REVIEW

Mortality Risk Reduction Associated With Smoking Cessation in Patients With Coronary Heart Disease

A Systematic Review

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Context As more interventions become available for the treatment of coronary heart disease (CHD), policy makers and health practitioners need to understand the benefits of each intervention, to better determine where to focus resources. This is particularly true when a patient with CHD quits smoking.

Objective To conduct a systematic review to determine the magnitude of risk reduction achieved by smoking cessation in patients with CHD.

Data Sources Nine electronic databases were searched from start of database to April 2003, supplemented by cross-checking references, contact with experts, and with large international cohort studies (identified by the Prospective Studies Collaboration).

Study Selection Prospective cohort studies of patients who were diagnosed with CHD were included if they reported all-cause mortality and had at least 2 years of follow-up. Smoking status had to be measured after CHD diagnosis to ascertain quitting.

Data Extraction Two reviewers independently assessed studies to determine eligibility, quality assessment of studies, and results, and independently carried out data extraction using a prepiloted, standardized form.

Data Synthesis From the literature search, 665 publications were screened and 20 studies were included. Results showed a 36% reduction in crude relative risk (RR) of mortality for patients with CHD who quit compared with those who continued smoking (RR, 0.64; 95% confidence interval [CI], 0.58-0.71). Results from individual studies did not vary greatly despite many differences in patient characteristics, such as age, sex, type of CHD, and the years in which studies took place. Adjusted risk estimates did not differ substantially from crude estimates. Many studies did not adequately address quality issues, such as control of confounding, and misclassification of smoking status. However, restriction to 6 higher-quality studies had little effect on the estimate (RR, 0.71; 95% CI, 0.65-0.77). Few studies included large numbers of elderly persons, women, ethnic minorities, or patients from developing countries.

Conclusions Quitting smoking is associated with a substantial reduction in risk of all-cause mortality among patients with CHD. This risk reduction appears to be consistent regardless of age, sex, index cardiac event, country, and year of study commencement.

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THE CAUSATIVE RELATIONSHIP between smoking and coronary heart disease (CHD) is well established, with relative risks (RRs) or odds ratios (ORs) estimated between 1.5 to 3 or higher.[1-5] Observational studies have estimated that smoking cessation reduces the risk of subsequent mortality and further cardiac events among patients with CHD by as much as 50%.[6-9] Stopping smoking therefore may have a greater effect on reducing the risk of mortality among patients with CHD who smoke than the effect of any other intervention or treatment. Simulation models in the United States have demonstrated that quitting smoking has short-term economic as well as health benefits.[10]

However, the speed and magnitude of risk reduction of mortality when a smoker quits have been debated.[11] Some authors suggest that risk can decline to that of a lifelong nonsmoker,[12,13] and others maintain some "remnant risk" always remains.[14] Moreover, some studies have found large reductions in risk after only 2 to 3 years.[9,10,12] Other studies estimate that risk is still higher than that in lifelong nonsmokers even 20 years after quitting.[14,15] The British Regional Heart Study found essentially no reduction in risk for ex-smokers after 7 years.[16] However, at 18 years, the Whitehall cohort showed no increase risk of mortality among ex-cigarette smokers (≤20 cigarettes/d) compared with never smokers.[17]

A number of possible explanations for disagreement between studies exist. The relationship between smoking cessation and mortality may depend on many other factors, such as age, sex, baseline risk from other CHD risk factors, and severity of disease. Survival is generally higher for patients with angina[18,19] than for those after myocardial infarction (MI)[19,20] or heart failure.[21-23] Further-

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more, smoking may be a more powerful risk factor for patients with MI than for those with angina pectoris.[24,25]

Differences in the accuracy of measurement of exposure status also may account for some uncertainty in the evaluation of risk of mortality. Prospective cohort studies may underestimate the risk reduction associated with stopping smoking, as an unknown proportion of quitters may start again, hence becoming misclassified as ex-smokers.[14,15,26] Furthermore, some patients originally classified as smokers will subsequently stop. Case-control studies may equally be subject to a number of additional biases, particularly for selection and recall. Other aspects of study quality, particularly the degree of control of confounding variables, or differences in the baseline risk among quitters and those who continue to smoke, also may be important.

As more interventions become available for the treatment of CHD, it is increasingly important to quantify the risk reduction associated with each. Policy makers need a better understanding of the costs and benefits of each intervention, to better determine where to focus efforts and scarce resources. Therefore, we conducted a systematic review of the benefits of smoking cessation in patients with CHD.

METHODS

Participants

Studies that had patients diagnosed with CHD (ie, previous MI or stable or unstable angina) were included. Ideally, CHD in the included studies should be defined according to the guidelines by the World Health Organization,[27] but we did include studies that gave no explicit definition of CHD. Smokers ideally should be defined in the article, such as those who smoke regularly (eg, smoking at least on average 1 cigarette/d during the preceding year). Not all studies reported precise definitions of smoking or even smoking cessation.

Studies

Any prospective cohort study was included if (1) the cohort included current smokers at baseline; (2) smoking status was measured to ascertain which smokers had quit; (3) the cohort was followed-up for at least 2 years; and (4) the study reported all-cause mortality as an outcome measure.

Outcome Measures

The primary outcome was total mortality rate for each group. Secondary outcomes included any further cardiovascular event, either fatal or nonfatal; CHD; or stroke, which ideally should be defined according to the *International Classification of Disease, Ninth Edition*[28] (eg, codes 410-414).

