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META-ANALYSIS

Evidence relating cigarettes, cigars and pipes to cardiovascular disease and stroke: Meta-analysis of recent data from three regions

Peter Nicholas Lee, Katharine J Coombs, Jan S Hamling

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Peter Nicholas Lee, Katharine J Coombs, Jan S Hamling, Medical Statistics and Epidemiology, P.N.Lee Statistics and Computing Ltd., Sutton SM2 5DA, Surrey, United Kingdom

Corresponding author: Peter Nicholas Lee, MA, Senior Statistician, Medical Statistics and Epidemiology, P.N.Lee Statistics and Computing Ltd., 17 Cedar Road, Sutton SM2 5DA, Surrey, United Kingdom. peterlee@pnlee.co.uk

Abstract

BACKGROUND

More recent data are required relating to disease risk for use of various smoked products and of other products containing nicotine. Earlier we published meta-analyses of recent results for chronic obstructive pulmonary disease and lung cancer on the relative risk (RR) of current compared to never product use for cigarettes, cigars and pipes based on evidence from North America, Europe and Japan. We now report corresponding up-to-date evidence for acute myocardial infarction (AMI), ischaemic heart disease (IHD) and stroke.

AIM

To estimate, using recent data, AMI, IHD and stroke RRs by region for current smoking of cigarettes, cigars and pipes.

METHODS

Publications in English from 2015 to 2020 were considered that, based on epidemiological studies in the three regions, estimated the current smoking RR of AMI, IHD or stroke for one or more of the three products. The studies should involve at least 100 cases of stroke or cardiovascular disease (CVD), not be restricted to populations with specific medical conditions, and should be of cohort or nested case-control study design or randomized controlled trials. A literature search was conducted on MEDLINE, examining titles and abstracts initially, and then full texts. Additional papers were sought from reference lists of selected papers, reviews and meta-analyses. For each study identified, we entered the most recent available data on current smoking of each product, as well as the characteristics of the study and the RR estimates. Combined RR estimates were derived using random-effects meta-analysis for stroke and, in the case of CVD, separately for IHD and AMI. For cigarette smoking, where far more data were available, heterogeneity was studied by a wide range of factors. For cigar and pipe smoking, a more limited heterogeneity analysis was carried out. A more limited assessment of variation in risk by daily number of cigarettes smoked was also conducted.

Results were compared with those from previous meta-analyses published since 2000.

RESULTS

Current cigarette smoking: Ten studies gave a random-effects RR for AMI of 2.72 [95% confidence interval (CI): 2.40-3.08], derived from 13 estimates between 1.47 and 4.72. Twenty-three studies gave an IHD RR of 2.01 (95%CI: 1.84-2.21), using 28 estimates between 0.81 and 4.30. Thirty-one studies gave a stroke RR of 1.62 (95%CI: 1.48-1.77), using 37 estimates from 0.66 to 2.91. Though heterogeneous, only two of the overall 78 RRs were below 1.0, 71 significantly ($P < 0.05$) exceeding 1.0. The heterogeneity was only partly explicable by the factors studied. Estimates were generally higher for females and for later-starting studies. They were significantly higher for North America than Europe for AMI, but not the other diseases. For stroke, the only endpoint with multiple Japanese studies, RRs were lower there than for Western studies. Adjustment for multiple factors tended to increase RRs. Our RR estimates and the variations by sex and region are consistent with earlier meta-analyses. RRs generally increased with amount smoked. Current cigar and pipe smoking: No AMI data were available. One North American study reported reduced IHD risk for non-exclusive cigar or pipe smoking, but considered few cases. Two North American studies found no increased stroke risk with exclusive cigar smoking, one reporting reduced risk for exclusive pipe smoking (RR 0.24, 95%CI: 0.06-0.91). The cigar results agree with an earlier review showing no clear risk increase for IHD or stroke.

CONCLUSION

Current cigarette smoking increases risk of AMI, IHD and stroke, RRs being 2.72, 2.01 and 1.62. The stroke risk is lower in Japan, no increase was seen for cigars/pipes.

Key Words: Cigarettes; Cigars; Pipes; Cardiovascular disease; Stroke; Meta-analysis; Review

Core Tip: Recent North American and European studies indicate that current, compared to never cigarette smoking, increases risk in each sex by about 3-fold for acute myocardial infarction, about 2-fold for ischaemic heart disease (IHD), and about 1.6-fold for stroke. More limited evidence from Japanese studies suggests a similar increase in risk for IHD, but a lower increase, of about 1.2-fold, for stroke. The increase in risk is greater in heavier smokers. Limited recent data for cigar or pipe smoking, all from North America, finds no evidence of an increased risk of IHD or stroke, one study reporting a significantly reduced risk of stroke in exclusive pipe smokers. Our findings are generally consistent with evidence from earlier studies. Cigarette smoking increases risk of all the three diseases studied, but by a much smaller factor than noted for lung cancer and chronic obstructive pulmonary disease in our companion publication. Any increase in risk from cigar and pipe smoking has not been demonstrated.

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INTRODUCTION

It is known that cigarette smoking increases risk of various diseases, particularly chronic obstructive pulmonary disease (COPD), lung cancer, stroke and various forms of cardiovascular disease (CVD), including ischaemic heart disease (IHD) and acute myocardial infarction (AMI)[1,2]. However, any risk increases from cigar or pipe smoking, or from using other products containing nicotine are less well investigated. In a project based on studies conducted in North America, Europe and Japan (regions commonly studied in predictive modelling exercises[3-8] and which do not include countries such as India, where a wide variety of other tobacco products are commonly used), we are comparing relative risks (RRs) of various diseases for current *vs* never use of different products. In this journal we earlier published two reviews with meta-analyses of recent epidemiological evidence. One related current use of snus (Swedish snuff) or smokeless tobacco to risk of the major smoking-related diseases[9]. Another related current cigarette, pipe and cigar smoking to risk of lung cancer and COPD[10]. Here we systematically review and meta-analyse evidence relating current smoking of cigarettes, pipes and cigars to risk of AMI, IHD and stroke, based on publications in 2015 to 2020. We do not consider either electronic cigarettes or heat-not-burn products in our project, because large long-term studies relating risk of the main smoking-related diseases to their use have not so far been conducted. As in our previous publications we aim only to carry out meta-analyses concerning current product use, and to study how the derived RRs vary by factors like sex and region, and not investigating in detail variation by amount smoked, duration of smoking, time quit, or age at onset.

The work described here partially updates two earlier meta-analyses of ours. One[5], based on data from 15 countries in Europe, Asia or North America, reported analyses comparing risk in current v never cigarette smoking, giving a RR of 2.05 (95%CI: 1.90-2.21) combining 92 estimates for IHD/AMI, and of 1.48 (95%CI: 1.37-1.60) combining 57 estimates for stroke. The other[11], limited to Japan, gave an RR of 2.21 (95%CI: 1.96-2.50) combining 20 estimates for IHD and of 1.40 (95%CI: 1.25-1.57) combining 16 estimates for stroke. Neither of these reviews considered cigar or pipe smoking specifically. We compare our derived RR estimates with those earlier results, and also with findings of other meta-analyses/reviews published between 2000 and 2020, some of IHD and stroke[12-18], one of IHD only[19], some of stroke only[20-23] and some limited to particular types of stroke[24-28]. These reviews generally relate to cigarette smoking, or to undefined smoking, but one[12] gives results for exclusive cigar smokers.

MATERIALS AND METHODS

Study inclusion and exclusion criteria

Attention was restricted to publications in English in the years 2015 to 2020 which provided RR estimates for stroke, IHD or AMI comparing current and never smokers of cigarettes, of cigars, or of pipes. These had to be based on epidemiological cohort or nested case-control studies or randomized controlled trials which were conducted in North America, Europe or Japan, and which involved at least 100 cases of the disease of interest. The studies were excluded if they were restricted to specific types of the diseases, or to patients with specific medical conditions, or if the results were superseded by corresponding later results from the same study. Studies providing estimates for equivalent diseases, such as cerebrovascular disease rather than stroke, coronary heart (or artery) disease rather than IHD, or myocardial infarction rather than AMI were also included. However, studies providing estimates only for disease subsets, such as specific types of stroke were not included.

Literature searches

Initially, at stage 0, literature searches were conducted on MEDLINE for publications in 2015 to 2020. Searches were carried out on November 13, 2021 and used the terms "smoking" OR "smoking [MeSH Major Topic]" AND "cardiovascular disease" OR "heart disease" OR "stroke".

Then, at stage 1, titles and abstracts were screened to select publications that appeared to describe studies satisfying the inclusion criteria, and both meta-analyses and reviews that may cite other relevant publications. The initial screening was usually carried out by PNL, with acceptances checked by KJC, though in some cases KJC did the initial screening and PNL the checking. Disagreements were resolved *via* discussion.

Then, at stage 2, the full texts of the selected publications (and of relevant Supplementary files and other publications linked to them in the MEDLINE search) were obtained, and examined by PNL, who classified the publication as being an acceptance (*i.e.* it appeared to include relevant data), a reject (giving reason), a relevant review or a relevant meta-analysis. The rejections were then checked by KJC, with any disagreements resolved.

