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Meta-analysis of the association between secondhand smoke exposure and stroke

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ABSTRACT

Background Active smoking is a recognized risk factor for stroke. We determined the evidence for an association with secondhand smoke exposure.

Methods A systematic review was undertaken according to PRISMA guidelines. Random effects meta-analysis provided a pooled estimate of risk, and heterogeneity quantified using I^2 values. Potential publication and study bias were assessed using a funnel plot and Egger's test. Meta-regression analyses were used to investigate sources of heterogeneity.

Results The 20 eligible studies provided 35 estimates of risk derived from 885 307 participants, of whom 5894 (0.7%) suffered a stroke. The pooled estimate of risk was 1.25 (95% CI: 1.12–1.38) with no evidence of significant publication or small-study bias. There was moderate heterogeneity ($I^2 = 54.2\%$, $P < 0.001$) but no study characteristics were statistically significant in the meta-regression analysis. There was a non-linear dose relationship. The relative risk increased from 1.16 (95% CI: 1.06–1.27) for exposure to 5 cigarettes/day to 1.56 (95% CI: 1.25–1.96) for exposure to 40 cigarettes/day.

Conclusions There is evidence of a strong, consistent and dose-dependent association between exposure to secondhand smoke and risk of stroke, suggestive of a causal relationship, with disproportionately high risk at low levels of exposure suggesting no safe lower limit of exposure.

Keywords meta-analysis, review, secondhand smoke, smoking, passive, tobacco smoke pollution

Introduction

Annually, 16 million people suffer a stroke worldwide and 5.7 million die from the condition.[1] The burden of stroke is likely to increase further as a result of demographic and economic transition. Around half of all stroke survivors have residual physical or cognitive impairment[2,3] placing considerable demands on both support services and informal caregivers. Almost all caregivers report adverse effects on their emotional health, social activities and leisure time, and more than half suffer adverse effects on family relationships.[4] In the UK, stroke accounts for 5% of National Health Service spending, and the total cost of treatment and lost productivity amounts to £8.9 billion per annum.[5] Hence, stroke is an important public health problem and priority should be given to preventable causes. There has long been general acceptance of a causal link between active smoking and risk of stroke. More recently, an increasing number of studies have examined the association between exposure to secondhand smoke and stroke. The aim of this study was to determine the strength and consistency of the existing literature and whether there is evidence of a dose relationship.

Methods

Two of the authors (I.P.O. and J.P.P.) undertook a systematic review in accordance with the Preferred Reporting Items for

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Systematic Reviews and Meta-analyses (PRISMA) guidelines (http://www.prisma-statement.org/). We used five journal databases (OVID Medline, NCBI PubMed, EBSCOHost Medline, ISI Web of Knowledge and Google Scholar) and applied the following search terms and Boolean connectors: (cerebral h?emorrhage OR cerebral infarction OR cerebral artery disease* OR cerebral isch?emia OR cerebrovascular disease OR cerebrovascular accident* OR stroke OR cerebrovascular lesion*) AND (environmental tobacco smok* OR second hand smok* OR passive smok*). The Google Scholar search was restricted to articles published from 2005 onwards and used primarily to check on the completeness of the searches using the other four databases. No date restrictions were applied to the other search engines. Only studies on humans and non-interventional studies were included. The electronic databases identified a total of 226 articles of which 163 were excluded as duplicates. A manual search of reference lists and lists of related items identified an additional 37 articles. Of the resultant 100 articles, only 28 had relevant abstracts. Following manual review of the full manuscripts, eight were excluded as ineligible because they did not provide quantified estimates of the risk associated with secondhand smoke exposure ($n = 6$), did not provide original data ($n = 1$) or were not published in nor translated into English ($n = 1$). Therefore, 20 articles were suitable for inclusion in the meta-analysis.

