Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study

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Summary

Background **Tobacco use is one of the major avoidable causes of cardiovascular diseases. We aimed to assess the risks associated with tobacco use (both smoking and non-smoking) and second hand tobacco smoke (SHS) worldwide.**

Methods **We did a standardised case-control study of acute myocardial infarction (AMI) with 27 089 participants in 52 countries (12 461 cases, 14 637 controls). We assessed relation between risk of AMI and current or former smoking, type of tobacco, amount smoked, effect of smokeless tobacco, and exposure to SHS. We controlled for confounders such as differences in lifestyles between smokers and non-smokers.**

Findings **Current smoking was associated with a greater risk of non-fatal AMI (odds ratio [OR] 2·95, 95% CI 2·77–3·14, p<0·0001) compared with never smoking; risk increased by 5·6% for every additional cigarette smoked. The OR associated with former smoking fell to 1·87 (95% CI 1·55–2·24) within 3 years of quitting. A residual excess risk remained 20 or more years after quitting (1·22, 1·09–1·37). Exclusion of individuals exposed to SHS in the never smoker reference group raised the risk in former smokers by about 10%. Smoking beedies alone (indigenous to South Asia) was associated with increased risk (2·89, 2·11–3·96) similar to that associated with cigarette smoking. Chewing tobacco alone was associated with OR 2·23 (1·41–3·52), and smokers who also chewed tobacco had the highest increase in risk (4·09, 2·98–5·61). SHS was associated with a graded increase in risk related to exposure; OR was 1·24 (1·17–1·32) in individuals who were least exposed (1–7 h per week) and 1·62 (1·45–1·81) in people who were most exposed (>21 h per week). Young male current smokers had the highest population attributable risk (58·3%; 95% CI 55·0–61·6) and older women the lowest (6·2%, 4·1–9·2). Population attributable risk for exposure to SHS for more than 1 h per week in never smokers was 15·4% (12·1–19·3).**

Conclusion **Tobacco use is one of the most important causes of AMI globally, especially in men. All forms of tobacco use, including different types of smoking and chewing tobacco and inhalation of SHS, should be discouraged to prevent cardiovascular diseases.**

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Introduction

Tobacco use is one of the most important avoidable causes of cardiovascular diseases worldwide.[1] The number of smokers worldwide is currently estimated to be 1·3 billion, of which 82% are in developing countries.[2] During the 20th century, 100 million individuals died worldwide as a result of tobacco-related diseases.[3] This number is expected to increase to 1 billion during the 21st century.[4] About half of these deaths will occur among middle-aged adults (35–69 years old), who will lose on average 22 years of life.[5] Most tobacco-related deaths occur among men, but female mortality from tobacco is expected to increase substantially as a result of large increases in smoking among women in many developed countries, and high rates of use of non-smoking tobacco, especially in women, in several developing countries.[2]

The risk of coronary heart disease associated with smoking has been documented in studies in developed countries,[6–8] few large studies have been done to examine the effects of tobacco in other geographical regions. The available studies are difficult to compare, and extrapolations from studies in developed countries to other regions of the world might not be appropriate because of varying methods and markedly different patterns of tobacco use (eg, the type of smoking varies in different countries: cigarettes or beedies, smoking or chewing, different ages at starting the habit, numbers smoked).[9–16] Moreover, the few studies that have been done in developing countries include relatively small numbers of cases, so that there is uncertainty about the magnitude of the risk associated with smoking in these countries.

Emerging data suggest that second hand smoke (SHS) is associated with adverse health effects, including coronary heart disease,[17,18] but the available studies recorded relatively few events, and might not have fully adjusted for other lifestyle factors such as diet. However, some of the research that suggested a failure to adjust for such confounders has itself been challenged on both methodological grounds and undisclosed links to the tobacco industry.[19] Therefore, considerable uncertainty exists about the size of the effect of SHS. We undertook a study to document the risks associated with various forms of active tobacco use (both smoking and non-smoking) and SHS in all regions of the world, controlling for potential confounders.

Methods

Participants

INTERHEART was a standardised case-control study of 15 152 cases of first acute myocardial infarction (AMI) and 14 820 age-matched and sex-matched controls who were recruited from 262 centers in 52 countries in Asia, Europe, Middle East Crescent, Africa, Australia, North and South America. Details have been published previously.[20,21] Consecutive cases of first AMI presenting within 24 h of symptom onset were eligible. We included all consenting cases without cardiogenic shock or history of major chronic diseases. At least one age-matched (plus or minus 5 years) and sex-matched control (without a history of heart disease or exertional chest pain) was recruited per case by use of specific criteria. A community-based control was either a visitor or relative of a patient from a non-cardiac ward or an unrelated visitor of another cardiac patient. A hospital-based control was selected from those at the same centre with illnesses not obviously related to coronary heart disease or its risk factors. Of the cases, 1531 were excluded because they had unstable angina alone and were recruited into a substudy, 205 did not have a confirmed AMI, 695 had a previous AMI, and 260 had insufficient data. Of the controls, 74 were excluded because of insufficient data, and 109 had a previous history of AMI. Therefore, 27 098 participants (12 461 cases and 14 637 controls) were available for the study; among these individuals, data on tobacco use was missing in 530, so that complete data were available in 12 133 cases and 14 435 controls.

Procedures

Trained staff administered a structured questionnaire and did physical examinations for cases and controls in the same manner. Participants were asked if they regularly used any of the following tobacco products: cigarettes, beedies, pipes or cigars, chewing tobacco, paan, snuff, sheesha or water pipe, and other forms of smoked or non-smoked tobacco. Beedies consist of a small amount of tobacco wrapped in a dried temburini leaf and tied with a string. Paan is a form of tobacco preparation that is used with lime, with areca nut or a betel quid. For cigarettes (and beedies), the number smoked per day, the type of cigarettes (filter, nonfilter, or both), and the brands of cigarettes commonly smoked were recorded. Categories of tobacco use were defined as follows: current smokers were individuals who smoked any tobacco (including beedies, pipes, and other forms) in the previous 12 months, and included those who had quit within the past year. Former smokers had quit more than a year earlier. Never smokers were those who responded that they had never used tobacco products regularly. Regular users were individuals who used at least one tobacco product daily. Exposure to SHS was recorded by asking about the smoking habits of family members, friends, or co-workers, whether these individuals smoked regularly in the participants' presence, the number of times per day that SHS exposure exceeded 5 consecutive minutes, the average number of hours per week of exposure over the past 12 months, and smoking habits of the spouse. Height, weight, waist and hip circumferences, blood pressure, and heart rate were measured with a standardised protocol. Concentrations of apolipoproteins B and A1 in serum were measured with standardised approaches. Information on dietary patterns, physical activity, alcohol consumption, education, income, psychosocial factors, personal and family history of cardiovascular disease, and risk factors (hypertension, diabetes mellitus) were recorded.

