DRAFT 1

A REVIEW OF THE EPIDEMIOLOGY

OF HEART DISEASE

RELATED TO ACTIVE SMOKING

THE ROLE OF AMOUNT SMOKED,

AGE AND TIME QUIT SMOKING

Peter N Lee
17 Cedar Road
Sutton
Surrey, SM2 5DA
UK

[July 2001]

EXECUTIVE SUMMARY

A compilation is presented of the epidemiological evidence concerning four aspects of the relative risk of heart disease associated with cigarette smoking:

1) How the relative risk in current smokers varies by amount smoked,
2) How the relative risk in current smokers varies by age,
3) How the relative risk in current smokers varies jointly with amount smoked and age, and
4) How the relative risk in ex-smokers varies by time given up smoking.

Data from 48 case-control and prospective studies providing relevant information have been systematically presented. Relative risks and 95% confidence intervals relating to all four aspects of smoking considered have been extracted, or calculated where necessary. Results were usually extracted for ischaemic (coronary) heart disease or acute myocardial infarction.

Of the 48 studies, 37 were prospective (3 with over 25 years follow-up) and 11 were case-control. Nineteen were conducted in the USA, 7 in the UK, 13 in the rest of Europe, 5 in Asia, 2 in Canada and 1 each in Argentina and Australia. The earliest study started in 1949. Six studies involved over 5000 heart disease cases, with 2 exceeding 30000. Fourteen further studies involved over 1000 cases. Twenty of the 48 studies were of both sexes, with 20 considering only males and 8 only females. Two studies restricted attention to the elderly (65+) while six studies restricted attention to younger subjects (55-). Many of the studies concerned special groups (e.g. doctors or war veterans) which were not necessarily representative of the population at large. Although all the studies adjusted for age (and sex where relevant) about half the studies took no other potential confounding variables into account in their analyses.

At this stage the data presented here have not been placed on a computer database to allow formal meta-analyses to be conducted and a more detailed evaluation of how differences between study findings depend on various aspects of the studies. For the present, conclusions were based on a simpler examination of the data. The main conclusions to be drawn are as follows:

1. Smoking is associated with an increased risk of heart disease.

2. The relative risk is dose-related, being quite consistently higher for heavy than for light smokers.

3. The slope of the dose-response relationship does not appear to rise smoothly. The increase in risk per cigarette smoked is markedly higher at lower levels of smoking than at higher levels of smoking.

4. The relative risk of smoking decreases markedly with increasing age. At ages under 50 relative risks exceeding 4 are commonly reported, but at ages over 70 relative risks are typically less than 2.

5. In most of those studies that relate risk jointly to age and amount smoked, risks can be seen to increase with increasing amount smoked for a given age and to decrease with age for a given amount smoked. though this pattern is very clear for some studies (e.g. CPSI for both sexes and CPSII for males) it is not always so clear (e.g. CPSII for females).

6. In ex-smokers risk is intermediate between that of never and current smokers and declines with increasing time given up. The idea that, on giving up, risk of heart disease rapidly declines to the level of never smokers seems not to be supported by the data taken at face value.

Possible sources of bias and confounding are discussed. The strength of the association of heart disease with smoking at younger ages suggests that it is unlikely to be explained by bias or confounding. The general conclusions that risk increases with amount smoked and decreases on giving up smoking and that the relative risk is greater in young men and women seem unlikely to be affected by more detailed analysis. However it seems possible that the observed shape of the dose-response relationship for current smokers may be biassed in some prospective studies by some subjects classified as light smokers increasing amount smoked during the follow-up period, and some subjects classified as heavy smokers decreasing it. Also, conclusions about risks in ex-smokers based on prospective studies may be biassed if some subjects classified as ex-smokers were actually still smoking or resumed smoking during follow-up.

INDEX

1. Introduction

1.1 Objective

The objective of this review is to provide a compilation of the epidemiological evidence from case-control and prospective studies concerning four aspects of the relative risk of heart disease associated with cigarette smoking:

1) How the relative risk in current smokers varies by amount smoked,
2) How the relative risk in current smokers varies by age,
3) How the relative risk in current smokers varies jointly with amount smoked and age, and
4) How the relative risk in ex-smokers varies by time given up smoking.

1.2 This review

In order to achieve a useful review in a reasonable time, it was decided to limit attention to studies present in our extensive literature files. Unlike the IESLC project, no attempt has been made to carry out formal literature searches to detect all studies which might have relevant data. For that study it took about a year to be reasonably confident that we had a virtually complete set of published data. The data on heart disease and smoking are about as voluminous as those for lung cancer and smoking. However our in-house files provided a very considerable amount of useful data, and it is very doubtful whether a complete data set would have affected the conclusions reached.

No attempt has been made at this stage to enter the relative risks and confidence intervals presented in this report onto computer with a view to conducting formal meta-analyses. Rather impressions are reached from a less formal overview of the data. If necessary, it would be possible at a later date to enter the data presented here onto computer for analysis and/or to extend the literature considered.

This report contains six further main sections.

Section 2 of this review concerns materials and methods, giving fuller details of how the studies were selected and the approaches used to extract relative risk estimates and confidence intervals.

The main characteristics of the 48 studies selected are summarized in section 3.

Section 4 considered in turn the evidence collected in relation to each of the four main objectives.

Section 5 discusses the overall evidence and draws conclusions.

Following acknowledgements in section 6 and references in section 7, the tables of results are presented, the first digit of the table number relating to the section of the text to which the table refers. Finally, appendices provide additional detail.

2. Methods

2.1 Selection of studies

In-house we have a literature database on smoking and health collected over many years which runs to over 20,000 references (the great majority in the English language). Papers in files that might have contained relevant data were screened manually, and those that did in fact contain data relevant to one or more of the four objectives were extracted for further study. The papers were then sorted according to the country where the study described was conducted, and then sorted further by study. A total of 48 studies were identified (but see also section 3.2).

2.2 Extraction of data

The objective was to present data to show how the relative risk of heart disease associated with cigarette smoking varied:

1) by amount smoked (in current smokers),
2) by age (in current smokers),
3) jointly by amount smoked and age (in current smokers), and
4) by time given up smoking (in ex-smokers).

Relative risks* were generally presented with never smokers as the base group (the denominator). However, in a few studies (as noted in the relevant tables), current smokers were compared to nonsmokers, i.e. ex-smokers were included in the base group.

The comparison groups (numerators) would generally be smokers of cigarettes. However, in some studies, noted in the text, pipe and cigar smokers were included in the comparison group, with amount smoked being expressed in terms of grams/day or cigarette equivalents. Also ex-smokers were included in the comparison group in some studies.

---

*For convenience the term "relative risk" is used not only for relative risks estimated directly in prospective studies but also for relative risks estimated approximately by odds ratios in case-control studies.

In the tables giving relative risks by time given up smoking, relative risks are also presented for current smokers where these are available.

Where prospective studies report at multiple time points, the latest data relevant to each of the four objectives have been used.

Where possible to do so risks have been extracted for coronary heart disease (CHD) or ischaemic heart disease (IHD) which is the same, or the nearest equivalent, e.g. arteriosclerotic heart disease (AHD) in older studies. In some studies results are only available under the wider category of cardiovascular disease (CVD). A number of estimates extracted are for acute myocardial infarction (AMI). Where studies present separate data for fatal and non-fatal AMI the combined data have been used.

Wherever possible 95% confidence intervals (95% CI) are presented along with the relative risk estimates. Relative risks and 95% CI have been estimated, where necessary, from the data as presented in the source papers. The following techniques have been used, as appropriate (sometimes in combination):

1) Conversion of 90% to 95% confidence limits, assuming the logarithm of the relative risk is normally distributed.
2) Estimation of the variance of the logarithm of the relative risk (V) for case-control studies using the formula $V = 1/A+1/B+1/C+1/D$ where A and B are the numbers of exposed and unexposed cases and C and D are the corresponding numbers of controls.
3) Estimation of V for prospective studies using the formula $V = 1/A+1/B$. (Note that where relative risks are adjusted, this (and the previous) formula may somewhat understate the true variance.)
4) Estimation of effective numbers of controls (M_i) by smoking group (i) where the author only presents the number of cases (N_i) and the adjusted relative risks (R_i) by smoking group and the total number of controls (M_0). Here the formula $M_i = (N_i*M_0)/(R_i\ \Sigma(N_i/R_i))$ was used.

5) Estimating relative risks in prospective studies using O/E as an indicator of risk, where O is the observed number of deaths and E that expected from a standard population.

6) Estimating deaths (D_i) in a smoking category (i) in prospective studies where the author only presents data on total deaths (D_0), giving rates (R_i) and person years (or populations at risk) (Y_i) by category. Here the formula used was $D_i = (R_i*Y_i*D_0)/\Sigma(R_i*Y_i)$.

7) For prospective studies, combining risk estimates over smoking levels using the formula $R_0 = \Sigma D_i/(\Sigma D_i/R_i)$, where R_i are the risk estimates and D_i the numbers of deaths by smoking level, and R_0 is the combined estimate.

8) For prospective studies where risk estimates are given separately for each age group, calculating overall age-adjusted risk estimates by direct standardization to the age distribution of the overall population being studied. Thus if w_i are the weights of the standard population (Σw_i), d_{ij} are the numbers of deaths and λ_{ij} are the rates, i referencing age and j smoking group, we calculate the standardized rate S_j as $S_j = \Sigma w_i \lambda_{ij}$ and its variance as var $S_j = \Sigma(w_i^2 \lambda_{ij}^2/d_{ij})$. The variance of the logarithm of the relative risk of smoking groups a and b is then given by $V = (\text{var } S_a)/S_a^2 + (\text{var } S_b)/S_b^2$.

Note that results are only presented to one decimal place where the author presents them to one decimal place or calculations start from data to one decimal place. Otherwise, data are presented to two decimal places (except for relative risks or 95% CI of 10 or more which are given to one decimal place).

Appendix A gives details of the source(s) from which each presented relative risk and 95% CI was obtained and indicates whether the data came directly from the source or required estimation. The actual details of the estimations are retained in-house on spreadsheets (Quattro Pro).

3. Study characteristics

3.1 Introduction

This review focuses on 48 studies which have presented relevant results. Table 3.1 gives, for each study, the study short name by which it will be referred, its title, its location and study type and the period during which the heart disease cases occurred. The main references used for each study [1-56] are given in Appendix B, although in a few studies other references were used to obtain some of the information in the tables in this section.

3.2 Overlap of studies

The 48 studies are not completely independent. In particular, some points should be noted:

(i) Combined results from the Seven Countries Study are reported under KEYS, but results are also reported separately for the Finnish cohorts (PEKKAN) and the Italian cohorts (CONTI).

(ii) Results from the Framingham study are reported under FRAMIN, but results are also reported for a combined analysis of the Framingham and Albany studies under DOYLE and for a combined analysis from these two studies and three additional studies under the pooling project (POOLIN).

(iii) PRESCO is a combined analysis of data from three studies in Denmark, not individually reported.

3.3 Location

Five studies (as defined in this review) were conducted in Asia (two in China, two in Japan, one in Taiwan), with one study conducted in Australia and 22 in the Americas (19 in the US, two in Canada and one in Argentina). The remaining 20 studies were conducted in Europe(seven in the UK, four in Sweden, three in Italy, two in Norway, one each in Denmark, Finland and Switzerland and one in seven countries). No studies included in this review have been conducted in Africa, USSR or Eastern Europe.

3.4 Study type

Of the 48 studies listed in Table 3.1, 11 were of case-control design (one nested within a prospective study). The remaining 37 studies were of prospective design.

3.5 Period of study

Table 3.1 includes information on the period during which the heart disease cases occurred. This period is of relevance given the considerable change over time in the type of cigarette smoked.

Case-control studies tended to report results relatively late, the earliest being the ALDERS, ROSENB1 and ROSENB2 studies published in 1985, and many not reporting until the 1990s.

Many of the prospective studies started much earlier, with FRAMIN starting in 1949 and DOLL, WEIR, DORN, HAMMON and the studies in POOLIN starting before 1955. The prospective studies with the longest follow-up periods were DOLL (40 years), FRAMIN (34 years) and DORN (26 years).

All the five-year periods from 1960-64 to 1985-89 were considered by at least 16 of the studies, with 1980-84 the period covered by the largest number, 27. Fewer studies covered the period earlier or later than this, with only two studies (DUNN, ROSENB4) considering deaths since 1995.

3.6 Heart disease cases in the 48 studies

Table 3.2 presents some relevant details relating to the heart disease cases in the 48 studies. Numbers of cases shown usually relate to the total number in the study, though in some studies they relate to the actual number included in the analyses considered by the source paper. Further details of numbers of cases for specific analyses are shown in later tables.

The largest studies in terms of numbers of heart disease cases were CPSI and DORN. CPSI had data on 41448 CHD cases, and while DORN had data on 164785 total deaths, with possibly around 30000 due to CHD. Other studies with over 5000 deaths were CPSII (20114), DOLL (6617), MRFIT (6327) and HAMMON (5297). There were also a further 14 studies with 1000 or more cases. The smallish studies, with less than 100 cases, were the two in China (CHEN, YUAN) and the one in Italy (CONTI). None of the case-control studies were based on more than 3000 cases, though four (CHUN, ROSENB2, ALDERS, SCHARG) were based on 1000 or more.

The case-control studies were most commonly based on hospital admissions with AMI, often first AMI, though some were based on other definitions (ALDERS used CHD and CHUN, DUNN and CROFT included heart attack or MI deaths). Of the prospective studies, most were based on death drom CHD, IHD or AHD, according to death certificates. The studies of SEMENC and LACROI used the wider definition of total CVD, while BRETT used deaths from coronary thrombosis. Some of the prospective studies (PRESCO, ROSENG, TANG, ROSENM, FRAMIN, KAWACH, DOYLE, POOLIN) included non-fatal AMI (or CHD) in their cases.

3.7 Populations at risk (or controls) in the 48 studies

Table 3.3 similarly presents some relevant details of the populations at risk (or controls for case-control studies).

Of the 48 studies, 20 were of both sexes, 20 considered males only (or virtually so as in DORN) and 8 considered females only. Studies considering males only tended to be conducted earlier while studies considering females only tended to be conducted later.

The prospective studies with the largest populations studied were CPSI and CPSII which each involved over 1 million men and women. Five other studies (HIRAYA, DORN, HAMMON, KAWACH, MRFIT) involved over 100000 subjects. Six of these largest seven studies were conducted in the USA. Other relatively large studies, with 50000-99999 subjects were BEST, TVERDA1, BRETT, FRIEDM and WEIR.

Table 3.3 also gives some details of what the populations studied were and the range of ages at the start of the study. Many of the studies had an age distribution typical of the working population, but excluding the young (e.g. 35-64), with a number also including subjects of older ages. Two studies (PAGANI, LACROI) were unusual in that they restricted attention to the elderly (65+). There were also some studies which restricted attention to the young - these included the prospective studies (TVERDA1 and TVERDA2 (35-49) and the case-control studies DUNN (16-44), ROSENB1 (25-49) and ROSENB2 (20-54). One study (HEDBLA) unusually restricted attention to subjects exactly 55 years old. Of course, in the prospective studies, data may be available on risk for older ages than the ranges indicated, as results are often presented by current age, not age at the start of the study.

3.8 Aspects of smoking considered

Table 3.4 shows which studies considered which of the four aspects of smoking with which this report is concerned. 45 of the 48 studies presented data on the smoking risk by number of cigarettes smoked, 25 presented data on risk by age and 20 presented data on risk jointly by amount smoked and age. 17 presented risk by time given up smoking for ex-smokers.

3.9 Potential confounding variables allowed for

All the studies adjusted for age in their analyses of risk by amount smoked or time of giving up (although not usually in their analyses of risk for specific age groups). Results were usually presented separately by sex, and where, on occasions, results for sexes combined were presented, they were always adjusted for sex.

