.24 (1.07-1.44)	NS	37.12	12	< 0.001
			Between continents		54.09	3	< 0.001
By publication period							
1984-1991	16	1.28 (1.17-1.39)	1.35 (1.18-1.54)	< 0.05	21.29	15	NS
1992-1998	18	1.04 (1.00-1.07)	1.06 (1.00-1.12)	< 0.1	24.86	17	< 0.1
1999-2005	13	1.08 (1.03-1.13)	1.13 (1.02-1.24)	< 0.1	28.86	12	< 0.01
2006-2009	13	1.24 (1.17-1.31)	1.19 (1.06-1.34)	NS	32.96	12	< 0.001
2010-2016	15	1.26 (1.11-1.41)	1.31 (1.11-1.55)	< 0.05	21.07	14	< 0.1
			Between periods		47.42	4	< 0.001
By number of heart disease cases ⁸							
1-99	13	1.62 (1.32-1.99)	1.66 (1.30-2.11)	NS	14.83	12	NS
100-199	14	1.33 (1.11-1.58)	1.33 (1.11-1.58)	NS	5.78	13	NS
200-999	30	1.26 (1.17-1.35)	1.27 (1.16-1.39)	NS	44.09	29	< 0.05
1000+	18	1.08 (1.05-1.10)	1.08 (1.02-1.15)	NS	76.70	17	< 0.001
			Between numbers		35.06	3	< 0.001
By study design							
Case-control	32	1.29 (1.21-1.36)	1.28 (1.15-1.42)	NS	52.18	31	< 0.05
Prospective	33	1.04 (1.01-1.07)	1.09 (1.03-1.14)	< 0.001	55.43	32	< 0.01
Cross-sectional	10	1.20 (1.14-1.28)	1.24 (1.12-1.37)	NS	16.78	9	< 0.1
			Between types		52.06	2	< 0.001
By number of confounders considered in the study							
0-2	15	1.03 (0.99-1.07)	1.05 (0.92-1.12)	< 0.1	17.51	14	NS
3-4	10	1.27 (1.16-1.39)	1.32 (1.13-1.55)	NS	16.65	9	< 0.1
5-9	38	1.13 (1.09-1.18)	1.19 (1.09-1.30)	< 0.05	94.55	37	< 0.001
10+	12	1.16 (1.10-1.22)	1.21 (1.10-1.32)	< 0.05	21.01	11	< 0.05
			Between groups		26.72	3	< 0.01
By results available in the study on dose-response							
No	24	1.15 (1.08-1.22)	1.19 (1.08-1.32)	< 0.05	44.81	23	< 0.01
Yes	51	1.10 (1.07-1.12)	1.18 (1.11-1.25)	< 0.01	129.74	50	< 0.001
			Between groups		1.90	1	NS
By spouse the index							
Yes	34	1.03 (1.00-1.06)	1.06 (1.01-1.12)	< 0.001	47.62	33	< 0.05
No	41	1.23 (1.19-1.28)	1.24 (1.16-1.32)	NS	72.59	40	< 0.01
			Between groups		56.24	1	< 0.001
Spouse the index, by whether unmarried subjects were excluded							
Yes	23	1.02 (0.99-1.05)	1.03 (0.99-1.07)	< 0.05	27.88	22	NS
No	11	1.30 (1.10-1.54)	1.35 (1.11-1.63)	< 0.01	12.00	10	NS
			Between groups		7.74	1	< 0.01
By heart disease fatality considered							
Fatal	31	1.04 (1.01-1.07)	1.07 (1.02-1.12)	< 0.001	46.74	30	< 0.05
Non-fatal	31	1.27 (1.22-1.33)	1.27 (1.19-1.36)	NS	39.58	30	NS
Both	13	1.25 (1.10-1.43)	1.34 (1.06-1.68)	NS	28.43	12	< 0.01
			Between groups		61.70	2	< 0.001
By heart disease definition							
IHD	32	1.06 (1.03-1.11)	1.12 (1.05-1.19)	< 0.001	56.92	31	< 0.01
MI	18	1.34 (1.25-1.43)	1.29 (1.14-1.46)	NS	23.10	17	NS
Other/Mixed	25	1.08 (1.05-1.12)	1.20 (1.10-1.30)	< 0.001	58.29	24	< 0.001
			Between definitions		38.14	2	< 0.001
By use of biomarker data to exclude smokers							
Yes	6	1.30 (1.08-1.57)	1.30 (1.08-1.57)	NS	3.89	5	NS
No	69	1.10 (1.08-1.13)	1.18 (1.12-1.24)	< 0.001	169.45	68	< 0.001
			Between groups		3.12	1	< 0.1
By any use of proxy respondents							
Yes	11	1.10 (0.99-1.23)	1.23 (0.98-1.53)	NS	26.38	10	< 0.01
No	64	1.10 (1.08-1.13)	1.18 (1.12-1.24)	< 0.001	150.07	63	< 0.001
			Between groups		0.00	1	NS

By type of control							
Healthy	15	1.30 (1.13-1.50)	1.38 (1.12-1.70)	< 0.1	27.67	14	< 0.05
Diseased/hospital	15	1.12 (1.01-1.24)	1.14 (1.01-1.28)	< 0.1	14.72	14	NS
Both	2	1.37 (1.27-1.48)	1.37 (1.27-1.48)	NC	0.29	1	NS
Prospective/cross-sectional	43	1.07 (1.05-1.10)	1.13 (1.08-1.19)	< 0.001	91.01	42	< 0.001
			Between types		42.78	3	< 0.001
			Between types, excluding prospective/cross-sectional		9.51	2	< 0.01
By source of diagnosis							
Death certificate only	27	1.04 (1.01-1.07)	1.06 (1.02-1.11)	< 0.01	41.57	26	< 0.05
Medical data used	41	1.35 (1.28-1.43)	1.34 (1.23-1.46)	NS	51.49	40	NS
Self-report only	7	1.17 (1.10-1.24)	1.17 (1.07-1.27)	NS	8.11	6	NS
			Between sources		75.29	2	< 0.001
By definition of never smoker							
Never any product	11	1.10 (1.05-1.15)	1.15 (1.05-1.27)	NS	32.42	10	< 0.001
Never, product unstated	33	1.05 (1.02-1.09)	1.15 (1.07-1.24)	< 0.001	49.99	32	< 0.05
Never cigarettes	12	1.17 (1.06-1.30)	1.21 (1.05-1.38)	NS	16.54	11	NS
Other	19	1.20 (1.14-1.25)	1.21 (1.07-1.37)	NS	57.89	18	< 0.001
			Between definitions		19.62	3	< 0.001
Sensitivity analyses							
Preferring unadjusted to adjusted estimates	75	1.06 (1.04-1.08)	1.16 (1.09-1.24)	< 0.01	321.31	74	< 0.001
Preferring current to ever exposure	75	1.12 (1.09-1.14)	1.19 (1.13-1.26)	< 0.001	176.96	74	< 0.001
Excluding studies 15 and 16	71	1.16 (1.12-1.19)	1.21 (1.15-1.28)	< 0.01	144.97	70	< 0.001
Excluding study 30	73	1.12 (1.10-1.15)	1.20 (1.14-1.26)	< 0.001	158.21	72	< 0.001
Excluding studies 15, 16 and 30	69	1.20 (1.17-1.24)	1.23 (1.17-1.29)	< 0.05	109.86	68	< 0.001

¹Nearest equivalent to IHD as shown in Tables 1 and 3; ²Heterogeneity relates to variation between studies within subgroup, except for results given in italics which relate to heterogeneity between subgroups; ³N: Number of estimates in meta-analysis; ⁴Egger test *P* expressed as < 0.001, < 0.01, < 0.05, < 0.1 or NS (*P* ≥ 0.1). NC indicates not calculable as too few data points; ⁵DF: Degrees of freedom; ⁶Expressed as < 0.001, < 0.01, < 0.05, < 0.1 or NS (*P* ≥ 0.1); ⁷Relative risks are adjusted for covariates if adjusted data are available, with estimates for ever exposure preferred to those for current exposure where there is choice; ⁸Number of cases was estimated for Nishtar^[57] (as category 1-99) and for Rostron^[80] (as category 100-199). MI: Myocardial infarction.

with a large weight, they do add to the difficulties in interpreting the overall estimate.