At stage 3, additional accepted publications not detected by the MEDLINE searches were sought by examination of reference lists of the accepted papers and of the relevant reviews and meta-analyses and, when obtained, dealt with as in stage 2.

Finally, at stage 4, copies of all the accepted publications (not the meta-analyses) were organized, first by country, and then by study within country, with studies conducted in multiple countries considered as a separate group. The aim was to eliminate from consideration those publications giving results for a study that were superseded by a later publication, and those publications which, on more detailed examination, did not fully satisfy the inclusion criteria.

Data entry

Data were entered into a study database and into an associated RR database. The study-specific information recorded was: Study name; country; region (North America, Europe, Japan or multiple); study design (cohort, nested case-control, or randomized controlled), study population (international, national, regional or specific, *e.g.* workers in a particular industry); study size (number of cases of the disease); year of start; length of follow-up; sexes considered (males only, females only, or both); and age range considered. Also recorded was a summary of the definition of each disease used in each study, including the international classification of disease (ICD) codes where they were provided in the source paper.

The information recorded relating to each RR was: The RR itself and its 95% confidence interval (CI), the RR and CI being estimated from the data provided if necessary; the study to which it related; an identifier for the paper providing the estimate; the year of publication of the paper; whether the RR related to exclusive use of the product; the sex to which it related (males, females or combined - combined RRs only being entered if sex-specific RRs were not available); the age range considered; the years of follow-up considered; the endpoint (from death certification only, or involving in-life diagnosis); whether a latency rule was applied (*i.e.* whether cases identified in the first few years of follow-up were ignored), the number of adjustment factors applied to the risk estimate, and whether the definition of disease was standard or not.

Meta-analyses

Meta-analyses could not be conducted for current cigar or current pipe smoking as the data proved to be too limited. Otherwise, individual study RR estimates were combined using fixed- and random-effects meta-analyses[29], with the

significance of between-study heterogeneity also estimated. For current cigarette smoking, where data were much more extensive, more detailed meta-analyses were conducted, separately for AMI, IHD and stroke, as described below.

Initially, meta-analyses were conducted based on either two RR estimates from each study, if separate RRs were available for males and females, or on a single estimate if the study reported only combined sex results or results for only one sex. Where there was a choice of RRs available for a study, those selected were based on a sequence of preferences applied in turn: (1) Exclusive rather than non-exclusive cigarette smoking; (2) a latency rule had been applied rather than not; and (3) adjustment for the most possible confounders.

Where the data permitted, heterogeneity was studied by the following factors: Sex; region; study population; year of start; study size; exclusive use; study design; lowest age considered; years of follow-up; endpoint; number of adjustment factors; and disease definition. Grouped levels of the variables were used as appropriate.

For each disease, forest plots were generated, with results separated by region, each line of the plot showing the study name (and sex where relevant) and giving the RR and 95%CI. Each RR is illustrated as a square with the area proportional to the weight of the estimate, surrounded by lines extending to the upper and lower 95% confidence limit. The plots also similarly present the overall RRs and 95%CIs for each region and for all the regions combined.

While these meta-analyses and heterogeneity investigations were based on between-study variation in RRs, some additional investigations were conducted on within-study variation in RRs, based on data from the same publication. For sex, these meta-analyses were based on the ratio of the RR for males to that for females, while for level of adjustment, results were compared based on the ratio of the RR adjusted for multiple potential confounding variables to the RR adjusted for no variables. Where multiple pairs of results were available within a publication, the pair selected was chosen based on the preferences described above.

Additional investigation of risk related to the number of cigarettes smoked. The papers selected for the meta-analyses relating cigarette smoking to risk of AMI, IHD and stroke were examined to identify those reporting RRs by number of cigarettes smoked. The results were then tabulated in order to assess those showing a tendency for RRs to increase with amount smoked. Formal meta-analyses of these results were not attempted in view of the various different ways in which the number of cigarettes smoked were grouped. Results by pack-years were not considered as this measure makes the invalid assumption that given increases in amount smoked and duration smoked have the same proportional effect on risk.

RESULTS

Literature searches

A flowchart of the searches is shown in Figure 1. Starting with 20,500 papers identified in the initial MEDLINE searches, the 49 papers identified provided results for AMI, IHD and stroke from respectively, 10, 23 and 31 studies (Figure 1).

For AMI, 20 RRs were available for analysis, all for cigarette smoking. For IHD, there were 53, 51 for cigarette smoking and one each for cigar and for pipe smoking. For stroke there were 76, 70 for cigarettes, four for cigars, and two for pipes. It should be noted that some studies provide more than one estimate, *e.g.* by sex, by level of covariate adjustment, or for different products.

Table 1 (AMI), Table 2 (IHD) and Table 3 (stroke) provide details of the studies considered. Some studies gave data for more than one disease.

The definitions of the diseases considered in each study are not shown in the tables, but can be found in Supplementary material 1.

AMI - cigarette smoking data available

Each study gave data for current cigarette smoking, with the data deriving from one publication per study. Of the total of ten studies, two were from North America [one United States of America (USA), one Canada], and eight were from Europe [two each from Sweden and United Kingdom (UK), and one from each of Estonia, Finland, Germany and Norway]. All were cohort studies. Three studies were national, six regional and one based on GP records. As can be seen in Table 1, the studies varied as regards different factors, including start year, length of follow-up, ages and sexes considered, numbers of AMI cases studied, whether cases were dead or diagnosed, and extent of adjustment for potential confounding factors. As shown in Supplementary material 1, the studies also varied in the definition of AMI, the standard definition being based on ICD-8 or ICD-9 code 410 or ICD-10 code I21.

AMI - cigarette smoking meta-analyses

Data were entered on 20 RRs, with at most four per study. The initial meta-analyses involved 13 RRs, these being selected using the preferences described above. As can be seen in Table 4 and Figure 2, the overall RR estimate (random-effects) was 2.72 (95%CI: 2.40-3.08), this being based on RR estimates that were extremely ($P < 0.001$) heterogeneous, though all exceeded 1.00 (range 1.47-4.72) and all but one of the RRs were significantly increased ($P < 0.05$).

Table 4 also shows RRs by level of ten different study or RR characteristics. The the most striking evidence of risk variation was for number of adjustment factors where the estimates adjusted for age only (2.52, 95%CI: 2.34-2.71) and for age and other factors (2.89, 95%CI: 2.48-3.37) were higher than that with no adjustment (1.47, 95%CI: 1.08-2.01). Estimates were also significantly higher for estimates from North America rather than Europe, for studies starting from 1988 onward than for earlier starting studies, for studies with shorter years of follow-up, and for studies using a standard disease definition. The RR for females exceeded that for males, but not significantly.

Table 1 Details of the 10 studies of acute myocardial infarction

Study ID[a]	Ref.	Country	Design	Study population	Start year	Yr followed	Age	Sex[b]	Cases	Adjust[c]	Excl[d]	Latency[e]	Endpoint	NRR[f]
BIOBANK	[37]	United Kingdom	Cohort	National	2006	12	40-69	M, F	5081	2	0	0	Diagnosed	2
CaCHS	[38]	Canada	Cohort	Regional	2001	13	20+	M, F	1133	15	0	0	Diagnosed	2
CALIBER	[39]	United Kingdom	Cohort	GP records	1997	13	30+	F	5628	1	0	0	Diagnosed	1
EPIC-GERM	[40]	Germany	Cohort	Regional	1994	14	35-65	C	507	0, 9	0	0	Diagnosed	2
ESTONGENOME	[41]	Estonia	Cohort	National	2002	13	18+	M, F	118	0, 1	0	0	Died	4[g]
KIHD	[42]	Finland	Cohort	Regional	1984	18	42-60	M	205	0	0	0	Diagnosed	1
TROMSO	[43]	Norway	Cohort	Regional	1979	33	20-94	F	854	0, 4	0	0	Diagnosed	2
VASTERBOTTEN	[44]	Sweden	Cohort	Regional	1990	19	30-60	C	2062	2, 9	0	0	Diagnosed	2
WHILA	[45]	Sweden	Cohort	Regional	1995	20	50-59	F	205	1, 7	0	0	Diagnosed	2
WHS	[46]	United States	Cohort	National	1992	26	45+	F	629	0, 14	0	0	Diagnosed	2

[a]Study IDs are BIOBANK: The UK Biobank Study; CaCHS: Canadian Community Health Survey; CALIBER: Cardiovascular disease research using linked bespoke studies and electronic health records; EPIC-GERM: European Prospective Investigation into Cancer and Nutrition, German component; ESTON-GENOME: Estonian Genome Center of the University of Tartu; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; TROMSO: Tromsø Study; VASTERBOTTEN: Västerbotten Intervention Programme; WHILA: Women's Health in the Lund Area Study; WHS: Women's Health Study.
[b]C: Results only for sexes combined.
[c]Number of adjustment factors for which relative risk (RR) available (0: Unadjusted, 1: Age adjusted, N > 1: Adjusted for N factors).
[d]No study had results available for exclusive use.
[e]No study excluded deaths in the early period of follow-up.
[f]Number of RRs available.
[g]Some of the RRs used from this study came from personal communication from Professor Koks.