A random effects meta-analysis was used to provide a pooled estimate of the risk of stroke associated with secondhand smoke exposure. Heterogeneity was quantified using I^2 values. Potential publication and study bias were assessed visually using a funnel plot and then tested, formally, using Egger's test. Univariate and multivariate meta-regression analyses were used to investigate possible sources of heterogeneity. Additional sub-group analysis was conducted on the cohort studies to assess whether duration of follow-up was associated with the estimate of effect size. Multiplicity

Table 1 Characteristics of studies examining the association between exposure to secondhand smoke and risk of stroke

Reference	*Country*	*Age (years)*	*Sex*	*Cases (n)*				*Controls (n)*	*Exposure*
				Stroke	*Ischaemic stroke*	*SAH*	*TIA*		
Cohort									
Gillis *et al.*[6]	UK	45–64	MF	12	–	–	–	2732	Household
Sandler *et al.*[7]	USA	≥25	MF	655	–	–	–	18 380	Total
Yamada *et al.*[8]	Asia	40–79	MF	–	–	72	–	81 237	Household
Iribarren *et al.*[9]	USA	30–85	MF	706	–	–	151	26 841	Household
Whincup *et al.*[10]	UK	25–74	M	41	–	–	–	904	Cotinine
Qureshi *et al.*[11]	USA	40–59	F	109	100	–	–	2823	Partner
Wen *et al.*[12]	Asia	40–70	F	157	–	–	–	72 489	Partner
Hill *et al.*[13]	Australasia	45–77	MF	1 152	–	–	–	546 447	Household
Glymour *et al.*[14]	USA	≥50	MF	266	–	–	–	15 959	Partner
Jefferis *et al.*[15]	UK	60–79	MF	176	–	–	–	5198	Cotinine
Case–control									
Lee *et al.*[16]	UK	35–74	MF	92	–	–	–	451	Partner
Donnan *et al.*[17]	Australasia	All	MF	–	142	–	–	207	Partner
Bonita *et al.*[18]	Australasia	35–74	MF	265	–	–	–	1336	Total
You *et al.*[19]	Australasia	All	MF	–	154	–	–	213	Partner
Anderson *et al.*[20]	Australasia	All	F	–	–	135	–	246	Household
McGhee *et al.*[21]	Asia	≥60	F	597	–	–	–	763	Household
Cross sectional									
Howard *et al.*[22]	USA	55–72	MF	77	–	–	–	715	Total
Iribarren *et al.*[23]	USA	≥15	MF	137	–	–	–	42 584	Total
Zhang *et al.*[24]	Asia	40–70	F	526	–	–	–	58 851	Partner
He *et al.*[25]	Asia	≥60	F	172	–	–	–	1037	Total
Overall				5 140	396	207	151	879 413	

n, number; SAH, subarachnoid haemorrhage; TIA, transient ischaemic attack; UK, United Kingdom; USA, United States of America; M, male; F, female.

adjustments (Monte Carlo simulation method) of up to 20 000 times were conducted in order to minimize the chances of a spurious or false-positive finding (type I error) and to check the robustness of effect size estimates. Monte Carlo simulations are based on random permutations of the covariates. The dose–response relationship between secondhand smoke and risk of stroke was examined by applying both linear and dose squared models to those studies that examined dose using the same measure of exposure. Where level of exposure was expressed as a range, the mid-point was used. All analyses were undertaken using Stata v11.0 software (STATA Corp, College Station, Texas, URL http://www.stata.com).

Results

The eligible studies were published between 1984 and 2010. Of the 20 studies,[6–25] 10 were cohort studies,[6–15] 6 were case–control studies[16–21] and 4 were cross-sectional studies[22–25] (Table 1). Six of the studies were conducted in the USA,[7,9,11,14,22,23] five in Australasia,[13,17–20] five in Asia[8,12,21,24,25] and four in the UK.[6,10,15,16] All of the studies reported results for non-smokers. In most studies, these were defined as never smokers,[6,7,9,12–14,16,17,19–24] but some also included ex-smokers,[8,10,11,15,18,25] or infrequent current smokers.[25] One of the case–control studies used hospital controls,[16] whilst the remainder used community controls. One study included only men,[10] four only women,[11,12,24,25] and fifteen both sexes.[6–9,13–23] The studies varied in their definition and measurement of secondhand smoke exposure. Only two measured cotinine concentration.[10,15] The remainder relied on self-reported exposure to secondhand smoke. Some focused on exposure in specific locations such as household exposure,[6,7,9,11–14,16–21,23–25] and exposure in the workplace,[12,18,25] whilst others collected information on overall exposure.[8,22,23] Eleven of the studies measured dose