Below, we comment on various aspects of the findings and discuss potential sources of bias.

Study size and publication bias

For the main exposure index, there was clear publication bias (*P* < 0.001), RRs from smaller studies (more likely not to be published if finding no association) being much greater than from larger studies. Thus, for studies of > 1000 cases of heart disease, the RR was 1.08 (95%CI: 1.02-1.15, *n* = 18) while for studies of < 100 cases it was 1.66 (1.30-2.11, *n* = 13). This variation by study size explains why the random-effects estimate (1.18, 1.12-1.24) was higher than the fixed-effect estimate (1.10, 1.08-1.13), as small studies contribute relatively more to random-effects analyses. The random-effects estimate may be an overestimate, due to publication bias.

Definition of never smoker

Some studies clarified that never smoking related to never smoking any product, and others that never smoking related only to cigarettes. However, many studies merely stated the subjects were never smokers. The distinction is more important in countries where smoking of other products is more common. Some studies also made it clear that the definition allowed inclusion of those with a limited history of smoking, and a few rejected individuals with cotinine levels typical of current smokers. However, the estimated RR for the

main index varied little depending on the definition.

Misclassification of never smoking status

No study attempted to determine whether self-reported never smokers had in fact smoked previously. However, as noted above and in Table 2, a few studies excluded those with cotinine levels indicative of current smoking. In our recent review of ETS and lung cancer^[96], we presented analyses demonstrating that correction for misclassification bias substantially reduced the estimated RR for husband's smoking. We did not attempt such correction here, partly because the extent of bias depends on the magnitude of the active smoking RR, which is much lower for heart disease than for lung cancer. However, we are aware of a study^[97] which reported particularly high heart disease mortality among smokers who deny smoking, which, if confirmed, suggests misclassification bias might be of some relevance.

Errors in determining ETS exposure

While random errors in determining ETS exposure will tend to underestimate any association with heart disease, errors may not be random. Thus, studies of case-control or cross-sectional design, are subject to recall bias if subjects with heart disease tend to overestimate their exposure relative to those without heart disease. Only two studies^[45,56] used biomarker data to try to avoid recall bias. Some support for the existence of recall bias arises from the RRs for the main index being higher for case-control and cross-sectional studies than for prospective studies.

Table 5 Dose-response evidence for heart disease among never smokers in relation to smoking by the spouse or household members in adulthood

Study No.	Ref. ¹	Sex	Exposure grouping	Relative risks by grouping ²	Significance (trend) ³
Smoking by the spouse					
1	Hirayama ^[29]	F	0, 1-19, 20+ (cigs/d)	1.00, 1.10, 1.31 ⁴	+
5	Svensden <i>et al</i> ^[33]	M	0, 1-19, 20+ (cigs/d)	1.00, 1.20, 1.75	
14	La Vecchia <i>et al</i> ^[42]	M + F	0, 1-14, 15+ (cigs/d)	1.00, 1.13, 1.30	
15	Layard ^[25]	M	0, 1-14, 15-34, 35+ (cigs/d)	1.00, 0.76, 1.07, 0.92	
		F	0, 1-14, 15-34, 35+ (cigs/d)	1.00, 0.85, 1.15, 1.06	
16	Le Vois <i>et al</i> ^[26] (CPS I)	M	0, 1-19, 20-39, 40+ (cigs/d)	1.00, 0.99, 0.98, 0.72	
		F	0, 1-19, 20-39, 40+ (cigs/d)	1.00, 1.04, 1.06, 0.95	
20	Steenland <i>et al</i> ^[46]	M	0, 1-19, 20, 21+ (cigs/d)	1.00, 1.33, 1.17, 1.09	
		F	0, 1-19, 20, 21-39, 40+ (cigs/d)	1.00, 1.15, 1.07, 0.99, 1.04	
		M	0, 1-12, 13-21, 22-29, 30+ (year)	1.00, 1.14, 1.13, 1.14, 1.25	
		F	0, 1-14, 15-25, 26-33, 34+ (year)	1.00, 0.84, 0.99, 1.20, 1.20	
		M	0, 1-5, 6-14, 15-27, 28+ (pack year)	1.00, 1.25, 1.33, 1.13, 1.00	
		F	0, 1-12, 13-25, 26-33, 34+ (pack year)	1.00, 0.83, 1.12, 1.09, 1.26	
21	Janghorbani <i>et al</i> ^[47]	F	0, 1-30, 31+ (year)	1.00, 1.74, 0.85	
		F	0, 1-19, 20+ (cigs/d)	1.00, 1.76, 1.11	
		F	0, 1-10, 11+ (pack year)	1.00, 1.95, 1.17	
23	Ciruzzi <i>et al</i> ^[49]	F	0, 1-20, 21+ (cigs/d)	1.00, 0.82, 3.00	
26	He <i>et al</i> ^[52]	F	0, 1-10, 11-20, 21+ (cigs/d)	1.00, 0.93, 1.40, 3.20	+
			0-5, 6-15, 16-30, 31+ (year)	1.00, 0.80, 2.10, 2.30	+
			0, 1-399, 400-799, 800+ (cigs/day × year)	1.00, 1.20, 1.90, 3.60	+
28	Rosenlund <i>et al</i> ^[54]	M + F	0, 1-19, 20+ (cigs/d)	1.00, 1.02, 1.58	
		M + F	0, 1-32, 33+ (year)	1.00, 1.11, 1.25	
		M + F	0, 1-20, 21+ (pack-year)	1.00, 1.09, 1.33	
30	Enstrom <i>et al</i> ^[27]	M	0, 1-9, 10-19, 20, 21-39, 40+ (cigs/d)	1.00, 0.98, 0.82, 0.89, 1.13, 1.24	
		F	0, 1-9, 10-19, 20, 21-39, 40+ (cigs/d)	1.00, 1.03, 0.99, 1.02, 0.88, 0.80	
39	Wen <i>et al</i> ^[64]	F	0, < 8.8, 8.8-17.9, 18.0+ (pack-year)	1.00, 1.10, 1.12, 1.22 ⁵	
47	Gallo <i>et al</i> ^[71]	M + F	0, 0.5, 1.0, 1.5+ (packs/d)	1.00, 1.87, 1.89, 2.46 ⁶	
Smoking by household members					
8	Hole <i>et al</i> ^[36]	F	0, 1-14, 15+ (cigs/d)	1.00, 2.09, 4.12	+
9	Jackson ^[37]	M	None, low, high (exposure)	1.00, 1.30, 0.90	
		F	None, low, high (exposure)	1.00, 2.10, 7.50	+
18	Muscat <i>et al</i> ^[44]	M	None, 1-20, 21-30, 31+ (year)	1.0, 1.7, 1.5, 1.1	
		F	None, 1-20, 21-30, 31+ (year)	1.0, 2.0, 0.9, 1.7	
22	Kawachi <i>et al</i> ^[48]	F	None, occasional, regular	1.00, 1.19, 2.11	+
		F	< 1, 1-9, 10-19, 20-29, 30+ (year)	1.00, 1.19, 1.54, 1.11, 1.50	
27	Iribarren <i>et al</i> ^[53]	M	0, 1-9, 10-39, 40+ (h/wk)	1.00, 1.12, 1.26, 1.20	+
		F	0, 1-9, 10-39, 40+ (h/wk)	1.00, 1.21, 1.31, 1.36	+
29	Pitsavos <i>et al</i> ^[55]	M + F	0, 1-4, 5-9, 10-19, 20-29, 30-39, 40+ (years living with a regular smoker)	1.00, 1.07, 1.16, 1.39, 1.75, 2.20, 3.09	+
34	McGhee <i>et al</i> ^[59]	M + F	0, 1, 2+ (smokers in the home)	1.00, 1.26, 1.68	+
40	Eisner <i>et al</i> ^[65]	M + F	Per 10 years exposure	1.10	
46	Ding <i>et al</i> ^[70]	F	0, < 1, 1+ (packs/d)	1.00, 1.14, 1.69	+
			0, < 5, 5+, (year)	1.00, 1.26, 1.52	+
			0, < 4, 4+, (h/d)	1.00, 1.28, 1.82	+
			0, < 5, 5+, (pack-year)	1.00, 1.44, 1.53	+
			0, < 20, 20+ (h-year)	1.00, 1.22, 1.61	+
47	Gallo <i>et al</i> ^[71]	M + F	0, < 1, 1-2, 3+ (h/d)	1.00, 1.39, 2.08, 1.94 ⁶	+
54	Iversen <i>et al</i> ^[78]	M	0, < 10, 10-19, 20-29, 30+ (year)	1.00, 0.70, 1.20, 0.70, 1.10	
		F	0, < 10, 10-19, 20-29, 30+ (year)	1.00, 1.00, 1.40, 1.30, 1.60	+