Table 3.5 shows which studies adjusted for other potential confounding variables. It can be seen that there were 22 studies which adjusted for no other variables at all, and a further 4 which adjusted for sub-study only (e.g. when the analysis was of risk in combined populations). Of the other 22 studies, the risk factors most often taken into account were hypertension (14 studies), cholesterol (10), diabetes (10), body mass index (7), alcohol (5) and education (5).

Table 3.5 also indicates, in the final column (P/C), how the smoking of pipes, cigars and products other than cigarettes were taken into account. There were 21 studies, indicated by “n” in the table, where this was not considered, so presumably both the smoking and never smoking groups in Tables 4.1-4.4 contain some pipe and cigar smokers. However, many of these studies were of women, or in countries where smoking of products other than cigarettes is rare.

There were 14 studies, indicated by an “i” in the table, where pipe and cigar smoking was considered but such smokers were not completely excluded. The normal procedure was to treat current smokers of pipes and/or cigars only as a separate group, and to compare cigarette smokers, regardless of whether they smoked pipes or cigars, with those who had never smoked any product.

There were 5 studies (DOLL, FRIEDM, CPSI, CPSII and DORN) where those who reported ever smoking pipes or cigars were excluded from analysis, so that cigarette only smokers were compared with those who had never smoked any product. There were also 2 others (ALDERS, ROSENG) which were similar except that only current pipe or cigar smokers were excluded.

There were 4 studies, all in countries where smoking of other products was common, where these smokers were included with the cigarette smokers, either by using cigarette-equivalents (HEDBLA, GSELL) or grams of tobacco smoked (PRESCO, CARSTE) as the dose measure.

Of the 2 remaining studies, TVERDA1 excluded those who were currently smoking other products from their smokers but used those who had never smoked cigarettes (rather than any product) as their base for comparison, while WEIR used a definition which explicitly included pipe and cigar smokers in their never smoking group and implicitly included them in their definition of smokers!

4. Results

4.1 Relative risk by amount smoked

Table 4.1 presents estimates from 45 of the studies of risk by amount smoked. For most studies the base (reference) group is never smokers and the comparison groups are current smokers, classified by number of cigarettes smoked per day. However, as noted in the tables, there are a number of exceptions to this, with the base group including ex-smokers or the comparison groups classified by grams of tobacco or cigarette equivalents (where the smokers include pipe and cigar smokers).

There are also variations in the groupings used to categorise subjects by amount smoked. There are 6 dose-response sets from 4 studies (CPSI, CPSII, KAWACH, MRFIT) where relative risks are presented by 5 or 6 levels of amount, and a further 8 dose-response sets by 4 levels. The most common situation, for 30 dose-response sets, is to have 3 levels of amount, with 14 dose-response sets presenting results by only 2.

To investigate the patterns in Table 4.1, I sorted the 60 dose-response sets according to the highest relative risk reported in the set. A number of impressions became clearly evident from an examination of the data.

First, it was clear that smoking was associated with an increased risk of heart disease. Of the 185 estimates in the table, only 9 were below 1 and only 1 (ALDERS, male, 1-17 cigs/day) was statistically significantly negative and that only marginally. In contrast, a very large number of significant increases were seen.

Second, there was clear evidence of dose-response. Of the 60 dose-response relationships, 40 showed a strictly monotonic increasing pattern with risk increased at the lowest amount smoked and continuing to rise with increasing amount. The highest risk was observed at the highest amount smoked in 51 of the studies, and the highest amount smoked was associated with an increased risk in all but two dose-response sets (FRAMIN and LACROI females).

Third, the magnitude of the relative risks varied markedly between dose-response sets. The highest relative risks observed in a dose-response set varied from a maximum of 16.5 (DUNN, females) to 1.18 (BUSH, males) and had a median value of 2.25. The maximum relative risk reported was in the range <1.5, 1.5-1.99, 2.0-2.49, 2.5-2.99, 3-3.99, 4-4.99 and 5+ in, respectively, 6, 14, 15, 6, 7, 5 and 7 dose-responses. It was evident that case-control studies reported higher relative risks; although the case-control studies provided only 10 of the 60 dose-response relationships, they provided the five with the largest maximum relative risks, ranging from 5.9 to 16.5. This was related to the fact that risks were higher in studies with younger populations - with some case-control studies restricting attention specifically to younger age-groups and case-control studies anyway not having the long-term follow-up of prospective studies during which the subjects age. The issue of age will be examined further in sections 4.2 and 4.3.

Finally, the shape of the dose-response relationship did not appear to rise smoothly. This is clearly seen looking at the results from the CPSI and CPSII studies where the relative risk rose quite markedly over the first two levels of amount smoked and then flattened out considerably. In an attempt to investigate this on the whole data we estimated the increase in risk associated with each successive increase in level. The lowest level of amount smoked was associated with a geometric mean increase of <u>1.55</u> based on 60 dose-response relationships, with 54 of the relative risks >1.0. Comparing the next level of amount smoked with the lowest level was associated with a geometric mean increase of <u>1.36</u>, again based on all 60 dose-response relationships, with 55 of the relative risks >1.0. Comparing level 3 with level 2 for those 44 relationships which presented data for 3 or more levels, the geometric mean increase was <u>1.22</u> with 39 of the relative risks >1.0. Comparing level 4 with level 3, the geometric mean increase was <u>0.99</u> with only a half of the 14 increases >1.0. Finally comparing level 5 with level 4, the geometric mean increases was <u>0.99</u>. Although there is an element of non-comparability between studies, due to the different categorisations used, the data show a clear tendency for the observed increase in risk to flatten out as dose increases.

4.2 Relative risk by age

Table 4.2 presents relative risks for current vs never smokers by age. In some studies the relative risks included ex-smokers in the numerator or in the denominator, and in others the relative risks are for specific categories of smokers (e.g. 15-24 cigs/day). The age groupings used vary markedly from study to study. In one study (FLODER) risks are presented by birth cohort rather than age. The most detailed age breakdowns are for the CPSI and CPSII study where data are available by 5 year age groups from 40-44 to 80-84.

In examining these results care should be taken to note that for the youngest age groups, 95% CI are often rather wide, due to the relative infrequency of heart disease deaths. However, a general impression in most studies of a decline in relative risk with increasing age is quite clear. For the 36 datasets by age (within study and sex) there are as many as 32 where the relative risk associated with the highest age group studied is less than that associated with the lowest age group studied, and in a number of the studies with more than two age groups, the relative risk declines continuously with increasing age. The heart disease relative risk associated with smoking is often substantially higher at younger than at older ages, with relative risks often exceeding 4 for ages under 50, but never as high as this and usually under 2 for ages over 70.

The CPSI study offers a good example of the pattern. In males the relative risk is 5.73 at age 40-44 and declines monotonically by 5-year age group, reaching 1.22 at age 80-84. In females the relative risk is lower at age 40-44, 2.90, and the decline not quite monotonic, but still very clear, reaching 1.23 at age 80-84.

A similar pattern is evident in CPSII males, with relative risks declining from 6.28 to 1.44, but interestingly not in CPSII females, where the pattern is erratic but showing no clear trend. Lack of a pattern is also seen in the Nurses study (KAWACH).

4.3 Relative risk jointly by age and amount smoked

Table 4.3 presents relative risks jointly by age and amount smoked from 20 studies, with a total of 27 sex-specific sets of data. For the CPSI, CPSII and DORN studies the data are quite detailed and are expanded in Tables 4.3A, B and C.

The pattern of results fits in with the data in Tables 4.1 and 4.2, with relative risk increasing with amount smoked and decreasing with age. This is most readily seen by comparing the relative risks for the youngest subjects smoking the most and the oldest subjects smoking the least (see Text-Table A). In all 27 sets of data the relative risk is higher in the former group of subjects and in many cases much higher. Thus the geometric mean relative risk of the 27 estimates for the "young heavy" smokers is 4.08, with only 5 of the values less than 2, while the geometric mean relative risk for the "old light" smokers is 1.31, with only 4 of the values above 2.

The pattern of relative risks increasing with amount smoked and decreasing with age is also clearly evident for CPSI in both sexes (see Table 4.3A) and in males for CPSII (Table 4.3B). The pattern is not nearly so clearly evident for CPSII females, especially in respect of the decrease with increasing age. For DORN (Table 4.3C) the decline in relative risk with increasing age is evident, but the increase with increasing amount is not so striking, though still seen. (This may be because DORN had a very long follow-up but only classified subjects by amount at baseline.)

TEXT-TABLE A. Comparison of smoking relative risks for youngest subjects smoking most and oldest subjects smoking least[1]

Study	Sex	Youngest subjects smoking most	Oldest subjects smoking least
SCHARG	M+F	10.3	1.4
BEST	M	1.85	1.71
GRAMEN	F	7.67	2.66
FLODER	M	2.9	1.6
	F	2.6	1.9
ALDERS	M	1.96	0.86
	F	3.02	1.03
BRETT	M	2.9	1.6
DOLL	M	14.9	1.12
	F	2.74	0.79
FRIEDM	M	1.8	0.6
	F	5.3	1.3
ROSENM	M	3.1	1.0
WEIR	M	7.93	1.17
BUSH	M	3.71	1.06
FRAMIN	M	1.95	0.71
	F	1.21	1.08
CPSI	M	9.03	0.97
	F	6.57	1.23
CPSII	M	9.38	1.31
	F	4.69	2.66
DORN	M	6.24	0.94
HAMMON	M	2.51	1.27
KAWACH	F	3.5	2.4
MRFIT	M	4.0	1.8
ROSENB1	F	13.0	1.72
POOLIN	M	2.6	2.1
Geometric mean		4.08	1.31

[1] See Table 4.3 for fuller details of age groups and smoking levels and 95% CI where available.

4.4 Relative risk by time given up

Table 4.4 presents evidence from 17 studies on risk by time given up smoking. For each of the 28 sex/study specific (and in some cases age specific) sets of results, never smokers are the base group, with relative risks and 95% CIs being shown for successively shorter times of giving up, ending with the relative risk for current smokers. The studies vary considerably in the categories of time by which ex-smokers are divided.

The general pattern is for risk to increase across the categories, i.e. for risk in ex-smokers to be intermediate between that of never and current smokers and to decrease with increasing time given up. However, there are exceptions, many no doubt due to sampling variation. To try to summarise the data more succinctly, Text-Table B presents estimates for giving up 10+ years, 5-9 years or 1-4 years and compares them with that for never and current smokers. For a given data set, if the data were more finely divided, the "10+ years" value was taken from the shorter period given up, e.g. for DOLL we took 10-14 years not 15+ years. The "5-9 years" value was taken from the period with midpoint closest to 7.5 years, while the "1-4 years" value was taken from the period with midpoint closest to 2.5 years.

As shown in Text-Table B, the risk in current smokers was clearly increased with all 28 data-sets showing a significant ($p<0.05$) difference from never smokers, and a geometric mean increase of 2.12. Those who had given up smoking for 1-4 years had a geometric mean increase of 1.56, with 17 of the estimates statistically significant. Those who had given up smoking for 5-9 years had a geometric mean increase of 1.32, with 11 of the estimates significant. Those who had given up smoking for 10+ years had a geometric mean increase of 1.16, with 6 of the estimates significant. Although there are some studies (e.g. HIRAYA females, NEGRI, LACROI, ROSENB2, ROSENB3) which give the impression that the excess risk is eliminated or virtually eliminated soon after giving up smoking, the overall data do not give that impression. The overall data suggest that the relative risk declines on giving up smoking, but the decline is gradual, with some excess evident even after 10 years.

This conclusion can also be reached if a comparison is made with risk in current smokers. As shown in Text-Table B, the geometric mean relative risks are 0.71 for giving up 1-4 years, 0.61 for giving up 5-9 years, 0.54 for giving up 10+ years and 0.47 for never smokers.

TEXT-TABLE B Relative risk by time given up smoking[1]

Study	Sex/Age	Never	10+ years	5-9 years	1-4 years	Current
HIRAYA	M	1.00	0.94	1.73*	1.50*	1.73*
	F	1.00	0.91	1.19	0.41	1.90*
CHUN	M	1.00	1.13	1.40*	1.95*	2.71*
	F	1.00	1.71	1.26	2.86*	4.70*
NEGRI	M+F	1.0	1.1	1.2	1.4	2.9*
TVERDA1	M	1.00	(1.37*)		1.77*	4.20*
ALDERS	M 35-54	1.00	0.89	1.21	2.27*	1.79*
	M 55-74	1.00	1.13	0.83	1.31*	0.73*
	F 35-54	1.00	1.00	1.37*	2.05*	2.44*
	F 55-74	1.00	0.92	1.23*	1.22*	1.67*
DOLL	M 30-54	1.0	1.4	1.3	1.9	3.5*
	M 55-64	1.0	1.7*	1.4	1.9*	1.7*
	M 65+	1.0	1.2	1.3	1.0	1.3*
BENSHL	M	1.0	1.19	(1.44*)		1.9*
TANG	M	1.0	1.3	1.0	1.8*	2.1*
FRIEDM	M	1.0	1.3	(1.3)		1.8*
	F	1.0	1.4	(1.4)		1.8*
PAGANI	M	1.0	1.21	1.43*	2.02*	1.41*
	F	1.0	1.53*	1.42	1.28	1.47*
CPSI	M	1.00	1.37*	1.64*	2.66*	-*
	F	1.00	0.98	1.53*	2.23*	-*
DORN	M	1.0	1.4*	1.5*	1.7*	-*
HAMMON	M	1.00	1.60*	2.06*	3.00*	2.20*
KAWACH	F	1.00	1.08	1.83*	1.92*	4.17*
LACROI	M	1.0	1.1	0.9	1.1	1.7*
	F	1.0	0.5	1.0	1.0	1.6*
ROSENB2	M	1.0	1.0	1.4	1.1	2.9*
ROSENB3	F	1.0	1.0	1.1	1.3	3.6*
Geometric mean (vs never smokers)		1.0	1.16	1.32	1.56	2.12
Geometric mean (vs current smokers)		0.47	0.54	0.61	0.71	1.00

1 See Table 4.4 for fuller details of time given up categories and 95% CI.
* indicates significant increase at 95% confidence level vs never smokers.
Bracketed numbers are estimates spanning two categories of time given up; value presented taken in both categories in calculation of geometric mean.
- Directly comparable estimates not available.

5. Discussion and conclusions

There are a number of problems in trying to come to an overall conclusion about effects of smoking on heart disease based on an overview of data from a relatively large number of epidemiological studies. Some of these are discussed briefly in the paragraphs that follow.

Diagnosis : One issue relates to comparability of the disease category chosen for analysis in the different studies. For many of the prospective studies considered, analyses were presented for death from ischaemic heart disease, representing codes 410-414 in the 8th and 9th revisions of the International Classification of Diseases (ICD). These deaths are mainly made up of ICD 410 = acute myocardial infarction and ICD 414 = other forms of chronic ischaemic heart disease, the latter category itself consisting mainly of coronary atherosclerosis and unspecified chronic ischaemic heart disease. The category ICD 410-414 is sometimes referred to as coronary heart disease rather than ischaemic heart disease. The 8th revision came into force in 1965. Before this, in the 6th and 7th revisions, arteriosclerotic and degenerative heart disease (ICD 420-422) forms a classification which is quite comparable. There are a number of variations from this category. In two studies (SEMENC and LACROI) the results available were for a broader group of total cardiovascular disease which includes cerebrovascular disease (stroke) and other forms of heart disease including chronic rheumatic heart disease and pulmonary heart disease. Arguably this category is too broad to be comparable. Another variation is that many of the studies, particularly the case-control studies, restricted attention to AMI. Also the studies vary according to whether they are considering only fatal cases, non-fatal cases or a mixture of the two. It is in theory possible that the relationship of smoking to fatal and non-fatal IHD may be different.

The other issue relating to diagnosis is whether, given the disease category, the classification of subjects is accurate. Many of the studies considered are prospective studies and in many of these, especially the large ones, reliance will be based wholly on death certificates, with no detailed knowledge of how the diagnosis was arrived at. In some prospective studies and in many of the case-control studies diagnosis would be based on standard criteria. It is likely that a variable proportion of subjects will be misdiagnosed. The effect this is likely to have is unclear and would depend on whether the diseases misclassified as IHD are more or less associated with smoking than is IHD.