Data Sources

The databases searched to obtain the articles included MEDLINE (1966 to February 2003), EMBASE (1980 to February 2003), Science Citation Index (April 26, 2003), Cochrane Controlled Trial Register (Issue 2 of 2003), CINAHL (1982 to April 2003), PsychLit (1971 to April 2003), Dissertation Abstracts (1861 to March 2003), BIDS ISI (Bath Information and Data Services-Index to Scientific and Technical Proceedings) (1982 to June 29, 2000), and the United Kingdom National Research Register (CD-ROM version, Issue 1 of 2003) (the information is available in appendix 1 from the authors' Web site at: http://www.liv.ac.uk/PublicHealth/sc/jama_article_appendices.html). The search was not restricted by language of articles. The search strategy used both key words and MeSH term searches and took the form of (CHD or synonyms) and (smoking cessation or smoking or synonyms) and ((mortality or synonyms) OR (Cochrane RCT filter)).

Reference lists of retrieved articles were inspected (the information is available in appendix 2 from the authors' Web site). Sixty-one large cohort studies concerned with cardiovascular risk were identified from a log maintained by the Prospective Studies Collaboration[29] and from any relevant publications. Authors of these studies were contacted to assess whether any relevant research had been carried out (see appendix 3, authors' Web site).

Study Selection and Data Extraction

Based on brief study details (eg, title, abstract) of identified articles, studies were excluded if they were not relevant. Two reviewers (J.A.C. and S.C.) independently assessed studies to determine eligibility and independently carried out data extraction using a prepiloted, standardized form. Any disagreement was resolved by discussion. Several authors were contacted to clarify details or provide additional information.

Criteria Used to Assess Quality

Unlike randomized controlled trials, no generally accepted lists of appropriate quality criteria for observational studies are available.[30-32] Rather than producing a simple quality score, which might be arbitrary, specific aspects of quality, such as control of confounding, minimization of selection biases, and sample size were used to assess the studies.

Data Synthesis

All analyses were carried out using RevMan 4.1 software[33] or STATA.[34] Studies were pooled using the DerSimonian and Laird random-effects model.[35]

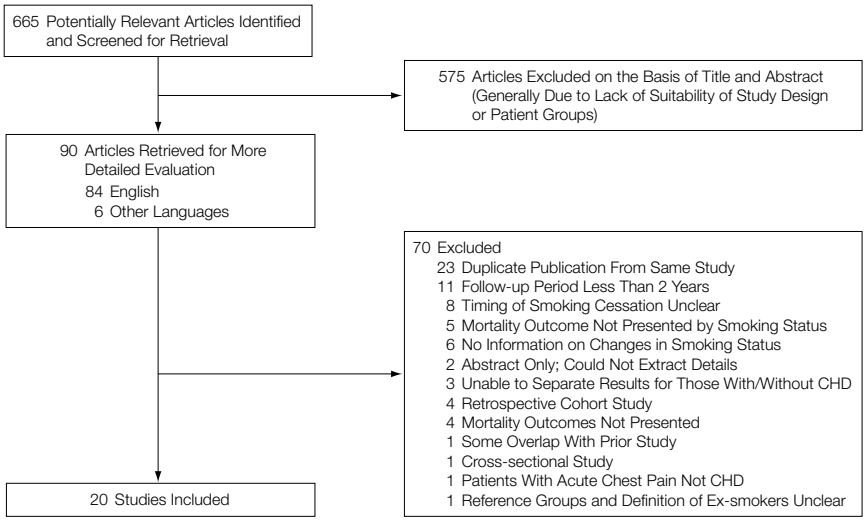
RESULTS

Description of Studies

Of the 665 articles screened, 90 were considered in depth for inclusion, but 70 were excluded because they did not meet inclusion criteria or were duplicate publications (FIGURE 1) (see appendix 4, authors' Web site). Twenty studies[7,8,19,36-52] met all inclusion criteria and had sufficient data available (see appendix 4, authors' Web site). Agreement between the 2 reviewers for study eligibility was very high (weighted $\kappa = 0.9$). These studies had a total sample size of 12 603 smokers at baseline, of whom 5659 ceased smoking and 6944 continued to smoke.

The majority of studies commenced data collection in the late 1960s or in the 1970s (TABLE 1). Most were conducted in Western countries, with 1 from Poland[36] and 1 from India.[37]

Figure 1. Flow Chart of the Study Selection Process



Women were underrepresented (20% of cases). Six studies included only men[8,36,38,41,43,45] and 1 small study was limited to women.[7] In most of the studies, the mean age of smokers was approximately 55 years, which was younger than the mean age of the general population of patients with CHD.[20] Reported cessation rates varied from 28% to 77% in the primary studies, with a mean of 45% (see appendix 5, authors' Web site).

Not all studies clearly stated when smoking cessation occurred. Some studies reported that patients who quit did so quickly after their CHD diagnosis or event.[19,41,45,47] However, some studies only reported changes in smoking status at later follow-up appointments (generally at 3, 6, or 12 months after the CHD event).[36,38,42,43,50,52] Evidence from some of the primary studies,[19,41] and other studies not included in this review,[18] suggested that patients who are likely to quit do so rapidly after their CHD diagnosis, as this is the main motivator for stopping.[53]

Mean length of follow-up ranged from 2 years[38] to 26 years,[39] with a mean of 5 years. The majority of studies included followed-up hospital case series. Most well-known, prospective, general-population CHD cohorts (such as the Whitehall[17] or the British Regional Heart Study[16]) (see appendix 3, authors' Web site) cannot address whether there was a reduction in mortality when a patient with CHD quits smoking. Ususally this is because they are unable to ascertain whether ex-smokers quit before or after experiencing a cardiac event. These studies therefore have not been included. Thirteen studies* followed up patients with MI only, and 4 studies[39,40,42,44] included patients in which some underwent coronary artery bypass graft (CABG) surgery or angioplasty. Of the 4 studies, 1 was a large (N=4165) and relatively high-quality study (see "Sensitivity Analyses" for evaluation of quality).[40] The other 3 studies included patients with MI and with other coronary diseases.[37,43,46]

Quality Assessment of Included Studies

Quality assessment criteria (TABLE 2) included the sample size, clear definitions of the cardiac events, smoking and smoking cessation, whether smoking status was confirmed during follow-up or validated, the adequacy of control of confounding, and minimization of selection biases.