¹First author of paper; ²Relative risks are adjusted for covariates if adjusted data are available; ³Significant ($P < 0.05$) positive (negative) trends are indicated by + (or -). Blank entries indicate non-significance. The trend test includes the unexposed group. Significant trends excluding the unexposed group are only evident for study 26 (all exposed indices); ⁴The 1-19 cigs/d group includes ex-smokers. Estimates are adjusted for the age of the husband. Alternative estimates, adjusted for the age of the subject are also given by Hirayama^[113]; ⁵Results for CVD. Not available for CVD - Stroke; ⁶Results for CVD. Not available for IHD. M: Male; F: Female; CVD: Cardiovascular disease; IHD: Ischaemic (coronary) heart disease.

Weaknesses in prospective studies

While prospective studies avoid recall bias, they may underestimate any true association if ETS exposure is determined only at baseline, and not updated. This was the case for the great majority of such studies.

Thus, RRs for the index “spouse current smoker” may be underestimated by inclusion of some spouses who give up after baseline. However, the similarity of the RR estimates preferring current to ever spousal exposure and preferring ever to current spousal exposure sug-

Table 6 Relative risk of heart disease among never smokers in relation to four other indices of environmental tobacco smoke exposure

Study No.	Ref. ¹	Sex	Exposure index ²	Relative risk (95%CI) ³	Exposure description
3	Lee <i>et al</i> ^[31]	M	Workplace	0.66 (0.26-1.66)	
		F	Workplace	0.69 (0.26-1.87)	
		M	Total	0.39 (0.17-0.90)	Home, work, travel, leisure
		F	Total	0.52 (0.24-1.09)	Home, work, travel, leisure
5	Svendsen <i>et al</i> ^[33]	M	Workplace	1.40 (0.80-2.50)	
		M	Total	1.17 (0.62-1.19)	Spouse, work
9	Jackson <i>et al</i> ^[37]	M	Workplace	1.80 (0.94-3.46)	
		F	Workplace	1.55 (0.48-5.03)	
		M	Total	1.14 (0.76-1.70)	Home, work
		F	Total	1.56 (0.76-3.20)	Home, work
12	Dobson <i>et al</i> ^[40]	M	Workplace	0.95 (0.51-1.78)	
		F	Workplace	0.66 (0.17-2.62)	
		M	Total	1.09 (0.72-1.63)	Home, work
		F	Total	2.24 (1.28-3.91)	Home, work
18	Muscat <i>et al</i> ^[44]	M	Workplace	1.20 (0.60-2.20)	
		F	Workplace	1.00 (0.40-2.50)	
		M	Childhood	0.79 (0.39-1.63)	Mother, father, other relatives
		F	Childhood	0.72 (0.30-1.72)	Mother, father, other relatives
19	Tunstall-Pedoe <i>et al</i> ^[45]	M + F	Total	1.34 (1.07-1.67)	Exposure to tobacco smoke from someone else in the previous three days
		M + F	Biomarker	1.13 (0.93-1.38)	Serum cotinine
20	Steenland <i>et al</i> ^[46]	M	Workplace	1.03 (0.89-1.19)	
		F	Workplace	1.06 (0.84-1.34)	
22	Kawachi <i>et al</i> ^[48]	F	Workplace	1.68 (0.81-3.47)	
		F	Total	1.71 (1.03-2.84)	Home, work
24	McElduff <i>et al</i> ^[50]	M	Total	0.82 (0.55-1.22)	Daily at home, work
		F	Total	2.15 (1.18-3.92)	Daily at home, work
26	He <i>et al</i> ^[52]	F	Workplace	1.85 (0.86-4.00) ⁴	
		F	Total	2.87 (1.36-6.05)	Spouse, work
27	Iribarren <i>et al</i> ^[53]	M	Total	1.07 (0.96-1.19)	Home, small spaces, large indoor areas
		F	Total	1.10 (1.01-1.20)	Home, small spaces, large indoor areas
28	Rosenlund <i>et al</i> ^[54]	M	Workplace	1.14 (0.78-1.67)	
		F	Workplace	0.94 (0.59-1.50)	
29	Pitsavos <i>et al</i> ^[55]	M + F	Total	1.18 (0.87-1.60)	Spouse, work
		M + F	Workplace	1.97 (1.16-3.34)	
31	Chen <i>et al</i> ^[56]	M	Total	1.33 (0.94-1.88)	Home, work
		F	Total	1.39 (0.87-2.23)	Home, work
		M + F	Workplace	1.70 (0.90-3.20)	
32	Nishtar <i>et al</i> ^[57]	M + F	Total	1.50 (1.03-2.20)	Other people's tobacco smoke in the previous three days
		M + F	Biomarker	0.86 (0.64-1.16)	Serum cotinine
32	Nishtar <i>et al</i> ^[57]	M + F	Total	2.87 (1.28-6.42)	Unspecified, but includes spouse and others
		M + F	Biomarker	0.86 (0.64-1.16)	Serum cotinine
33	Whincup <i>et al</i> ^[58]	M	Biomarker	1.67 (1.03-2.72)	Serum cotinine
36	Hedblad <i>et al</i> ^[61]	M	Biomarker	2.22 (1.21-4.09)	Blood carboxyhaemoglobin
37	Stranges <i>et al</i> ^[62]	M	Workplace	0.97 (0.64-1.48)	
		F	Workplace	0.96 (0.60-1.55)	
		M	Childhood	1.04 (0.72-1.52)	Unspecified
		F	Childhood	0.93 (0.57-1.51)	Unspecified
		M	Total	1.11 (0.69-1.77)	Lifetime; home, work, public places; RR is compared to lower tertile of exposure
		F	Total	0.58 (0.33-1.03)	Lifetime; home, work, public places; RR is compared to lower tertile of exposure
38	Teo <i>et al</i> ^[63]	M + F	Total	1.37 (1.27-1.48)	Family, friends, co-workers
39	Wen <i>et al</i> ^[64]	F	Workplace	1.21 (0.74-2.01) ⁵	
		F	Childhood	1.49 (1.01-2.22) ⁵	In early life from family members
		F	Total	1.25 (0.69-2.25) ⁵	Spouse, work, early life
43	He <i>et al</i> ^[67]	F	Total	1.69 (1.31-2.18)	Home, work
45	Vozoris <i>et al</i> ^[69]	M + F	Total	1.00 (0.80-1.20)	Exposed on most days in the previous month
47	Gallo <i>et al</i> ^[71] (EPIC)	M	Workplace	0.93 (0.46-1.90) ⁶	
		F	Workplace	0.76 (0.47-1.24) ⁶	
		M	Childhood	1.11 (0.72-1.69) ⁶	Parents
		F	Childhood	1.18 (0.88-1.57) ⁶	Parents
48	Hamer <i>et al</i> ^[72]	M	Biomarker	1.50 (0.85-2.64)	Salivary cotinine
49	Jefferis <i>et al</i> ^[73]	M + F	Biomarker	0.94 (0.59-1.51)	Serum cotinine
50	Peinemann <i>et al</i> ^[74]	M + F	Total	1.27 (0.84-1.92)	Home, work, other