Exposure : Again one issue relates to definition, the other issue to obtaining that information reliably. In a simple world someone may start to smoke cigarettes at a given age and then smoke at a steady rate until either the time of interview or the time at which cigarette smoking is stopped. In practice life is not so simple; smokers may modify the number they smoke, they may give up smoking more than once and they may smoke products other than cigarettes (such as pipes or cigars) which may increase risk of heart disease.

In a number of studies it was possible to present analyses comparing risks in those who had never smoked at all (or less than some very small amount in their lifetime) with those in current or former smokers of cigarettes only. These are the most clear-cut comparisons. In a number of countries smoking of pipes and cigars is rare (and essentially nonexistent in women) and classifications ignoring pipe and cigar smoking, based on cigarette smoking only, may be satisfactory. Where pipe and cigar smoking are common a variety of approaches have been used. Some studies attempt to lump all smokers together quantifying amount in terms of cigarette equivalents based on weight, a dubious approach if cigars and pipes have different effects on heart disease than do cigarettes. Some studies remove those who smoke pipes or cigars only from analysis but include mixed smokers of pipes/cigars and cigarettes in the cigarette group; this is also somewhat dubious.

Another problem is that though we have tried to obtain information on the current/never smoker comparison for assessing variation in heart disease risk in relation to amount smoked, for some studies data were only available in terms of the current/noncurrent or ever/never comparisons, i.e. ex-smokers were included in either the base group or the comparison group. Given ex-smokers have intermediate risk, this will tend to dilute the strength of associations observed.

The reliability of reported exposure is also a potentially important issue. Smokers are known to understate the amount they smoke, so distorting the observed dose-response relationship. Some also deny smoking, so distorting the simple association of heart disease with smoking. The studies considered generally did not attempt to validate reported smoking habits by cotinine or by secondary information from other sources.

It is important to realise a particular problem specific to prospective studies. This is that subjects are often categorized into groups based on smoking habits determined at baseline, the analysis implicitly assuming that material changes will not occur during the follow-up period. Especially where the follow-up period is a long one (and where additional smoking data are not collected at intervals to allow recategorization), this implicit assumption may be a false one. This may affect all the analyses considered here:

(i) Simple comparisons of risk in current and never smokers may be affected if some of the "current smokers" have given up smoking during the follow-up period and (less likely) some of the "never smokers" start smoking.

(ii) Dose-response analyses may be biassed if smokers vary the amount they smoke. Those classified as light smokers based on an answer at a single time point may on average smoke more than indicated by the answer, while those classified as heavy smokers may on average smoke less. The effect may be to distort the shape of the dose-relationship relationship, pushing risk estimates for low levels of smoking up and for high levels down.

(iii) Analyses based on time given up smoking may be biassed in two ways. First, as already noted, because some ex-smokers may resume smoking during the follow-up period. Second, because classifying subjects as age given up for 3-5 years at the start will imply longer periods of giving up as the follow-up period continues. An excess risk seen in such a group suggests a risk may be incurred more than 5 years after follow-up, unless the method of analysis recategorizes subjects into different time given up periods as they age. However, many studies classify subjects solely based on the data recorded at baseline.

Representativeness of populations studied : Prospective studies are often drawn from special populations, such as doctors (DOLL), nurses (KAWACH), war veterans (DORN) or civil servants (BENSHL). Other studies, such as CPSI and CPSII, are unrepresentative (more whites, more middle class) due to the way the subjects were collected. Such representativeness is more likely to affect absolute heart disease rates rather than relative risks associated with smoking.

In case-control studies bias may arise if the controls have smoking habits that are unrepresentative of the population from which the cases were drawn. Generally, the studies considered have used as controls either healthy population samples or subjects with diseases unrelated to smoking, so this should not be a particular problem.

Confounding : In order to arrive at an unbiassed estimate of the risk of heart disease associated with the aspects of smoking considered in this review it is important that potential confounding factors are taken into account. Inasmuch as all those studies that have presented results for the sexes combined have adjusted for sex, and all the studies have adjusted for age, these two factors are not an issue.

It is interesting to note that the analyses have generally not taken other aspects of smoking into account. Variation in risk by amount smoked, age and time given up smoking may in theory be to some extent explained by other smoking related factors such as age at starting to smoke, inhalation and type of cigarette smoked, but this has not been investigated.

About half the studies did not take any non-smoking potential confounding variables into account at all. At this stage we have not attempted to extract data relevant to the effect adjustment did have in those studies that presented results adjusted and unadjusted for confounding variables. The list of confounding variables considered in those studies that did adjust was in any case very variable (see Table 3.5).

Extraction of data : For a number of the studies (see Appendix A) it was necessary to perform calculations to derive estimates of relative risk and 95% CI in the form required. Such calculations involved a number of assumptions, leading to uncertainty, particularly in respect of the 95% CI. However, these are unlikely to have any material effect on the conclusions reached.

Analysis : At this stage no attempt has been made to perform meta-analysis. Rather, impressions have been gained from the consistency of the pattern of relative risks over the studies. In some cases geometric means have been calculated giving equal weight to each study. These can be seen as approximate indicators, though obtaining precise overall estimates based on a heterogeneous mix of studies may not be achievable.

Although, in some ways, the approach used in this review may be regarded as "quick and dirty" and more useful information may be derived from a more detailed investigation, the consistency of findings from study to study allows a number of conclusions to be drawn:

1. Smoking is associated with an increased risk of heart disease.

2. The relative risk is dose-related, being quite consistently higher for heavy than for light smokers.

3. The slope of the dose-response relationship does not appear to rise smoothly. The increase in risk per cigarette smoked is markedly higher at lower levels of smoking than at higher levels of smoking.

4. The relative risk of smoking decreases markedly with increasing age. At ages under 50 relative risks exceeding 4 are commonly reported, but at ages over 70 relative risks are typically less than 2. [Our review has concentrated on relative risks. It should be noted that various prospective studies have shown that the absolute excess risk associated with smoking is in fact higher at older than at younger ages.]

5. In most of those studies that relate risk jointly to age and amount smoked, risk can be seen to increase with increasing amount smoked for a given age and to decrease with age for a given amount smoked. Though this pattern is very clear for some studies (e.g. CPSI for both sexes and CPSII for males) it is not always so clear (e.g. CPSII for females).

6. In ex-smokers risk is intermediate between that of never and current smokers and declines with increasing time given up. The idea that, on giving up, risk of heart disease rapidly declines to the level of never smokers seems not to be supported by the data taken at face value.

The strength of the association of heart disease with smoking at younger ages suggests that it is unlikely to be explained by bias or confounding. The general conclusions that risk increased with amount smoked and decreases on giving up smoking, and that the relative risk is greater in young men and women seem unlikely to be affected by more detailed analysis. However, it seems possible that the observed shape of the dose-response relationship and of the relationship with time given up smoking may be affected by biases. These areas may merit more detailed work.

6. Acknowledgements

This report would not have been possible without the help of many of my colleagues. Barbara Forey, Yvonne Cooper, Pauline Wassell and Diana Morris have helped to maintain the in-house reference database. Pauline and Di typed the various drafts rapidly and accurately. John Fry and Barbara assisted with computing. I thank them all, and also Philip Morris who provided financial support.

7. References

1 Schargrodsky H, Rosloznik J, Ciruzzi M, Pramparo P, Prado AH, Cesar J, Soifer S, Negri E, Tognoni G, La Vecchia C: Cigarette smoking and acute myocardial infarction: a case-control study from Argentina. Tob Control 1993;2:127-131.

2 Department of National Health and Welfare Canada: A Canadian Study of Smoking and Health. Canada, Department of National Health and Welfare, 1966.

3 Semenciw RM, Morrison HI, Johansen H, Davies JW, Wigle DT: Major risk factors for cardiovascular disease mortality in adults: Results from the Nutrition Canada Survey Cohort. Int J Epidemiol 1988;17:317-323.

4 Chen Z-M, Xu Z, Collins R, Li W-X, Peto R: Early health effects of the emerging tobacco epidemic in China. JAMA 1997;278:1500-1504.

5 Yuan J-M, Ross RK, Wang X-L, Gao Y-T, Henderson BE, Yu MC: Morbidity and mortality in relation to cigarette smoking in Shanghai, China: a prospective male cohort study. JAMA 1996;275:1646-1650.

6 Hirayama T: Wahrendorf J (ed): Life-Style and Mortality: A Large Scale Census Based Cohort Study in Japan. Contributions to Epidemiology and Biostatistics. Basle, Karger, 1990. 6.

7 Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M: Smoking and mortalities from cancer, coronary heart disease and stroke in male Japanese physicians. J Cancer Res Clin Oncol 1985;110:161-164.

8 Liaw K-M, Chen C-J: Mortality attributable to cigarette smoking in Taiwan: a 12-year follow-up study. Tob Control 1999;7:141-148.

9 Chun BY, Dobson AJ, Heller RF: Smoking and the incidence of coronary heart disease in an Australian population. Med J Aust 1993;159:508-512.

10 Dobson AJ, Alexander HM, Heller RF, Lloyd DM: How soon after quitting smoking does risk of heart attack decline? J Clin Epidemiol 1991;44:1247-1253.

11 Prescott E, Hippe M, Hein HO, Schnohr P, Vestbo J: Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998;316:1043-1047.

12 Pekkan J, Nissinen A, Puska P, Karvonen MJ: Risk factors and 25 year risk of coronary heart disease in a male population with a high incidence of the disease: the Finnish cohorts of the seven countries study. BMJ 1989;299:81-85.

13 Conti S, Farchi G, Menotti A: Coronary risk factors and excess mortality from all causes and specific causes. Int J Epidemiol 1983;12:301-307.

14 Gramenzi A, Gentile A, Fasoli M, D'Avanzo B, Negri E, Parazzini F, La Vecchia C: Smoking and myocardial infarction in women: a case-control study from northern Italy. J Epidemiol Community Health 1989;43:214-217.

15 Negri E, La Vecchia C, D'Avanzo B, Nobili A, La Malfa RG: Acute myocardial infarction: association with time since stopping smoking in Italy. J Epidemiol Community Health 1994;48:129-133.

16 Tverdal A, Thelle D, Stensvold I, Leren P, Bjartveit K: Mortality in relation to smoking history: 13 years' follow-up of 68,000 Norwegian men and women 35-49 years. J Clin Epidemiol 1993;46:475-487.

17 Tverdal A: Calculation of risk for the development of acute myocardial infarction in the normal population based on long-term follow-up studies: smokers compared with non-smokers. J Cardiovasc Risk 1999;6:287-291.

18 Carstensen J, Pershagen G, Eklund G: Mortality in relation to cigarette and pipe smoking: 16 years' observation of 25,000 Swedish men. J Epidemiol Community Health 1987;41:166-172.

19 Floderus B, Cederlöf R, Friberg L: Smoking and mortality: a 21-year follow-up based on the Swedish Twin Registry. Int J Epidemiol 1988;17:332-340.

20 Hedblad B, Ogren M, Isacsson S-O, Janzon L: Reduced cardiovascular mortality risk in male smokers who are physically active. Results from a 25-year follow-up of the

prospective population study men born in 1914. Arch Intern Med 1997;157:893-899.

21 Rosengren A, Wilhelmsen L, Wedel H: Coronary heart disease, cancer and mortality in male middle-aged light smokers. J Intern Med 1992;231:357-362.

22 Gsell O, Abelin TH, Wieltschnig E: Rauchen und mortalität der Schweizer ärzte: resultate nach 18 jähriger beobachtung (Smoking and mortality of Swiss doctors: results after 18 years' observation). Bulletin of the Swiss Academy of Medical Science 1979;35:71-82.

23 Alderson MR, Lee PN, Wang R: Risks of lung cancer, chronic bronchitis, ischaemic heart disease, and stroke in relation to type of cigarette smoked. J Epidemiol Community Health 1985;39:286-293.

24 Brett GZ, Benjamin B: Smoking habits of men employed in industry, and mortality. BMJ 1968;3:82-85.

25 Dunn N, Thorogood M, Faragher B, de Caestecker L, MacDonald TM, McCollum C, Thomas S, Mann R: Oral contraceptives and myocardial infarction: results of the MICA case-control study. BMJ 1999;318:1579-1583.

26 Croft P, Hannaford PC: Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. BMJ 1989;298:165-168.

27 Doll R, Peto R: Mortality in relation to smoking: 20 years' observations on male British doctors. BMJ 1976;2:1525-1536.

28 Doll R, Gray R, Hafner B, Peto R: Mortality in relation to smoking: 22 years' observations on female British doctors. BMJ 1980;i:967-971.

29 Doll R, Peto R, Wheatley K, Gray R, Sutherland I: Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 1994;309:901-911.

30 Ben-Shlomo Y, Davey Smith G, Shipley MJ, Marmot MG: What determines mortality risk in male former cigarette smokers? Am J Public Health 1994;84:1235-1242.

31 Reid DD, McCartney PM, Hamilton PJS, Rose G: Smoking and other risk factors for coronary heart disease in British civil servants. Lancet 1976;2:979-983.

32 Tang JL, Cook DG, Shaper AG: Giving up smoking: how rapidly does the excess risk of eschaemic heart disease disappear? Journal of Smoking-Related Disorders 1992;3:203-215.

33 Keys A: Seven Countries: a Multivariate Analysis of Death and Coronary Heart Disease. Harvard University Press, 1980.

34 Friedman GD, Tekawa I, Sadler M, Sidney S: Smoking and mortality: the Kaiser Permanente experience; in Burns D, Garfinkel L, Samet JM (eds): Changes in Cigarette-Related Disease Risks and Their Implications for Prevention and Control. Monograph 8. (Smoking and Tobacco Control.) US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997, pp 477-499. NIH Publication No. 97-4213.

35 Paganini-Hill A, Hsu G: Smoking and mortality among residents of a California retirement community. Am J Public Health 1994;84:992-995.

36 Rosenman RH, Brand RJ, Jenkins D, Friedman M, Straus R, Wurm M: Coronary heart disease in the western collaborative group study. Final follow-up experience of 8½ years. JAMA 1975;233:872-877.

37 Weir JM, Dunn JE, Jr.: Smoking and mortality: A prospective study. Cancer 1970;25:105-112.

38 Bush TL, Comstock GW: Smoking and cardiovascular mortality in women. Am J Epidemiol 1983;118:480-488.

39 Freund KM, Belanger AJ, D'Agostino RB, Kannel WB: The health risks of smoking. The Framingham Study: 34 years of follow up. Ann Epidemiol 1993;3:417-424.

40 Burns DM, Shanks TG, Choi W, Thun MJ, Heath CW, Jr., Garfinkel L: The American Cancer Society cancer prevention study I: 12-year follow-up of 1 million men and women; in Burns D, Garfinkel L, Samet JM (eds): Changes in Cigarette-Related

Disease Risks and Their Implications for Prevention and Control. Monograph 8. (Smoking and Tobacco Control.) US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997, pp 113-304. NIH Publication No. 97-4213.

41 Thun MJ, Day-Lally C, Myers DG, Calle EE, Dana F, Zhu B-P, Namboodiri MM, Heath CW, Jr.: Age and the exposure-response relationships between cigarette smoking and premature death in Cancer Prevention Study II; in Burns D, Garfinkel L, Samet JM (eds): Changes in Cigarette-Related Disease Risks and Their Implications for Prevention and Control. Monograph 8. (Smoking and Tobacco Control.) US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997, pp 383-475. NIH Publication No. 97-4213.

42 Kahn HA: The Dorn study of smoking and mortality among U.S. veterans: report on eight and one-half years of observation; in Haenszel W (ed): Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases. Bethesda, Maryland, U.S. Department of Health, Education, and Welfare. Public Health Service National Cancer Institute, 1966, pp 1-125. National Cancer Institute Monograph 19.

43 Rogot E, Murray JL: Smoking and causes of death among US Veterans: 16 years of observation. Public Health Rep 1980;95:213-222.