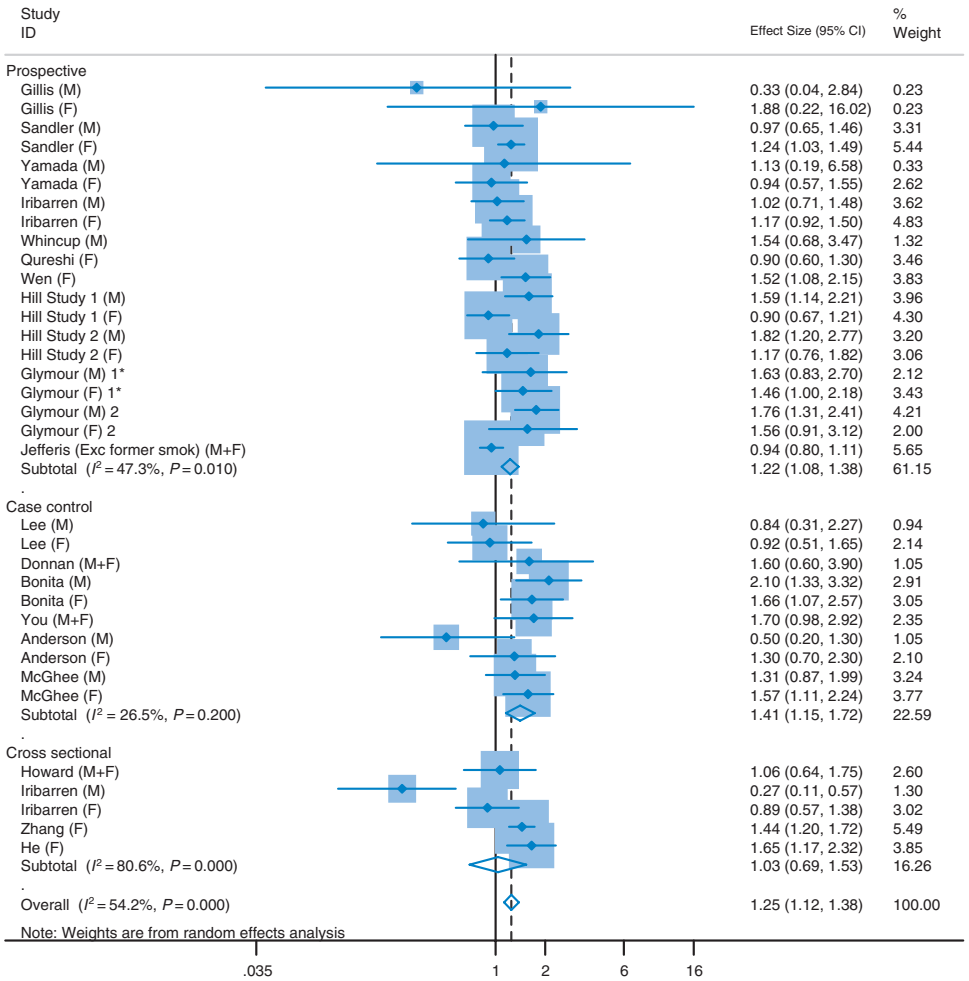


Fig. 1 Forest plot of studies examining the association between exposure to secondhand smoke and risk of stroke, stratified by study design. ES, effect size; CI, confidence interval; M, male; F, female.

of exposure to secondhand smoke.[9,10,12,15,16,18,19,21,23–25] Dose was measured in various ways including number of smokers,[21] cigarettes per day,[19,24,25] hours per week,[9,22,23] pack years,[12] cotinine concentration[10,15] and score.[16]