All data were transferred to the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Canada, where extensive data checks were done. The study protocol was approved by appropriate regulatory and ethics committees in all participating countries and centres. All participants provided informed consent before participating in the study.

	Cases	Controls
Number of individuals	12 461	14 637
Female	3005 (24%)	3786 (26%)
Mean age (SD)	58·1 (12·2)	56·9 (12·2)
Current smokers	45·2%	26·8%
Diabetes	18·5%	7·5%
Hypertension	39·0%	21·9%
Daily consumption of vegetables and fruits	35·8%	42·4%
Daily exercise	14·3%	19·3%
Mean body-mass index, kg/m^2 (SD)	26·1 (4·2)	25·8 (4·2)
Mean waist-hip ratio (SD)	0·93 (0·08)	0·91 (0·08)
Median ApoB, g/L (IQR)	0·95 (0·78–1·13)	0·90 (0·74–1·07)
Median ApoA1, g/L (IQR)	1·10 (0·96–1·36)	1·19 (1·03–1·37)
Median ApoB/ApoA1 ratio (IQR)	0·87 (0·70–1·05)	0·75 (0·60–0·93)

Apo=apolipoprotein.

Table 1: **Demographics and prevalence of risk factors in cases and controls**

Statistical methods

Details of statistical analysis have been described in previously published reports.[20,21] Univariate associations were investigated with frequency tables. For comparisons of prevalence of tobacco use across subgroups (eg, by region or ethnicity), the potential differences in age structure of the populations were accounted for by direct standardisation of the frequencies to the overall INTERHEART age distribution with a five-level age stratification (<45, 45–55, 56–65, 66–70, >70 years). Continuous variables were summarised by means or medians. For comparison of means across subgroups, values were adjusted for age and sex with analysis of covariance (ANCOVA) models. Sex-specific quintile values in controls were used to categorise continuous variables. Unconditional logistic regression with adjustment for matching factors (ie, age, sex, and geographic region included in all models as block effects) was used to control for confounding by other risk factors.

	Ever		Former		Current							
					Any		1–9 cig/day		10–19 cig/day		≥20 cig/day	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Overall												
Young	21·9	57·3	10·8	16·0	11·1	41·3	4·6	11·9	3·6	11·9	2·8	17·6
Older	19·2	57·9	12·7	29·9	6·5	28·0	2·6	7·0	2·1	9·2	1·8	11·8
North America												
Young	63·5	51·8	40·5	35·7	23·0	16·1	10·8	7·1	8·1	1·8	4·1	7·1
Older	40·7	80·0	39·1	62·8	1·6	17·2	0·0	4·1	0·0	2·1	1·6	11·0
Western Europe												
Young	47·1	56·7	24·0	18·9	23·1	37·8	7·7	11·1	9·6	10·0	5·8	16·7
Older	28·8	65·1	17·3	43·1	11·5	22·0	4·3	6·5	5·0	6·9	2·2	8·6
Australia/New Zealand												
Young	42·4	53·9	28·9	31·3	13·5	22·6	3·9	3·5	2·9	3·5	6·7	15·7
Older	36·0	64·1	28·8	54·4	7·2	9·7	3·6	1·2	0·9	2·6	2·7	6·0
Eastern/central Europe												
Young	35·0	71·4	16·8	18·8	18·2	52·6	4·2	3·8	6·4	12·1	7·6	36·7
Older	18·2	65·6	10·1	33·1	8·1	32·5	2·9	3·3	1·7	12·0	3·5	17·2
Middle East												
Young	4·4	53·8	1·0	15·4	3·4	38·4	1·9	9·2	1·0	6·9	0·5	22·4
Older	0·0	64·5	0·0	17·3	0·0	37·2	0·0	7·7	0·0	8·1	0·0	21·4
Africa												
Young	38·8	67·7	11·6	14·8	27·2	52·9	19·2	33·5	5·4	13·6	2·7	5·8
Older	29·8	65·2	21·3	27·1	8·5	38·1	4·3	19·4	4·3	9·3	0·0	9·3
South Asia												
Young	4·8	45·1	0·9	12·8	3·9	32·3	0·9	15·6	3·0	10·6	0·0	6·2
Older	3·4	47·9	1·7	22·1	1·7	25·8	1·7	10·0	0·0	10·4	0·0	5·4
China/Hong Kong												
Young	5·5	64·7	1·6	5·9	3·9	58·8	1·0	7·0	1·8	22·4	1·0	29·4
Older	11·3	49·9	5·2	16·9	6·1	33·0	1·4	5·8	3·3	12·4	1·4	14·8
Japan/southeast Asia												
Young	8·3	65·5	5·9	21·0	2·4	44·5	0·6	12·3	0·6	15·4	1·2	16·9
Older	16·2	70·9	10·3	35·8	5·9	35·1	5·9	7·7	0·0	11·6	0·0	15·8
Latin America												
Young	28·2	54·0	18·0	26·7	10·2	27·3	4·9	13·5	3·2	7·4	2·1	6·4
Older	21·6	57·6	16·8	41·0	4·8	16·6	2·9	7·7	1·0	4·7	1·0	4·3

Young: female ≤65 years, male ≤55 years. Older: female >65 years, male >55 years. cig/day=cigaretters per day.

Table 2: **Percentages of ever (former+current), former, and current smokers in controls by region, sex, and age**

Results from unconditional analyses were similar to those from conditional and mixed effect models analyses (<5% variation). Analyses adjusted for the other modifiable INTERHEART risk factors (apolipoprotein B/apolipoprotein A ratio, obesity, history of hypertension, history of diabetes, dietary pattern, activity, and alcohol use) are also presented.

Population attributable risks (PAR) and their 95% CI were calculated by a method based on unconditional logistic regression using the methods of Benichou and Gail,[22,23] and with the Interactive Risk Attributable Program by the US National Cancer Institute, 2002.[24] The PAR presented are adjusted for confounders in a similar fashion to the corresponding logistic regression models for odds ratio (OR) estimates and, where indicated, stratified by subgroups of interest. The PAR calculation uses the prevalence rates of risk factors reported in the control group, as well as the estimate of relative risk. In the analysis of PAR in subgroups (eg, males *vs* females or by age groups, etc) the actual prevalence and relative risks observed in the specific subgroups were used and are presented here.