AMI - cigarette smoking within-study comparisons

There were three comparable pairs of sex-specific RRs from the same study (see Supplementary material 1). The male RR was less than the female one in two pairs, and the overall estimate of the male/female ratio was not significant (ratio 0.74, CI 0.50-1.09).

There were four studies where comparison could be made between estimates adjusted for 2 or more covariates and estimates that were unadjusted or adjusted for age only. In only one of these did adjustment for multiple covariates materially increase the RR.

Within the studies considered, no study has pairs of estimates varying by other factors.

Table 2 Details of the 23 studies of ischaemic heart disease

Study ID[a]	Ref.	Country	Design	Study population	Start year	Yr followed	Age[b]	Sex[c]	Cases[d]	Adjust[e]	Excl[f]	Latency[g]	Endpoint	NRR[h]
7CNTRY-ITALY	[47]	Italy	Cohort	Regional	1960	50	40-59	M	319	3	0	0	Died	1
ARIC	[48]	United States	Cohort	National	1987	30	45-64	C	1798	0, 15	0	0	Diagnosed	2
BIOBANK	[49]	United Kingdom	Cohort	National	2006	12	40-69	C	547	0	0	0	Diagnosed	1
CALIBER	[39]	United Kingdom	Cohort	GP records	1997	13	30+	F	16800	1	0	0	Diagnosed	1
CPS-II	[50]	United States	Cohort	National	1982	22	30+	C	13478	0, 23	0	0	Died	2
CoCHS	[51]	Denmark	Cohort	Regional	1991	22	20-93	F	900	1	0	0	Diagnosed	1
ELSA	[52]	United Kingdom	Cohort	National	2004	13	52+	C	352	0, 7	0	0	Diagnosed	2
EPIC-10	[53]	Multi	Cohort	International	1991	19	35-70	M, F	7198	0	0	0	Diagnosed	2
	[54]	Multi	Nested CC	International	1991	19	35-70	C	7198	0	0	0	Diagnosed	1
EPIC-UK	[55]	United Kingdom	Cohort	Regional	1993	14	45-79	C	2332	0, 2, 6	0	0	Diagnosed	3
ESTON-GENOME	[41]	Estonia	Cohort	National	2002	13	18+	M, F	696	0, 1	0	0	Died	4[i]
FINRISK	[56]	Finland	Cohort	National	1982	25	25-74	F	NR	3, 8	0	0	Died	2
HAPIEE	[57]	Multi	Cohort	International	2002	9	NAR	C	225	0	0	0	Died	1
HSE-SHS	[58]	United Kingdom	Cohort	National	1994	17	NAR	C	1412	0, 7	0	0	Died	2
JACC	[59]	Japan	Cohort	Regional	1988	21	40-79	M, F	1554	0, 7, 9	x	0	Died	4
MALMO	[60]	Sweden	Cohort	Regional	1991	22	46-67	M, F	3217	0, 6	0	0	Diagnosed	4
MESA	[61]	United States	Cohort	Regional	2000	11	45-84	C	449	1, 14	0	0	Diagnosed	3
	[62]	United States	Cohort	Regional	2000	11	45-84	C	449	0	0	0	Diagnosed	1
NAS	[63]	United States	Cohort	Regional	1991	20	NAR	F	137	0	0	0	Diagnosed	1
NHS	[64]	United States	Cohort	Medical workers	1989	17	43-68	F	3874	0	0	0	Diagnosed	1
NHS-II	[65]	United States	Cohort	Medical workers	1991	20	25-42	F	456	1, 15	0	0	Diagnosed	2
PREVEND	[66]	Netherlands	Cohort	Regional	2001	9	32-80	C	212	0, 2, 10	0	0	Diagnosed	3
USA5	[67]	United States	Cohort	Regional	2000	11	55+	M, F	29931	0, 5	0	0	Died	4
WHI	[68]	United States	Cohort	National	1993	20	50-79	F	2975	11	0	0	Died	1
WHITEHALL	[69]	United Kingdom	Cohort	Civil servants	1967	43	40-69	M	3250	1	0	0	Died	1

[a]Study IDs are 7CNTRY-ITALY: Italian Rural Areas of the Seven Countries Study; ARIC: Atherosclerosis Risk in Communities Study; BIOBANK: The UK Biobank Study; CALIBER: Cardiovascular disease research using linked bespoke studies and electronic health records; CPS-II: Cancer Prevention Study 2; CoCHS: The Copenhagen City Heart Study; ELSA: The English Longitudinal Study of Ageing; EPIC-10: European Prospective Investigation Into Cancer and Nutrition; EPIC-UK: The European Prospective Investigation of Cancer -Norfolk; ESTON-GENOME: Estonian Genome Center of the University of Tartu; FINRISK: The National FINRISK Study; HAPIEE: Health, Alcohol and Psychosocial Factors in Eastern Europe (HAPIEE) project; HSE-SHS: Health Survey for England and the Scottish Health Survey; JACC: Japanese Collaborative Cohort Study; MALMO: Malmö Diet and Cancer Study; MESA: Multi-Ethnic Study of Atherosclerosis; NAS: Normative Aging Study; NHS: Nurses' Health Study I; NHS-II: Nurses' Health Study II; PREVEND: Prevention of Renal and Vascular End-Stage Disease; USA5: Cancer Prevention Study II Nutrition, Nurses' Health Study I Women's Health Initiative cohort, National Institutes of Health–AARP Diet and Health Study, and Health Professionals Follow-up Study; WHI: Women's Health Initiative; WHITEHALL: The Whitehall Study.

[b]NAR: No age restriction specified.

[c]C: Results only for sexes combined.

[d]NR: Not reported.

[e]Number of adjustment factors for which relative risk (RR) available (0 = unadjusted, 1 = age adjusted, N>1 = adjusted for N factors).

[f]x: Results available for exclusive use.

[g]No study excluded deaths in the early period of follow-up.

[h]Number of RRs available.

[i]Some of the RRs used from this study came from personal communication from Professor Koks.

IHD – cigarette smoking data available

Each study gave data for current cigarette smoking, with the data deriving from two publications for one study. Of the total of 23 studies, eight were from the USA, 14 from Europe (six UK, two from more than one country, and one from each of Denmark, Estonia, Finland, Italy, Netherlands, and Sweden), and one from Japan. One was a nested case-control study, the rest being of cohort design. Two studies were international, eight national, nine regional, two of medical workers, one of civil servants and one based on general practitioner records.

As demonstrated in Table 2, the studies varied by various factors, including start year, length of follow-up, ages and sexes considered, numbers of IHD cases studied, whether results were available for exclusive cigarette use, whether cases were dead or diagnosed, and the extent of adjustment for potential confounding factors. As shown in Supplementary material 1, the studies also varied with the definition of IHD used to identify cases, the standard definition being based on ICD-8 or ICD-9 codes 410-414 or ICD-10 codes I20-I25.

IHD - cigarette smoking meta-analyses

Data were entered on 49 RRs, with at most four per study. The initial meta-analyses involved 28 RRs, these being selected using the preferences described above. As can be seen in Table 5 and Figure 3, the overall RR estimate (random-effects) was 2.01 (95%CI: 1.84-2.21), this being based on RR estimates that were extremely ($P < 0.001$) heterogeneous, though all but one exceeded 1.00 (range 0.81-4.30), and 27 were significantly increased ($P < 0.05$).

Table 5 also shows RRs by level of 11 different study or RR characteristics. There was significant ($P < 0.05$) variation for two of these. One was endpoint, where the RR was higher for cases that had died compared to where it had been diagnosed. The other related to the number of adjustment factors where the RR was lower for those adjusted for age only, than for those that were unadjusted or adjusted for multiple factors. As for AMI, the RR for females exceeded that for males, but not significantly.

IHD – cigarette smoking within-study comparisons

There were five comparable pairs of sex-specific RRs from the same study (see Supplementary material 1). The male RR was lower in all five pairs, and the overall estimate of the male/female ratio was significant (ratio 0.85, 95%CI: 0.80-0.91).