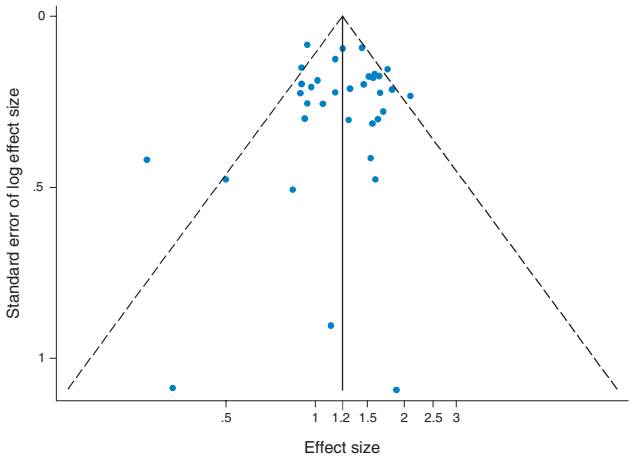


Fig. 2 Funnel plot of studies examining the association between exposure to secondhand smoke and risk of stroke.

There was a wide range in the number of study participants with stroke. The largest cohort study reported 1152 strokes,[13] but five studies reported fewer than 100,[6,8,10,16,22] with the smallest recording only 12.[6] The studies varied in their case definition. Seven studies included only fatal events,[6–8,12,13,21] six included only non-fatal events[16,19,22,23–25] and eight included both.[9–11,14,15,17,18,20] Most studies reported results for all strokes or all cerebrovascular events,[6,7,9–16,18,21–25] but some reported results for specific types, including ischaemic stroke,[11,17,19] subarachnoid haemorrhage[8,20] and transient ischaemic attack.[9] The studies varied in the extent to which they adjusted or matched for potential confounding factors. Two studies adjusted for only age.[6,8] Five studies adjusted for from two to five potential confounders,[16–19,21] and the remaining 13 studies adjusted for six or more including age, sex, socioeconomic status, alcohol consumption, physical activity and medication.[7,9–15,20,22–25] Some of these studies over-adjusted by adjusting for hypertension, which is a potential mediator rather than a potential confounder.[9–11,15,20,22–25]

Table 2 Meta-regression analysis of studies examining the association between exposure to secondhand smoke and risk of stroke

Study characteristics		*Univariate*			*Multivariate*		
		Coefficient (95% CI)	*P-value*	*Multiplicity adjusted P-value*	*Coefficient (95% CI)*	*P-value*	*Multiplicity adjusted P-value*
Location	USA[a]	–	–	–	–	–	–
	Asia	0.164 (−0.071, 0.400)	0.171	0.188	0.356 (−0.038, 0.750)	0.074	0.477
	UK	−0.279 (−0.588, 0.030)	0.077	0.099	−0.306 (−0.926, 0.313)	0.315	0.956
	Australasia	0.156 (−0.076, 0.387)	0.188	0.203	0.200 (−0.202, 0.602)	0.312	0.955
Year	1980–1989[a]	–	–	–	–	–	–
	1990–1999	0.276 (−0.048, 0.601)	0.095	0.111	0.294 (−0.593, 1.180)	0.531	0.998
	2000–2009	−0.047 (−0.291, 0.197)	0.706	0.712	0.044 (−0.904, 0.993)	0.923	1.000
Design	Cohort[a]	–	–	–	–	–	–
	Case–control	0.146 (−0.096, 0.389)	0.237	0.257	−0.046 (−0.445, 0.352)	0.811	1.000
	Cross sectional	−0.121 (−0.412, 0.170)	0.416	0.421	−0.267 (−0.725, 0.191)	0.238	0.891
Sex	Both[a]	–	–	–	–	–	–
	Male only	0.046 (−0.176, 0.267)	0.686	0.703	0.089 (0.528, 0.706)	0.766	1.000
	Female only	0.004 (−0.208, 0.215)	0.972	0.974	0.065(−0.523, 0.653)	0.821	1.000
Exposure	Total (reported)[a]	–	–	–	–	–	–
	Household (reported)	−0.056 (−0.267, 0.155)	0.604	0.612	−0.009 (−0.587, 0.570)	0.976	1.000
	Spouse (reported)	0.079 (−0.140, 0.300)	0.480	0.490	0.187 (−0.303, 0.678)	0.435	0.993
	Total (cotinine)	0.218 (−0.700, 1.128)	0.646	0.803	0.630 (−0.570, 1.829)	0.287	0.939
End-point	All stroke[a]	–	–	–	–	–	–
	Ischaemic stroke	−0.068 (−0.347, 0.211)	0.632	0.673	−0.013 (−0.470, 0.444)	0.953	1.000
	Subarachnoid haemorrhage	−0.286 (−0.717, 0.146)	0.194	0.209	−0.385 (−0.957, 0.187)	0.175	0.787