Results

A previous report showed that abnormal lipid profiles, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and physical activity accounted for most of the risk of AMI worldwide.[21] The demographic, health history and characteristics for the 27098 participants

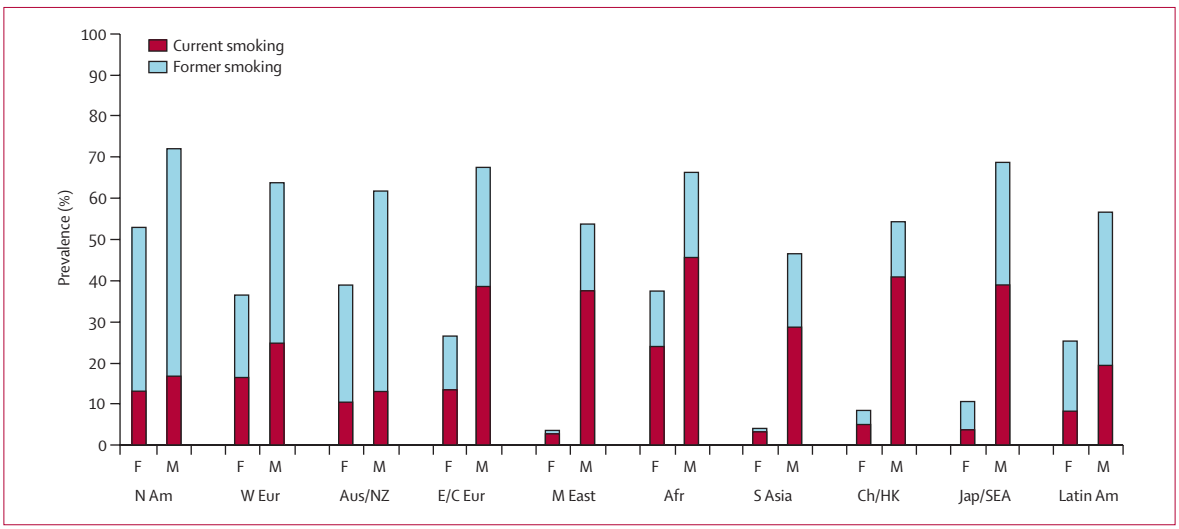

Figure 1: **Prevalence of smoking by region and sex**
F=female. M=male. N Am=North America. W Eur=western Europe. Aus/NZ=Australia and New Zealand. E/C Eur=eastern and central Europe. M East=Middle East. Afr=Africa. S Asia=South Asia. Ch/HK=China and Hong Kong. Jap/SEA=Japan and southeast Asia. Latin Am=Latin America.

(12 461 cases and 14 637 controls) have been reported.[21] The distribution of various risk factors between cases and controls are summarised in table 1. Here, we focus on the use of tobacco by participants in the study.

Smoking habits varied greatly among controls and cases, between men and women, and in different regions of the world. Table 2 summarises the smoking status in controls overall and by region, sex and age. In control women, nearly 80% never smoked and less than 10% were current smokers. Younger (≤65 years of age) women were more likely to have smoked at any time compared with older (>65 years) women (21·9% *vs* 19·2%), and were more likely to be current smokers (11·1% *vs* 6·5%). Smoking patterns varied markedly by region, especially in younger women. Prevalence of current smoking was fairly high (>20%) among younger women in three regions (North America, western Europe, and Africa), very low (<5%) in Asia and the Middle East, and intermediate (10–20%) in Australia/New Zealand, eastern and central Europe, and Latin America (figure 1, table 2). Among older women, the prevalence of current smoking was very low in most regions, with the highest rate (11·5%) in Western Europe (table 2)

The pattern of smoking in female controls differed substantially from that in male controls, among whom about a third were current smokers with a tendency to smoke heavily, and only about two fifths never smoked. The prevalence of ever smoking did not differ between younger (≤55 years of age) and older (>55 years) male controls (57·3% *vs* 57·9%), but current smoking was more frequent in younger than in older men (41·3% *vs* 28·0%)—a pattern seen in every region except North America. The highest rates of current smoking among young male controls were reported in China and Hong Kong, eastern and central Europe, and Africa (all >50%). The lowest rates were in North America and Australia and New Zealand (<25%), which were also regions with the highest proportions of former smokers in both younger (>30%) and older men (>50%). By contrast, in South Asia, the Middle East, and China and Hong Kong, only 15% or less of younger men and less than 25% of older men were former smokers. (figure 1, table 2)

Overall, current smoking was associated with a three-fold increase in odds of a non-fatal AMI, compared with never smokers (odds ratio [OR] 2·95, 95% CI 2·77–3·14, p<0·0001). The risks were higher depending on the number of cigarettes smoked, with people who smoked one to nine cigarettes per day having an OR of 1·63 (95% CI 1·45–1·82, p<0·0001), 10–19 per day an OR

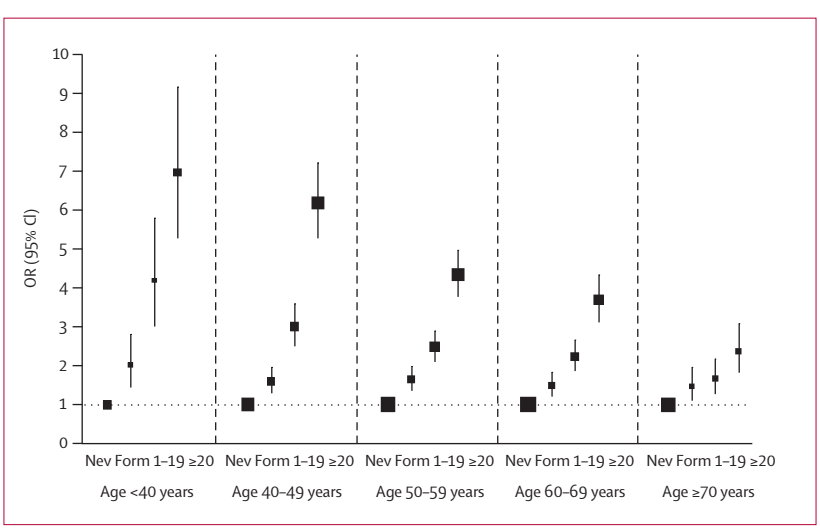

Figure 2: **Risk of AMI associated with numbers smoked, by age group**
p for interaction < 0·0001. Nev=never smokers. Form=former smokers. 1–19=currently smoking 1–19 cigarettes per day. ≥20=currently smoking 20 or more cigarettes per day.

of 2·59 (2·35–2·85, p<0·0001), and 20 or more per day an OR of 4·59 (4·21–5·00, p<0·0001). Similar trends were noted in men and women. Women who smoked 1–19 cigarettes per day had an OR of 2·11 (1·77–2·52, p<0·0001) and 20 or more per day an OR of 5·11 (3·98–6·56, p<0·0001) for AMI. For men, the corresponding ORs were 2·06 (1·90–2·24, p<0·0001) and 4·48 (4·13–4·87, p<0·0001), respectively.