The number of smokers at baseline in the primary studies varied from 77 to 4165. Most studies had small sample sizes and only 8 contained more than 500 smokers at baseline.[19,36,38-42,45] The Coronary Artery Surgery Study included a large sample (N=4165) of patients with angiographically proved coronary artery disease who underwent CABG surgery.[40] The other larger studies contained more than 900 smokers who were male patients after MI from Gothenburg, Sweden, from 1968 to 1977[41]; male patients after MI in the UK Diet and Reinfarction Trial, from the mid-1980s[38]; male patients with a first MI between 1968 and 1975 from Poland[36]; and male patients undergoing angioplasty at the Mayo clinic between 1979 and 1995.[42]

Minimization of Selection Biases

Losses to follow-up for mortality were generally small (Table 2). Most studies, however, recruited patients some weeks after their first cardiac event and frequently did not report how many smokers and nonsmokers died before entry into the study. The pooled RR in this review is therefore best regarded as an estimate of the reduction in risk for quitters who survived the initial cardiac event. A sensitivity analysis was carried out including only those studies that were able to ascertain smoking status rapidly (within 1 month) of the initial cardiac event.[19,41,45,47] The risk reduction estimated by this analysis (RR, 0.63; 95% CI, 0.53-0.74) and the analysis including all 20 studies (RR, 0.64; 95% CI, 0.58-0.71) did not differ significantly.

Definitions of Events and Smoking Status

Most studies defined the index cardiac event, but they did not clearly define who was considered a current smoker or a quitter (Table 2). Eleven[7,8,41,43-50] of the 20 studies attempted to verify smoking status during the follow-up time period (ie, whether or not the authors contacted patients during the follow-up period to check their smoking status. Mostly this was by self-report); only 2 attempted to assess smoking status biochemically.[41,43]

*References 7, 8, 19, 36, 38, 41, 45, 47-52.

Table 1. Characteristics of the Studies Included

Study	Setting	Index Cardiac Event	Years of Enrollment	No. of Smokers	Sex	Age, Mean (SD) or Range, y	Follow-up, mo	Study Results*
Aberg et al,[41] 1983	Gothenburg, Sweden	MI (primary)	1968 to 1977	985	100% Male	Quit: 53.2 Continued: 52.0	Range: 60-144	In patients who ceased smoking, 84% survived 5 years, compared with 78% of those who continued
Baughman et al,[51] 1982	Boston, Mass	MI	Nov 1968 to Jul 1971	77	72% Male	41-93	Mean: 99	No outcome reported for smoking status (not principle objective of study)
Bednarzewski,[36] 1984	Lubin, Poland	MI (primary)	1968 to 1975	1010	100% Male	22-84	Mean: 42	45% Ceased and 55% continued smoking Of patients who stopped, 30% died vs 37% of those who continued Mean time to subsequent MI was longer in those who stopped vs those who continued (36 mo vs 26 mo)
Burr et al,[38] 1992	United Kingdom	MI	Mid-1980s	1186	100% Male	Quit: 55.4 Continued: 55.0	24	7.9% mortality rate for continued smoking group vs 4.1% for ceased smoking group
Daly et al,[43] 1983	Ireland	MI And unstable angina	Jan 1965 to Dec 1975	374	100% Male	Continued: 50.3 Quit: 50.5	84	Smokers who continued had 2.8-fold higher mortality than those who stopped ($P<.01$)
Greenwood et al,[19] 1995	English hospitals	MI	Nov 1986 to Feb 1988	532	Not reported	Not reported	Median: 75.6	RR of 0.76 (95% CI, 0.51-1.12) for patients who stopped vs those who continued smoking
Gupta et al,[37] 1993	Jaipur, India	CHD Patients enrolled at KD Gupta Medical Centre	1980	225	Not reported	Quit: 52.4 (9.9) Continued: 51.8 (10.1)	Median for smokers: 98.5 Median for ex-smokers 88.7	Survival was similar in current smokers and ex-smokers for the first 3 years
Hallstrom et al,[46] 1986	Seattle, Wash	Survivors of out-of-hospital cardiac arrest	Mar 1970 to Mar 1981	310	80% Male	Quit: 56 Continued: 56	Average 47.5†	Stratified direct adjustment across all strata yielded a significance level for the 1-sided log-rank test of $P = .038$; after excluding patients with incomplete follow-up, the difference was not significant ($P = .12$)
Hasdai et al,[42] 1997	Mayo Clinic, Rochester, Minn	Angioplasty	Sep 1979 to Dec 1995	1169	Not reported	Quit: 56 (10) Continued: 55 (10)	Mean (SD): 54 (40.8)	After adjustment, persistent smokers had significantly greater risk of overall mortality (RR, 1.44; 95% CI, 1.02-2.11) and death from cardiac causes (RR, 1.49; 95% CI, 0.89-2.51)
Hedback et al,[52] 1993	Oskarsham District Hospital, Sweden	MI	Aug 1997 to Dec 1980	157	85% Male	Reference group: 57.2 Intervention group: 57.3	120	Mortality was significantly lower among nonsmokers in the intervention group and even among those who stopped smoking
Herlitz et al,[50] 1995	Sahlgrenska Hospital, Gothenburg, Sweden	MI	Feb 1986 to Nov 1987	217	69% Male of initial case series, not study population	Not reported	Not reported	Patients who continued to smoke after 1 year had higher mortality during the subsequent 4 years than patients who quit; but when corrected for comorbidity, continuation of smoking was no longer associated with mortality during subsequent years (no data presented)

(continued)

Table 1. Characteristics of the Studies Included (cont)