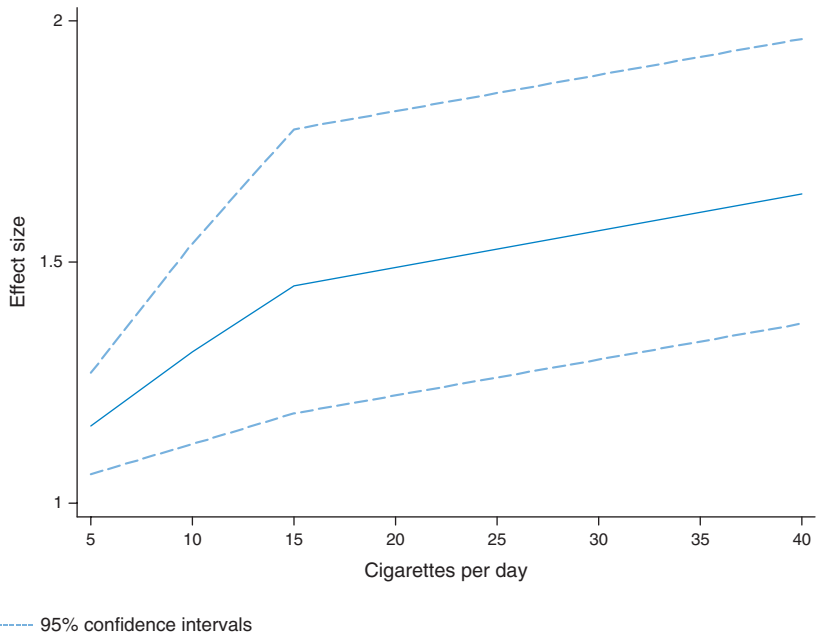
CI, confidence interval.

[a]Referent categories.

The 20 eligible studies comprised a total of 885 307 study participants, of whom 5894 (0.7%) suffered stroke. As a result of sub-group analyses, they provided 35 estimates of risk. Twenty-four of the estimates suggested an increased risk associated with exposure to secondhand smoke and 11 achieved statistical significance. Cohort studies contributed the most weight (61%) to the overall meta-analysis. The pooled estimates were statistically significant for both cohort studies and case–control studies. There was a high level of heterogeneity between the cross-sectional studies and the pooled estimate for cross-sectional studies did not reach statistical significance. Overall, the pooled estimate of the relative risk was 1.25 (95% CI: 1.12–1.38) with a moderate level of heterogeneity ($I^2 = 54.2\%$, $P < 0.001$) (Fig. 1).

The funnel plot appeared symmetrical (Fig. 2). Egger's test confirmed that there was no evidence of significant publication or small-study bias ($P = 0.836$). In the cumulative meta-analysis, the pooled estimate increased up to 1989 as more studies were published, but has remained fairly constant since, and year group was not a statistically significant predictor of effect size in the meta-regression analysis. Similarly, location, study design, sex, method of measuring exposure and case definition were all non-significant in both the univariate and multivariate analyses. In a sub-group analysis of cohort studies, length of follow-up was not a significant predictor of effect size (coefficient: 0.129, 95% CI: −0.013, 0.271, unadjusted $P = 0.076$, multiplicity adjusted $P = 0.266$) (Table 2).