Table 3 Details of the 31 studies of stroke

Study ID[a]	Ref.	Country	Design	Study population	Start year	Yr followed	Age[b]	Sex[c]	Cases	Adjust[d]	Excl[e]	Latency[f]	Endpoint	NRR[g]
7CNTRY-ITALY	[47]	Italy	Cohort	Regional	1960	50	40-59	M	225	3	0	0	Died	1
ARIC	[48]	USA	Cohort	National	1987	30	45-64	C	1106	0, 14	0	0	Diagnosed	2
BIOBANK	[70]	UK	Cohort	National	2006	12	40-69	M, F	4662	2	0	0	Diagnosed	2
CALIBER	[39]	UK	Cohort	GP records	1997	13	30+	F	11842	1	0	0	Diagnosed	1
CPS-II	[50]	USA	Cohort	National	1982	22	30+	C	5582	0, 23	0	0	Died	2
CaCHS	[38]	Canada	Cohort	Regional	2001	13	20+	M, F	1636	15	0	0	Diagnosed	2
	[71]	Canada	Cohort	Regional	2001	11	20+	M, F	1636	0	0	0	Diagnosed	2
ELSA	[52]	UK	Cohort	National	2004	13	52+	C	326	0, 7	0	0	Diagnosed	2
EPIC-10	[54]	Multi	Nested CC	International	1991	19	35-70	C	2187	0	0	0	Diagnosed	1
EPIC-ITALY	[72]	Italy	Cohort	Regional	1993	15	35-74	M, F	386	0, 2, 10	0	0	Diagnosed	6
EPIC-SPAIN	[73]	Spain	Cohort	Regional	1992	16	29-69	F	301	0	0	0	Diagnosed	1
EPIC-UK	[55]	UK	Cohort	Regional	1993	14	45-79	C	385	0, 2, 6	0	0	Diagnosed	3
ESTON-GENOME	[41]	Estonia	Cohort	National	2002	13	18+	M, F	156	0, 1	0	0	Died	4[h]
HAPIEE	[57]	Multi	Cohort	International	2002	9	NAR	C	109	0	0	0	Died	1
HSE-SHS	[58]	UK	Cohort	National	1994	17	NAR	C	690	0, 7	0	0	Died	2
JACC	[59]	Japan	Cohort	Regional	1988	21	40-79	M, F	3163	0, 7, 9	x	0	Died	4
JHS	[74]	USA	Cohort	Regional	2000	15	21-84	C	183	0, 11	0	0	Diagnosed	2
JP8	[75]	Japan	Cohort	National	1983	30	40+	M	3487	0	0	0	Died	1
MALMO	[76]	Sweden	Cohort	Regional	1991	22	46-67	C	305	0	0	0	Diagnosed	1
MESA	[62]	United States	Cohort	Regional	2000	11	45-84	C	180	0	0	0	Diagnosed	1
MILLION	[28]	United Kingdom	Cohort	National	1996	19	46-66	F	8103	8	0	0	Diagnosed	1
NFBC	[77]	Finland	Cohort	Regional	1966	49	14-46	C	352	0, 10	0	0	Diagnosed	2
NHIS	[78]	United States	Cohort	National	1987	24	18-95	C	2046	0, 5	x	0	Died	2
	[79]	United States	Cohort	National	1987	14	18-95	C	2046	0, 8, 9	0	x	Died	3
	[80]	United States	Cohort	National	1987	28	40-79	M	2046	0, 1, 9	0	x	Died	3

NHS	[64]	United States	Cohort	Medical workers	1989	17	43-68	F	3288	0	0	0	Diagnosed	1
NIH-AARP	[81]	United States	Cohort	Regional	2004	7	70+	C	1369	0, 4	0	0	Died	2
NLMS	[82]	United States	Cohort	National	1985	26	35-80	C	3083	0, 1, 5	x	0	Died	3
OHASAMA	[83]	Japan	Cohort	Regional	1998	12	60+	C	293	2	x	0	Diagnosed	1
PREVEND	[66]	Netherlands	Cohort	Regional	2001	9	32-80	C	83	0, 2, 10	0	0	Diagnosed	3
SCCS	[84]	United States	Cohort	Regional	2002	11	40-79	C	389	7	0	0	Died	1
USA5	[67]	United States	Cohort	Regional	2000	11	55+	M, F	9821	0, 5	0	0	Died	4
WHITEHALL	[69]	United Kingdom	Cohort	Civil servants	1967	43	40-69	M	1061	1	0	0	Diagnosed	1
WHS	[46]	United States	Cohort	National	1992	26	45+	F	887	0, 14	0	0	Diagnosed	2

[a]Study IDs are 7CNTRY-ITALY: Italian Rural Areas of the Seven Countries Study; ARIC: Atherosclerosis Risk in Communities Study; BIOBANK: The UK Biobank Study; CALIBER: cardiovascular disease research using linked bespoke studies and electronic health records; CPS-II: Cancer Prevention Study 2; CaCHS: Canadian Community Health Survey; ELSA: The English Longitudinal Study of Ageing; EPIC-10: European Prospective Investigation into Cancer and Nutrition; EPIC-ITALY: Italian European Investigation into Cancer and Nutrition; EPIC-SPAIN: Spanish European Investigation into Cancer and Nutrition; EPIC-UK: The European Prospective Investigation of Cancer -Norfolk; ESTON-GENOME: Estonian Genome Center of the University of Tartu; HAPIEE: Health, Alcohol and Psychosocial Factors in Eastern Europe (HAPIEE) project; HSE-SHS: Health Survey for England and the Scottish Health Survey; JACC: Japanese Collaborative Cohort Study; JHS: Jackson Heart Study; JP8: Pooled analysis of eight prospective studies in Japan; MALMO: Malmö Diet and Cancer Study; MESA: Multi-Ethnic Study of Atherosclerosis; MILLION: Million Women Study; NFBC: Northern Finland Birth Cohort; NHIS: National Health Interview Survey; NHS: Nurses' Health Study; NIH-AARP: National Institutes of Health–AARP Diet and Health Study; NLMS: National Longitudinal Mortality Study; OHASAMA: The Ohasama Study; PREVEND: Prevention of Renal and Vascular End-Stage Disease; SCCS: Southern Community Cohort Study; USA5: Cancer Prevention Study II Nutrition, Nurses' Health Study I, Women's Health Initiative cohort, National Institutes of Health–AARP Diet and Health Study, and Health Professionals Follow-up Study; WHITEHALL: The Whitehall Study, and WHS: Women's Health Study.

[b]NAR: No age restriction specified.

[c]C: Results only for sexes combined.

[d]Number of adjustment factors for which relative risk (RR) available (0 = unadjusted, 1 = age adjusted, N>1 = adjusted for N factors).

[e]x: Results available for exclusive use.

[f]x: Results available with deaths excluded in early period of follow-up.

[g]Number of RRs available.

[h]Some of the RRs used from this study came from personal communication from Professor Koks.

There were 14 study/sex combinations where comparison could be made between estimates adjusted for two or more covariates and estimates that were unadjusted or adjusted for age only. In all but two of the 14, adjustment for multiple covariates increased the RR ($P < 0.05$).

Within the studies considered, no study has pairs of estimates varying by other factors.

Stroke - cigarette smoking data available

Each study gave data for current cigarette smoking, with the data deriving from three publications for one of these studies, and from two for another. Of the 31 studies, 12 were from North America (11 from USA, one from Canada), 16 from Europe (seven UK, two Italy, two from multiple countries, and one each from Estonia, Finland, Netherlands, Spain and Sweden), and three from Japan. One was a nested case-control study, the rest being of cohort design. Two studies were international, 11 national, 15 regional, one of medical workers, one of civil servants and one based on general practitioner records.

Table 4 Acute myocardial infarction and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of studies	RR (95%CI)	Test of heterogeneity by level (NS = $P \geq 0.1$) and trend if relevant, *P* value
	All		13	10	2.72 (2.40-3.08)	< 0.001
5	Sex	Combined	2	2	2.98 (2.20-4.04)	
		Males	4	4	2.30 (1.57-3.37)	
		Females	7	7	2.83 (2.40-3.34)	NS
6	Region	N. America	3	2	3.42 (2.93-3.99)	
		Europe	10	8	2.54 (2.22-2.90)	< 0.01
7	Study population	National	5	3	2.85 (2.16-3.77)	
		Regional	7	6	2.69 (2.18-3.33)	
		Other	1	1	2.51 (2.33-2.71)	NS
8	Year of start of baseline	< 1988	2	2	1.81 (1.28-2.56)	
		1988+	11	8	2.93 (2.58-3.32)	< 0.05
9	Number of cases	< 1000	7	6	2.52 (1.96-3.25)	
		1000+	6	4	2.87 (2.46-3.35)	NS
10	Lowest age considered	< 30	5	3	3.02 (2.09-4.35)	
		30-44	6	5	2.58 (2.20-3.04)	
		45+	2	2	2.88 (2.40-3.46)	NS trend NS
11	Yr of follow-up	10-< 20	10	7	2.78 (2.40-3.23)	
		20-< 30	2	2	2.88 (2.40-3.46)	
		30+	1	1	2.11 (1.81-2.46)	< 0.05 trend < 0.01
12	Endpoint	Died	2	1	2.99 (1.34-6.67)	
		Diagnosed	11	9	2.71 (2.38-3.08)	NS
13	Number of adjustment factors	None	1	1	1.47 (1.08-2.01)	
		Age only	3	2	2.52 (2.34-2.71)	
		More	9	7	2.89 (2.48-3.37)	< 0.001
14	Disease definition standard	No	6	7	2.43 (2.06-2.87)	
		Yes	7	5	3.14 (2.63-3.74)	< 0.05

As can be seen in Table 3, the studies varied as regards different factors, including start year, length of follow-up, ages and sexes considered, numbers of stroke cases studied, whether results were available for exclusive cigarette use, or for cases being excluded during the early period of follow-up, whether cases were dead or diagnosed, and the extent of adjustment for potential confounding factors. As shown in Supplementary material 1, the studies also varied with the definition of stroke used to identify cases, the standard definition being based on ICD-8 or ICD-9 codes 430-438 or ICD-10 codes I60-I69.

Stroke - cigarette smoking meta-analyses

Data were entered on 70 RRs, with at most six per study. The initial meta-analyses involved 37 RRs, these being selected using the preferences described above. As can be seen in Table 6 and Figure 4, the overall RR estimate (random-effects) was 1.62 (95%CI: 1.48-1.77), this being based on RR estimates that were extremely ($P < 0.001$) heterogeneous, though all but one of the 37 RRs exceeded 1.00 (range 0.66-2.91), and 32 were significantly increased ($P < 0.05$).