The effect of current smoking was much larger in younger (OR 3·53, 95% CI 3·23–3·86) than in older individuals (2·55, 22·35–2·76; p<0·0001 for interaction); especially in heavy smokers (≥20 cigarettes per day) in whom ORs were 5·60 (95% CI 5·1–6·20) for younger and 3·60 (3·25–3·98, p<0·0001 for interaction) for older smokers. A consistent interaction between age and smoking was noted in risk of AMI (figure 2), with groups of smokers younger than 40 years and those aged 40–49 years of age showing much higher levels of risk of AMI associated with number of cigarettes smoked. The excess risks associated with tobacco were similar between smokers who used filter cigarettes (OR 2·92, 95% CI 2·73–3·12) and non-filter cigarettes (2·35, 1·96–2·82; figure 3).

A clear dose-response relation existed between number of cigarettes smoked per day and risk of AMI (figure 4). Regression analysis of the number of cigarettes smoked per day as a continuous variable showed that the odds of developing AMI were increased by 1·056 (95% CI 1·05–1·06) for every additional cigarette smoked per day. This risk did not change when exposure to SHS was removed in the control never smokers. The odds were nine-fold higher in those who smoked 40 or more cigarettes a day (OR 9·16, 95% CI 6·79–12·36) than in never smokers.

Compared with never smokers, former smokers had a moderately higher risk (OR 1·49, 95% CI 1·39–1·59). There was an apparent difference in risks between female (1·04, 0·89–1·22, p=0·62) and male former smokers (1·62, 1·49–1·75, p<0·0001; p=0·0002 for heterogeneity) after adjusting for age, region, physical activities, and consumption of fruits, vegetables, and alcohol. After further adjustment for numbers of cigarettes smoked per day before quitting, this interaction was only marginally significant (p=0·03), and therefore might be simply due to chance. This apparent difference in risk cannot be readily explained.

The risk associated with smoking was much reduced within a few years of quitting (table 3, figure 5). When compared with control never smokers as the reference, the OR for AMI for those who quit smoking 1–3 years earlier was substantially lower than that observed among current smokers after similar adjustment. Risk of AMI fell progressively with time after smoking cessation but even in people who had quit 20 or more years ago, there was a residual excess risk of about 22%.

When these analyses were repeated after removing individuals who had been exposed to SHS from the control reference never smokers group, the risks in former smokers were higher by about 10%, with a similar graded lowering in risks the longer the individuals had quit smoking (table 3). When individuals exposed to SHS were removed from both reference never smokers and former smokers, the levels of risk in the former smokers were lower by about 5% compared with the levels of risk observed when there was no adjustment for SHS (table 3). In these analyses, the risks for current smokers were not affected substantially when adjusted for exposure to SHS (table 3).

Among those who smoked 20 or more cigarettes per day before quitting, the largest decrease in risk occurred

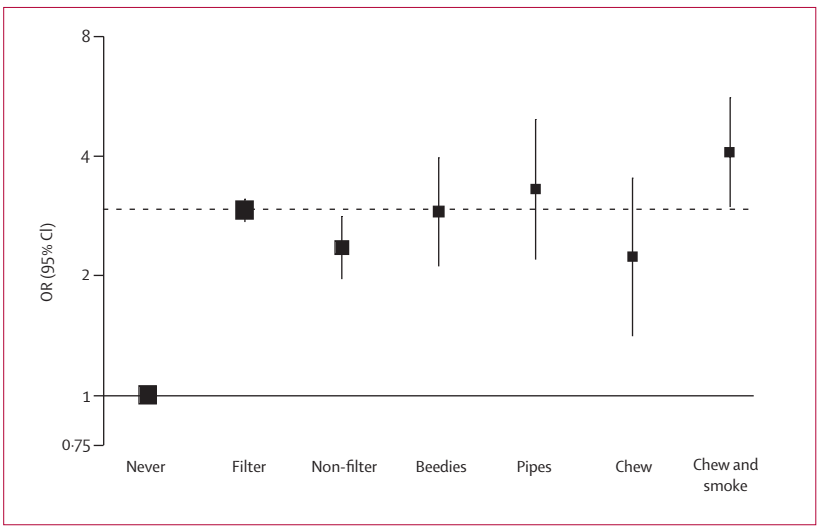

Figure 3: **Risk of AMI associated with type of tobacco used**
OR for current smokers=2·95 (95% CI 2·77–3·14) indicated by broken horizontal line. Never=never smokers. Filter=filter cigarettes. Non-filter=non-filter cigarettes. Beedies=smoking beedies alone. Pipes=smoking pipes/cigars. Chew=chewing tobacco alone. Chew and smoke=both chewing and smoking tobacco.

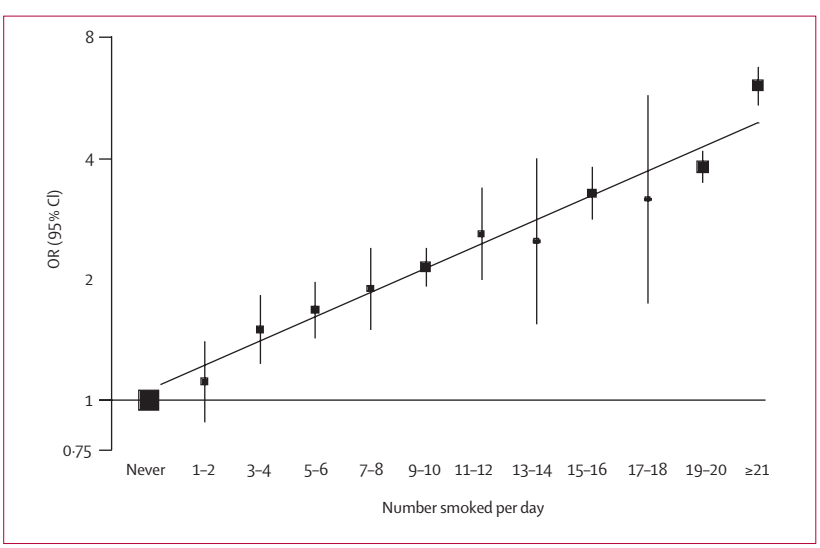

Figure 4: **Risk of AMI with increasing numbers of cigarettes smoked, compared with never smokers**
≥21 cigarettes smoked per day represents about 1·5 pack of cigarettes per day, associated with OR 6·00–7·00.