44 Hrubec Z, McLaughlin JK: Former cigarette smoking and mortality among U.S. veterans: a 26-year followup, 1954 to 1980; in Burns D, Garfinkel L, Samet JM (eds): Changes in Cigarette-Related Disease Risks and Their Implications for Prevention and Control. Monograph 8. (Smoking and Tobacco Control.) US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997, pp 501-530. NIH Publication No. 97-4213.

45 Hammond EC, Horn D: Smoking and death rates - Report of forty-four months of follow-up of 187,783 men II. Death rates by cause. JAMA 1958;166:1294-1308.

46 Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH: Smoking cessation and time course of decreased risks of coronary heart

disease in middle-aged women. Arch Intern Med 1994;154:169-175.

47 Willett WC, Green A, Stamper MJ, Speizer FE, Colditz GA, Rosner B, Monson RR, Stason W, Hennekens CH: Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. N Engl J Med 1987;317:1303-1309.

48 LaCroix AZ, Lang J, Scherr P, Wallace RB, Cornoni-Huntley J, Berkman L, Curb JD, Evans D, Hennekens CH: Smoking and mortality among men and women in three communities. N Engl J Med 1991;324:1619-1625.

49 Kuller LH, Ockene JK, Meilahn E, Wentworth DN, Svendsen KH, Neaton JD: Cigarette smoking and mortality. Prev Med 1991;20:638-654.

50 Neaton JD, Wentworth D: Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316099 white men. Arch Intern Med 1992;152:56-64.

51 Rosenberg L, Kaufman DW, Helmrich SP, Miller DR, Stolley PD, Shapiro S: Myocardial infarction and cigarette smoking in women younger than 50 years of age. JAMA 1985;253:2965-2969.

52 Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S: The risk of myocardial infarction after quitting smoking in men under 55 years of age. N Engl J Med 1985;313:1511-1514.

53 Rosenberg L, Palmer JR, Shapiro S: Decline in the risk of myocardial infarction among women who stop smoking. N Engl J Med 1990;322:213-217.

54 Rosenberg L, Palmer JR, Rao RS, Adams-Campbell LL: Risk factors for coronary heart disease in African American women. Am J Epidemiol 1999;150:904-909.

55 Doyle JT, Dawber TR, Kannel WB, Kinch SH, Kahn HA: The relationship of cigarette smoking to coronary heart disease. The second report of the combined experience of the Albany, NY, and Framingham, Mass, studies. JAMA 1964;190:886-890.

56 The Pooling Project Research Group: Relationship of blood pressure, serum

cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the pooling project. Journal of Chronic Diseases 1978;31:201-306.

TABLE 3.1

The 48 studies selected

Continent (Country)	Country (State)	Study name	Study title	Study type[a]	Period of deaths/cases
America	Argentina	SCHARG	Buenos Aires case-control study of AMI[b]	CC	1984-89
	Canada	BEST	Canadian veterans study	P	1955-62
		SEMENC	Nutrition Canada study	P	1970-81
Asia	China	CHEN	First Shanghai prospective study	P	1972-93
		YUAN	Second Shanghai prospective study	P	1986-93
	Japan	HIRAYA	Six prefecture prospective study	P	1965-82
		KONO	Japanese doctors study	P	1965-77
	Taiwan	LIAW	Twelve town prospective study	P	1982-93
Australasia	Australia	CHUN	Hunter region case-control study of AMI[b] or fatal heart attack	CC	1986-90
Europe	Denmark	PRESCO	Pooled results from:		
			(i) Copenhagen city heart study	P	1976-93
			(ii) Glostrup population studies	P	1976-93
			(iii) Copenhagen male study	P	1985-93
	Finland	PEKKAN	Finnish cohorts of Seven Countries Study (KEYS)	P	1959-84
	Italy	CONTI	Italian cohorts of Seven Countries Study (KEYS)	P	1960-75
		GRAMEN	Northern Italy case-control study of AMI[b]	CC	1983-87
		NEGRI	GISSI-2 trial: case-control study of AMI[b]	CC	1988-89
	Norway	TVERDA1	Five area prospective study	P	1972-88
		TVERDA2	Three counties prospective study	P	1974-94
	Sweden	CARSTE	Swedish random sample prospective study	P	1963-79

TABLE 3.1 (Continued)

Continent (Country)	Country (State)	Study name	Study title	Study type[a]	Period of deaths/cases
Europe	Sweden	FLODER	Swedish twin registry study	P	1961-82
		HEDBLA	Malmo prospective study	P	1968-93
		ROSENG	Göteborg multicentre primary prevention trial (intervention group)	P	1970-83
	Switzerland	GSELL	Swiss doctors study	P	1955-73
	UK	ALDERS	10 hospital regions in-patients study	CC	1978-82
		BRETT	Industrial workers study in London and Home Counties	P	1960-63
		DUNN	MICA case-control study	CC	1993-95
		CROFT	Royal College of General Practitioners oral contraceptive study	NCC	1968-87
		DOLL	British doctors study	P	1951-91
		BENSHL	Whitehall study of male civil servants	P	1967-87
		TANG	British Regional Heart Study	P	1978-88
	7 Countries	KEYS	Seven Countries Study	P	1958-74
USA	California	FRIEDM	Kaiser Permanente study	P	1979-87
		PAGANI	Leisure World cohort study	P	1981-91
		ROSENM	Western Collaborative group study	P	1960-69
		WEIR	Study of occupational groups	P	1954-62
	Maryland	BUSH	Washington County study	P	1963-75
	Massachusetts	FRAMIN	Framingham study	P	1948-86
	25 states	CPS I	American Cancer Society Cancer Prevention Study I	P	1959-72
	Nationwide	CPS II	American Cancer Society Cancer Prevention Study II	P	1982-88
	Nationwide	DORN	US Veterans study	P	1953-80
	9 states	HAMMON	US Nine State Study	P	1952-55
	Nationwide	KAWACH	Nurses' Health Study	P	1976-88

TABLE 3.1 (Continued 2)

Continent (Country)	Country (State)	Study name	Study title	Study type[a]	Period of deaths/cases
	3 states	LACROI	Study of the elderly	P	1981-88
USA	Nationwide	MRFIT	Multiple Risk Factor Intervention Study	P	1973-86
	3 states	ROSENB1	Study of MI in young women	CC	1976-79
	4 states	ROSENB2	Study of MI in young men	CC	1980-83
	4 states	ROSENB3	Study of MI in women	CC	1985-88
	Nationwide	ROSENB4	Black Women's Health Study	CC	1995
	2 states	DOYLE	Combined analysis from Albany and Framingham studies	P	1949-62
	4 states	POOLIN	Combined analysis from Albany, Framingham, Chicago Gas Co., Chicago Western Electric Co and Tecumseh studies	P	1950s[c]

[a] CC = case-control, CS = cross-sectional, NCC = nested case-control (within prospective), P = prospective.
[b] AMI = acute myocardial infarction.
[c] Follow-up periods ranged from 6 to 10 years, exact periods not given.

TABLE 3.2

Heart disease cases in the 48 studies

Study	Number of cases[a] Men	Women	Total	Definition of cases[b]
SCHARG	873	127	1000	Hospital admissions with first AMI
BEST	1380[c]	46[c]	1426[c]	Died of CHD
SEMENC	157	107	264	Died of CVD
CHEN	69	-[d]	>69	Died of CHD
YUAN	68	-	68	Died of IHD
HIRAYA	2170	1378	3548	Died of IHD
KONO	121	-	121	Died of CHD
LIAW	143[e]	23[e]	166[e]	Died of IHD
CHUN	1882	863	2645	Hospitalised with first AMI or died of HA
PRESCO	1251	512	1763	Fatal and non-fatal AMI
PEKKAN	335	-	335	Died of CHD
CONTI	78	-	78	Died of CHD
GRAMEN	-	262	262	Hospital admissions with AMI
NEGRI	801	115	916	Hospital admissions with first AMI
TVERDA1	1313	68	1381	Died of CHD
TVERDA2	1021	193	1214	Died of CHD
CARSTE	2479	-	2479	Died of IHD
FLODER	1136	830	1966	Died of CHD
HEDBLA	154	-	154	Died of CHD
ROSENG	473	-	473	Fatal or non-fatal CHD
GSELL	280	-	280	Died of AMI
ALDERS	811	712	1523	Hospital patients with IHD
BRETT	422	-	422	Died of CT
DUNN	-	448	448	Fatal or non-fatal MI
CROFT	-	158	158	First fatal or non-fatal AMI
DOLL	6438	179	6617	Died of IHD
BENSHL	1695	-	1695	Died of CHD

TABLE 3.2 (Continued)

Study	Number of cases[a] Men	Women	Total	Definition of cases[b]
TANG	611	-	611	AMI or sudden death from IHD
KEYS	283	-	283	Died of CHD
FRIEDM	358	219	577	Died of CHD
PAGANI	2015[f]	1987[f]	4002[f]	Died of CHD
ROSENM	257	-	257	Clinical CHD
WEIR	1718	-	1718	Died of AHD
BUSH	-	852	852	Died of AHD
FRAMIN	709	595	1304	Diagnosed CHD
CPS I	29086	12362	41448	Died of CHD
CPS II	13232	6882	20114	Died of CHD
DORN	Less than ½% women in population		164785[f]	Died of CHD
HAMMON	5297	-	5297	Died of CAD
KAWACH	-	970	970	Fatal or non-fatal CHD
LACROI	-	-	729[g]	Died from CVD
MRFIT	6327[h]-		6327[h]	Died of CHD
ROSENB1	-	555	555	Hospital admissions with first MI
ROSENB2	1873	-	1873	Hospital admissions with first MI
ROSENB3	-	910	910	Hospital admissions with first MI
ROSENB4	-	352	352	Reported having heart attack
DOYLE	243	-	243	Fatal or non-fatal CHD
POOLIN	658	-	658	First major coronary event

[a] Total number included in study except where stated.
[b] AHD = arteriosclerotic heart disease, AMI = acute myocardial infarction, CAD = coronary artery disease, CHD = coronary heart disease, CT = coronary thrombosis, CVD = cardiovascular disease, HA = heart attack, IHD = ischaemic heart disease.
[c] Numbers of cases among current cigarette smokers.
[d] Women were included in the study but relevant results for CHD death not provided.
[e] Numbers of cases among current and never smokers combined.
[f] Numbers are of deaths for all causes; numbers by cause not given.
[g] Numbers by sex not given.
[h] Numbers of cases among Whites.

TABLE 3.3

Populations at risk (or controls) in the 48 studies

	Number at risk[a]				
Study	Men	Women	Total	Population studied	Age range[b]
SCHARG	[873]	[127]	[1000]	Hospital admissions with diseases unrelated to smoking or risk factors for AMI; matched to cases (broadly) on age, sex, hospital	35-65
BEST	77541	14226	91767	Canadian Veteran pension recipients	Unrestricted
SEMENC	3146	3971	7117	Free of self-reported heart disease or stroke	35-79
CHEN	6494	2857	9351	Factory workers in urban Shanghai	35-64
YUAN	18244	-	18244	Male residents of four areas in Shanghai with no history of cancer	45-64
HIRAYA	122261	142857	265118	Census sample in six prefectures	40+
KONO	5477	-	5477	Doctors in 17 prefectural medical associations in West Japan	Unrestricted
LIAW	11096	3301	14397	Residents in 12 townships and precincts in Taiwan with no history of cancer or major diseases	40+
CHUN	[?]	[?]	[?]	Random sample in Hunter region of New South Wales	35-69
PRESCO	13191	11472	24663	(i) population sample of central Copenhagen (ii) population sample of Glostrup (iii) male workers in 14 Copenhagen factories Subjects with past MI excluded	20-93 30-60 45-64
PEKKAN	1711	-	1711	All men in two rural areas	40-59
CONTI	1712	-	1712	All men in two rural areas	40-59
GRAMEN	-	[519]	[519]	Hospital admissions with acute disorders unrelated to IHD	<70
NEGRI	[976]	[130]	[1106]	Hospital admissions with acute conditions unrelated to smoking or risk factors for AMI	<75
TVERDA1	44290	24535	68825	Random sample of Oslo men. Men in Tromsø and population in Finnmark, Sogn og Fjordane and Oppland	35-49
TVERDA2	25077	24546	49623	Populations of Finnmark, Sogn og Fjordane and Oppland	35-49

TABLE 3.3 (Continued)

Study	Number at risk[a] Men	Women	Total	Population studied	Age range[b]
CARSTE	25129	-	25129	Random sample of Swedish men born between 1894 and 1945	<70
FLODER	?	?	21890[c]	Like-sexed Swedish twin pairs born between 1886 and 1925	<75
HEDBLA	642	-	642	Men in Malmo with no history of CHD or stroke	=55
ROSENG	6879	-	6879	Men in Göteborg free of previous MI	47-55
GSELL	3749	-	3749	Male doctors	Unrestricted
ALDERS	[811]	[712]	[1523]	Hospital patients with diseases definitely or probably not associated with smoking, matched on age, sex, hospital, ward	35-74
BRETT	54660	-	54660	Volunteers for routine x-ray examination randomly drawn from 119 industrial establishments in Greater London and the Home Counties	40+
DUNN	-	[1728]	[1728]	Women without MI, matched for age and general practice	16-44
CROFT	-	[474]	[474]	Women in cohort study with no previous MI, individually matched (3:1) on date of birth and still under observation when infarction diagnosed in index subject	20-65
DOLL	34439	6194	40633	British doctors living in the UK	Unrestricted
BENSHL	19018	-	19018	Male British civil servants	40-69
TANG	7735	-	7735	Men randomly selected from group practices in 24 towns in the UK	40-59
KEYS	12509	-	12509	Men in 16 groups in Finland, Greece, Italy, Japan, the Netherlands, USA and Yugoslavia free of CHD at entry	40-59
FRIEDM	24803	36035	60838	Attending Kaiser Permanente Medical Care Program in Northern California	35+
PAGANI	4999	8869	13868	Residents of Leisure World, Laguna Hills, a retirement community near Los Angeles	65+
ROSENM	3154	-	3154	Men in 10 California companies	35-59
WEIR	68153	-	68153	Workers in various occupations in California	30-64
BUSH	-	20158	20158	Census sample in Washington County	25-74

TABLE 3.3 (Continued 2)

Study	Number at risk[a] Men	Women	Total	Population studied	Age range[b]
FRAMIN	2282	2845	5127	Inhabitants of Framingham free of CHD at initial examination	30-62
CPS I	456476	594526	1051002	Recruited by American Cancer Society volunteers in 25 states, mainly Eastern. Household had to contain 1+ person aged 45+	30+
CPS II	508579	676527	1185106	Recruited by American Cancer Society volunteers in all 50 states and in DC, Guam and Puerto Rico. Household had to contain 1+ person aged 45+	30+
DORN	Less than ½% women		248046	Policyholders of insurance available only to persons serving in the US Armed Forces between 1917 and 1940. Nearly all white males	31-84
HAMMON	187783	-	187783	Receuited by American Cancer Society volunteers in 9 states[d], white men, not seriously ill	50-69
KAWACH	-	117006	117006	Female registered nurses free of CHD, cancer or stroke	30-55
LACROI	?	?	7178[c]	Without history of MI, cancer or stroke living in communities in Massachusetts, Iowa and Connecticut	65+
MRFIT	361662	-	361662	Men screened in 22 clinical centres in order to select them for randomized intervention trial. Nearly all white	35-57
ROSENB1	-	[1864]	[1864]	Hospital admissions with diseases unrelated to smoking in Boston, New York and Philadelphia	25-49
ROSENB2	[2775]	-	[2775]	Hospital admissions with diseases unrelated to smoking in 4 states[e]	20-54
ROSENB3	-	[2375]	[2375]	Hospital admissions with nonmalignant diseases unrelated to smoking in 4 states[e]	25-64
ROSENB4	-	[1760]	[1760]	Women returning questionnaires mailed to Essence magazine, read largely by African American women. Controls matched on age (5:1) to cases. Subjects did not report stroke or clot in leg or lungs	21-69

TABLE 3.3 (Continued 3)

Study	Number at risk[a]			Population studied	Age range[b]
	Men	Women	Total		
DOYLE	4120	-	4120	Combined analysis of data from FRAMIN (see above) and study of male civil servants in Albany, NY. Men originally free of heart disease	30-62
POOLIN	8503	-	8503	Combined analysis of data from 5 studies; 3 employment groups (Civil servants - Albany, Gas company employees - Chicago, Electric company employees - Chicago) and 2 community samples (Framingham and Tecumseh). All white men with no history of angina or MI	35-59

[a] For case-control studies, numbers at risk are shown in square brackets; numbers are total included in the study except where stated.
[b] For prospective studies, range is as at baseline.
[c] Numbers by sex not given.
[d] California, Illinois, Iowa, Michigan, Minnesota, New Jersey, New York, Pennsylvania and Wisconsin.
[e] Massachusetts, Rhode Island, Connecticut and New York.