Table 6 also shows RRs by level of 11 different study or RR characteristics, there being highly significant evidence ($P < 0.001$) of variation for three of them. One related to the RR being higher for studies in North America and Europe than for studies in Japan, one to the RR being higher for non-exclusive cigarette smokers than it was for exclusive cigarette smokers, and one to the RR being higher for studies with a shorter follow-up period.

Table 5 Ischaemic heart disease and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of studies	RR (95%CI)	Test of heterogeneity by level (NS = $P \geq 0.1$) and trend if relevant, *P* value
	All		28	23	2.01 (1.84-2.21)	< 0.001
19	Sex	Combined	10	10	1.94 (1.71-2.21)	
		Males	7	7	1.86 (1.53-2.26)	
		Females	11	11	2.23 (1.86-2.69)	NS
20	Region	N. America	9	8	2.23 (1.92-2.58)	
		Europe	17	14	1.90 (1.67-2.15)	
		Japan	2	1	2.15 (1.73-2.69)	NS
21	Study population	National	9	8	2.10 (1.92-2.30)	
		Regional	12	9	1.85 (1.56-2.19)	
		Other	7	6	2.18 (1.77-2.69)	NS
22	Year of start of baseline	< 1988	5	5	1.89 (1.56-2.27)	
		1988+	23	18	2.04 (1.83-2.28)	NS
23	Number of cases	< 1000	12	11	1.97 (1.58-2.45)	
		1000+	16	12	2.04 (1.83-2.27)	NS
24	Exclusive cigarettes	No	26	22	2.00 (1.82-2.21)	
		Yes	2	1	2.15 (1.73-2.69)	NS
25, 26	Lowest age considered	< 30	5	4	2.45 (1.77-3.39)	
		30-44	11	9	1.81 (1.61-2.05)	
		45+	9	7	2.06 (1.76-2.42)	NS trend without missing NS
		Missing	3	3	2.09 (1.16-3.78)	
27	Yr of follow-up	< 10	2	2	2.52 (1.07-5.90)	
		10-< 20	13	10	2.04 (1.77-2.35)	
		20-< 30	10	8	1.99 (1.78-2.23)	
		30+	3	3	1.68 (1.23-2.29)	NS trend NS
28	Endpoint	Died	13	10	2.23 (1.94-2.57)	
		Diagnosed	15	13	1.83 (1.62-2.05)	< 0.05
29	Number of adjustment factors	None	6	5	2.11 (1.78-2.50)	
		Age only	5	4	1.64 (1.39-1.93)	
		More	17	14	2.10 (1.88-2.35)	< 0.05
30	Disease definition standard	No	13	12	1.83 (1.59-2.10)	
		Yes	15	11	2.17 (1.93-2.45)	< 0.1

Stroke - cigarette smoking within-study comparisons

There were six comparable pairs of sex-specific RRs from the same study (see Supplementary material 1). The male RR was less than the female one in five of the pairs, and the overall estimate of the male/female ratio was significant (ratio 0.90, 95%CI: 0.82-1.00).

There were 18 study/sex combinations where comparison could be made between estimates adjusted for 2 or more covariates and estimates that were unadjusted or adjusted for age only. In all but one of the 18, adjustment for multiple covariates increased the RR ($P < 0.001$). Within the studies considered, no study has pairs of estimates varying by other factors.

Results relating cigarette smoking to daily amount smoked

The detailed results are given in Supplementary material 3. Fifteen of the studies provided data on RR by amount

Table 6 Stroke and current *vs* never cigarette smoking – results from random effects meta-analyses

Full output table	Factor	Level	No. of RRs	No. of Studies	RR (95%CI)	Test of heterogeneity by level (NS = $P \geq 0.1$) and trend if relevant, *P* value
	All		37	31	1.62 (1.48-1.77)	< 0.001
35	Sex	Combined	17	17	1.65 (1.52-1.50)	
		Males	9	9	1.48 (1.21-1.80)	
		Females	11	11	1.66 (1.39-1.99)	NS
36	Region	N. America	14	12	1.64 (1.48-1.83)	
		Europe	19	16	1.71 (1.51-1.94)	
		Japan	4	3	1.18 (1.04-1.34)	< 0.001
37	Study population	National	13	11	1.76 (1.47-2.11)	
		Regional	19	15	1.55 (1.36-1.78)	
		Other	5	5	1.51 (1.39-1.65)	N.S.
38	Yr of start of baseline	< 1988	8	8	1.43 (1.23-1.67)	
		1988+	29	23	1.68 (1.52-1.85)	< 0.1
39	Number of cases	< 1000	18	16	1.66 (1.44-1.91)	
		1000+	19	15	1.59 (1.41-1.78)	NS
40	Exclusive cigarettes	No	32	27	1.67 (1.52-1.84)	
		Yes	5	4	1.31 (1.19-1.45)	< 0.001
41, 42	Lowest age considered	< 36	8	6	1.59 (1.19-2.14)	
		30-44	16	13	1.48 (1.35-1.62)	
		45+	11	10	1.89 (1.68-2.12)	< 0.01 trend without missing < 0.01
		Missing	2	2	1.87 (1.54-2.28)	
43	Yr of follow-up	< 10	3	3	2.13 (1.80-2.53)	
		10-< 20	22	17	1.69 (1.52-1.89)	
		20-< 30	7	6	1.43 (1.29-1.60)	
		30+	5	5	1.44 (1.10-1.89)	< 0.001 trend < 0.001
44	Endpoint	Died	16	13	1.60 (1.41-1.81)	
		Diagnosed	21	18	1.63 (1.46-1.83)	NS
45	Number of adjustment factors	None	7	7	1.32 (1.08-1.62)	
		Age only	4	3	1.70 (1.31-2.20)	
		More	26	21	1.69 (1.53-1.88)	< 0.1
46	Disease definition standard	No	20	18	1.68 (1.51-1.88)	
		Yes	17	13	1.55 (1.36-1.77)	NS

smoked for one or more of the three diseases, with four giving results for AMI, six for IHD and ten for stroke. Given that some studies presented results separately for females and males, there were a total of 29 independent dose relationships. Twelve of these gave RRs (compared to never smokers) by two levels of amount smoked, and fifteen by three or more levels, with the remaining two dose relationships expressed as risk per daily amount smoked. Fifteen of the relationships came from North American studies, the others coming from European studies. With two minor exceptions (where the stroke results from the ARIC and NHIS studies showed virtually the same RR in heavier smokers as in lighter smokers,) the RR was always greater in the heaviest smoking group than in the lightest smoking group, and in the relationships with three or more levels, the risk increase was usually monotonic. These data demonstrate that a dose-response relationship exists between daily amount smoked and the risk of each of the three diseases.