	OR (95% CI)		
	Adjustment 1	Adjustment 2	Adjustment 3
Current smokers	3·04 (2·85–3·25)	3·08 (2·86–3·33)	2·83 (2·54–3·15)
Quit 1–3 years	1·87 (1·55–2·24)	1·93 (1·60–2·32)	1·49 (1·09–2·02)
Quit >3–5 years	1·57 (1·25–1·97)	1·65 (1·32–2·07)	1·51 (1·07–2·12)
Quit >5–10 years	1·51 (1·29–1·76)	1·63 (1·40–1·91)	1·36 (1·09–1·70)
Quit >10–15 years	1·45 (1·25–1·69)	1·60 (1·37–1·87)	1·40 (1·13–1·74)
Quit >15–20 years	1·55 (1·30–1·84)	1·69 (1·42–2·02)	1·47 (1·15–1·97)
Quit >20 years	1·22 (1·09–1·37)	1·41 (1·25–1·59)	1·31 (1·13–1·51)
p for slope	<0·0001	<0·0001	<0·0001

Adjustment 1=adjusted for age, sex, region, physical activities and consumption of fruits, vegetables, and alcohol. Adjustment 2=never smokers not exposed to SHS as reference group; adjusted for sex, region, physical activities, and consumption of fruits, vegetables, and alcohol. Adjustment 3=included only reference group (never smokers) and former smokers not exposed to SHS; adjusted for sex, region, physical activities, and consumption of fruits, vegetables, and alcohol.

Table 3: **Risk of AMI associated with various durations of cessation in former smokers**

during the first 3 years after quitting. Thereafter, the ORs decreased more gradually. However, in this group, the risk of AMI was still raised 20 or more years after quitting (figure 5). In light smokers (<10 cigarettes per day), the excess risk fell rapidly, with no apparent excess risk 3 years after quitting (figure 5). When levels of risk were assessed at 1, 2, and 3 years after quitting, we found that the risks remained high at 1 year, with a rapid lowering of risk at 2 years after quitting.

The use of other forms of tobacco was largely confined to specific regions. Smoking of beedies was reported in 5·9% of male controls in South Asia (Bangladesh, India, and Sri Lanka). Of these, 51% also smoked cigarettes. In western Europe and North America, 3·1% and 4·4% male controls, respectively, reported smoking cigars, pipes, or both; 67% and 73% of these individuals also smoked cigarettes. In the Middle East, 0·4% of female controls smoked sheesha (none smoked cigarettes), and 3·1% male controls smoked sheesha; 53% also smoked cigarettes. In Iran, 2·3% female controls (no male controls) smoked sheesha, but none of these women also smoked cigarettes. Conversely, in Egypt, 8·2% men smoked sheesha, with 56% also smoking cigarettes.

In South Asia, 4·7% of controls chewed tobacco (3·4% women, 5·0% men). Of these, 40% (8% women and 44% men) also smoked cigarettes. Chewing tobacco was most frequently reported in India (4·6%; 2·3% women, 5·1% men), Nepal (4·2%; 2·1%, 5·1%), Pakistan (4·8%; 5·3%, 5·9%) and Sri Lanka (11·6%; 11·1%, 11·7%). In these countries, very few or none of the women who chewed tobacco also smoked cigarettes or beedies, whereas men who chewed tobacco often also smoked cigarettes or beedies (ranging from 17% in India to 86% in Sri Lanka). In the USA, 1·7% of male controls both chewed tobacco and smoked cigarettes. The use of paan in controls who also smoked cigarettes or beedies was mostly reported in Bangladesh (7·3%; 4·5% women, 7·5% men), India (3·1%; 1·6%, 3·4%), Nepal (3·4%, only in men), and Pakistan (5·9%; 7·7% women, 5·4% men). All individuals who used paan without other forms of chewing tobacco also smoked cigarettes or beedies.

The use of non-smoking tobacco, including chewing tobacco and paan, was reported mainly from South Asia (7·3% controls; of whom 40% also smoked cigarettes or beedies). This high rate of use was observed in women (5·5%; 5% also smoked) and men (7·6%; 44% also smoked). Countries with the highest rates of use of non-smoking tobacco included Bangladesh (7·6%; 87% also smoked), India (6·4%; 24% smoked), Nepal (5·6%; 73% smoked), Pakistan (7·6%; 28% smoked), and Sri Lanka (13·6%; 77% smoked). In these countries, very few women who used non-smoking tobacco also smoked cigarettes or beedies, whereas men chewed and smoked tobacco frequently, ranging from 23% in India to 88% in Sri Lanka. In Western Europe, 7·4% Scandinavian men reported using non-smoking tobacco, mostly snuff (6·8%), and 35% of these individuals also smoked cigarettes. The use of snuff was reported in Africa, mainly in Nigeria (in 6·8%, 100% also smoked cigarettes) and Cameroon (15·6%, 57% also smoked cigarettes) but the numbers of participants from these countries were relatively small.

Significant risks were associated with forms of tobacco use other than cigarette smoking. Smoking beedies alone, without cigarette smoking, was associated with an age-adjusted and sex-adjusted OR of 2·89 for AMI (95% CI 2·11–3·96) compared with never smokers who did not use other tobacco products. The risk for South Asia alone did not differ (OR 2·73, 95% CI 1·90–3·92). This risk was similar to that associated with current cigarette smoking. The risk was graded; the ORs for people who smoked one

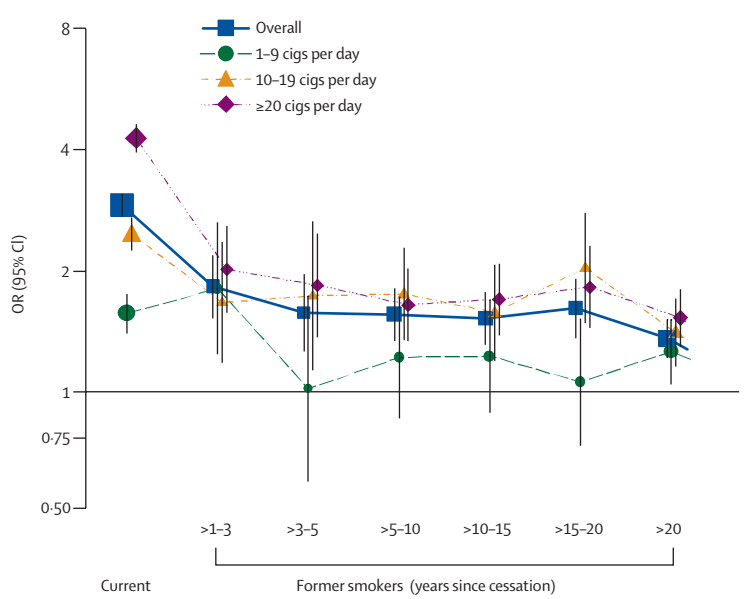

Figure 5: **Diminishing risk of AMI associated with quitting in former smokers, with never smokers as reference**
ORs adjusted for sex, region, diet, alcohol, and physical activity.