Study	Setting	Index Cardiac Event	Years of Enrollment	No. of Smokers	Sex, %	Age, Mean (SD) or Range, y	Follow-up, mo	Study Results*
Johansson et al,[7] 1985	Gothenburg, Sweden	MI (primary)	1968 to 1977	156	100% Female	Quit: 53.0 (6.2) Continued: 53.5 (5.6)	Range: 12-144	RR was 2.3 (95% CI, 1.2-4.4) for patients who continued to smoke compared with those who stopped
Perkins and Dick,[47] 1985	Leigh Infirmary and Astley Hospital, UK	MI (primary)	Jan 1974 to Jun 1977	119	76% Male	Males: quit, 54.9 and continued, 56.5 Females: quit, 61.4 and continued, 60.8	60	Decrease of 55% in mortality after adjusting for age and sex, in favor of those who quit smoking
Salonen,[45] 1980	North Karelia, Finland	MI	1972 to 1975	523	100% Male	<65	36	Crude all-cause mortality rate was 1.7-fold (95% CI, 1.1-2.6) greater in patients who continued smoking compared with those who quit Suggests bigger benefit ratios in younger men and in those at lowest risk
Sato et al,[8] 1992	Japan	MI	Not clear	87	100% Male	Quit: 56.6 (9.2) Continued: 52.9 (9.6)	Mean 37.2	RR for total cardiac events for those who continued compared with those who ceased was 3.4 (95% CI, 1.1-9.8) RR for cardiac death was 2.5 (95% CI, 0.7-9.1)
Sparrow and Dawber,[48] 1978	Framingham, Mass	MI	1949 to 1975	195	85% Male	Quit: 55 Continued: 57.6	Maximum: 264 Mean: 72	6-Year mortality rate of 18.8% (95% CI, 8.2-29.4) in quitters and 30.4% (95% CI, 22.6-38.2) among those who continued smoking
Tofler et al,[49] 1993	MILIS, US	MI		393	Approximately 72% male	Not presented by smoking status	48	Main outcome was survival for high school graduates compared with those who did not graduate Authors supplied crude number for smoking status (see Table 3)
Van Domburg et al,[39] 2000	Rotterdam, Netherlands	CABG	Feb 1971 to Jun 1986	556	88% Male	Males: 53 Females: 55	Median: 240 Range: 156-312	Persistent smokers had higher risks of death from all causes and cardiac death compared with quitters Survival curves diverged after approximately 4 years and the difference increased throughout the follow-up period
Vlietstra et al,[40] 1986‡	CASS study, US	Angio-graphically proved CAD	1975 to 1977	4165	24% Female†	Men: 53 Women: 54†	60	15% Of quitters died compared with 22% of those who continued smoking
Voors et al,[44] 1996	Utrecht, Netherlands	CABG	Apr 1, 1976 to Apr 1, 1977	167	90% Male	Mean: 52.5 Range: 20-73	Mean: 184.8	No significant difference in survival between smokers and quitters at 1-5 years, but mortality from 5-15 years was higher among smokers

Abbreviations: CABG, coronary artery byass graft; CAD, coronary artery disease; CASS, Coronary Artery Surgery Study; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; MILIS, Multicenter Investigation of the Limitation of Infarct Size; OR, odds ratio; RR, relative risk; UK, United Kingdom; US, United States.
*Estimates are for mortality
†Unclear in orginal article.
‡Relates to entire CASS registry of 24 959 patients, not just those in this report.

Table 2. Quality Assessments of Studies Included in the Systematic Review

Study	Clear Definition of Cardiac Event*	Clear Definitions of Smoking and Cessation†	Smoking Status Verified During Follow-up‡	Smoking Cessation Validated	Control of Confounding§	Minimization of Selection Bias	No. Lost to Follow-up
Aberg et al,[41] 1983	Yes	Yes	Yes, at 1, 3, 12, 24, 60, and 120 mo	Yes, carboxyhemoglobin in subsample of 100 patients in 1973 at various stages of follow-up from 3 months to 5 years; 1 patient had values above normal	Good	96% Of case series included (983/1023 smokers)	None
Baughman et al,[51] 1982	Yes	Yes	Unclear	Unclear	Poor	89% Of original cohort (123 of original, 138 included)	None
Bednarzewski,[36] 1984	No	No	Unclear	No	Adequate	Complete case series of male smokers	None
Burr et al,[38] 1992	Yes	No	No	No	Poor	92% Of eligible patients (1877/2033)	None
Daly et al,[43] 1983	Yes	Yes	Yes, at annual check	Yes, reliability tested on a subsample	Poor	92% Of smokers (374 of initial 408 smokers included)	2
Greenwood et al,[19] 1995	Yes	No	No	No	Good	Of case series of 3458, only 1557 (45% of eligible patients) completed questionnaire	None
Gupta et al,[37] 1993	Yes	Yes	Uncertain	No	Adequate	Unclear, but 40 lost to follow-up and 41 opted for CABG and were excluded Potentially only 79% of initial case-series included (225 smokers plus 60 exclusions)	At least 40
Hallstrom et al,[46] 1986	No	No	Yes, but unclear when	No	Poor	94% (310/331)	31 (10%) had incomplete follow-up
Hasdai et al,[42] 1997	Yes	Yes	No	No	Adequate	Complete data available for 97% (6424/6600)	None stated
Hedback et al,[52] 1993	Yes	No	No	No	Poor	Consecutive and nonselected case series, implies 100%, but unclear	None
Herlitz et al,[50] 1995	Yes	No, stopping smoking not defined	Yes, at 1 y and 5 y	No	Poor, adjusted results not presented	62 Smokers died before entry to study (1 year after MI) and smoking status unknown for 71 patients; approximately 87% of case series included	No further losses
Johansson et al,[7] 1985	Yes	Yes	Yes, at 1, 3, 24, 60, and 120 mo	No	Good	97% Smokers (156/161)	None stated
Perkins and Dick,[47] 1985	Yes	Yes	Yes, at 3 mo, and then annually	No	Poor	119 Of possible 219 smokers: 24 died before entry, 39 pipe and cigar smokers, and 37 "variable" smokers were excluded	4
Salonen,[45] 1980	Yes	Yes	6 mo and 12 mo	No	Adequate	523 (98%) Of possible 536 Data on smoking status missing for 13	None
Sato et al,[8] 1992	Yes	Yes	Yes, annual by telephone review	No	Adequate	Complete case series	3
Sparrow and Dawber,[48] 1978	Yes	Yes	Every 2 y	No	Poor	195 (95%) Of possible 205 33 deaths prior to inclusion	None