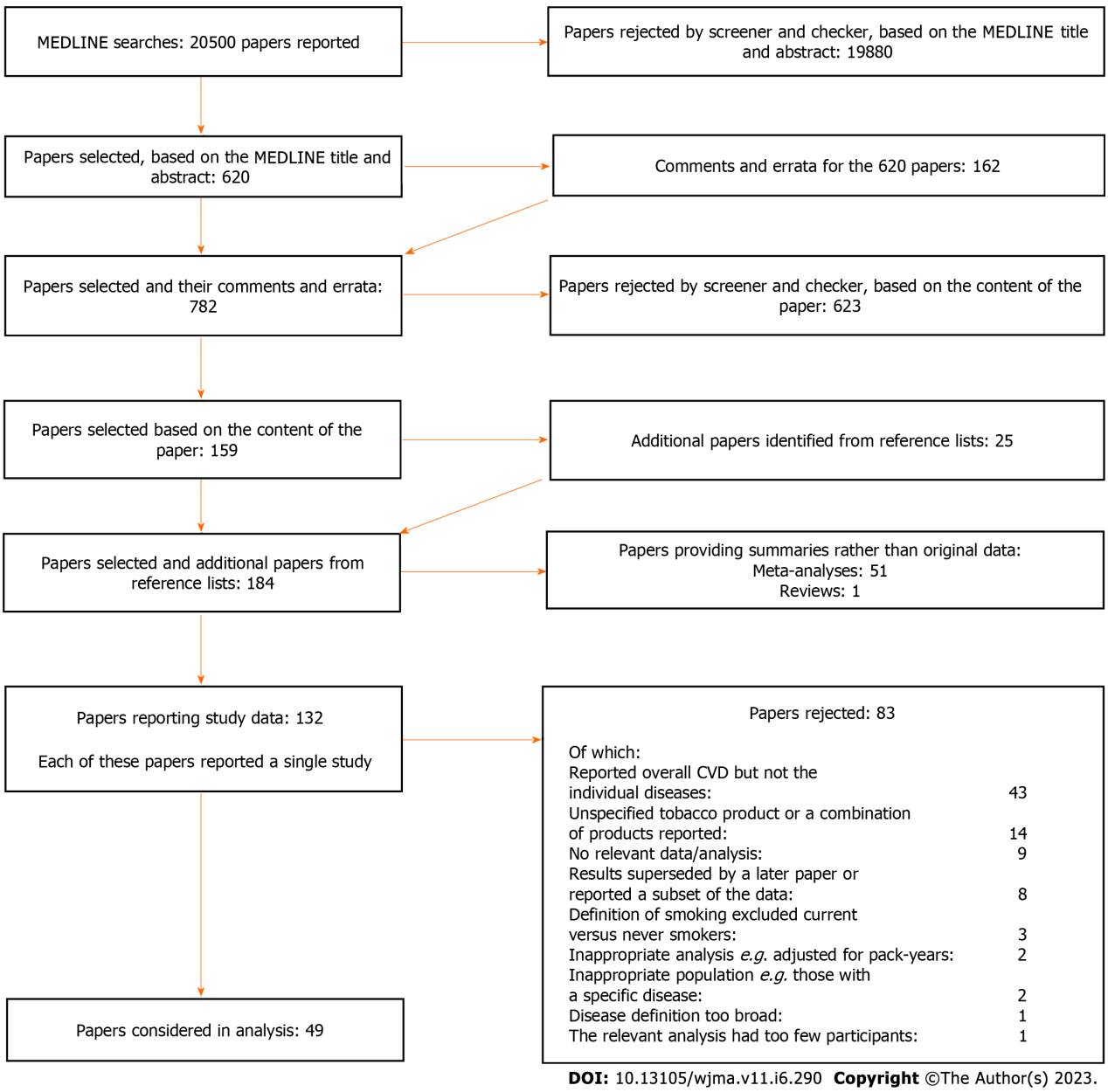

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Figure 1 Flowchart of the literature searches. CVD: Cardiovascular disease.

Results for cigar and pipe smoking

The detailed output for current smoking of cigars or pipes is given in Supplementary material 2. The data are very limited. There are no data at all for AMI. For IHD the only data come from study MESA, where the RRs compared to never smokers are 0.71 (95%CI: 0.35-1.45) for current smoking of cigars and 0.81 (95%CI: 0.26-4.55) for current smoking of pipes, both estimates being reduced but with very wide 95%CI. For stroke, the available data relates to exclusive product use. For exclusive cigar smoking, an estimate from study NHIS of 1.60 (95%CI: 0.72-3.57) is non-significantly increased, but that from study NLMS of 0.50 (95%CI: 0.21-1.22) is non-significantly reduced. For exclusive pipe smoking, the only study providing data is NLMS, where the RR of 0.24 (95%CI: 0.06-0.91) is significantly reduced.

DISCUSSION

Comparison with earlier reviews - cigarettes

We could find no other meta-analysis published in 2001 to 2020 that related cigarette smoking to the risk of AMI. However, there were various published meta-analyses for the other two diseases, as shown in Table 7 (IHD) and Table 8 (stroke) where their results are summarized and compared with our findings.

For IHD (see Table 7) the nine meta-analyses summarized[5,11,13-19] vary by the year of publication, the regions of the world considered, the definition of what is smoked and the comparison group, and the methodology used. However, the

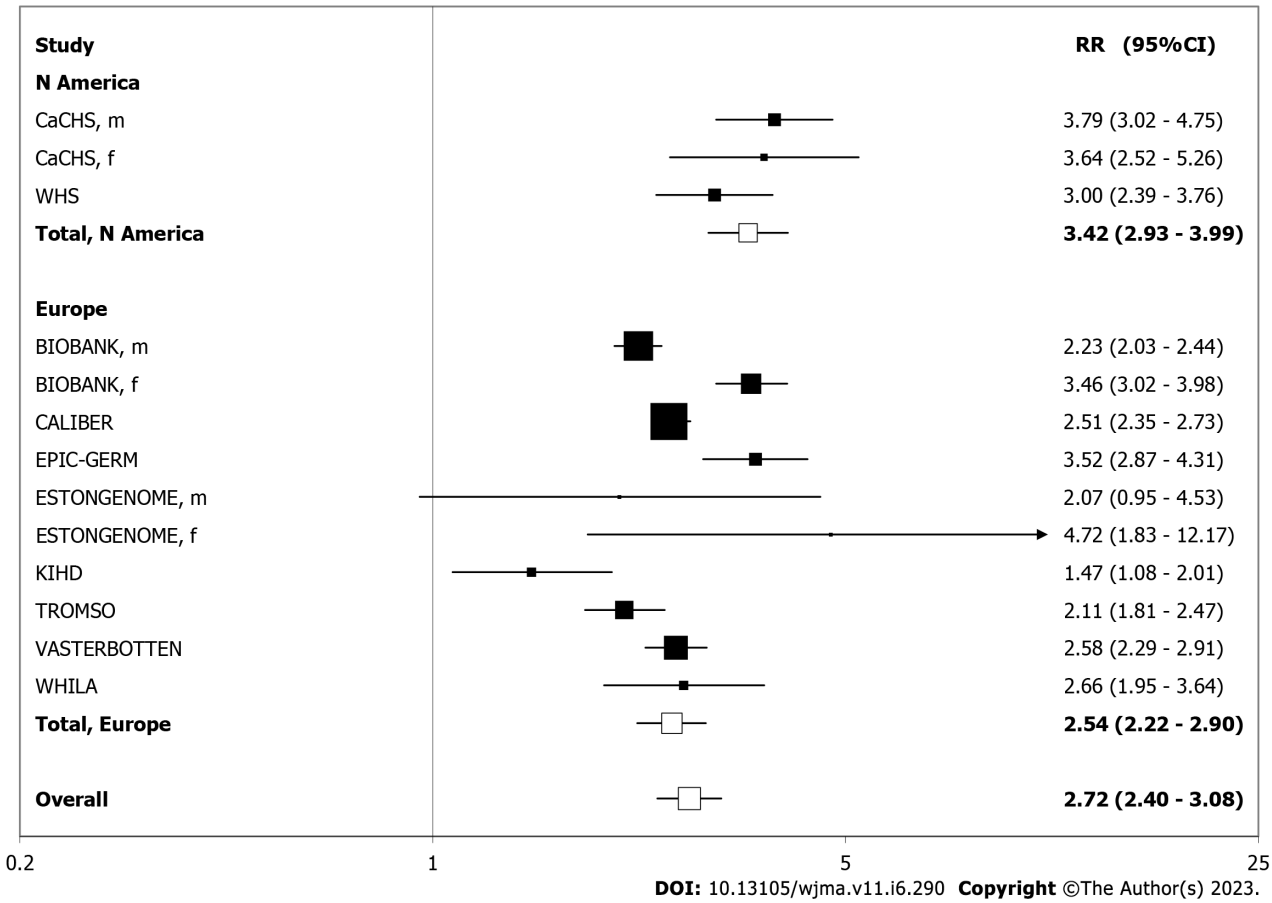

Figure 2 Forest plot for acute myocardial infarction and current *vs* never cigarette smoking, by region.

results are remarkably consistent, with the overall RR estimates varying only from 1.60 to 2.34, as compared with our estimate of 2.01 (95%CI: 1.84-2.21), and all the meta-analyses reporting a somewhat higher RR in females than in males. The consistency of the results, despite the variation in regions considered, also aligns with our finding of similar RRs by continent, though our analysis only included a single study in Japan. Variation in the current smoking RR by any of the factors other than sex or region considered in Table 5 is hardly mentioned at all in any of the earlier meta-analyses. One meta-analysis[11] found no clear relationship, as we did, with study size or number of variables that were adjusted for.

For stroke (see Table 8) data from 11 other meta-analyses[5,11,13-17,20-23] were summarized, these meta-analyses varying by the same factors mentioned above for IHD. Again, the results are quite consistent, with the RRs all significantly raised and varying from 1.32 to 2.27, compared to our estimate of 1.62 (95%CI: 1.48-1.77), and all the meta-analyses reporting a higher RR for females than for males. As previously noted, our analyses found a lower RR for studies in Japan than for studies in North America or Europe (see Table 6), and the earlier results also show relatively low meta-analysis RRs for studies conducted in, or predominantly in, Asia[11,16,17,23]. Few of the earlier meta-analyses considered any of the factors other than sex and region which we had considered in Table 6. One meta-analysis[11] reported higher RRs in studies involving fewer cases, a finding not seen in our analyses (see Table 6) or in another meta-analysis[21]. That meta-analysis reported a non-significantly higher RR in studies with a longer term (> 10 years) follow-up, whereas our analyses reported that the RR declined significantly with increasing follow-up. Our analyses did not consider type of stroke, but a number of the earlier meta-analyses did[17,18,24-28]. It was clear from the RRs reported in these meta-analyses, that the association with smoking was stronger for subarachnoid haemorrhage, where meta-analysis RRs varied from 2.20 to 3.46, than it was for other types of stroke, where RRs varied from 1.19 to 2.17 (data not shown).

For all three diseases our results show strong evidence of a dose-response relationship with amount smoked, a finding consistent with results from earlier meta-analyses (*e.g.*[14]).