to nine beedies per day was 2·06 (95% CI 0·96–4·42), for 10–19 beedies was 2·51 (1·60–3·94), and for 20 or more beedies was 3·99 (2·37–6·74). The risk of AMI associated with pipe and cigar smoking, in the absence of smoking cigarettes or beedies, was also high (3·30, 2·20–4·96; figure 3). Similarly, the use of sheesha was associated with an excess risk (2·16, 1·06–4·39). Participants who were current smokers of cigarettes or beedies and who chewed tobacco had an OR of 4·09 for AMI (95% CI 2·98–5·61). When adjusted for smoking status, the OR in all participants who chewed tobacco was 1·57 (1·24–2·00). Individuals who chewed tobacco alone had an OR of 2·23 (1·41–3·52) compared with those who never used tobacco (figure 3). This effect of chewing tobacco was undiminished after further adjustment for diabetes, abdominal obesity, hypertension, exercise, and diet. Because of the small number of users of paan and snuff in this study, we were unable to draw conclusions about the effects of these forms of tobacco on AMI risk.

Overall, 44% of controls reported no exposure to SHS, 39% of controls reported exposures of between 1 to 7 hours/week, 8·2% exposed for 8 to 14 hours, 3·6% for 15 to 21 hours and 5·3% for 22 or more hours per week. Slightly lower proportions of females reported exposures to SHS than males (table 4). Half (53·6%) of controls who were never smokers were also not exposed to SHS, whereas slightly less than half of former smokers and much fewer of the current smokers were not also exposed to SHS. Current smokers reported much greater exposure to SHS than never and former smokers (table 4)

Exposure to SHS increased the risk of non-fatal AMI in a graded manner. For example, after adjusting for age, sex, region, physical activity, and consumption of fruits, vegetables, and alcohol, individuals with the lowest level of exposure (1–7 h per week), compared with those who had never used tobacco or been exposed to SHS, had an OR of 1·24 (95% CI 1·17–1·32). The levels of risk then increased in a graded manner with increasing exposure (figure 6). These patterns were most marked among never smokers (figure 6) and in former smokers. The risk due to SHS was least marked among heavy smokers (20 or more cigarettes per day), with an OR of 1·05 (0·88–1·26) for those with the lowest exposure and 1·30 (1·04–1·62) at the highest level of exposure to SHS (p=0·128 for slope). About a fifth of controls were exposed to SHS from a spouse's tobacco smoking, with women more frequently exposed than men. The risk of AMI associated with exposure to SHS due to spousal smoking was significant (OR 1·28, 95% CI 1·12–1·47) and did not differ from the overall risks due to SHS exposure. The increased risk of AMI associated with tobacco use was consistently noted in the presence or absence of the other risk factors (table 5).

Current smoking, compared with never smoking, was responsible for 37·6% (95% CI 35·9–39·4) of the PAR of AMI in the overall population. In women the PAR was 15·4% (13·4–17·6) and in men, it was 46·3% (44·1–48·5).

	Overall	Female	Male	Never smokers	Former smokers	Current 1–19 cig/day	Current >20 cig/day
Never	44·0	48·9	42·2	53·6	47·3	27·0	18·0
1–7 h	39·0	37·5	39·5	35·7	39·0	48·1	40·6
8–14 h	8·2	7·7	8·4	5·7	6·9	12·0	16·9
15–21 h	3·6	2·3	4·0	2·1	2·7	5·5	9·4
>21 h	5·3	3·6	5·8	2·9	4·2	7·4	15·2

cig/day=cigaretters per day.

Table 4: **Prevalence (%) of exposure to SHS (per week) in controls by sex and smoking status**

In younger individuals (women aged <65 years and men aged <55 years), the PAR was 45·4% (42·8–47·9) and for older individuals (women ≥65 years, men ≥55 years), it was 30·8% (28·5–33·1). The PAR for younger women was 22·4% (19·4–25·7) and for younger men was 58·3% (55·0–61·6). For older women, the PAR was 6·2% (4·1–9·2) and for older men, it was 37·9% (35·1–40·8). The PAR was much lower in women than in men, reflecting the lower prevalence of smoking in women, even though they had the same odds of AMI as in men.

The PAR for current smokers ranged from a low of 33·1% (95% CI 29·7–36·6) in China/Hong Kong to a high of 53·3% (46·2–60·3) in Australia/New Zealand. The PAR for the other regions fell within this narrow range, showing that the PAR for current tobacco smoking is consistent and high across all the regions. When the PAR for current smoking was examined by sex and age in each of the regions, we noted that in men and in younger smokers, and to some degree in older smokers, the PAR was consistently high. In female current smokers, higher PAR was seen in North America, Australia/New Zealand,

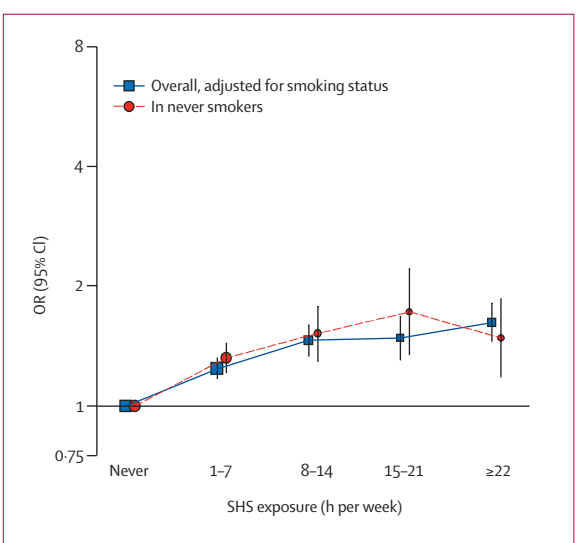

Figure 6: **Risk of AMI associated with extent of exposure to SHS, adjusted for smoking status in all individuals and in never smokers**
Graded increase in risk occurs with increasing exposure. In never smokers, the decreasing number of individuals who were exposed to higher levels of SHS resulted in loss of robustness of the data at the highest level of exposure.