(continued)

Table 2. Quality Assessments of Studies Included in the Systematic Review (cont)

Study	Clear Definition of Cardiac Event*	Clear Definitions of Smoking and Cessation†	Smoking Status Verified During Follow-up‡	Smoking Cessation Validated	Control of Confounding§	Minimization of Selection Bias	No. Lost to Follow-up
Tofler et al,[49] 1993	Yes	No	3 mo and 6 mo after randomization	No	Poor, not main objective of article	393 (88%) Of possible 443 Of 9450 patients screened, only 985 randomized into trial	None
Van Domburg et al,[39] 2000	Yes	Yes	No	No	Adequate	56 Lost to follow-up and 20 nonsmokers started smoking after undergoing CABG surgery 93% Of case series (965/1041)	56 Lost to follow-up
Vlietstra et al,[40] 1986	Yes	Yes	No	No	Good	293 Of total registry of 14 517 not included due to incomplete data (98% were accounted for) 2891 With a "mixed" smoking history excluded (865 who quit smoking initially then restarted and 2026 who continued smoking but quit later)	None
Voors et al,[44] 1996	No	Yes	Yes, at 1 y and 5 y later	No	Good	93% (167/179)	None

Abbreviation: CABG, coronary artery bypass graft; MI, myocardial infarction.
*Clear definition of cardiac event was determined if authors had clearly defined the event, and if so, did the definition relate to the guidelines of the World Health Organization or other national guidelines.
†Clear definition of smoking was determined if authors had clearly defined smoking, and if so, what definitions were used (eg, smoking at least 1 cigarette per day for at least 1 year). Similarly, a clear definition of cessation was determined if authors had provided definitions of cessation.
‡Smoking status was verified during follow-up if authors contacted patients at least once during the follow-up period to check their smoking status. Verification was mostly done by self-report.
§Control of confounding was classified as poor if little or no attempt was made to measure or control for known basic confounders such as age, and sex; adequate control considered at least these basic confounders; and good control considered the majority of the clinical variables.

Control of Confounding

Assessing control of confounding was carried out independently by 2 reviewers using prespecified criteria. These criteria included age, sex, socioeconomic status, education, secondary prevention drug treatments, measurement and levels of other CHD risk factors, history of previous MI or angina, comorbidities, severity of the initial cardiac event (ie, measures reported in the individual studies, eg, severity of infarct, presence of left ventricular function) or any prognostic indices (see appendix 6, author's Web site). Control of confounding was classified as poor if little or no attempt was made to measure or control for known basic confounders such as age and sex (Table 2). Adequate control considered at least these basic confounders, and good control considered the majority of the clinical variables previously listed. Most of the studies were old, so little information on modern secondary preventive therapies, such as prescribing β-blockers, was reported. Only 1 study included any information on psychosocial outcomes.[19]

Reviewer agreement was good (weighted $\kappa = 0.72$). Control of confounding was poor in 9 studies (Table 2).[38,43,46-52] Only 5 studies were classified as good.[7,19,40,41,44] Many of the studies provided only crude estimates of the reduction in mortality (TABLE 3).

Total Mortality

A random-effects meta-analysis was carried out, and the pooled RR for all 20 studies was 0.64 (95% CI, 0.58-0.71) (FIGURE 2). Although all 95% CIs for the primary studies overlapped, some heterogeneity was observed (χ^2 for heterogeneity, $P = .009$), hence the need for the random-effects meta-analysis. The pooled estimate was dominated by the 3 larger CABG studies[39,40,44] which together provided about half the total patients. However, the results did not differ when the analysis was limited to 13 studies, including only patients after having an MI (RR, 0.63; 95% CI, 0.56-0.72).†

A Begg funnel plot was created to compare the log OR with the SE of the log OR of the 20 studies, revealing possible publication bias. Larger, more precise studies with smaller SEs tended to find smaller reductions in risk of mortality on quitting smoking than did smaller studies with fewer deaths, and therefore larger SEs ($P = .006$) (FIGURE 3).

Sensitivity Analyses

Sensitivity analyses were carried out, as planned, using the following 3 criteria: (1) an initial sample size of at least 500 smokers at baseline; (2) at least 85% of the initial case series included in the analyses; and (3) adequate or good control of confounding. Only 6 of the 20 studies met all these criteria.[36,39,40-42,45] However, the pooled RR for these 6 studies (RR, 0.71; 95% CI, 0.65-0.77)

†References 7, 8, 19, 36, 38, 41, 45, 47-49, 50-52.