TABLE 3.4

Aspects of smoking considered

	Current/never smoker risk by			Ex-smoker risk by
Study	amount	age	age and amount	time given up
SCHARG	✓	✓	✓	
BEST	✓	✓	✓	
SEMENC	✓			
CHEN	✓			
YUAN	✓			
HIRAYA	✓			✓
KONO	✓			
LIAW	✓			
CHUN		✓		✓
PRESCO	✓	✓		
PEKKAN	✓			
CONTI	✓			
GRAMEN	✓	✓	✓	
NEGRI	✓	✓		✓
TVERDA1	✓			✓
TVERDA2		✓		
CARSTE	✓			
FLODER	✓	✓	✓	
HEDBLA	✓			
ROSENG	✓			
GSELL	✓	✓		
ALDERS	✓	✓	✓	✓
BRETT	✓	✓	✓	
DUNN	✓			
CROFT	✓			
DOLL	✓	✓	✓	✓
BENSHL	✓			✓
TANG	✓			✓

TABLE 3.4 (Continued)

Study	Current/never smoker risk by amount	age	age and amount	Ex-smoker risk by time given up
KEYS	✓			
FRIEDM	✓	✓	✓	✓
PAGANI	✓			✓
ROSENM	✓	✓	✓	
WEIR	✓	✓	✓	
BUSH	✓	✓	✓	
FRAMIN	✓	✓	✓	
CPS I	✓	✓	✓	✓
CPS II	✓	✓	✓	
DORN	✓	✓	✓	✓
HAMMON	✓	✓	✓	✓
KAWACH	✓	✓	✓	✓
LACROI	✓			✓
MRFIT	✓	✓	✓	
ROSENB1	✓	✓	✓	
ROSENB2				✓
ROSENB3	✓			✓
ROSENB4	✓			
DOYLE	✓			
POOLIN	✓	✓	✓	

TABLE 3.5

Potential nonsmoking confounding variables adjusted for (other than age or sex)[1]

Study	None	SUB	CHO	HYP	BMI	DIA	ALC	EDU	HIS	FHS	OES	Other	P/C
SCHARG				h	✓	✓				c			n
BEST	✓												i
SEMENC				h		✓							i
CHEN			✓	s			✓						n
YUAN							✓						n
HIRAYA	✓												n
KONO	✓												i
LIAW				b									n
CHUN[2]									i				n
PRESCO		✓	✓	sd	✓	✓	✓	✓				HGT, PHY, TRI	g
PEKKAN		✓											i
CONTI	✓												n
GRAMEN				h	✓	✓	✓	✓			o	COF, HYL	n
NEGRI			✓		✓	✓		✓		m		COF	i
TVERDA1		✓											xn
TVERDA2			✓	s									n
CARSTE												RES	g

TABLE 3.5 (Continued)

Study	None	SUB	CHO	HYP	BMI	DIA	ALC	EDU	HIS	FHS	OES	Other	P/C
FLODER		✓											i
HEDBLA				h	✓	✓			r			HYL	c
ROSENG			✓	s	✓	✓	✓			m		ECP, OCC, PHY, STR	xc
GSELL	✓												c
ALDERS	✓												xc
BRETT	✓												n
DUNN												GNP	n
CROFT											o	SCL	n
DOLL	✓												x
BENSHL[3]												SCL	i
TANG			✓	s									i
KEYS	✓												i
FRIEDM	✓												x
PAGANI	✓												n
ROSENM	✓												i
WEIR	✓												j
BUSH								✓				CHU, HOU, MAR	i
FRAMIN[4]			✓	s		✓						LVH	n
CPS I	✓												x
CPS II	✓												x
DORN	✓												x

TABLE 3.5 (Continued 2)

Study	None	SUB	CHO	HYP	BMI	DIA	ALC	EDU	HIS	FHS	OES	Other	P/C
HAMMON	✓												i
KAWACH[5]			✓	h	✓	✓					op	MEN	n
LACROI		✓											n
MRFIT			✓	d								RAC	n
ROSENB1	✓												n
ROSENB2	✓												n
ROSENB3	✓												n
ROSENB4			✓	h	✓	✓		✓		m		AFB, AME, HGT, PAR	n
DOYLE	✓												i
POOLIN	✓												i

[1] Abbreviations (and codes) used for confounding variables
SUB = sub-study
CHO = cholesterol
HYP = hypertension : h = hypertension unspecified, s = systolic blood pressure, d = diastolic blood pressure, b = blood pressure unspecified
BMI = body mass index
DIA = diabetes
ALC = alcohol
EDU = education
HIS = history : i = of IHD, r = of chronic respiratory disease
FHS = family history : c = of CHD, m = of MI
OES = oestrogen use : o = of oral contraceptive use, p = postmenopausal oestrogen therapy
P/C = pipe/cigar : n = not considered, i = included in smokers, g = included as grams, xn = excluded from numerator, c = included as cigarette equivalents, xc = excluded completely, j = included in never smokers
Other : AFB = age at first birth, AME = age at menarche, COF = coffee, CHU = church attendance, ECP = exertional chest pain, GNP = general practice, HGT = height, HOU = housing quality, HYL = hyperlipidaemia, LVH = left ventricular hypertrophy, MAR = marital status, MEN = menopausal status, OCC = occupation, PAR = parity, PHY = physical activity, RAC = race, RES = residence, SCL = social class, STR = stress, TRI = triglycerides.

[2] Adjustment for HIS only made in analyses in Table 4.4.

[3] Adjustment for SCL only made in analyses in Table 4.4.

[4] Adjustment for CHO, HYP, DIA and LVH only made in analyses in Table 4.2.

[5] Adjustment for CHO, HYP, BMI, DIA, OES and MEN only made in analyses in Tables 4.1 and 4.4.

T15

TABLE 4.1

Relative risk (95% CI) of heart disease by amount smoked (base = never smokers and comparison groups = current smokers unless indicated)

Study/adjustment factors[a]	Number of cases[b]	Sex	Relative risk (95% CI)[c] by amount smoked			
SCHARG/			0	<15	15-24	25+cigs/day
Age, sex, other	819M+F	M+F	1.0	1.6(1.1-2.4)	2.2 (1.6-3.0)	5.9(4.2-8.3)
BEST/			0	<10	10-20	21+ cigs/day
Age	1380M[d]	M	1.00	1.55 [337]	1.58 [766]	1.78 [277]
SEMENC/			0	1-19		20+ cigs/day
Age, other	106M,	M	1.00	2.42(1.40-4.17)		3.47(2.14-5.62)
	98F	F	1.00	0.94(0.50-1.77)		2.11(1.19-3.72)
CHEN/			0	1-19		20+cigs/day
Age, other	69M	M	1.0	1.7(0.9-3.1)		2.0(1.1-3.7)
				(base group includes ex-smokers)		
YUAN/			0	<20		20+ cigs/day
Age, other	68M	M	1.0	1.8(1.0-3.3)		2.1(1.2-3.8)
HIRAYA/			0	1-9	10-19	20+cigs/day
Age	2170M[d],	M	1.00	1.68(1.39-2.02)	1.63(1.41-1.88)	1.95(1.69-2.24)
	1378F[d]	F	1.00	1.69(1.38-2.07)	2.25(1.85-2.73)	3.77(2.77-5.13)
KONO/			0	1-9	10-19	20+ cigs/day
Age	90M	M	1.00	1.51(0.68-3.36)	2.12(1.13-3.97)	3.01(1.61-5.65)
LIAW/			0	1-10	11-20	21+ cigs/day
Age, sex, other	143M, 23F	M+F	1.0	1.9(1.2-2.9)	1.6(1.0-2.4)	2.8(1.4-5.5)
PRESCO/			0	1-14	15-24	25+ grams/day
Age, other	1251M[d],	M	1.00	1.60(1.24-2.07)	1.75(1.37-2.23)	2.09(1.58-2.77)
	512F[d]	F	1.00	2.76(2.08-3.68)	3.27(2.42-4.42)	2.82(1.45-5.46)
				(comparison group = inhaling smokers of any product)		
PEKKAN/			0	1-9	10-19	20+ cigs/day
Age, other	280M	M	1.00	0.92(0.59-1.43)	1.80(1.27-2.54)	1.95(1.36-2.79)
CONTI/			0	1-9	10-19	20+ cigs/day
Age	74M	M	1.0	1.2(0.6-2.4)	2.5(1.4-4.4)	1.6(0.8-3.4)
				(base group includes ex-smokers)		
GRAMEN/			0	1-14	15-24	25+ cigs/day
Age, other	252F	F	1.00	2.28(1.41-3.68)	5.93(3.16-9.27)	11.0(5.13-23.7)
NEGRI/			0	1-19		20+ cigs/day
Age, sex, other	744M+F	M+F	1.0	2.3(1.7-3.1)		4.1(3.0-5.4)

TABLE 4.1 (Continued)

Study/adjustment factors[a]	Number of cases[b]	Sex	Relative risk (95% CI)[c] by amount smoked			
TVERDA1/			0	1-9	10-19	20+ cigs/day
Age, other	891M,	M	1.00	3.25(2.49-4.25)	4.32(3.43-5.43)	5.10(3.98-6.54)
	60F		0	1-9	10+ cigs/day	
		F	1.00	1.81(0.96-3.41)	2.34(1.29-4.24)	
CARSTE/			0	1-7	8-15	16+ grams/day
Age, other	2000M	M	1.00	1.31(1.15-1.49)	1.44(1.29-1.60)	1.66(1.46-1.89)
				(comparison group = smokers of any product)		
FLODER/			0	1-9		10+ cigs/day
Age, period of birth	704M,	M	1.0	1.4(1.2-1.6)		1.8(1.5-2.1)
	178F	F	1.0	1.7(1.4-2.1)		1.4(0.9-2.2)
HEDBLA/			0	1-14	15-24	25+ grams/day
Other	131M	M	1.0	2.6(1.5-4.6)	3.4(1.9-6.2)	4.2(1.9-9.5)
				(comparison group = smokers of any product)		
ROSENG/			0	1-4	5-14	15-24
Age, other	290M	M	1.0	2.8(1.7-4.7)	2.8(2.0-3.9)	3.1(2.2-4.4)
				25+cigs/day		
			...	2.1(1.1-4.2)		
			0	1-4	5-14	15+ cigs/day
	121M	M	1.0	4.6(2.1-10.1)	3.6(2.2-6.0)	4.5(2.2-7.5)
				(first analysis is based on smoking habits at baseline, second on subset who gave consistent smoking data at later screening)		
GSELL/			0	1-19		20+ cig units/day
Age	280M	M	1.0	1.15(0.85-1.56)		1.35(0.97-1.88)
				(comparison group = smokers of any product, base group includes ex-smokers)		
ALDERS/			0	1-17	18-27	28+ cigs/day
Age	426M,	M	1.00	0.84(0.71-0.99)	1.16(1.01-1.33)	1.48(1.31-1.68)
	688F	F	1.00	1.11(1.00-1.23)	1.99(1.80-2.21)	2.92(2.61-3.26)
				(comparison group = ever smoked manufactured cigarettes only, amounts at time of heaviest smoking)		
BRETT/			0	1-14	15-24	25+ cigs/day
Age	351M	M	1.0	1.7(1.1-2.5)	2.1(1.4-3.1)	2.5(1.6-4.0)
DUNN/			0	1-9	10-19	20+ cigs/day
Age, other	448F	F	1.00	2.54(1.30-4.94)	6.27(4.40-8.94)	16.5(12.2-22.8)
				(base group includes ex-smokers)		
CROFT/			0	1-14	15+ cigs/day	
Age, other	158F	F	1.0	1.7(1.1-2.7)	4.3(2.6-6.9)	
				(base group includes ex-smokers)		
DOLL/			0	1-14	15-24	25+ cigs/day
Age	2268M,	M	1.00	1.40(1.26-1.57)	1.56(1.40-1.74)	1.79(1.59-2.02)
	147F	F	1.00	0.96(0.60-1.52)	2.20(1.44-3.37)	2.12(1.17-3.84)

TABLE 4.1 (Continued 2)

Study/adjustment factors[a]	Number of cases[b]	Sex	Relative risk (95% CI)[c] by amount smoked			
BENSHL/			0	1-19		20+ cigs/day
Age	188M	M	1.00	1.64(1.10-2.43)		1.75(1.15-2.66)
TANG/			0	1-19	20	20-39 cigs/day
Age, other	319M	M	1.0	3.0(1.7-5.2)	3.2(1.8-5.8)	4.0(2.2-7.1)
				40+ cigs/day		
			...	2.2(0.9-5.3)		
KEYS/			0	1-9	10-19	20+ cigs/day
Age	284M[d]	NE[e]M	1.00	2.34(0.83-6.57)	3.78(1.47-9.73)	4.38(1.67-11.5)
		SE[e]M	1.00	0.70(0.29-1.67)	1.42(0.80-2.52)	1.82(1.03-3.20)
		US[e]M	1.00	1.65(0.55-4.98)	2.84(1.40-5.76)	3.10(1.51-6.35)
FRIEDM/			0	1-19		20+ cigs/day
Age	259M,	M	1.0	1.4(1.1-1.8)		2.0(1.6-2.4)
	184F	F	1.0	1.4(1.0-2.0)		2.2(1.7-2.9)
PAGANI/			0	1-19		20+ cigs/day
Age	?M,	M	1.00	1.19(0.96-1.47)		1.21(1.01-1.44)
	?F	F	1.00	1.15(0.93-1.43)		1.65(1.32-2.07)
ROSENM/			0	1-15	16-25	26+ cigs/day
Age	193M	M	1.0	1.2(0.7-2.1)	2.1(1.4-3.2)	2.7(1.8-4.0)
WEIR/			0	1-19	20	21+ cigs/day
Age	1718M	M	1.00	1.39	1.67	1.74
				(comparison group includes ex-smokers, base group includes pipe and cigar smokers, confidence intervals not available)		
BUSH/			0	1-9	10-20	21+ cigs/day
Age, other	833M	M	1.00	1.12(0.76-1.63)	1.16(0.84-1.59)	1.18(0.85-1.64)
FRAMIN/			0	1-10	11-20	21-30 cigs/day
Age	709M,	M	1.00	0.80(0.59-1.08)	1.27(1.06-1.53)	1.30(1.01-1.67)
	595F	F	1.00	1.06(0.82-1.36)	1.30(1.04-1.62)	0.79(0.46-1.37)
				31+ cigs/day		
		M	...	1.41(1.09-1.81)		
		F	...	0.57(0.24-1.34)		
CPS I/			0	1-9	10-19	20 cigs/day
Age	22612M,	M	1.00	1.34(1.26-1.43)	1.62(1.55-1.69)	1.76(1.70-1.82)
	16537F	F	1.00	1.14(1.05-1.23)	1.63(1.52-1.75)	1.66(1.54-1.79)
				21-39 cigs/day	40+ cigs/day	
		M	...	1.76(1.68-1.85)	2.01(1.90-2.14)	
		F	...	1.96(1.63-2.36)	1.45(1.09-1.92)	
				(data are for 30-84 year old Whites)		

TABLE 4.1 (Continued 3)