	OR (95% CI)	
	Current smokers	Former smokers
Overall	2·95 (2·77–3·14)	1·49 (1·39–1·59)
Diabetes	2·35 (1·92–2·88)	1·30 (1·07–1·58)
Hypertension	2·53 (2·24–2·87)	1·31 (1·60–1·48)
No regular fruits or vegetables	2·95 (2·53–3·43)	1·45 (1·22–1·73)
No regular physical activities	2·79 (2·46–3·16)	1·43 (1·24–1·65)
1st tertile ApoB/ApoA1	2·41 (2·08–2·78)	1·74 (1·47–2·06)
2nd tertile ApoB/ApoA1	2·79 (2·46–3·16)	1·43 (1·24–1·65)
3rd tertile ApoB/ApoA1	2·95 (2·65–3·29)	1·47 (1·30–1·67)
1st tertile waist-hip ratio	2·90 (2·57–3·27)	1·64 (1·42–1·90)
2nd tertile waist-hip ratio	2·97 (2·65–3·32)	1·42 (1·25–1·62)
3rd tertile waist-hip ratio	3·14 (2·83–3·48)	1·45 (1·30–1·62)
1st tertile BMI	3·00 (2·68–3·35)	1·57 (1·38–1·80)
2nd tertile BMI	2·91 (2·62–3·24)	1·53 (1·35–1·72)
3rd tertile BMI	3·18 (2·85–3·55)	1·39 (1·24–1·56)

Apo=apolipoprotein. BMI=body-mass index.

Table 5: **Effect of tobacco use in strata defined by presence of other risk factors**

Africa, and Latin America than in the other regions (table 6) Although the odds for AMI in beedies smokers did not differ from that of cigarette smokers, the PAR for beedies smoking alone in South Asia, where this form of tobacco use was more common, was about 6%.

The PAR for former smokers was much smaller, reflecting the lower risks found in former smokers, and to low prevalence of former smokers in most regions. Overall, the PAR for former smokers was 12·4% (10·4–14·6); for women it was 2·5% (1·2–5·4) and for men 18·2% (15·4–21·3). In younger former smokers, PAR was 8·1% (5·8–11·2) and in older individuals, it was 15·2% (12·7–18·2). In younger women who were former smokers, PAR was 2·8% (1·1–6·8) and in younger men, it was 15·3% (11·1–20·6). In older women who had quit smoking, PAR was 2·5% (0·7–7·9) and in older men it was 20·0% (16·7–23·8).

For never smokers who were exposed to SHS for 1 hour per week or longer, compared with never smokers who were not exposed to SHS, the overall PAR was 15·4% (95% CI 12·1–19·3); for women in this group, it was 10·8% (6·2–18·1) and for men, it was 18·6% (14·4–23·6). In the younger individuals in the group, the PAR was 13·7% (8·6–21·1) and for older people it was 14·9% (11·0–19·9). In younger women who were never smokers but were exposed to SHS, PAR was 9·6% (3·8–22·4) and for younger men, it was 18·2% (10·7–29·0). The corresponding PAR for older women was 10·8% (5·1–21·4) and for older men was 17·0% (12·3–23·0).

Discussion

Our study resulted in several key findings about tobacco use. First, use of tobacco is associated with increased risk of AMI, consistently across all regions. Tobacco use is one of the largest contributors to AMI worldwide. The risk is greater in the young than in the old, for men and women. Although the PAR of AMI was low in women because of the low prevalence of smoking, the excess risk associated with smoking in women was similar to that in men. Second, smoking patterns differed significantly between men and women and across different regions. Third, the magnitude of risk is closely, and linearly, related to the number of cigarettes smoked, with even low levels of smoking (eg, five cigarettes per day) being associated with an appreciable risk of AMI. Fourth, former smokers have a higher risk of AMI than do non-smokers, but this risk decreases with time after stopping smoking. A large part of the excess risk of AMI associated with smoking dissipates within 5 years, and among light smokers there was no excess risk after 3–5 years of quitting. By contrast, moderate and heavy smokers still had an increased risk even 20 years after quitting. Fifth, exposure to SHS increases the risk of AMI, in non-smokers and former smokers. The effect of tobacco use on AMI risk was consistent in the presence and absence of the other risk factors.

Several epidemiological studies done in developed countries, mainly with European populations, have

	Current smokers	Current female smokers	Current male smokers	Current younger smokers	Current older smokers
Overall	37·6 (35·9–39·4)	15·4 (13·4–17·6)	46·3 (44·1–48·5)	45·4 (42·8–47·9)	30·8 (28·5–33·1)
North America	45·4 (33·7–57·6)	37·6 (20·8–58·0)	51·1 (36·4–65·7)	61·4 (46·0–74·8)	32·4 (16·9–53·1)
Western Europe	34·6 (26·8–43·3)	13·3 (5·1–30·3)	44·8 (35·1–55·0)	53·2 (39·2–66·7)	26·2 (17·6–37·1)
Australia/New Zealand	53·3 (46·2–60·3)	42·9 (30·4–56·4)	56·4 (47·9–64·6)	65·7 (55·0–75·0)	45·1 (36·9–53·6)
Eastern/central Europe	34·6 (29·5–40·0)	16·1 (11·3 –22·3)	45·2 (37·8–52·7)	51·5 (43·5–59·5)	20·9 (14·8–28·6)
Middle East	45·5 (41·4–50·0)	5·7 (2·6–12·1)	52·7 (47·5–57·8)	49·0 (43·6–54·4)	40·2 (32·8–48·0)
Africa	39·3 (30·4–48·8)	28·9 (18·4–42·3)	45·0 (32·6–58·1)	42·6 (31·5–54·5)	32·7 (19·5–49·3)
South Asia	36·1 (32·0–40·4)	1·6 (0·1–16·7)	42·2 (37·5–47·2)	38·8 (33·4–44·5)	32·6 (26·5–39·2)
China/Hong Kong	33·1 (29·7–36·6)	10·6 (8·1–13·9)	43·6 (38·9–48·4)	38·7 (32·8–45·1)	29·0 (25·0–33·2)
Japan/southeast Asia	38·1 (31·1–45·7)	14·4 (8·9–22·6)	43·2 (34·2–52·8)	45·7 (36·8–54·9)	29·4 (19·1–42·3)
Latin America	40·3 (33·7–57·6)	27·1 (20·7–34·7)	45·3 (39·1–51·7)	53·2 (45·8–60·5)	31·4 (25·7–37·8)

Younger: female ≤65 years, male ≤55 years. Older: female >65 years, male >55 years.