51	Chen ^[75]	M + F	Total	1.16 (0.93-1.45) ⁷	Home, work, other
52	He <i>et al</i> ^[76]	M	Total	2.24 (0.76-6.59)	Lifetime; home, work
		F	Total	2.10 (0.69-6.33)	Lifetime; home, work
54	Iversen <i>et al</i> ^[78]	M	Total	0.97 (0.61-1.55)	Time spent in smoke-filled rooms
		F	Total	0.70 (0.44-1.12)	Time spent in smoke-filled rooms
55	Kastorini <i>et al</i> ^[79]	M + F	Total	4.33 (1.52-12.38)	Partner, parents, children, roommates, colleagues; 30+ min/d
56	Rostron ^[80]	M + F	Biomarker	1.02 (0.70-1.47)	Serum cotinine
57	Batty <i>et al</i> ^[81]	M	Biomarker	0.49 (0.19-1.25)	Salivary cotinine
		F	Biomarker	1.26 (0.70-2.24)	Salivary cotinine
58	Shiue ^[82]	M + F	Total	1.47 (0.96-2.24)	Home, work, other

¹First author of paper; ²Biomarker RRs are all based on cotinine measurement except for study 36 which is based on COHb; ³Relative risks are adjusted for covariates if adjusted data are available. Some of the RRs are repeats of those given in Table 3; ⁴Estimate given by an earlier report of the same study^[117]; ⁵Results for CVD-Stroke. Results also available for CVD: workplace 0.92 (0.64-1.32), childhood 1.26 (0.94-1.69), total 1.45 (0.95-2.22); ⁶Results for CVD-Stroke. Not available for IHD; ⁷Result for IHD. Result for MI also available: 0.93 (0.66-1.31). M: Male; F: Female; CVD: Cardiovascular disease; IHD: Ischaemic (coronary) heart disease; MI: Myocardial infarction.

Table 7 Meta-analyses of heart disease¹ risk among never smokers in relation to four other indices of environmental tobacco smoke exposure

Index of exposure	n ²	Fixed-effect	Random-effects	Publication bias	Heterogeneity	DF ⁴	P ⁵ value
		Relative risk (95%CI)	Relative risk (95%CI)	P ³	χ ²		
Workplace	22	1.08 (0.99-1.19)	1.08 (0.99-1.19)	NS	20.12	21	NS
Childhood	7	1.12 (0.95-1.31)	1.12 (0.95-1.31)	< 0.1	4.77	6	NS
Total	33	1.21 (1.16-1.26)	1.23 (1.12-1.35)	NS	90.21	32	P < 0.001
Biomarker	9	1.11 (0.98-1.26)	1.15 (0.94-1.40)	NS	15.40	8	P < 0.1

¹Nearest equivalent to IHD as shown in Tables 1 and 6; ²n: Number of estimates in meta-analysis; ³Egger test P expressed as < 0.001, < 0.01, < 0.05, < 0.1 or NS (P ≥ 0.1); ⁴DF: Degrees of freedom; ⁵Expressed as < 0.001, < 0.01, < 0.05, < 0.1 or NS (P ≥ 0.1).

gests this is not a major issue.

Inappropriate controls in case-control studies

In some case-control studies using population controls, the control group may not have been fully representative of the population from which the cases derived, while some hospital studies merely ensured that the controls were not suffering from heart disease, and may have included patients with other diseases associated with ETS exposure.

Weaknesses of cross-sectional studies

Ten of the 58 studies considered were of cross-sectional design. Apart from the possibility of recall bias, this design does not exclude the theoretical possibility that disease onset might have occurred before ETS exposure.

Diagnosis and classification of heart disease

A major determinant of heterogeneity for the main index related to source of diagnosis, with RRs substantially lower for estimates based only on death certificates (1.06, 95%CI: 1.02-1.11), than when based on medical data (1.34, 1.23-1.46), the few estimates based on self-report giving intermediate results (1.17, 1.07-1.27). Note, however, that this classification correlates considerably with that for study type. Thus, all the estimates based on self-report are from cross-sectional studies, nearly all those based only on death certificates are from prospective studies, with case-control studies contributing largely to estimates based on medical data.

The actual disease for which results are available

varies by study, with some studies presenting results for multiple definitions. Higher RRs were seen for the main index where the definition was based on MI (1.29, 95%CI: 1.14-1.46) rather than on IHD (1.12, 1.05-1.19) or other/mixed definitions (1.20, 1.10-1.30). However, again there is a correlation with study type, there being few prospective studies using a definition of MI.

Confounding by other risk factors

There are manifold risk factors for heart disease, a study published in 1986^[98] mentioning over 300. As several studies^[53,99-103] showed differences in many lifestyle factors between smoking and non-smoking households, a potential for confounding is certainly present. Though difficult to assess precisely, partly because of the numerous risk factors involved, and partly because studies rarely present results showing the effect of adjustment for individual factors, some insight can be gained by comparing RR estimates across studies according to the number of risk factors adjusted for. Though the number of risk factors may be correlated with other aspects of the study, the results did not suggest the association was due to confounding, RRs being somewhat higher where more confounders were accounted for.

Inclusion of studies rejected in other meta-analyses

Three meta-analyses published in the late 1990s^[2-4] deliberately excluded results reported by Layard^[25], based on the National Mortality Followback Survey (NMFS), and by LeVois and Layard^[26], based on the American Cancer Society (ACS) Cancer Prevention Studies I (CPS I) and

Table 8 Other indices of environmental tobacco smoke exposure - dose response results among never smokers