Study/adjustment factors[a]	Number of cases[b]	Sex	Relative risk (95% CI)[c] by amount smoked			
CPS II/			0	1-9	10-19	20 cigs/day
Age	4947M,	M	1.00	1.71(1.50-1.95)	1.94(1.75-2.14)	2.16(2.00-2.34)
	3380F	F	1.00	1.67(1.42-2.03)	2.03(1.76-2.34)	2.41(2.13-2.73)
				21-39 cigs/day		40+ cigs/day
		M	...	1.87(1.68-2.08)		1.87(1.66-2.11)
		F	...	2.24(1.76-2.84)		2.25(1.65-3.07)
				(data are for age 40-84 for males and for age 45-84 for females)		
DORN/			0	1-9	10-20	21-39 cigs/day
Age	20333M[f]	M[f]	1.00	1.24(1.18-1.30)	1.56(1.51-1.61)	1.76(1.69-1.83)
				40+ cigs/day		
		M	...	1.94(1.81-2.08)		
HAMMON/			0	<½	½-1	1-2 packs/day
Age	2369M	M		1.29(1.10-1.51)	1.89(1.71-2.09)	2.15(1.92-2.41)
				2+ packs/day		
		M	...	2.41(1.98-2.93)		
				(comparison group includes ex-smokers)		
KAWACH/			0	1-4	5-14	15-24 cigs/day
Age, other	752F	F	1.00	1.94(1.23-3.08)	2.53(1.96-3.26)	4.22(3.56-5.00)
				25-34	35-44	45+ cigs/day
		F	...	4.97(4.06-6.08)	5.57(4.36-7.11)	5.74(3.36-9.81)
LACROI/			0	1-19	20-39	40+ cigs/day
Age, other	729M+F[d]	M	1.0	1.4(1.0-2.1)	1.9(1.3-2.8)	2.2(1.1-4.3)
		F	1.0	1.8(1.2-2.6)	1.5(0.9-2.4)	0.8(0.2-3.1)
MRFIT/			0	1-15	16-25	26-35 cigs/day
Age, other	6417M	M	1.00	1.61(1.47-1.77)	2.14(2.00-2.29)	2.47(2.28-2.66)
				36-45	46+ cigs/day	
		M	...	2.43(2.24-2.64)	2.44(2.14-2.78)	
				(base group includes ex-smokers)		
ROSENB1/			0	1-14	15-24	25-34 cigs/day
Age	519F	F	1.0	1.4(0.9-2.1)	2.4(1.8-3.3)	5.0(3.6-8.9)
				35+cigs/day		
		F	...	7.0(5.2-9.4)		
ROSENB3/			0	1-14	15-24	25-34 cigs/day
Age	761F	F	1.0	2.0	2.8	4.7
				35+ cigs/day		
		F	...	7.2		
				(confidence intervals not available)		
ROSENB4/			0	1-14	15+ cigs/day	
Age, other	187F	F	1.0	1.6(1.1-2.5)	2.3(1.4-3.7)	

TABLE 4.1 (Continued 4)

Study/adjustment factors[a]	Number of cases[b]	Sex	Relative risk (95% CI)[c] by amount smoked			
DOYLE/			0	<20	20	>20 cigs/day
Age	214M	M	1.00	1.79(1.08-2.96)	1.85(1.15-2.98)	2.74(1.73-4.34)
POOLIN/			0	½	1	>1 packs/day
Age	510M	M	1.0	1.9(1.3-2.8)	2.2(1.7-3.0)	3.4(2.5-4.6)

[a] See Table 3.5 for “other” factors adjusted for.
[b] Numbers in never and current smokers included in analysis, except where stated.
[c] Data given in square brackets are cases, not 95% CI.
[d] Total cases in study.
[e] NE = Northern Europe, SE = Southern Europe, US = United States.
[f] Population is >99.5% male.

TABLE 4.2

Relative risk (95% CI) of heart disease for current vs never smokers for different age-groups

Study/adjustment factors[a]	Number of cases[b]	Sex	Relative risk (95% CI)[c] for current vs never smokers			
SCHARG/			Age 30-44	Age 45-54	Age 55-65	
Sex, other	819M+F	M+F	4.6 (2.1-9.8)	3.6 (2.3-5.6)	2.1 (1.6-2.7)	
BEST/			Age 30-49	Age 50-69	Age 70+	
None	1380M[d],	M	1.49 [198]	1.66 [961]	1.50 [221]	
	46F[d]	F	2.07 [3]	1.65 [35]	0.62 [8]	
			(for females, data are for ever vs never smokers)			
CHUN/	1882M[d],		Age 35-39	Age 40-44	Age 45-49	Age 50-54
None	863F[d]	M	4.7(2.6-8.4)	4.6(3.1-6.9)	6.1(3.9-8.6)	3.1(2.4-4.6)
		F	28.1(6.3-124)	9.6(4.3-17)	4.2(2.6-7.3)	2.8(1.8-4.4)
			Age 55-59	Age 60-64	Age 65-69	
		M	3.0(2.4-3.9)	2.1(1.6-2.7)	2.0(1.6-2.6)	
		F	3.6(2.6-5.1)	3.6(2.8-4.8)	2.6(1.9-3.4)	
PRESCO/			Age <55	Age 55-64	Age 65-74	Age 75-84
Other	1251M[d],	M	2.9	2.1	1.2	1.4
	512F[d]	F	6.8	3.4	2.8	1.9
GRAMEN/			Age <50	Age 50+		
Other	252F	F	4.57	7.28		
			(data are for current smokers of 15-24 cigs/day)			
NEGRI/			Age <50	Age 50+		
Sex, other	744M+F	M+F	8.8	2.6		
TVERDA2/			Age 35-39	Age 40-44	Age 45-49	
Other	1021M,	M	2.8(2.0-3.8)	2.9(2.3-3.8)	1.9(1.6-2.4)	
	193F	F	3.8(1.9-7.8)	2.5(1.5-4.2)	3.1(2.0-4.7)	
			(base = ever smoked)			
FLODER/			Born 1911-1925	Born 1901-1910		
None	352M[e]	M	2.9(2.1-4.0)	1.8(1.4-2.5)		
	89F[e]	F	2.6(1.4-4.9)	1.2(0.6-2.3)		
			(data are for current smokers of >10 cigs/day)			
GSELL/			Age 35-54	Age 54-65	Age 66-74	Age 75+
None	117M[f]	M	2.27	2.16	1.94	0.99
			(data are for "heavy" smokers based on 9 years follow-up)			
ALDERS/			Age 35-54	Age 55-74		
None	426M,	M	1.63(1.38-1.93)	0.91(0.78-1.07)		
	688F	F	2.13(1.86-2.44)	1.30(1.17-1.44)		
			(data are for ever smokers of manufactured cigarettes only)			
BRETT/			Age 40-54	Age 55+		
None	351M	M	2.1(1.2-3.6)	1.8(1.1-3.1)		

TABLE 4.2 (Continued)

Study/adjustment factors[a]	Number of cases[b]	Sex	Relative risk (95% CI)[c] for current vs never smokers			
DOLL/			Age <45	Age 45-54	Age 55-64	
None	1383M,	M	9.89(3.09-31.6)	3.27(2.26-4.74)	1.99(1.57-2.54)	
	68F		Age 65-74	Age 75+		
		M	1.81(1.43-2.29)	1.65(1.31-2.09)		
			Age <65	Age 65+		
		F	1.94(1.00-3.77)	1.48(1.02-2.15)		
FRIEDM/			Age 35-49	Age 50-64	Age 65-74	
None	227M,	M	1.8(0.7-4.6)	3.0(2.1-4.2)	1.7(1.2-2.4)	
	164F	F	5.3(1.5-19.0)	3.2(1.9-5.4)	2.2(1.4-3.6)	
			Age 75+			
		M	1.1(0.7-1.8)			
		F	1.0(0.5-2.0)			
			(data are for smokers of 20+ cigs/day)			
ROSENM/			Age 39-49	Age 50-59		
None	193M	M	2.5(1.5-4.0)	1.8(1.0-3.2)		
WEIR/			Age 35-44	Age 45-54	Age 55-64	Age 65-69
None	1718M	M	6.24	2.95	1.56	1.24
			(comparison group includes ex-smokers, base group includes pipe and cigar smokers)			
BUSH/			Age 25-44	Age 45-64	Age 65-74	
Other	833M	M	2.21(1.09-4.47)	1.60(1.32-1.95)	0.83(0.59-1.16)	
FRAMIN/			Age 45-64	Age 65-84		
Age, other	709M,	M	1.6(1.3-2.0)	1.0(0.8-1.4)		
	595F	F	1.2(1.0-1.6)	1.2(0.9-1.6)		
CPS I/			Age 40-44	Age 45-49	Age 50-54	
None	23337M,	M	5.73(3.02-10.9)	3.73(2.88-4.83)	2.97(2.60-3.39)	
	16677F	F	2.90(1.59-5.29)	2.83(2.07-3.87)	2.96(2.47-3.55)	
			Age 55-59	Age 60-64	Age 65-69	
		M	2.26(2.07-2.47)	1.79(1.67-1.93)	1.61(1.51-1.72)	
		F	2.43(2.15-2.74)	1.78(1.61-1.96)	1.58(1.45-1.72)	
			Age 70-74	Age 75-79	Age 80-84	
		M	1.47(1.37-1.57)	1.25(1.16-1.35)	1.22(1.01-1.35)	
		F	1.45(1.33-1.59)	1.26(1.14-1.39)	1.23(1.08-1.41)	
			(data are for Whites)			

TABLE 4.2 (Continued 2)

Study/adjustment factors[a]	Number of cases[b]	Sex	Relative risk (95% CI)[c] for current vs never smokers		
CPS II/			Age 40-44	Age 45-49	Age 50-54
None	4947M,	M	6.28(1.85-21.3)	5.47(3.30-9.07)	3.78(2.91-4.91)
	3380F	F	2.52(0.56-11.2)	3.20(1.77-5.78)	1.97(1.41-2.76)
			Age 55-59	Age 60-64	Age 65-69
		M	2.72(2.26-3.27)	2.39(2.07-2.76)	1.90(1.67-2.17)
		F	1.69(1.33-2.15)	2.00(1.67-2.40)	2.08(1.78-2.44)
			Age 70-74	Age 75-79	Age 80-84
		M	1.69(1.49-1.92)	1.36(1.17-1.58)	1.44(1.16-1.78)
		F	2.01(1.72-2.36)	2.30(1.94-2.75)	2.66(2.07-3.42)
DORN/			Age 35-44	Age 45-54	Age 55-64
None	7147M[g]	M	5.02(2.18-11.6)	5.51(2.76-11.0)	1.71(1.59-1.84)
		M	Age 65-74	Age 75-84	
			1.64(1.53-1.75)	1.24(0.97-1.58)	
HAMMON/			Age 50-54	Age 55-59	Age 60-64
None	2369M	M	1.93(1.67-2.24)	1.86(1.65-2.09)	1.66(1.52-1.82)
			Age 65-69		
		M	1.41(1.31-1.52)		
			(comparison group includes ex-smokers)		
KAWACH/			Age 30-39	Age 40-49	Age 50-59
None	145F	F	4.3(1.3-13.7)	3.6(2.4-5.5)	4.1(2.9-5.9)
			(data are for smokers of 15-24/day)		
MRFIT/			Age 35-39	Age 40-44	Age 45-59
Other	6327M	M	3.2(2.6-4.0)	3.1(2.7-3.7)	2.7(2.4-3.0)
			Age 50-54	Age 55-57	
		M	2.4(2.2-2.6)	2.0(1.8-2.2)	
			(base group includes ex-smokers)		
ROSENB1/			Age 25-39	Age 40-44	Age 45-59
None	519F	F	5.13(2.57-10.2)	3.55(2.10-6.02)	3.13(2.20-4.46)
POOLIN/			Age 40-44	Age 45-49	Age 50-54
None	510M	M	2.2(0.7-7.1)	13(3.2-52)	4.7(2.3-9.7)
			Age 55-59	Age 60-64	
		M	1.9(1.2-3.0)	2.1(1.3-3.3)	

[a] See Table 3.5 for "other" factors adjusted for.
[b] Numbers in never and current smokers included in analysis, except where stated.
[c] Data given in square brackets are cases, not 95% CI. Confidence intervals not always available.
[d] Total cases in study.
[e] Numbers are for current smokers only.
[f] Total cases in first 9 years follow-up.
[g] Population is >99.5% male

TABLE 4.3

Relative risk (95% CI) of heart disease by amount smoked for different age groups (base = never smokers and comparison groups = current smokers unless indicated)

Study/adjustment factors[a]	Number of cases[b]	Sex	Age	Relative risk (95% CI)[c] by amount smoked			
SCHARG/				0	<15	15-24	25+cigs/day
Sex, other	819M+F	M+F	30-44	1.0	2.4(0.9-6.7)	2.6 (1.1-6.0)	10.3(4.3-24.5)
			45-54	1.0	2.2(1.3-3.9)	2.7(1.6-4.6)	7.0(4.0-12.2)
			55-64	1.0	1.4(0.9-2.1)	1.7(1.2-2.4)	4.3(2.8-6.5)
BEST/				0	<10	10-20	20+ cigs/day
None	1380M[d]	M	30-49	1.00	0.97 [18]	1.45 [115]	1.85 [65]
			50-69	1.00	1.56 [220]	1.67 [557]	1.76 [184]
			70+	1.00	1.71 [99]	1.29 [94]	1.73 [28]
GRAMEN/				0	<15	15-24	25+ cigs/day
Other	252F	F	<50	1.00	2.14	4.57	7.67
			50+	1.00	2.66	7.28	-[e]
FLODER/			Born	0	1-9		10+ cigs/day
None	352M[f], 89F[f]	M	1911-25	1.0	2.2(1.6-2.9)		2.9(2.1-4.0)
			1901-10	1.0	1.6(1.3-2.0)		1.8(1.4-2.5)
		F	1911-25	1.0	2.4(1.6-3.6)		2.6(1.4-4.9)
			1901-10	1.0	1.9(1.4-2.6)		1.2(0.6-2.3)
ALDERS/			Age	0	1-17	18-27	28+ cigs/day
None	426M, 788F	M	35-54	1.00	0.79(0.59-1.06)	1.51(1.24-1.85)	1.96(1.64-2.34)
			55-74	1.00	0.86(0.70-1.06)	0.90(0.74-1.09)	1.11(0.93-1.33)
		F	35-54	1.00	1.28(1.06-1.54)	2.55(2.18-2.99)	3.02(2.57-3.55)
			55-74	1.00	1.03(0.91-1.17)	1.65(1.44-1.90)	2.82(2.41-3.30)
			(comparison group = ever smokers of manufactured cigarettes only, amounts at time of heaviest smoking)				
BRETT/				0	1-14	15-24	25+ cigs/day
None	351M	M	40-54	1.0	1.8(1.0-3.2)	2.1(1.2-3.8)	2.9(1.5-5.6)
			55+	1.0	1.6(0.9-2.8)	2.0(1.2-3.5)	2.2(1.1-4.2)
DOLL/				0	1-14	15-24	25+ cigs/day
None	1383M, 68F	M	<45	1.00	6.57(1.85-23.3)	8.71(2.61-29.1)	14.9(4.38-50.4)
			45-54	1.00	1.86(1.16-2.98)	3.12(2.08-4.67)	3.33(2.19-5.06)
			55-64	1.00	1.40(1.03-1.89)	1.54(1.16-2.05)	1.93(1.46-2.56)
			65-74	1.00	1.57(1.19-2.06)	1.27(0.95-1.70)	1.45(1.07-1.98)
			75+	1.00	1.12(0.85-1.47)	1.01(0.72-1.43)	1.34(0.87-2.05)
		F	<65	1.00	1.42(0.62-3.24)	2.55(1.11-5.86)	2.74(0.94-7.99)
			65+	1.00	0.79(0.44-1.41)	2.19(1.33-3.59)	2.76(1.48-5.16)

TABLE 4.3 (Continued)