Table 3. Summary of Principle Results

	Total Mortality		Nonfatal MI		
Study	Crude RR (95%CI)	Adjusted Estimate (95% CI)	Crude RR (95%CI)	Adjusted Estimate (95% CI)	Confounders*
Aberg et al,[41] 1983	0.63 (0.51-0.79)	Previous light smokers, HR = 2.29 Previous heavy smokers, HR = 1.46	0.67 (0.53-84)	None	Age and a logistic severity index (previous hypertension dyspnea on infarction, left ventricular failure, atrial flutter/fibrillation, mean peak AST levels, relative heart volume)
Baughman, et al,[51] 1982	0.46 (0.23-0.92)	None	None	None	None
Bednarzewski,[36] 1984	0.81 (0.68-0.97)	*P* value only	None	None	None
Burr et al,[38] 1992	0.52 (0.32-0.83)	None	None	None	None
Daly et al,[43] 1983	0.45 (0.37-0.54)	None	None	None	None
Greenwood et al,[19] 1995	0.76 (0.51-1.12)	0.56 (0.33-0.98)	None	None	Age, history of angina pectoris, history of DM, treatment with anti-arrythmic drugs on discharge
Gupta et al,[37] 1993	0.70 (0.49-1.01)	HR = 0.78	None	None	Age, sex, cholesterol levels, hypertension, diabetes, history of previous MI, CHF
Hallstrom et al,[46] 1986	0.79 (0.58-1.06)	None	None	None	None
Hasdai et al,[42] 1997	0.71 (0.50-1.01)	HR = 1.44 (1.02-2.11)	Q-wave for MI unclear whether fatal, nonfatal, or combined, 0.69 (0.32-1.49)	None	Age, sex, severe angina, prior coronary bypass surgery, prior MI, CHF, history of DM, history of hypertension, complete revascularization, multivessel CAD, number of vessels dilated, family history of CAD, unstable angina; unclear as to which ones were actually included in the final model
Hedback et al,[52] 1993	0.69 (0.49-0.98)	None	None	None	None
Herlitz et al,[50] 1995	0.57 (0.35-0.94)	States adjustment made, but not reported	0.99 (0.42-2.33) Events are reported at 1 y only	None	None
Johansson et al,[7] 1985	0.48 (0.27-0.84)	RR = 2.7 from Cox regression	0.79 (0.46-1.37)	None	Mean peak serum AST levels, Q waves, angina pectoris prior to MI
Perkins and Dick,[47] 1985	0.39 (0.20-0.74)	None	3.87 (0.81-18.37)	None	None
Salonen,[45] 1980	0.59 (0.39-0.91)	RR = 1.6	None	None	Number of selected factors (age group, diagnostic category of infarction, history of previous MI, prodromal or previous angina pectoris, acute HF at onset of MI or during hospital treatment, and cardiac arrest during hospital treatment)
Sato et al,[8] 1992	0.34 (0.12-0.97)	RR = 3.1 (1.0-9.8)	0.1 (0-1.95)	Only for total cardiovascular events	Age, hypertension, total cholesterol
Sparrow and Dawber,[48] 1978	0.62 (0.33-1.15)	None	0.76 (0.37-1.58)	None	None
Tofler et al,[49] 1993	0.48 (0.27-0.86)	None	None	None	None
Van Domburg et al,[39] 2000	0.72 (0.06-0.85)	HR = 1.68 (1.33-2.13) for total mortality HR = 1.75 (1.3-2.37) for cardiac mortality	None	None	Age, sex, vessel disease, ejection fraction, complete revascularization
Vliestra et al,[40] 1986	0.68 (0.59-0.78)	HR = 1.55 (1.29-1.85)	Hospitalization for MI	OR = 0.63 (0.51-0.78) Article states adjusted for prognostic factors, reported as percentage, ie, 7.1% of those who quit smoking, 11.3% of those who continued	CHF score (0-4, with 1 point given for each of the following factors: symptoms of HF, chest rales, use of digitalis, and use of a diuretic), left ventricular wall motion score, CAGE 50 (number of segments [of a total of 26] with coronary artery stenosis of at least 50%), bypass surgery performed, age at entry, left ventricular end-diastolic pressure

(continued)

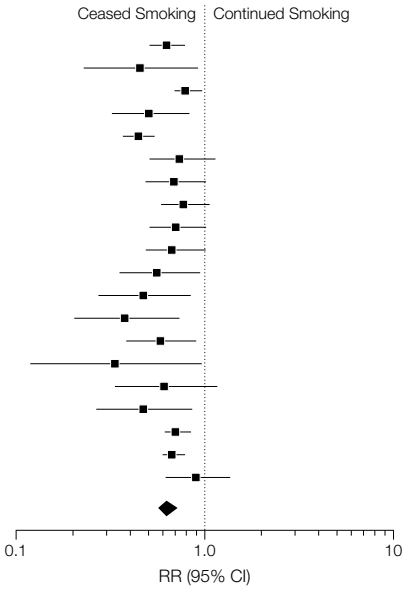
Table 3. Summary of Principle Results (cont)

Study	Total Mortality: Crude RR (95%CI)	Total Mortality: Adjusted Estimate (95% CI)	Nonfatal MI: Crude RR (95%CI)	Nonfatal MI: Adjusted Estimate (95% CI)	Confounders*
Voors et al,[44] 1996	0.93 (0.62-1.38)	For smokers compared with quitters 1-15 years after surgery, HR = 0.9 (0.5-1.6) HR = 1.7 (0.8-3.5) for smokers vs quitters 5-15 years after surgery	0.54 (0.29-1.01)	HR = 2.3 (1.1-5.1)	Age, sex, obesity (BMI), DM, elevated levels of serum cholesterol and triglycerides, hypertension, history of HF, preoperative angina pectoris, family history of CAD, number of vessels diseased, completeness of revascularization, number of distal anastomoses, left ventricular function, history of MI, operation indication, presence of collateral arteries, left main CAD and proximal left anterior descending artery disease All variables with a significance level of $P<.10$ in at least 1 univariate test were introduced into the multivariate model Age and sex were always included

Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; CHF, congestive heart failure; CAD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; RR, risk ratio.
*Confounders are those included in the final model.