Study No.	Author ¹	Sex	Exposure grouping	Relative risk by grouping (95%CI) ²	Significance ³
Workplace exposure					
22	Kawachi <i>et al</i> ^[48]	F	No, occasional, regular	1.00, 1.49, 1.92	
26	He <i>et al</i> ^[52]	F	0-5, 6-10, 11-20, 21+ cigs/d	1.00, 0.87, 2.95, 3.56	+
		F	0-5, 6-15, 16+ year	1.00, 3.08, 1.56	
		F	0, 1-2, 3, 4+ smokers	1.00, 1.16, 5.06, 4.11	+
		F	0, 1-2, 3-4, 5+ h/d	1.00, 0.62, 4.03, 21.32	+
		F	0, 1-2000, 2001-4000, 4000+, cigs/d × year × smokers × h	1.00, 1.00, 2.05, 9.23	+
28	Rosenlund <i>et al</i> ^[54]	M + F	0, 1-31, 32+ yr	1.00, 1.04, 1.30	
		M + F	0, 1-68, 69+ h-year (= h/d × year)	1.00, 0.99, 1.48	
39	Wen <i>et al</i> ^[64]	F	0, < 10, 10-24, > 24 yr	1.00, 0.86, 0.96, 0.93 ⁴	
40	Eisner <i>et al</i> ^[65]	M + F	Per 10 yr exposure	1.04	
Childhood exposure					
18	Muscat <i>et al</i> ^[44]		Exposure to mother, father, other relatives		
		M	None, 1-17, > 17 yr	1.0, 0.9, 0.7	
		F	None, 1-17, > 17 yr	1.0, 0.6, 0.8	
39	Wen <i>et al</i> ^[64]	F	In early life from family members ⁵		
			0, < 20, 20+, year	1.00, 1.21, 1.36 ⁴	+
Total exposure					
3	Lee <i>et al</i> ^[31]		Home, work, travel, leisure combined index		
		M	Score: 0-1, 2-4, 5-12	1.00, 0.43, 0.43	
		F	Score: 0-1, 2-4, 5-12	1.00, 0.59, 0.81	
5	Svendsen <i>et al</i> ^[33]		Spousal and/or workplace exposure		
		M	Neither, spouse, work, both	1.0, 1.2, 1.0, 1.7	
9	Jackson ^[37]		Exposure at home and/or work ⁶		
		M	No, yes	1.00, 1.14 (0.76-1.70)	
		F	No, yes	1.00, 1.56 (0.76-3.20)	
12	Dobson <i>et al</i> ^[40]		Exposure at home and/or work		
		M	No, yes	1.00, 1.09 (0.72-1.63)	
		F	No, yes	1.00, 2.24 (1.28-3.91)	+
19	Tunstall-Pedoe <i>et al</i> ^[45]		Exposure to tobacco smoke from someone else in the previous three days		
		M + F	None, little, some, a lot, (self-classified)	1.00, 1.2, 1.5, 1.6	+
22	Kawachi <i>et al</i> ^[48]	F	Exposure at home and/or work		
			None, occasional, regular	1.00, 1.58, 1.91	+
26	He <i>et al</i> ^[117]	F	ETS exposure from spouse and/or work		
			Neither, spouse, work, both	1.00, 2.07, 2.53, 4.18	+
27	Iribarren <i>et al</i> ^[53]		Exposure at home, in small spaces, in large indoor areas		
		M	0, 1-9, 10-39, 40+ total h/wk	1.00, 0.90, 1.08, 1.13	+
		F	0, 1-9, 10-39, 40+ total h/wk	1.00, 0.86, 1.07, 1.17	+
28	Rosenlund <i>et al</i> ^[54]		Exposure from spouse and/or work		
		M + F	0, > 16, 7-16, 1-6, < 1, year ago	1.00, 0.92, 1.11, 1.30, 1.39	
		M + F	0, 1-12, 13-23, 24-34, 35+, year	1.00, 0.72, 0.97, 1.54, 1.48	+
		M + F	0, 1-17, 18-41, 42-89, 90+, h-year, (= year × h/d)	1.00, 0.70, 1.22, 1.27, 1.55	+
29	Pitsavos <i>et al</i> ^[55]		Exposure at home and/or work		
		M	None, occasional, regular	1.00, 1.25, 1.47	+
		F	None, occasional, regular	1.00, 1.29, 1.56	+
31	Chen <i>et al</i> ^[56]		Exposure to tobacco smoke from someone else in the previous three days		
		M + F	None, a little, some, a lot	1.00, 1.30, 1.50, 1.80	+
			Exposure to other people's tobacco smoke		
		M + F	0, > 0-2, 3-5, ≥ 6 h/d	1.00, 1.20, 1.60, 1.70	
37	Stranges <i>et al</i> ^[62]		Cumulative lifetime ETS exposure at home, work and in public settings		
		M	Tertile: 1, 2, 3	1.00, 0.93, 1.40	
		F	Tertile: 1, 2, 3	1.00, 0.50, 0.67	
38	Teo <i>et al</i> ^[63]		Exposure from family, friends, co-workers		
		M + F	< 1, 1-7, 8-14, 15-21, 22+ h/wk	1.00, 1.32, 1.52, 1.73, 1.49	+
43	He <i>et al</i> ^[67]		Exposed at home and/or work		
		F	0, 1-9, 10-19, 20+, cigs/d	1.00, 1.41, 1.85, 1.77	+
			0, 1-20, 21-40, 41+, min/d	1.00, 1.46, 1.78, 1.86	+
52	He <i>et al</i> ^[76]		Exposed at home and/or work ⁷		
		M + F	None Low Moderate High	1.00, 1.74, 2.25, 3.79	+
54	Iversen <i>et al</i> ^[78]		Time spent in a smoke-filled rooms		
		M	0, 1-6, > 6, h/d	1.00, 1.00, 0.80	
		F	0, 1-6, > 6, h/d	1.00, 0.70, 0.70	
58	Shiue ^[82]		Exposed at home, work, other people's home		
		M + F	0, 1, 2+ of these places	1.00, 1.37, 2.64	+

Biomarker	Study	Sex	Exposure	Relative Risk (95% CI)	Significance
19	Tunstall-Pedoe <i>et al.</i> ^[45]	M + F	Serum cotinine (ng/mL) 0, > 0-1.05, 1.06-3.97, 3.98-17.49	1.00, 1.00, 1.30, 1.20	
31	Chen <i>et al.</i> ^[56]	M + F	Serum cotinine (ng/mL) 0, > 0-1.05, 1.06-3.97, 3.98-17.49	1.00, 0.70, 1.00, 1.10	
33	Whincup <i>et al.</i> ^[58]	M	Serum cotinine (ng/mL) ≤ 0.7, 0.8-1.4, 1.5-2.7, 2.8-14.0	1.00, 1.54, 1.89, 1.67	+
36	Hedblad <i>et al.</i> ^[61]	M	Blood carboxyhaemoglobin (%) 0.13-0.49, 0.50-0.57, 0.58-0.66, 0.67-5.47 (quartiles)	1.00, 1.26, 1.77, 3.71	+
48	Hamer <i>et al.</i> ^[72]	M + F	Salivary cotinine (ng/mL) ≤ 0.05, 0.06-0.70, 0.71-14.99	1.00, 1.33, 2.00	+
49	Jefferis <i>et al.</i> ^[73]	M + F	Per unit increase in log cotinine Serum cotinine (ng/mL) ≤ 0.05, 0.06-0.19, 0.20-0.70, 0.71-15	1.60 (1.11-2.31) 1.00, 0.91, 0.99, 0.94	
56	Rostron ^[80]	M + F	Per doubling of cotinine Serum cotinine (ng/mL) < 0.1, 0.1- < 1, 1- < 15	1.00 (0.86-1.16) 1.00, 0.97, 1.41	
57	Batty <i>et al.</i> ^[81]	M F	Salivary cotinine (ng/mL) ≤ 0.3, 0.4-1.2, 1.3-15.0 ≤ 0.3, 0.4-1.2, 1.3-15.0	1.00, 0.41, 0.62 1.00, 0.99, 1.70	

¹First author; ²Relative risks presented are adjusted for covariates if adjusted data are available. When two groups only are being compared (or results for log cotinine are given), the relative risk and 95%CI limits for the exposed group (per unit increase) are shown; when more than two exposure groups are being compared, only the set of relative risks is shown; ³Significant ($P < 0.05$) positive (or negative) differences or trends are indicated by + (or -). ? indicates not known whether significant or not. Blank entries indicate non-significance. The trend test includes the unexposed group; ⁴Results for CVD. Not available for CVD - Stroke; ⁵For study 39 the results for any childhood exposure (yes/no) shown in Table 4 relate to CVD minus stroke but the results by years exposed shown here relate to CVD as a whole; ⁶The data shown here for study 9 come from the publication describing study 24; ⁷The index of exposure was a combination of exposure at home (four categories of pack-years) and exposure at work (four categories of pack-years × h/d). M: Male; F: Female; CVD: Cardiovascular disease.

II (CPS II). The results from these studies showed no evidence of a relationship of spousal smoking to heart disease mortality. Though we have not used the cited CPS II results, more detailed results being reported later by the ACS^[46], we included the results from NMFS^[25] and CPS I^[26]. Apart from wishing to consider all the evidence, and particularly not omit data from the very large CPS I, we found the reasons for excluding these studies to be unconvincing.

One reason given^[2] was that their results were inconsistent with other data, and reported by tobacco industry consultants. As regards inconsistency, it seems better to include all data, and investigate reasons for inconsistency, than to reject results not fitting in with preconceptions. As regards tobacco industry support, the test is whether the analyses presented were sound. We note no attempt was made by any critic to check the results from the publicly available NMFS, or by the ACS to check results from their CPS I. The ACS did conduct their own analyses of CPS II^[46] using somewhat different methodology, their findings failing to indicate errors in the results of LeVois and Layard^[26].