Study/adjustment factors[a]	Number of cases[b]	Sex	Age	Relative risk (95% CI)[c] by amount smoked			
FRIEDM/				0	1-19		20+ cigs/day
None	259M, 184F	M	35-49	1.0	2.3(0.8-6.4)		1.8(0.7-4.6)
			50-64	1.0	2.1(1.3-3.3)		3.0(2.1-4.2)
			65-74	1.0	1.4(0.9-2.2)		1.7(1.2-2.4)
			75+	1.0	0.6(0.3-1.2)		1.1(0.7-1.8)
		F	35-49	1.0	No deaths		5.3(1.5-19.0)
			50-64	1.0	1.4(0.7-2.9)		3.2(1.9-5.4)
			65-74	1.0	1.6(0.9-2.8)		2.2(1.4-3.6)
			75+	1.0	1.3(0.7-2.3)		1.0(0.5-2.0)
ROSENM/				0	1-15	16-25	26+ cigs/day
None	193M	M	39-49	1.0	1.4(0.7-3.0)	2.3(1.3-4.1)	3.1(1.8-5.2)
			50-59	1.0	1.0(0.4-2.3)	1.9(1.0-3.6)	2.3(1.2-4.2)
WEIR/				0	1-19	20	21-39 cigs/day
None	1718M	M	35-44	1.00	4.22	6.14	8.57
			45-54	1.00	2.05	3.17	3.33
			55-64	1.00	1.41	1.64	1.66
			65-69	1.00	1.17	1.26	1.36
					40+ cigs/day		
			35-44	...	7.93		
			45-54	...	3.15		
			55-64	...	1.42		
			65-69	...	1.42		
					(comparison group includes ex-smokers, base group includes pipe and cigar smokers)		
BUSH/				0	1-9	10-20	21+ cigs/day
Other	833M	M	25-44	1.00	1.57(0.51-4.87)	1.90(0.82-4.41)	3.71(1.52-9.09)
			45-64	1.00	1.16(0.82-1.63)	1.46(1.12-1.90)	2.25(1.73-2.92)
			65-74	1.00	1.06(0.67-1.66)	0.86(0.53-1.40)	0.14(0.02-1.00)
FRAMIN/				0	1-10	11-20	21-30 cigs/day
Age	709M, 595F	M	45-64	1.00	0.89(0.60-1.32)	1.67(1.33-2.10)	1.51(1.11-2.05)
			65-84	1.00	0.71(0.44-1.17)	0.89(0.61-1.31)	1.10(0.60-2.00)
		F	45-64	1.00	1.03(0.73-1.43)	1.21(0.90-1.62)	0.96(0.52-1.78)
			65-84	1.00	1.08(0.71-1.66)	1.38(0.95-2.01)	0.64(0.17-2.43)
					31+ cigs/day		
		M	45-64	...	1.95(1.46-2.60)		
			65-84	...	0.89(0.47-1.66)		
		F	45-64	...	1.21(0.58-2.53)		
			65-84	...	No deaths		
CPS I/ None	22612M, 16537F				See Table 4.3A		
CPS II/ None	4947M, 3380F				See Table 4.3B		
DORN/ None	7096M[g]				See Table 4.3C		

TABLE 4.3 (Continued 2)

Study/adjustment factors[a]	Number of cases[b]	Sex	Age	Relative risk (95% CI)[c] by amount smoked			
HAMMON/				0	<½	½-1	1+ pack/day
None	2369M	M	50-54	1.00	1.38(0.93-2.03)	2.00(1.57-2.56)	2.51(1.95-3.21)
			55-59	1.00	1.38(1.00-1.90)	2.04(1.66-2.50)	2.47(1.99-3.06)
			60-64	1.00	1.17(0.86-1.60)	1.91(1.59-2.31)	1.92(1.54-2.40)
			65-69	1.00	1.27(0.96-1.69)	1.58(1.30-1.92)	1.56(1.20-2.02)
				(comparison group includes ex-smokers)			
KAWACH/				0	1-14	15-24	25+ cigs/day
None	252F	F	30-39	1.0	No deaths	4.3(1.3-13.7)	3.5(0.8-14.5)
			40-49	1.0	1.6(1.1-2.4)	3.6(2.4-5.5)	7.0(4.8-10.5)
			50-59	1.0	2.4(1.5-3.9)	4.1(2.9-5.9)	5.3(3.7-7.6)
MRFIT/				0	1-25	26+ cigs/day	
Other	6327M	M	35-39	1.0	2.4(1.8-3.1)	4.0(3.2-5.0)	
			40-44	1.0	2.7(2.3-3.2)	3.5(3.0-4.1)	
			45-49	1.0	2.2(1.9-2.5)	3.1(2.8-3.5)	
			50-54	1.0	2.1(1.9-2.3)	2.7(2.4-3.0)	
			55-57	1.0	1.8(1.6-2.0)	2.2(1.9-2.5)	
				(base group includes ex-smokers)			
ROSENB1/				0	1-14	15-24	25-34 cigs/day
None	519F	F	25-39	1.00	1.00(0.30-3.33)	2.90(1.33-6.32)	9.97(4.25-23.4)
			40-44	1.00	1.24(0.51-3.01)	2.25(1.24-4.10)	4.33(2.23-8.44)
			45-49	1.00	1.72(1.02-2.89)	2.53(1.67-3.81)	4.32(2.65-7.04)
		F			35+ cigs/day		
			25-39	...	13.0(5.92-28.4)		
			40-44	...	8.24(4.50-15.1)		
			45-49	...	5.18(3.34-8.04)		
POOLIN/				0	½	1	>1 pack/day
None	510M	M	40-44	1.0	1.6(0.3-8.1)	2.1(0.6-7.1)	2.6(0.7-9.4)
			45-49	1.0	7.1(1.5-34)	12(2.9-49)	17(4.2-72)
			50-54	1.0	2.5(1.0-6.4)	4.1(2.0-8.6)	7.0(3.3-14.6)
			55-59	1.0	1.8(1.0-3.3)	1.6(1.0-2.6)	2.6(1.5-4.3)
			60-64	1.0	2.1 (1.1-4.1)	1.9(1.1-3.3)	2.4(1.3-4.3)

[a] See Table 3.5 for "other" factors adjusted for.
[b] Numbers in never and current smokers included in analysis, except where stated.
[c] Data given in square brackets are cases, not 95% CI. Confidence intervals not always available.
[d] Total cases in study.
[e] Not estimable.
[f] Numbers are for current smokers only.
[g] Population is >99.5% male

TABLE 4.3A

Relative risk (95% CI) of heart disease by amount smoked (compared to never smokers) for different age groups in CPS I (data are for Whites; smokers are of cigarettes only)

Sex	Age	Relative risk (95% CI) by amount smoked					
		0	1-9	10-19	20	21-39	40+ cigs/day
Male	40-44	1.00	2.71(0.85-8.64)	3.76(1.69-8.37)	5.50(2.81-10.8)	5.89(2.94-11.8)	9.03(4.43-18.4)
	45-49	1.00	2.07(1.24-3.45)	3.31(2.38-4.61)	3.57(2.70-4.73)	3.88(2.90-5.20)	4.48(3.27-6.12)
	50-54	1.00	1.66(1.25-2.20)	2.34(1.94-2.81)	3.04(2.63-3.52)	3.06(2.62-3.57)	3.50(2.95-4.14)
	55-59	1.00	1.69(1.41-2.02)	2.14(1.90-2.42)	2.26(2.05-2.50)	2.19(1.97-2.44)	2.75(2.44-3.09)
	60-64	1.00	1.35(1.15-1.57)	1.63(1.47-1.81)	1.81(1.67-1.97)	1.81(1.65-1.99)	2.15(1.93-2.39)
	65-69	1.00	1.35(1.17-1.55)	1.58(1.43-1.74)	1.66(1.53-1.80)	1.67(1.51-1.84)	1.75(1.55-1.98)
	70-74	1.00	1.18(1.02-1.36)	1.45(1.31-1.60)	1.54(1.41-1.67)	1.61(1.43-1.81)	1.63(1.40-1.91)
	75-79	1.00	1.30(1.13-1.50)	1.22(1.08-1.37)	1.28(1.15-1.42)	1.28(1.07-1.54)	1.42(1.12-1.81)
	80-84	1.00	0.97(0.78-1.19)	1.28(1.10-1.50)	1.36(1.17-1.58)	1.25(0.92-1.71)	1.68(1.16-2.45)
Female	40-44	1.00	0.70(0.16-3.04)	2.13(0.90-5.01)	3.43(1.66-7.10)	5.88(2.49-13.9)	6.57(1.90-22.7)
	45-49	1.00	1.95(1.16-3.28)	2.76(1.83-4.18)	3.21(2.17-4.74)	3.18(1.77-5.70)	3.41(1.37-8.31)
	50-54	1.00	1.64(1.18-2.29)	2.54(1.98-3.26)	3.70(2.96-4.63)	4.30(3.12-5.93)	4.42(2.68-7.26)
	55-59	1.00	1.40(1.11-1.77)	2.44(2.06-2.89)	2.90(2.47-3.40)	2.80(2.14-3.67)	3.67(2.52-5.33)
	60-64	1.00	1.14(0.94-1.39)	1.89(1.64-2.18)	2.04(1.77-2.35)	2.35(1.83-3.00)	2.86(2.01-4.07)
	65-69	1.00	1.07(0.90-1.27)	1.74(1.51-1.99)	1.89(1.65-2.17)	1.72(1.29-2.30)	1.80(1.16-2.80)
	70-74	1.00	0.97(0.82-1.16)	1.58(1.36-1.83)	1.76(1.52-2.05)	1.91(1.39-2.62)	1.22(0.65-2.27)
	75-79	1.00	1.13(0.96-1.34)	1.48(1.25-1.75)	1.16(0.94-1.43)	1.89(1.24-2.87)	0.83(0.31-2.21)
	80-84	1.00	1.23(1.01-1.51)	1.36(1.08-1.71)	1.29(0.97-1.72)	1.62(0.77-3.41)	0.64(0.09-4.52)

Note: Underlined estimates are based on less than 10 deaths in the smoking group.

TABLE 4.3B

Relative risk (95% CI) of heart disease by amount smoked (compared to never smokers) for different age groups in CPS II (smokers are of cigarettes only)

Sex	Age	Relative risk (95% CI) by amount smoked					
		0	1-9	10-19	20	21-39	40+ cigs/day
Male	40-44	1.00	3.84(0.40-36.9)	2.64(0.27-25.3)	7.80(1.95-31.2)	4.22(0.85-20.9)	9.38(2.43-36.3)
	45-49	1.00	6.59(2.96-14.7)	5.24(2.48-11.1)	5.27(2.84-9.77)	3.68(1.88-7.21)	7.13(4.01-12.7)
	50-54	1.00	2.61(1.47-4.62)	4.46(2.98-6.68)	3.80(2.73-5.30)	3.75(2.68-5.24)	3.84(2.76-5.33)
	55-59	1.00	2.36(1.57-3.55)	2.61(1.89-3.60)	3.03(2.40-3.82)	2.39(1.85-3.10)	2.87(2.25-3.65)
	60-64	1.00	2.16(1.57-2.97)	2.49(1.96-3.18)	2.80(2.34-3.35)	2.02(1.62-2.51)	2.25(1.82-2.77)
	65-69	1.00	1.61(1.18-2.19)	1.90(1.51-2.38)	2.03(1.71-2.41)	2.02(1.65-2.48)	1.69(1.34-2.14)
	70-74	1.00	1.67(1.25-2.21)	1.61(1.29-2.02)	1.94(1.64-2.30)	1.48(1.14-1.91)	1.45(1.08-1.94)
	75-79	1.00	1.05(0.73-1.50)	1.21(0.92-1.59)	1.43(1.15-1.79)	1.81(1.34-2.44)	1.34(0.89-2.02)
	80-84	1.00	1.31(0.87-1.97)	1.48(1.03-2.12)	1.63(1.18-2.27)	1.07(0.55-2.06)	1.39(0.66-2.94)
Female	40-44	1.00	No deaths	No deaths	3.89(0.65-23.3)	3.19(0.33-30.7)	4.69(0.49-45.1)
	45-49	1.00	2.37(0.70-8.05)	3.79(1.58-9.06)	3.18(1.43-7.08)	2.39(0.81-7.06)	4.40(1.63-11.8)
	50-54	1.00	1.45(0.67-3.16)	1.79(0.99-3.23)	1.73(1.05-2.87)	2.93(1.75-4.92)	2.13(1.06-4.25)
	55-59	1.00	0.52(0.21-1.26)	1.26(0.78-2.02)	2.12(1.54-2.93)	1.77(1.11-2.82)	2.61(1.64-4.15)
	60-64	1.00	1.37(0.87-2.16)	1.66(1.19-2.31)	2.33(1.82-2.98)	2.44(1.74-3.42)	1.91(1.20-3.04)
	65-69	1.00	1.53(1.05-2.23)	2.06(1.59-2.67)	2.40(1.93-2.98)	1.98(1.37-2.85)	2.01(1.28-3.15)
	70-74	1.00	1.50(1.04-2.16)	2.21(1.73-2.83)	2.07(1.64-2.63)	2.16(1.42-3.29)	2.01(1.18-3.42)
	75-79	1.00	1.98(1.37-2.87)	2.09(1.55-2.82)	2.57(1.97-3.35)	2.81(1.68-4.69)	2.45(1.27-4.73)
	80-84	1.00	2.66(1.67-4.23)	2.39(1.54-3.71)	3.12(2.11-4.62)	1.70(0.55-5.30)	2.68(0.86-8.36)

Note: Underlined estimates are based on less than 10 deaths in the smoking group.

TABLE 4.3C

Relative risk (95% CI) of heart disease by amount smoked (compared to never smokers) for different age groups in the US Veteran's Study (DORN) (smokers are of cigarettes only)

Sex	Age	Relative risk (95% CI) by amount smoked				
		0	1-9	10-20	21-39	40+ cigs/day
Male	35-44	1.00	3.39(0.85-13.6)	4.31(1.80-10.3)	6.47(2.71-15.5)	6.24(1.56-24.9)
	45-54	1.00	5.72(2.04-16.1)	4.71(2.25-9.89)	6.40(3.07-13.3)	7.93(2.82-22.3)
	55-64	1.00	1.39(1.19-1.63)	1.78(1.63-1.93)	1.71(1.55-1.87)	2.08(1.76-2.44)
	65-74	1.00	1.41(1.23-1.61)	1.70(1.57-1.84)	1.71(1.55-1.89)	1.58(1.27-1.96)
	75-84	1.00	0.94(0.57-1.54)	1.30(0.96-1.75)	1.44(0.92-2.27)	2.00(0.82-4.86)

Note: Underlined estimates are based on less than 10 deaths in the smoking group; the number of deaths in the never smoking group was less than 10 for the age groups 35-44 and 45-54. The population studied was over 99.5% male but included some females.