Comparison with earlier reviews – cigars and pipes

As noted above, recent data relating to current cigar or pipe smoking are very limited, with no data for AMI, only one study for IHD, and only two for stroke. None of the RRs are significantly increased compared to never smokers, and one, that for stroke and exclusive pipe smoking, 0.24 (95%CI: 0.06-0.91), is significantly reduced. Though there appears to be no recent review for pipe smoking, a recent review[12] reports results from five studies relating current cigar smoking to IHD and from two studies relating current cigar smoking to stroke. From the RRs presented (and using those for primary rather than secondary cigar smoking where both RRs are given for a study) we estimate overall RRs of 1.06 (95%CI: 0.98-1.14) for IHD and 1.00 (0.90-1.11) for stroke, indicating that if any association exists it is much weaker than for cigarettes. It should be noted, however, that all of the RRs cited related to publications in the last century.

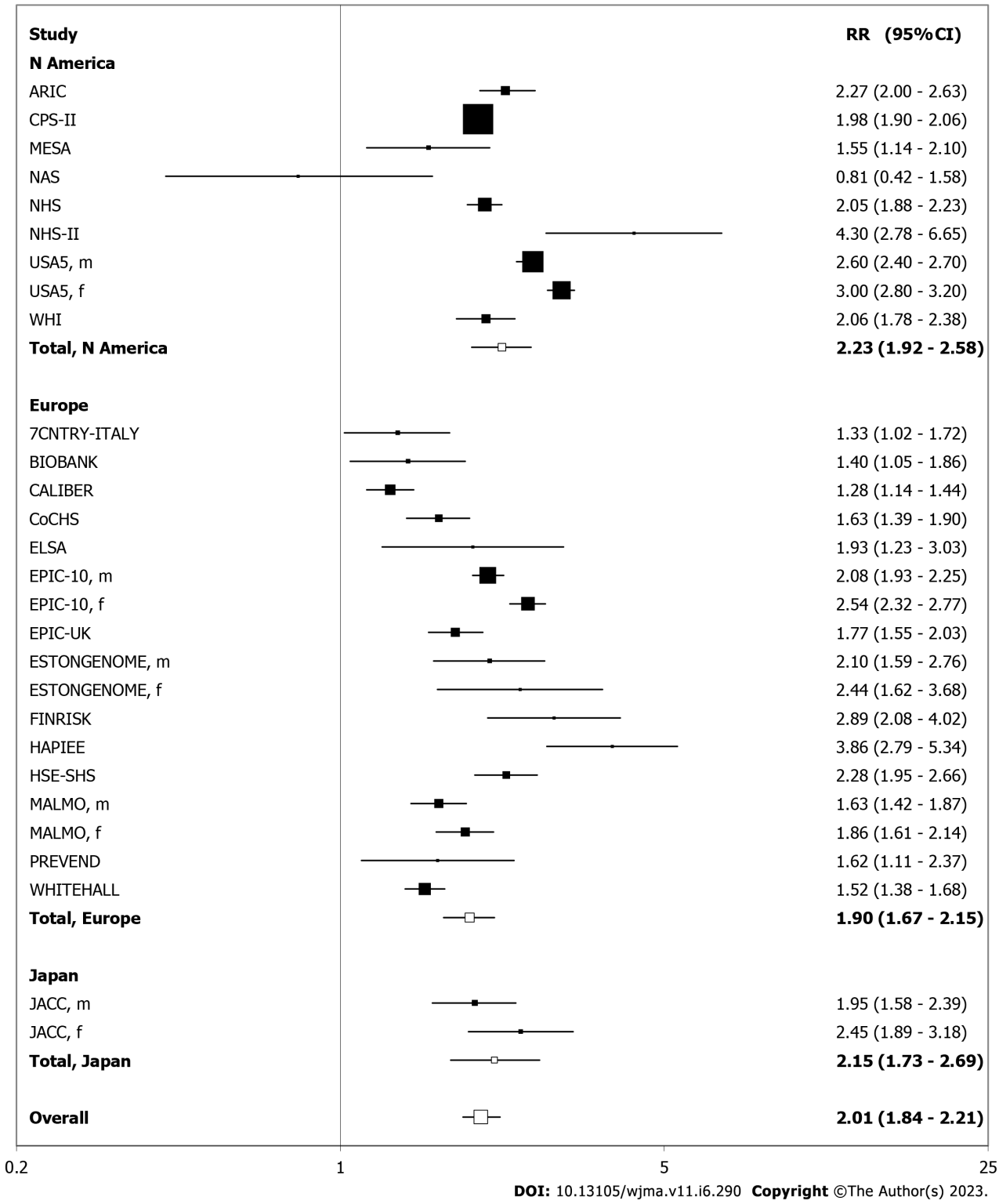

Figure 3 Forest plot for ischaemic heart disease and current *vs* never cigarette smoking, by region.

General considerations

While it is clear that cigarette smoking increases the risk of AMI, IHD and stroke (though by a much smaller factor than for lung cancer and COPD[10]) the RR estimates for all three diseases show highly significant ($P < 0.001$) heterogeneity between the studies. Of the possible reasons for this, many of which are inter-related, we have only investigated some. Thus, populations considered in different studies may vary by race and age, which may affect the product used and extent of exposure. Males and females may also smoke a different amount. The extent of exposure to other risk factors may also vary between studies, as may the extent to which analyses adjust for these factors. As noted previously[10], studies may vary in the definition of exposure, the detail in which changes in smoking over time are monitored or taken into account, the extent to which questions on smoking are answered accurately, the precise definition of disease, and the procedures for diagnosing and treating disease. These factors, not always recorded in the source publications, may help

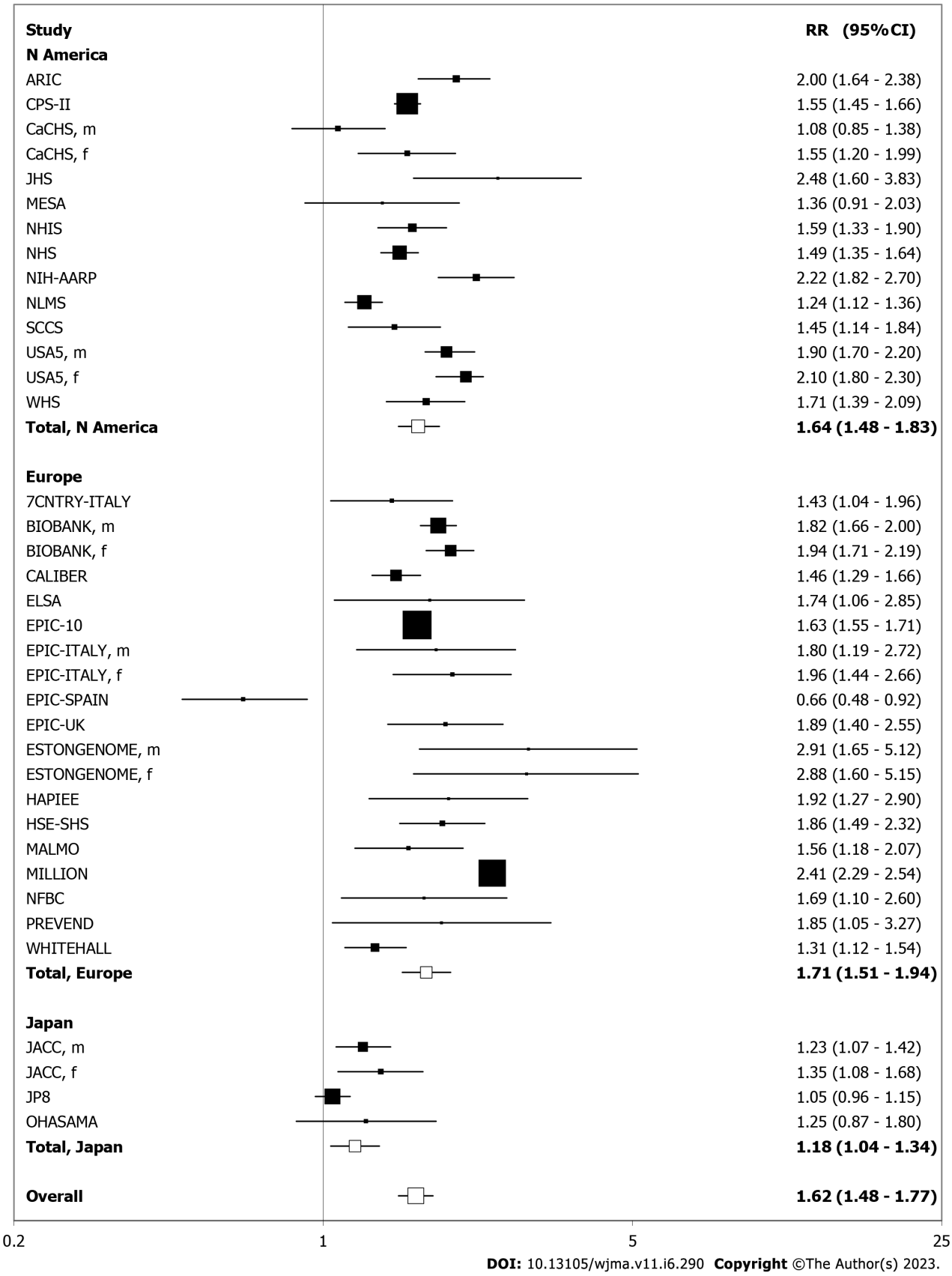

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Figure 4 Forest plot for stroke and current *vs* never cigarette smoking, by region.