Another reason^[4] given was that results were only presented for ever spousal exposure, rather than current spousal exposure. Apart from not noting that results for current spousal exposure were readily available from the CPSI data presented^[26], the results being included in our analysis, Thun *et al.*^[4] also did not mention that their own analyses included results from other studies (studies 1, 2 and 8) based on ever spousal exposure! In fact, as we show, the overall RRs as can be seen in our main analysis, are very similar whether preferring ever to current spousal exposure (1.18, 95%CI: 1.12-1.24),

or preferring current to ever spousal exposure (1.19, 1.13-1.26).

We have also included results reported by Enstrom and Kabat^[27] in our analysis (Study 30), despite publication of the paper in the BMJ being subject to a large number of critical responses. As the authors noted in a final rapid response in the BMJ, none of the responses identified “any impropriety, bias, or omission in the review process” with “only about 3%” referring to “actual data in the paper”. “No one has identified a single error in the paper, not even Thun, who is in a position to check our findings”. We agree with Enstrom and Kabat that “the unethical tactics used by the ACS and others, including *ad hominem* attacks and condemnation of legitimate research based solely on the source of funding, have no place in scientific discourse”. The authors noted that “Our current research funding comes from Philip Morris USA and three other sources not connected with the tobacco industry”. As shown in Table 4, exclusion from our meta-analysis of the three studies in question (studies 15, 16 and 30) slightly increased the RR estimate for our main index, from 1.18 (95%CI: 1.12-1.24) to 1.23 (95%CI: 1.17-1.29), but did not affect the conclusion that there was a clear association of ETS exposure with heart disease risk.

Evidence from studies of smoking bans

Since the first study in 2004^[104], which reported a 40% reduction in hospital admissions from AMI following introducing a local law banning smoking in public places and workplaces, numerous further studies have investigated ban effects at national, regional and local level. In a recent review^[105], based on 45 studies, we used a

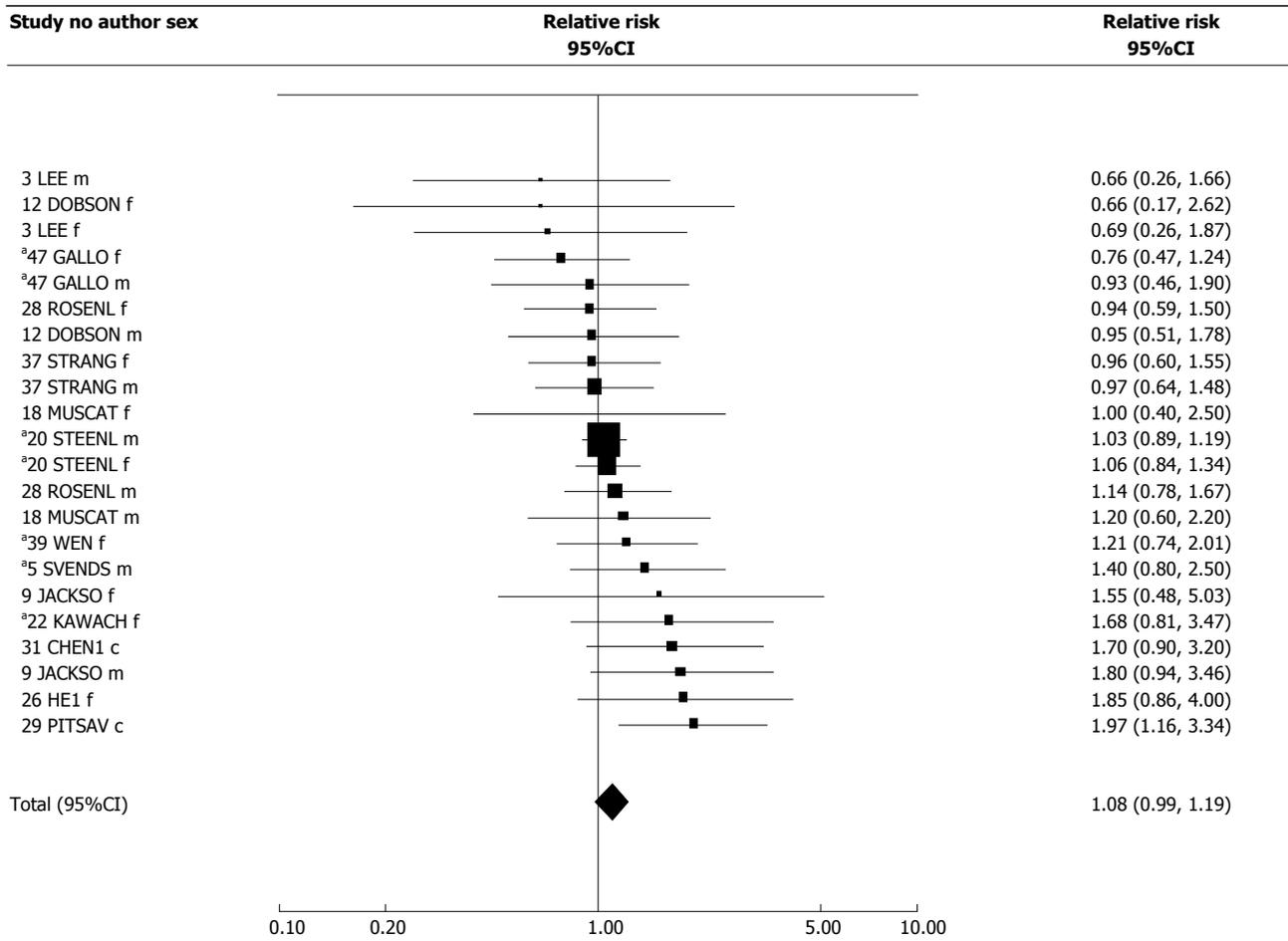


Figure 2 Forest plot for workplace exposure. Estimates of the RR and its 95%CI are shown sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). The overall random-effects estimate (RRs and 95%CI) is shown, represented graphically by a diamond whose width indicates the confidence interval. ^aProspective study.

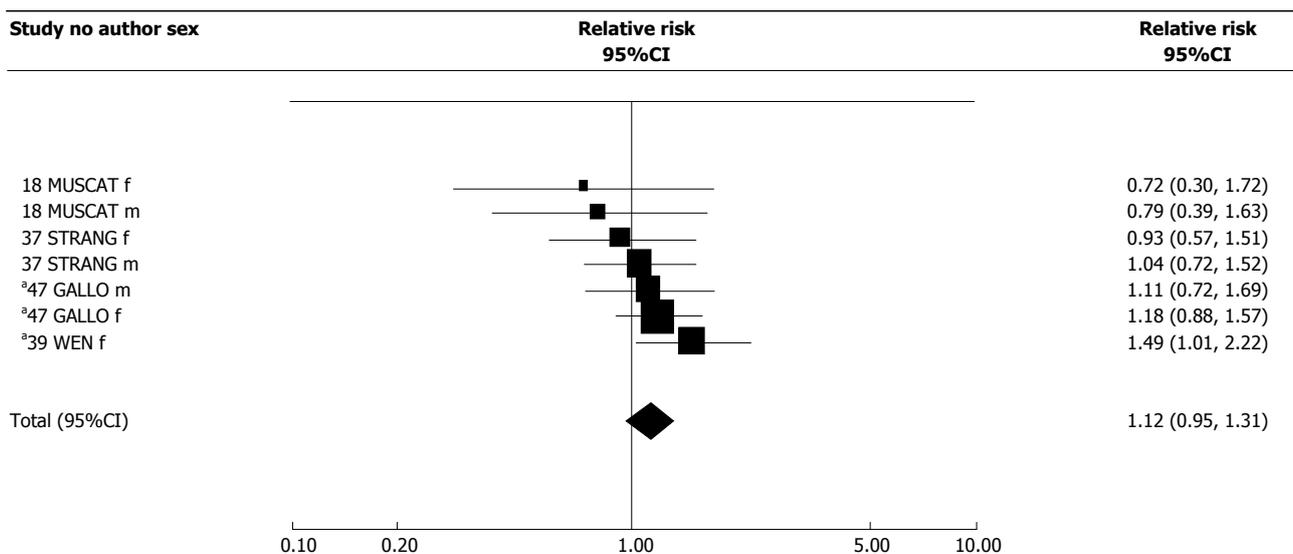


Figure 3 Forest plot for childhood exposure. Estimates of the RR and its 95%CI are shown sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). The overall random-effects estimate (RRs and 95%CI) is shown, represented graphically by a diamond whose width indicates the confidence interval. ^aProspective study.