Figure 2. Pooled Relative Risks of Mortality Reduction When Patients With CHD Stop Smoking: Random-Effects Meta-analysis of All 20 Studies

Study	Ceased Smoking: Patients, No.	Ceased Smoking: Deaths, No.	Continued Smoking: Patients, No.	Continued Smoking: Deaths, No.	Weight, %	RR (95% CI)
Aberg et al,[41] 1983	542	110	443	142	8.3	0.63 (0.51-0.79)
Baughman et al,[51] 1982	45	9	32	14	1.8	0.46 (0.23-0.92)
Bednarzewski et al,[36] 1984	455	136	555	205	9.3	0.81 (0.68-0.97)
Burr et al,[38] 1992	665	27	521	41	3.5	0.52 (0.32-0.83)
Daly et al,[43] 1983	217	80	157	129	9.0	0.45 (0.37-0.54)
Greenwood et al,[19] 1995	396	64	136	29	4.5	0.76 (0.51-1.12)
Gupta et al,[37] 1993	173	56	52	24	4.9	0.70 (0.49-1.01)
Hallstrom et al,[46] 1986	91	34	219	104	6.1	0.79 (0.58-1.06)
Hasdai et al,[42] 1997	435	41	734	97	5.2	0.71 (0.50-1.01)
Hedback et al,[52] 1993	83	31	74	40	5.2	0.69 (0.49-0.98)
Herlitz et al,[50] 1995	115	20	102	31	3.2	0.57 (0.35-0.94)
Johansson et al,[7] 1985	81	14	75	27	2.6	0.48 (0.27-0.84)
Perkins and Dick,[47] 1985	52	9	67	30	2.1	0.39 (0.20-0.74)
Salonen,[45] 1980	221	26	302	60	4.0	0.59 (0.39-0.91)
Sato et al,[8] 1992	59	5	28	7	0.9	0.34 (0.12-0.97)
Sparrow and Dawber,[48] 1978	56	10	139	40	2.3	0.62 (0.33-1.15)
Tofler et al,[49] 1993	173	14	220	37	2.5	0.48 (0.27-0.86)
Van Domburg et al,[39] 2000	238	109	318	202	9.8	0.72 (0.61-0.85)
Vlietstra et al,[40] 1986	1490	223	2675	588	10.4	0.68 (0.59-0.78)
Voors et al,[44] 1996	72	26	95	37	4.4	0.93 (0.62-1.38)
Overall	**5659**	**1044**	**6944**	**1884**	**100.0**	**0.64 (0.58-0.71)**



CHD indicates coronary heart disease; RR, relative risk. χ^2 for heterogeneity, $P=.009$.

was essentially the same as for all 20 (RR, 0.64; 95% CI, 0.58-0.71).

Morbidity Outcomes

Nonfatal Myocardial Reinfarctions. Eight studies presented information on nonfatal myocardial reinfarctions (Table 3; FIGURE 4; see appendix 5, authors' Web site).[7,8,40,41,44,47,48,50] The pooled RR for nonfatal reinfarctions was 0.68 (95% CI, 0.57-0.82). Ideally, we would analyze a combined outcome of cardiac deaths and nonfatal reinfarction, but it was not possible to extract this information as reinfarctions were mostly reported as total events rather than for individuals.

Other Outcomes. A few studies reported other cardiovascular outcomes, such as other cardiovascular disease (unspecified), new angina cases,

or stroke/transient ischemic attack (see appendix 5, authors' Web site).

COMMENT

This systematic review strongly suggests that quitting smoking is associated with reduced risk of total mortality. The pooled crude RR was 0.64 (95% CI, 0.58-0.71). This 36% reduction appears at least as great as other secondary preventive therapies, such as use of statins for lowering cholesterol levels (a 29% reduction),[54] aspirin (15%),[55] β-blockers (23%),[56] or angiotenin-converting enzyme inhibitors (23%),[57] which have received greater attention in recent years. Moreover, evidence from the United States and the United Kingdom has shown that quitting smoking has considerable short-term economic as well as health benefits because of reductions in hospitalizations for MI and stroke.[10,58]

This review was not able to assess how quickly the risk of mortality was reduced. Only 20 studies were included, and most of these had a mean length of follow-up between 3 and 7 years.[7,8,19,36,43,45-49] One possible implication is that the risk reduction occurs relatively quickly after stopping smoking, as early as 2 years (the minimum follow-up period for the review), and hence greater risk reductions over time are not observed. Another possibility is increasing misclassification with time, as discussed below.

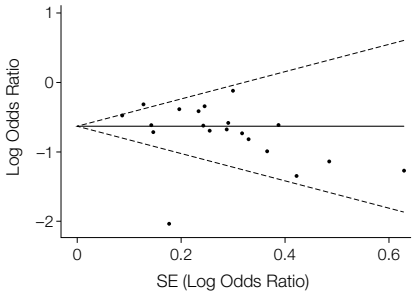
The risk reduction associated with quitting smoking appears relatively consistent, regardless of the type of index cardiac event or years in which the study was conducted. Other measured features of the studies, such as the age, population, or aspects of quality, did not appear to influence the results. However, relatively few studies have included many women, ethnic minorities, or older patients. The majority of studies were also conducted in Western countries. The generalizability to these groups is therefore uncertain.

Limitations of Review

Observational Data. This review has a number of limitations. First, we are considering observational data. Smokers who quit after MI may well differ from those who continue to smoke in a number of ways, including their age, sex, socioeconomic status, psychological characteristics, and other factors. However the direction of this potential difference is not obvious. Some studies found that subsequent mortality risk in quitters was higher,[19,41] lower,[8,46,50] or showed little difference from those who continued to smoke.[37,39,42,47,49] The one study that considered psychosocial factors in detail found these factors had little influence on rates of quitting smoking, or mortality.[19]

Second, meta-analysis was carried out using crude estimates. The 10 studies that presented adjusted outcome measures for total mortality used markedly different adjustment methods (some used Cox hazards regression models and others used Mantel-Haenszel stratification or logistic regression) to consider different covariates and were measured in varying ways.[7,8,19,37,39-42,44,45] However, results of these 10 studies found surprisingly small differences between adjusted and crude estimates (Table 3) (table of confounders are in appendix 6, authors' Web site). If anything, the risk reduction appeared greater after adjustment in most studies, suggesting our estimates may slightly underestimate the true risk reduction associated with smoking cessation in patients with CHD.