Table 7 Comparison of meta-analysis relative risks for ischaemic heart disease in this study and in other publications

Ref.	Region	What is smoked	Comparison group[a]	RR (95%CI) males	RR (95%CI) females	RR (95%CI) any
Woodward *et al*[17], 2005	Asia-Pacific	Cigarettes	Non	1.56 (1.44-1.70)	1.73 (1.50-2.01)	1.60 (1.49-1.72)
Woodward *et al*[18], 2005	Asia, Australia, New Zealand	Cigarettes	Non			1.86 (1.69-2.06)
Nakamura *et al*[16], 2009	Asia	Undefined	Never			1.97 (1.66-2.33)
Huxley *et al*[19], 2011	Any	Cigarettes	Non	1.72 (1.57-1.88)	1.92 (1.66-2.23)	1.79 (1.61-1.98)
Mons *et al*[15], 2015	Any	Undefined	Never	1.80 (1.51-2.15)	2.26 (1.98-2.59)	2.03 (1.63-2.54)[b]
Lee *et al*[5], 2017[c]	North America, Europe, Asia	Cigarettes[d]	Never	1.99 (1.81-2.19)	2.12 (1.87-2.40)	2.05 (1.90-2.21)
Colpani *et al*[13], 2018	Any	Cigarettes[e]	Never		3.12 (2.15-4.52)	
Hackshaw *et al*[14], 2018	Any	20 cigarettes per day	Never	2.04 (1.86-2.24)	2.84 (2.21-3.64)	2.34 (1.96-2.79)
Lee *et al*[11], 2018[c]	Japan	Cigarettes[d]	Never	1.98 (1.74-2.25)	2.59 (2.06-3.27)	2.21 (1.96-2.50)
This meta-analysis	North America, Europe, Japan	Cigarettes	Never	1.86 (1.53-2.26)	2.23 (1.86-2.69)	2.01 (1.84-2.21)

[a]Former smokers are included among nonsmokers, but are not included among never smokers.
[b]Estimated from data provided.
[c]Includes results for coronary heart disease and acute myocardial infarction.
[d]Includes results for any product if those for cigarettes not available.
[e]Assumed to be cigarettes as study in women.

Table 8 Comparison of meta-analysis relative risks for stroke in this study and in other publications

Ref.	Region	What is smoked	Comparison group[a]	RR (95%CI) males	RR (95%CI) females	RR (95%CI) any
Woodward *et al*[17], 2005	Asia-Pacific	Cigarettes	Non	1.29 (1.20-1.38)	1.42 (1.26-1.62)	1.32 (1.24-1.40)
Nakamura *et al*[16], 2009	Asia	Undefined	Never			1.34 (1.12-1.48)
Peters *et al*[22], 2013	Any	Cigarettes	Non	1.67 (1.49-1.88)	1.83 (1.58-2.12)	1.73 (1.58-1.89)
Chen *et al*[20], 2014	Western	Cigarettes	Never			2.27 (1.76-2.93)
Mons *et al*[15], 2015	Any	Undefined	Never	1.44 (1.23-1.68)	1.78 (1.46-2.17)	1.59 (1.29-1.95)[b]
Lee *et al*[5], 2017	North America, Europe, Asia	Cigarettes[c]	Never	1.42 (1.29-1.56)	1.54 (1.33-1.78)	1.48 (1.37-1.60)
Wang *et al*[23], 2017	China	Undefined	Undefined			1.53 (1.06-2.20)[b]
Colpani *et al*[13], 2018	Any	Cigarettes[d]	Never		2.09 (1.51-2.89)	
Hackshaw *et al*[14], 2018	Any	20 cigarettes per day	Never	1.64 (1.48-1.82)	2.16 (1.69-2.75)	1.90 (1.54-2.35)
Lee *et al*[11], 2018	Japan	Cigarettes[c]	Never	1.32 (1.16-1.51)	1.50 (1.16-1.94)	1.40 (1.25-1.57)
Pan *et al*[21], 2019	Any	Cigarettes[c]	Never[e]	1.54 (1.11-2.13)	1.88 (1.45-2.44)	1.92 (1.49-2.48)
This meta-analysis	North America, Europe, Japan	Cigarettes	Never	1.48 (1.21-1.80)	1.66 (1.39-1.99)	1.62 (1.48-1.77)

[a]Former smokers are included among non smokers, but are not included among never smokers.
[b]Estimated from data provided.
[c]Includes results for any product if those for cigarettes not available.
[d]Assumed to be cigarettes as study in women.

[e]Sex-specific relative risks (RRs) are compared to non-smokers.

to explain variations between studies, and between our results and earlier meta-analyses.

Limitations of our work

Though limited to specific regions, and not providing any information relevant to developing countries, our meta-analyses provide a good idea of the size of the RR for current *vs* never cigarette smoking for all three diseases studied, which was our main objective. Although heterogeneity of the individual RR estimates limits the precision of the overall estimates, we have studied various factors that could contribute in part to the heterogeneity. However, we have not carried out multivariate analyses investigating how RRs vary jointly by the studied factors. For smoking of cigars and pipes, our estimates are limited by the paucity of available information. Our analyses are also limited by the lack of clear description of the factors considered in some studies. Notably, in some studies we cannot always tell with certainty whether the term "smoking" relates to any tobacco product use, to cigarette smoking or to exclusive cigarette smoking.

Other limitations arose as the objectives of our study were limited. Thus we did not consider RRs by duration of smoking, age of starting to smoke or individual types of the product smoked (such as tar level of cigarettes). Nor did we consider RRs for former smokers or users of multiple products, and we carried out only a limited assessment relating to amount smoked. Nor did we study variation by the age when the endpoint was diagnosed or when the subject died from it. Nor did we try to determine the extent of bias arising from misclassification of exposure, disease, or confounding variables.

We did not consider results for different types of stroke, which might have given insight into, for example, whether smoking increases risk differently for lacunar and non-lacunar stroke, a stronger association for lacunar stroke being reported in some studies (*e.g.*[30,31]), but being not clearly evident in others (*e.g.*[32-36]). Clearly there is scope for more detailed investigation.

CONCLUSION

Results from 10 studies of AMI, 23 of IHD and 31 of stroke published in 2015-2020 confirm a dose-related association of current cigarette smoking with all three diseases, with RRs somewhat higher for females than males, and for stroke only, and lower for studies in Japan than for studies in North America and Europe. Very limited evidence for current cigar and current pipe smoking shows no increase in risk for IHD and stroke, no data being available for AMI. Our findings seem generally consistent with data from other reviews and meta-analyses published this century. As noted in our companion paper on lung cancer and COPD, cigarettes smokers should quit to most effectively reduce the risks, though switching to other products containing nicotine, may greatly reduce these risks, as as has been most clearly demonstrated for Swedish snuff ("snus").

ARTICLE HIGHLIGHTS

Research background

While there are considerable data on risks from smoking, such risks may change with time, and recent evidence is required for smoking of cigarettes, cigars and pipes.

Research motivation

To take into account recent data on the risks of acute myocardial infarction (AMI), ischaemic heart disease (IHD) and stroke associated with current smoking of cigarettes, cigars and pipes.

Research objectives

To summarize recent data on the risk of AMI, IHD and stroke related to current cigarette, cigar and pipe smoking in North America, Europe and Japan.

Research methods

Searches on MEDLINE identified publications in English in 2015-2020 giving data on risks of the three diseases associated with current (*vs* never) cigarette, cigar or pipe smoking in studies conducted in the three regions. Studies were accepted which were of cohort or nested case-control design or were randomized controlled trials, which involved at least 100 cases of the disease of interest, and were not restricted to specific disease subsets, to patients with specific medical conditions or which reported results superseded by later reports of the study. Relative risk estimates were extracted from each study and overall estimates derived using random-effects meta-analyses.

Research results

There were available results from 10 studies for AMI, from 23 studies for IHD, and from 31 studies for stroke, the studies

being mainly conducted in North America and Europe. Overall relative risk (RR) estimates for current cigarette smoking were 2.72 for AMI, 2.01 for IHD and 1.62 for stroke. Estimates were dose-related to daily cigarette consumption, and somewhat higher for females than males. Estimates were relatively low in Japan for stroke. RR estimates tended to be higher for studies starting later and with a shorter follow-up period and where adjusted for multiple covariates. Only a few studies in the United States provided findings for current cigar or current pipe smoking, and then only for IHD and stroke. There was no evidence from these studies that smoking either of these products increased risk of these diseases.

Research conclusions

Consistent with evidence from earlier studies, increased risks for all three diseases are clearly seen for current cigarette smoking, but not for current cigar or pipe smoking.

Research perspectives

Cigarette smoking increases the risks of developing AMI, IHD and stroke, though by a factor much lower than for lung cancer and chronic obstructive pulmonary disease. To reduce these risks most effectively, cigarette smokers should quit, though switching to other products containing nicotine, such as Swedish snuff ("snus"), may also materially reduce these risks.

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FOOTNOTES

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Country/Territory of origin: United Kingdom

ORCID number: Peter Nicholas Lee 0000-0002-8244-1904; Katharine J Coombs 0000-0003-0093-7162; Jan S Hamling 0000-0001-7788-4738.

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