TABLE 4.4

Relative risk (95% CI) of heart disease by time given up (base = never smokers and comparison groups = current smokers unless indicated)

Study/adjustment factors[a]	Number of cases[b]	Sex(Age)	Relative risk (95% CI)[c] by time given up			
HIRAYA/			Never	10+ years	5-9 years	1-4 years
Age	2179M[d],	M	1.00	0.94(0.54-1.64)	1.73(1.10-2.72)	1.50(1.02-2.20)
	1378F[d]	F	1.00	0.91(0.13-6.74)	1.19(0.20-6.94)	0.41(0.05-3.37)
				Current		
		M	...	1.73(1.52-1.97)		
		F	...	1.90(1.66-2.17)		
CHUN/			Never	13+ years	10-12 years	7-9 years
Age, other	570M,	M	1.00	0.96(0.69-1.34)	1.13(0.67-1.89)	1.40(0.77-2.53)
	259F	F	1.00	0.71(0.37-1.35)	1.71(0.59-4.94)	1.26(0.49-3.21)
				4-6 years	1-3 years	6-12 months
		M	...	1.02(0.60-1.74)	1.95(1.15-3.20)	2.38(0.91-6.20)
		F	...	1.29(0.49-3.37)	2.86(1.23-6.66)	9.97(2.11-47.1)
				<6 months	Current	
		M	...	4.31(1.89-9.85)	2.71(2.07-3.53)	
		F	...	3.24(1.15-9.19)	4.70(3.35-6.58)	
NEGRI/			Never	>10 years	6-10 years	2-5 years
Age, sex, other	744M+F	M+F	1.0	1.1(0.8-1.8)	1.2(0.7-2.1)	1.4(0.9-2.1)
				1 year	Current	
			...	1.6(0.8-3.2)	2.9(2.2-3.9)	
TVERDA1/			Never	5+ years	1-5 years	3-12 months
Age, other	1199M	M	1.00	1.37(1.02-1.85)	1.77(1.28-2.15)	2.48(1.58-3.90)
				<3 months	Current	
			...	3.83(2.44-6.02)	4.20(3.37-5.23)	
ALDERS/			Never	>10 years	5-10 years	1-3 years
Age	426M,	M35-54	1.00	0.89(0.65-1.22)	1.21(0.89-1.65)	2.27(1.83-2.82)
	688F	M55-74	1.00	1.13(0.93-1.38)	0.83(0.64-1.09)	1.31(1.04-1.65)
		F35-54	1.00	1.00(0.69-1.45)	1.37(1.03-1.80)	2.05(1.68-2.50)
		F55-74	1.00	0.92(0.76-1.10)	1.23(1.03-1.48)	1.22(1.01-1.46)
				Current		
		M35-54	...	1.79(1.49-2.14)		
		M55-74	...	0.73(0.61-0.88)		
		F35-54	...	2.44(2.11-2.81)		
		F55-74	...	1.67(1.48-1.88)		
			(comparison group = smokers of manufactured cigarettes only)			
DOLL/			Never	15+ years	10-14 years	5-9 years
Age	2152M	M30-54	1.0	1.3(0.6-2.9)	1.4(0.7-2.9)	1.3(0.6-2.6)
		M55-64	1.0	1.3(0.9-1.9)	1.7(1.2-2.5)	1.4(0.9-2.1)
		M65+	1.0	1.1(0.9-1.4)	1.2(0.9-1.6)	1.3(1.0-1.7)
				1-4 years	Current	
		M30-54	...	1.9(0.8-4.3)	3.5(2.4-5.0)	
		M55-64	...	1.9(1.1-3.1)	1.7(1.3-2.2)	
		M65+	...	1.0(0.7-1.5)	1.3(1.1-1.5)	
BENSHL/			Never	30+ years	20-29 years	10-19 years
Age, other	1485M	M	1.00	1.15(0.91-1.46)	1.13(0.89-1.43)	1.19(0.94-1.50)
				1-9 years	Current	
		M	...	1.44(1.03-2.03)	1.90(1.62-2.24)	

TABLE 4.4 (Continued)

Study/adjustment factors[a]	Number of cases[b]	Sex(Age)	Relative risk (95% CI)[c] by time given up				
TANG/			Never	21+ years	11-20 years	6-10 years	
Age, other	430M	M	1.0	0.8(0.5-1.5)	1.3(0.8-2.0)	1.0(0.6-1.7)	
				3-5 years	1-2 years	Current	
		M	...	1.5(0.9-2.6)	1.8(1.0-3.1)	2.1(1.6-2.8)	
FRIEDM/			Never	20+ years	11-20 years	2-10 years	
Age	358M,	M	1.0	1.0(0.8-1.3)	1.3(1.0-1.7)	1.3(0.9-1.8)	
	219F	F	1.0	1.1(0.7-1.7)	1.4(0.9-2.1)	1.4(0.9-2.3)	
				Current			
		M	...	1.8(1.5-2.1)			
		F	...	1.8(1.4-2.3)			
PAGANI/			Never	20+ years	11-20 years	6-10 years	
Age	?M,	M	1.00	1.03(0.85-1.25)	1.21(0.96-1.53)	1.43(1.02-1.99)	
	?F	F	1.00	1.09(0.83-1.42)	1.53(1.14-2.04)	1.42(0.93-2.15)	
				1-5 years	Current		
		M	...	2.02(1.44-2.84)	1.41(1.03-1.93)		
		F	...	1.28(0.81-2.01)	1.47(1.10-1.95)		
CPS I/			Never	35-39	30-34	25-29	20-24 years
Age	24920M,	M	1.00	0.55	0.93	0.96	0.99
	20820F	F	1.00	0.63	0.63	0.96	0.88
				15-19	10-14	5-9	2-4 years
		M	...	1.13	1.37	1.64	2.66
		F	...	0.84	0.98	1.53	2.23
				(Data are for whites; 95% CI and comparable rate ratio for current smokers not available)			
DORN/			Never	40+ years	30-39 years	20-29 years	
Age	23626M[e]	M	1.0	1.0(1.0-1.1)	1.1(1.0-1.1)	1.2(1.1-1.2)	
				10-19 years	5-9 years	<5 years	
		M	...	1.4(1.3-1.4)	1.5(1.4-1.6)	1.7(1.5-1.9)	
				(comparable estimates for current smokers not available)			
HAMMON/			Never	10+ years	1-10 years	<1 year	
Age	1435M	M	1.00	1.60(1.16-2.20)	2.06(1.60-2.66)	3.00(1.88-4.79)	
				Current			
			...	2.20(1.97-2.45)			
KAWACH/			Never	15+ years	10-14 years	5-9 years	
Age, other	941F	F	1.00	1.17(0.81-1.68)	1.08(0.60-1.96)	1.83(1.22-2.76)	
				2-4 years	<2 years	Current	
		F	...	1.92(1.19-3.10)	3.13(2.01-4.85)	4.17(3.52-4.93)	
LACROI/			Never	>20 years	11-20 years	6-10 years	
Age, other	729M+F[d]	M	1.0	1.0(0.7-1.4)	1.1(0.8-1.6)	0.9(0.5-1.5)	
		F	1.0	0.8(0.4-1.4)	0.5(0.2-1.1)	1.0(0.5-2.0)	
				≤5 years	Current		
		M	...	1.1(0.7-1.8)	1.7(1.3-2.3)		
		F	...	1.0(0.5-2.1)	1.6(1.2-2.2)		
ROSENB2/			Never	20+ years	15-19 years	10-14 years	
Age	1873M	M	1.0	0.8(0.6-1.2)	1.3(0.9-1.8)	1.0(0.8-1.4)	
				5-9 years	3-4 years	24-35 mo	
		M	...	1.4(1.0-2.0)	1.0(0.7-1.6)	1.1(0.7-1.9)	
				12-23 mo	Current		
		M	...	2.0(1.1-3.8)	2.9(2.4-3.4)		
				(current smokers includes all smokers in previous years)			

TABLE 4.4 (Continued 2)

Study/adjustment factors[a]	Number of cases[b]	Sex(Age)	Relative risk (95% CI)[c] by time given up			
ROSENB3/			Never	10+ years	6-9 years	3-5 years
Age	910F	F	1.0	1.0(0.7-1.3)	1.1(0.7-1.8)	0.8(0.4-1.8)
				24-35 mo	12-23 mo	7-11 mo
		F	...	1.3(0.7-2.6)	2.0(1.1-3.7)	2.3(0.9-5.8)
				4-6 mo	1-3 mo	Current
		F	...	3.6(1.8-7.2)	3.0(1.5-5.7)	3.6(3.0-4.4)
				(current smokers includes all smokers in previous years)		

[a] See Table 3.5 for "other" factors adjusted for.
[b] Numbers in never and current smokers included in analysis, except where stated.
[c] Data given in square brackets are cases, not 95% CI.
[d] Total cases in study.
[e] Population is >99.5% male.

APPENDIX A

Sources for the main tables

This appendix gives details of the sources used for each of the main tables in section 4. For each study included in each table, the appendix provides details of:

(i) the reference number (in square brackets) of the publication which was used as source,

(ii) the tables in that reference that were used, and

(iii) whether the relative risks and CIs used were taken directly from the source or whether some calculation was necessary. Details of the calculations used are available on request on spreadsheets (Quattro Pro).

A2

Sources for Table 4.1

Study	Source
SCHARG	Table 2 of [1]
BEST	Estimated from Table 8.2 of [2]
SEMENC	Table 2 of [3]
CHEN	Estimated from Table 1 of [4]
YUAN	Estimated from Table 3 of [5]
HIRAYA	Estimated from Table 16 of [6]
KONO	Table 4 of [7]
LIAW	Table 5 of [8]
PRESCO	Table 3 of [11]
PEKKAN	Table II of [12]
CONTI	Estimated from Table 3 of [13]
GRAMEN	Table 2 of [14]
NEGRI	Table 3 of [15]
TVERDA1	Estimated from Tables 1, 2, 5 and 6 of [16]
CARSTE	Estimated from Table 1 of [18]
FLODER	Table 4 of [19]
HEDBLA	Table 4 of [20]
ROSENG	Tables 1 and 2 of [21]
GSELL	Estimated from Tables 4 and 5a of [22]
ALDERS	Estimated from Tables 7 and 8 of supplement to [23]
BRETT	Estimated from Table VI of [24]
DUNN	Table 1 of [25]
CROFT	Table II of [26]
DOLL	Estimated from Table IV of [29] for men and from Table III of [28] for women
BENSHL	Estimated from Table II of [31]
TANG	Approximate estimates from Figure1 of [32]
KEYS	Estimated from Appendix 4 of [33]

Sources for Table 4.1 (Continued)

FRIEDM	Estimated from Tables 3 and 4 of [34]
PAGANI	Tables 2 and 3 of [35]
ROSENM	Estimated from Table 1 of [36]
WEIR	Table 4 of [37]
BUSH	Estimated from Table 3 of [38]
FRAMIN	Estimated from Tables 1 and 3 of [39]
CPS I	Estimated from Appendix B (pages 185-193, 245-253) and Appendix C of [40]
CPS II	Estimated from Appendices 26, 27 and 30 of [41]
DORN	Estimated from Figure 1 and Table 4 of [43]
HAMMON	Estimated from Figure 7 of [45]
KAWACH	Table 1 of [46]
LACROI	Table 4 of [48]
MRFIT	Estimated from Table 1 of [49]
ROSENB1	Table 1 of [51]
ROSENB3	Text, p 214 of [53]
ROSENB4	Table 3 of [54]
DOYLE	Estimated from Table 2 of [55]
POOLIN	Estimated from Table 25 in [56]

Sources for Table 4.2

Study	Source
SCHARG	Estimated from Table 3 of [1]
BEST	Estimated from Tables 8.2 and 14.3 of [2]
CHUN	Tables 2 and 3 of [9]
PRESCO	Approximate data from Figure 2 of [11]
GRAMEN	Table 3 of [14]
NEGRI	Table 4 of [15]
TVERDA2	Table 2 of [17]
FLODER	Table 4 of [19]
GSELL	Table 5b of [22]
ALDERS	Estimated from Tables 7 and 8 of supplement to [23]
BRETT	Estimated from Table VI of [24]
DOLL	Estimated from Table V of [27] for men and from Table IV of [28] for women
FRIEDM	Estimated from Tables 3 and 4 of [34]
ROSENM	Estimated from Table 1 of [36]
WEIR	Table 6 of [37]
BUSH	Estimated from Table 3 of [38]
FRAMIN	Table 3 of [39]
CPS I	Estimated from Appendix C of [40]
CPS II	Estimated from Appendices 26, 27 and 30 of [41]
DORN	Estimated from Appendix A of [42]
HAMMON	Estimated fro Table 1 of [45]
KAWACH	Table 3 of [47]
MRFIT	Estimated from Table 2 of [50]
ROSENB1	Estimated from Table 1 of [51]
POOLIN	Estimated from Table 25 of [56]

Sources for Table 4.3

Study	Source
SCHARG	Estimated from Table 3 of [1]
BEST	Estimated from Table 8.2 of [2]
GRAMEN	Table 3 of [14]
FLODER	Table 4 of [19]
ALDERS	Estimated from Tables 7 and 8 of supplement to [23]
BRETT	Estimated from Table VI of [24]
DOLL	Estimated from Table V of [27] for men and from Table IV of [28] for women
FRIEDM	Estimated from Tables 3 and 4 of [34]
ROSENM	Estimated from Table 1 of [36]
WEIR	Table 6 of [37]
BUSH	Estimated from Table 3 of [38]
FRAMIN	Estimated from Tables 1 and 3 of [39]
CPS I	Estimated from Appendix B (pages 285-293, 245-253) and Appendix C of [40]
CPS II	Estimated from Appendices 26, 27 and 30 of [41]
DORN	Estimated from Appendix A of [42]
HAMMON	Estimated from Tables 1 and 2 of [45]
KAWACH	Table 3 of [47]
MRFIT	Estimated from Table 2 of [50]
ROSENB1	Estimated from Table 1 of [51]
POOLIN	Estimated from Table 25 of [56]

Sources for Table 4.4

Study	Source
HIRAYA	Estimated from Table 19 of [6]
CHUN	Tables 2 and 3 of [10]
NEGRI	Table 2 of [15]
TVERDA1	Estimated from Tables 1 and 3 of [16]
ALDERS	Estimated from Tables 7 and 8 of supplement to [23]
DOLL	Estimated from Tables IX and X of [27]
BENSHL	Tables 4 and 5 of [30]
TANG	Approximate estimates from Figure 2 of [32]
FRIEDM	Estimated from Tables 7 and 8 of [34]
PAGANI	Tables 2 and 3 of [35]
CPS I	Tables 3 and 4 of [40]
DORN	Table 5 of [44]
HAMMON	Estimated from Figure 7 of [45]
KAWACH	Estimated from Table 2 of [46]
LACROI	Table 5 of [48]
ROSENB2	Figure 1 of [52]
ROSENB3	Figure 1 of [53].

APPENDIX B

Main references for studies

For each of the 48 studies considered in this report, this appendix gives the references to the publication(s) which provided the source(s) of the relative risks and 95% CIs presented. On occasion, additional publications may have been used to provide information on the study details presented in section 3.

B2

Main references for studies

Continent (Country)	Country (State)	Study	Main references
America	Argentina	SCHARG	[1]
	Canada	BEST	[2]
	Canada	SEMENC	[3]
Asia	China	CHEN	[4]
	China	YUAN	[5]
	Japan	HIRAYA	[6]
	Japan	KONO	[7]
	Taiwan	LIAW	[8]
Australasia	Australia	CHUN	[9,10]
Europe	Denmark	PRESCO	[11]
	Finland	PEKKAN	[12]
	Italy	CONTI	[13]
	Italy	GRAMEN	[14]
	Italy	NEGRI	[15]
	Norway	TVERDA1	[16]
	Norway	TVERDA2	[17]
	Sweden	CARSTE	[18]
	Sweden	FLODER	[19]
	Sweden	HEDBLA	[20]
	Sweden	ROSENG	[21]
	Switzerland	GSELL	[22]
	UK	ALDERS	[23] and supplement
	UK	BRETT	[24]
	UK	DUNN	[25]
	UK	CROFT	[26]

Main references (continued)

Continent (Country)	**Country (State)**	**Study**	**Main references**
Europe	UK	DOLL	[27-29]
	UK	BENSHL	[30,31]
	UK	TANG	[32]
	7 Countries	KEYS	[33]
USA	California	FRIEDM	[34]
	California	PAGANI	[35]
	California	ROSENM	[36]
	California	WEIR	[37]
	Maryland	BUSH	[38]
	Massachusetts	FRAMIN	[39]
	25 states	CPS I	[40]
	Nationwide	CPS II	[41]
	Nationwide	DORN	[42-44]
	9 states	HAMMON	[45]
	Nationwide	KAWACH	[46,47]
	3 states	LACROI	[48]
	Nationwide	MRFIT	[49,50]
	3 states	ROSENB1	[51]
	4 states	ROSENB2	[52]
	4 states	ROSENB3	[53]
	Nationwide	ROSENB4	[54]
	2 states	DOYLE	[55]
	4 states	POOLIN	[56]