Of the 11 studies that examined dose effect,[9,10,12,15,16,19,21–25] seven demonstrated evidence of a dose effect either overall,[10,19,21,24,25] or in only men[16] or only women.[9] Four studies reported no evidence of a dose relationship.[12,15,22,23] In the meta-analysis, we examined dose response measured by number of cigarettes as this definition enabled us to include the maximum number of studies ($n = 3$).[19,24,25] The crude plot of effect size against dose suggested that the relationship was non-linear. Therefore, the relationship was tested using the 'glst' command in Stata. The coefficients of the dose (coefficient: 0.032, 95% CI: 0.012, 0.053, $P = 0.02$) and dose squared (coefficient, 0.0005, 95% CI: −0.0010, −0.00002, $P = 0.043$) terms confirmed a statistically significant, non-linear dose response. There was a disproportionately high risk of stroke at levels of exposure lower than 15 cigarettes per day. Compared with people exposed to 0 cigarettes per day, the risk of stroke associated with secondhand smoke exposure was 1.16 (95% CI: 1.06–1.27) for exposure to 5 cigarettes per day increasing to 1.56 (95% CI: 1.24–1.96)



	Number of cigarettes / day			
	5	10	15	40
RR (95% CI)	1.16 (1.06-1.27)	1.31 (1.12-1.54)	1.45 (1.19-1.78)	1.56 (1.25-1.96)
p value	0.001	0.001	<0.001	<0.001

RR relative risk, CI confidence interval

Fig. 3 Relationship between dose of exposure to secondhand smoke and risk of stroke.

for those exposed to around 40 cigarettes per day (Fig. 3). The goodness-of-fit test (Q = 6.20, Pr = 0.9055) suggested that the model used for the analysis was appropriate.

Discussion

Main findings of this study and what is already known

Our meta-analysis demonstrated a strong, consistent association between secondhand smoke exposure and risk of stroke. Our pooled estimate was consistent with an earlier meta-analysis published in 2006,[26] at which time the US Surgeon General concluded that there was sufficient evidence to 'suggest, but not infer, a causal relationship'.[27]

What this study adds

Since then an additional five studies (four cohort studies[12–15] and one cross-sectional study[25]) have been published adding to the strength of evidence supporting the existence of a true association.[26] Furthermore, the existence of a dose–response relationship provides additional evidence that the association may be causal. Our findings suggested that the dose relationship between secondhand smoke exposure and stroke is non-linear, with disproportionately high risk at low levels of exposure. This result is consistent with coronary artery disease. Many gases that are toxic to the vascular system are present in higher concentrations in sidestream smoke than mainstream smoke. Exposure to secondhand smoke rapidly induces platelet aggregation, thrombosis, endothelial dysfunction and inflammation,[28] and is associated with plasma concentrations of homocysteine, C reactive protein, fibrinogen and oxidized LDL cholesterol comparable to those in active smokers.[29]

Limitations of this study

Our study has a number of strengths and weaknesses. The meta-analysis was based on published aggregate results. We did not have access to individual patient data. The pooled result was derived from 35 individual estimates of risk obtained from a very large total population. The individual studies varied in their inclusion criteria, design, definition of exposure, case definition and ascertainment, and statistical adjustment. Use of a random effects model enabled us to take account of these variations between studies and produce a more robust estimate of effect with only a moderate level of heterogeneity. There was no statistical evidence of publication or small-study bias. The pooled estimate for the sub-group of case–control studies was slightly higher than for cohort studies. This may be due to selection or recall bias in the former. Nonetheless, the pooled estimate for cohort studies alone suggested a statistically significant association.

Conclusions

Published studies suggest a strong, consistent, dose-dependent association between secondhand smoke and stroke, suggestive of a causal relationship. This supports the need to protect non-smokers from the harmful effects of exposure to secondhand smoke and adds to the evidence that there are no safe lower limits of exposure. Our study provides further evidence of the need for effective worldwide tobacco control measures.

Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

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Appendix

PRISMA flowchart