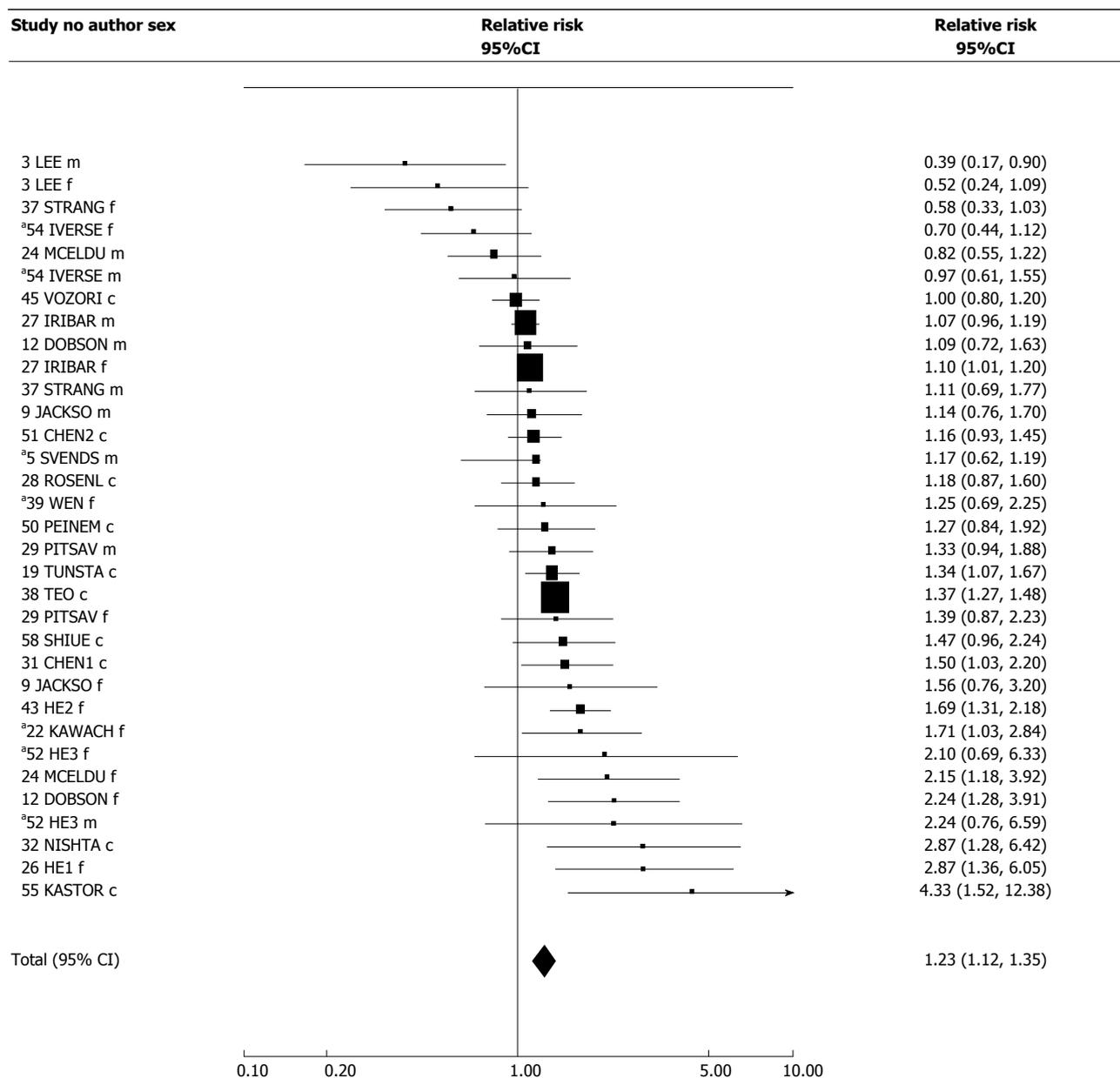


Figure 4 Forest plot for total environmental tobacco smoke exposure. Estimates of the RR and its 95%CI are shown sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). The overall random-effects estimate (RRs and 95%CI) is shown, represented graphically by a diamond whose width indicates the confidence interval. ^aProspective study.

consistent approach to adjust for time trends and seasonal effects. We estimated the post-ban risk reduction as 4.2% (95%CI: 1.8%-6.5%) initially, which reduced to 2.6% (1.1%-4.0%) after excluding regional studies where national estimates were available, and also studies where adjustment for the underlying trend in the heart disease rate was not possible. Although these estimates are much less than those from some earlier reviews^[106-108] which used less precise techniques, they do suggest a small true ban effect. However, the effect cannot be directly attributed to reductions in risk arising from reduced ETS exposure. Some of the estimated effect might be because smokers reduced their daily cigarette

consumption due to the more limited number of places where they are allowed to smoke.

Experimental evidence

The Institute of Medicine (IOM) report^[7] discussed “pathophysiologic experiments that have investigated the cardiovascular effects of mainstream and sidestream tobacco smoke in cells, in animals and in humans”, noting that cigarette smoke could produce CVD by various “interrelated modes of action, including oxidative stress, hemodynamic and autonomic effects, endothelial dysfunction, thrombosis, inflammation, hyperlipidemia or other effects”. While beyond the scope of this paper to

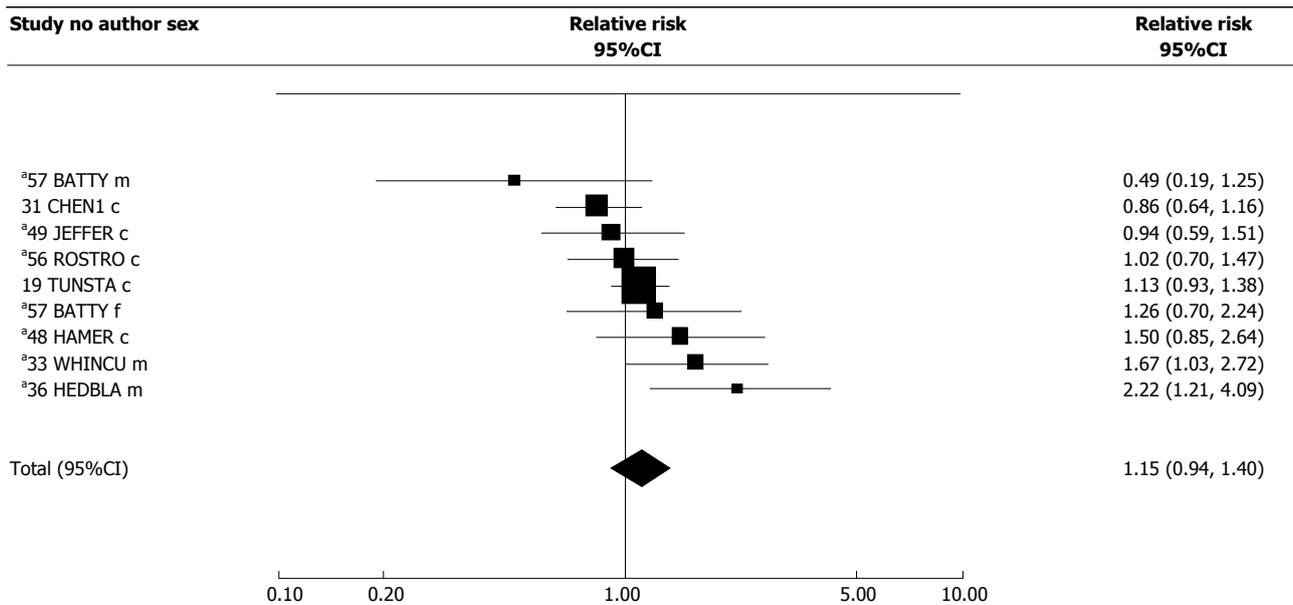


Figure 5 Forest plot for biomarker based indices of environmental tobacco smoke exposure. Estimates of the RR and its 95%CI are shown sorted in increasing order of RR. These are shown numerically and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). The overall random-effects estimate (RRs and 95%CI) is shown, represented graphically by a diamond whose width indicates the confidence interval. ^aProspective study.

consider such evidence, we note that the report states most of the observed changes “have not been formally validated as clinical tests and there is not a consensus within the scientific community that they are predictive of actual clinical disease.” While the IOM Committee considered that these effects can “contribute to the biological plausibility that decreasing second-hand smoke could lead to a decrease in acute myocardial infarction”, they did not consider that the results, on their own, demonstrated a causal relationship of ETS exposure to heart disease.