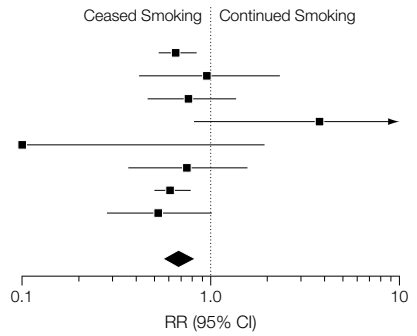
Figure 3. Begg Funnel Plot



Log odds ratio vs SE of the log odds ratio for each study are presented. The horizontal solid line indicates the log odds ratio of the pooled estimate; the sloping dashed lines are expected 95% confidence intervals. The funnel plot appears asymmetric and shows that larger, more precise studies with smaller SEs tended to find smaller reductions in risk of mortality on quitting smoking than smaller studies with fewer deaths ($P = .006$).

Figure 4. Pooled Relative Risks of Reduction in Nonfatal Myocardial Reinfarction When Patients With CHD Stop Smoking: Random-Effects Meta-analysis of 8 Studies

Study	Ceased Smoking		Continued Smoking		Weight, %	RR (95% CI)
	Patients, No.	Deaths, No.	Patients, No.	Deaths, No.		
Aberg et al,[41] 1983	542	104	441	127	34.4	0.67 (0.53-0.84)
Herlitz et al,[50] 1995	115	10	102	9	4.2	0.99 (0.42-2.33)
Johansson et al,[7] 1985	81	18	75	21	9.6	0.79 (0.46-1.37)
Perkins and Dick,[47] 1985	52	6	67	2	1.3	3.87 (0.81-18.37)
Sato et al,[8] 1992	59	0	28	2	0.4	0.10 (0.00-1.95)
Sparrow and Dawber,[48] 1978	56	8	139	26	5.7	0.76 (0.37-1.58)
Vlietstra et al,[40] 1986	1490	106	2675	302	36.9	0.63 (0.51-0.78)
Voors et al,[44] 1996	72	11	95	27	7.5	0.54 (0.29-1.01)
Overall	2467	263	3622	516	100.0	0.68 (0.57-0.82)



CHD indicates coronary heart disease; RR, relative risk.

Misclassification. A further limitation is the potential for bias from misclassification of smoking status. Patients who continued to smoke may have falsely claimed cessation. Only 2 studies attempted to validate self-reported smoking status biochemically and only then on a subset of patients.[41,43] Although self-reporting appears generally accurate when compared with biochemical markers of tobacco inhalation,[59] it may be less accurate for patients with CHD.[60,61]

Not all the primary studies clearly stated when smoking cessation occurred among smokers who quit. However, the magnitude of risk reduction among studies able to report that quitting took place rapidly after the cardiac event (RR, 0.63; 95% CI, 0.53-0.74) compared with that from all studies (RR, 0.64; 95% CI, 0.58-0.71) was the same. This suggests that most smokers who quit do so quickly after their CHD diagnosis.

A further potential for misclassification arises over time. Many studies relied on baseline assessments of smoking status only. Clearly, some patients who had reported quitting might have started again.[9,62] Conversely, patients who had not initially stopped smoking might have quit later on, and thus be erroneously regarded as continuers. Such nondifferential misclassification may dilute the differences between the 2 groups and therefore underestimate the true RR. Only 3 of the studies incorporated more than 1 follow-up and excluded patients who reported mixed smoking histories (ie, those who quit smoking after their cardiac event but then started smoking again later on, or those who quit did not quit initially, but did later on).[41,45,52] The risk reduction in these 3 studies was not statistically significantly different from that in all 20 studies (RR, 0.73; 95% CI, 0.63-0.86).

Our analyses were repeated assuming that an arbitrary 10% of those who reported to have ceased smoking actually had continued. In this case, the pooled crude RR would be reduced slightly to 0.61 (95% CI, 0.54-0.68).

As with any systematic review, there is always a possibility of publication bias, as suggested by the funnel plot (Figure 3).[63] However, exclusion of the smaller studies in a sensitivity analysis made essentially no difference to the pooled RR.

Statistical pooling of RR for observational data is itself controversial because of the many biases that can arise in observational studies, compared with those in randomized controlled trials.[63] It has been argued that presenting a single pooled estimate without additional detail may give a simple statistic that could be misleading.[63] However, a single summary statistic is highly appealing for clinicians and other health care professionals working with cardiac patients. Furthermore, these studies showed relatively little heterogeneity, particularly for the sensitivity analysis of the 6 higher-quality studies (χ^2 for heterogeneity, $P=.51$). The implication is that the risk reduction associated with quitting smoking in these studies is essentially the same, regardless of the differences between these studies in terms of factors, such as the type of index cardiac event (MI, CABG, angioplasty, or other) and the time period during which patients were recruited.

Given the overwhelming evidence of the benefits of stopping smoking and the growing evidence of the best methods of helping patients to achieve this goal, it is unlikely that substantial further work exploring the magnitude or speed of effect of smoking cessation is needed. People who stop smoking following onset of CHD or after undergoing revascularization have a considerably lower risk of death. Advice and support for smoking cessation should be provided routinely to all patients with a diagnosis of CHD.

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Acquisition of data: Critchley, Capewell.
Analysis and interpretation of data: Critchley, Capewell.
Drafting of the manuscript: Critchley, Capewell.
Critical revision of the manuscript for important intellectual content: Critchley, Capewell.
Statistical expertise: Critchley.
Obtained funding: Capewell.
Administrative, technical, or material support: Critchley, Capewell.
Study supervision: Capewell.

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