Comment on a recent systematic review

In the introduction we referred to various other, conflicting, reviews of ETS and heart disease. Though it is beyond our scope to consider all these in detail, it is worth referring to a recently published systematic review^[109] which concluded that ETS exposure “significantly increased the risk for ...CVD”. This review was limited to prospective and case-control studies, but included studies of stroke, which we have reviewed separately^[110]. While the authors’ combined RR estimate for cardiovascular disease of 1.23 (95%CI: 1.16-1.31) was similar to our main analysis estimate of 1.18 (1.12-1.24), we note they excluded a number of prospective and case-control studies we included. While some omissions were because they excluded abstracts and theses, and biomarker studies using COHb, we noted eight studies (13, 16, 21, 25, 32, 38, 46 and 55) where there seemed no good reason for the omission. Also, they did not separate results by source of ETS exposure or present any dose-response results.

Association of ETS with other diseases

In recent years, our group has carried out systematic reviews and meta-analyses of the relationship of ETS with various diseases in never smoking adults. These include lung cancer^[111], breast cancer^[112], other cancers^[113], stroke^[110] and COPD (submitted for publication). It is of interest to note that spousal smoking is associated with about 20% increased risk in never smokers, not only for heart disease, as we report here, but most studied diseases - stroke, COPD, lung cancer and breast cancer. Estimates are more limited for other cancers, many sites not showing any evidence of an effect, though significant increases were noted for cervix, nasosinus and kidney cancer. Whether evidence of an association for other diseases adds support to the argument that ETS exposure causes heart disease is unclear, as many of the problems of bias noted to affect the association with heart disease may also affect the association with other diseases.

Some, but not all, of the biases may be removed by limiting attention to prospective studies of ETS and total mortality. However, at this point in time, we have not carried out a review of the evidence, though we note that about half the prospective studies cited in Table 1 do give results for total mortality.

Overall assessment

Do the results show that ETS exposure increases risk of heart disease? Here one can usefully cite the classic paper by Hill^[114] which specified nine criteria to be considered when attempting to conclude causation. We consider these in turn below.

Strength: The observed association is clearly weak, with our main analyses estimating only an 18% increase in risk associated with ETS exposure.

Consistency: While some studies report no increased risk and a number do not report a statistically significant increased risk, this may reflect the difficulty in demonstrating a weak association, particularly with limited data. Even though there is clear heterogeneity for our main index of exposure, the meta-analysis estimates by level of a range of factors are all increased, and nearly always significantly increased. Thus, for example, significant increases are seen in each sex, in four continents, in prospective, case-control and cross-sectional studies, and in smaller and larger studies. There is certainly an element of consistency.

Specificity: ETS exposure is certainly not a necessary or sufficient cause of heart disease. While it is much easier to demonstrate causation where an agent is such a cause, this criterion is not really relevant here.

Temporality: While theoretically possible in the cross-sectional studies that some cases of heart disease might have preceded exposure to ETS, this could not be so for most cases in the 58 studies we considered.

Biological gradient: Though not all the studies demonstrate a dose-response relationship, many do. However, the significant trends observed are generally calculated including the unexposed group, and evidence of a dose-response within ETS exposed subjects is less clear.

Plausibility: There is clearly plausibility, given smoking causes heart disease and given the experimental evidence referred to above. However, the dose of smoke constituents from ETS is very much less than that from smoking, and it is unclear whether the short-term effects of ETS observed experimentally are actually predictive of heart disease.

Coherence: A cause-and-effect interpretation of the data does not, as far as we are aware, seriously conflict with other generally known facts concerning the history and biology of heart disease.

Experiment: The epidemiological evidence considered lacks any useful material to determine how the risk of heart disease varies following cessation of ETS exposure. However, the evidence from studies of smoking bans suggests that the introduction of smoking bans in public places has caused a modest reduction in risk of heart disease though, as noted, such studies, generally do not separate out effects of reduced ETS exposure in never smokers and of reduced opportunities to smoke in smokers.

Analogy: Whether effects of smoking and of ETS can be regarded as analogous is doubtful, given the

substantial differences in extent of exposure and the somewhat different distribution of chemicals for the two types of exposure.

Considering all these points, there seems some inconclusive support for ETS exposure causing heart disease. An important issue not specifically considered in the Bradford Hill criteria, much more relevant for weak than strong associations, is whether the association might be explained by confounding or bias. As regards confounding, the observation that many studies adjusted for numerous risk factors for heart disease, and that RR estimates if anything, increase as more factors are adjusted for, suggests that confounding could not explain the relationship. Nor does it seem likely that the relationship could be fully explained by publication bias or recall bias, though the smaller estimates for large studies and for prospective studies suggest that these biases might have led to some overestimation of the association. Nor is it probable that misclassification of smoking status, or the inclusion of some smokers of products other than cigarettes or occasional or ex-smokers could explain the observed association. While we feel there may well be a true effect of ETS on heart disease risk, it is clear that it is difficult to come to a definitive conclusion, and even more difficult to estimate any true effect precisely.

In conclusion, Taken together with the known relationship of heart disease with smoking, the significantly increased risk for various indices of ETS exposure which can be seen in many study subsets, the evidence of a dose-response relationship, and the lack of any source of bias or confounding that can clearly explain the relationship, the evidence suggests that ETS exposure may cause some increase in the risk of heart disease. That said, the weakness of the overall relationship, the evidence of heterogeneity, the limitations of some of the studies, and the various possibilities of bias, certainly mean that any true effect of ETS exposure is very difficult to quantify precisely.

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COMMENTS

Background

The authors consider evidence that environmental tobacco smoke (ETS)

exposure might cause heart disease by presenting an up-to-date meta-analysis of the available evidence.

Research frontiers

Based on 58 studies providing relevant data, the authors demonstrate an increase in heart disease risk in never smokers associated with ETS exposure by the spouse (or nearest equivalent), with an overall RR estimate of 1.18 (1.12-1.24). While increases were observed in all data subsets considered, there was evidence of heterogeneity, with risk estimates lower for North American studies, larger studies, prospective studies, and when based on fatal cases or death certificate data. Positive associations, not all significant at $P < 0.05$, were also seen with spousal exposure specifically (1.10, 1.04-1.17), workplace exposure (1.08, 0.99-1.19), childhood exposure (1.12, 0.95-1.31), total exposure (1.23, 1.12-1.35) and biomarker-based exposure (1.15, 0.94-1.40) and there was evidence of a dose-response relationship. Although the evidence has various limitations, it is suggestive of a causal relationship. However, the various possibilities of bias mean that any true effect of ETS exposure is very difficult to quantify precisely.

Innovations and breakthroughs

The new feature of the paper is the extent of the evidence considered, and the detail of the analyses conducted.

Applications

The authors analyses emphasise the difficulties in drawing inferences from weak associations seen in non-randomized epidemiological studies, where various biases may exist.

Peer-review

This is a meta-analysis of 58 studies that address the issue of environmental tobacco smoke and the development of heart disease. Overall, the authors found an association between exposure and heart disease risk.

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