Table 6: **PAR as percentage (95% CI) from current smoking by region, sex, and age**

documented the risks for cardiovascular disease and cancers associated with tobacco smoking.[6–8] These studies generally include populations where the average levels of other risk factors are high. Few data come from non-European populations, among whom the levels of other risk factors might be lower. INTERHEART used a standardised approach across several countries, and showed that the increased risk for AMI associated with smoking is seen in individuals from several ethnic groups and regions of the world. The present study provides useful data on the association of tobacco use with risk of AMI from all regions of the world. The similarity of the increased risks in all regions lends strong support to the need for a global approach to tobacco control.

World Bank data from 2000 indicate that globally, 48% of men and 10% of women aged 15 years and older smoked daily with wide variations by region and sex.[25] Our data also show a decrease in the prevalence of current smoking with increasing age. In view of the higher mean age of subjects in INTERHEART (55·7 years for men and 62·6 years for women), compared with the average age in the populations of the participating countries, the rates of smoking we present here reflect behaviour among older individuals. Our data for prevalence of current smoking in controls in various regions are close to those noted among older individuals in some of the national surveys that reported such data.[26–28] For example, whereas overall smoking prevalence among Australian adults is about 23%, in 2001 the prevalence in those aged 50–59 years was 20% and in those older than 60 years was 10%,[27] rates that are consistent with the prevalence of smoking in controls (14%) in INTERHEART. A national population health survey in the Russian Federation reported that 34% of males over the age of 65 years smoked,[28] which is similar to the 35% rate of smoking in male controls older than 65 years in the Russian INTERHEART sample. Therefore, the estimates of smoking prevalence in the control group of INTERHEART are generally similar to those in populations at risk of AMI in the regions studied.

In this study, the higher prevalence of smoking in men than in women in low and middle income countries, and the similarity between rates in men and women in high income countries, show changing patterns of smoking habits. These patterns are consistent with the stages in the evolving pandemic described by WHO.[2] In several developed countries, the gap between the sexes is narrowing because of an increase in smoking among women and a decline among men.[29] In the older age groups represented in INTERHEART, lower smoking rates were observed in women than in men in Western Europe, North America, Australia, and New Zealand, although smoking prevalence among women in these regions were high. This pattern probably reflects trends 40 years ago, since smoking rates in these countries tend to be higher in younger women than in older women. In Asia and the Middle East, smoking rates in women at all ages were very low, but the rates of smoking in younger women in Africa and Latin America were higher than in older women, suggesting an increase in the rates of smoking at younger ages. It is projected that the prevalence of smoking among women in developing countries will more than double from 8% to about 20% by the year 2025.[30] If smoking rates increase in women in the future, AMI rates in women are also likely to increase greatly, especially in developing countries, and tobacco could become a much bigger cause of cardiovascular disease among women in several parts of the world.

The odds ratio for AMI associated with smoking was markedly raised in younger age groups. Because of the higher prevalence of smoking, and the higher numbers of cigarettes smoked per day among smokers, the PAR for AMI in young male smokers is higher than in middle-aged or older men. Even though the PAR for younger women was smaller than that for younger men, it was much higher than that for older women. This finding suggests that there is a need and opportunity to drastically reduce the high risks faced by younger smokers, through active and effective tobacco control programmes that encourage smoking cessation.

Our data show the benefits of stopping smoking. Detailed analyses showed that the excess risk remained high during year 1 and fell substantially during year 2. The rate of change was almost identical to that reported previously.[31] However, the excess risk does not seem to have completely disappeared even 20 years after quitting in those who are moderate or heavy smokers. By contrast, it seems to completely dissipate in light smokers (<10 cigarettes per day) after about 3–5 years of cessation. By removing from our analyses individuals who reported exposure to SHS in the never smoker reference group, and then in the former smokers group, we found that the effects of SHS could explain some, but not all, of the long-term excess risk persisting in former smokers.

Our findings show that use of tobacco in any form is harmful. Beedies smoking is eight to ten times more prevalent than cigarette smoking in South Asia.[12–15] Beedies are not subject to taxes, and the packages do not carry health warnings. Sheesha smoking is now used by many affluent people from the Middle East and by women in developed countries, as many people wrongly think that the water removes the toxins. Control of all forms of tobacco should be as an integral part of any programme to reduce use, but use of indigenous forms of inexpensive tobacco is probably much more difficult to control than that of other tobacco products.

Findings of other studies have also shown enhanced risk of mortality associated with use of non-smoking tobacco.[15] Our study provides important new data on

the link between use of non-smoking tobacco and increased risk of AMI. Men in the two Cancer Prevention Studies (CPS I and II)[32] who chewed tobacco at baseline had significantly increased risk of death from ischaemic heart disease, with relative risks 1·12 in CPS I and 1·26 in CPS II.[32] A large study in Swedish construction workers found a 40% increased risk of death from cardiovascular disease in users of non-smoking tobacco.[33] Previous case-control studies have not, however, shown a significant association.[34,35] However, despite the size of the present study, the number of individuals who used paan and snuff was still too few to allow conclusive results on the risks associated with the use of these specific forms of tobacco.

The mechanisms by which non-smoking tobacco increases the risk of AMI are poorly understood. The increase in risk of AMI associated with use of non-smoking tobacco and smoked tobacco suggests a role for toxins that are intrinsic to tobacco itself, and not just confined to the smoked form. It seems that tobacco use is associated not only with arterial damage[36] but also with short-term increases in blood pressure.[37] The risk of AMI associated with both chewing and smoking tobacco is higher than either habit alone. This pattern of dual tobacco use is common in several parts of South Asia, especially in rural areas, and could lead to a large health burden in these countries.

Our findings clearly show the harmful effects of SHS, a conclusion that has been widely accepted by authoritative scientific bodies for about 10 years.[38] Smokers, as well as non-smokers, are exposed to SHS, thus possibly compounding these adverse effects. Non-smokers exposed to a spouse's SHS had an increased risk of AMI, suggesting that SHS has an important adverse effect, on family members of the individual who smokes. Our findings are consistent with those of many previous studies that have shown increased risk of AMI in non-smokers reporting exposure to SHS,[17,18] with a graded increase in risk associated with extent of exposure. However, the method used in this study to assess SHS exposure might underestimate the dangers of SHS. When degree of exposure is more precisely specifiied, using cotinine levels, a graded increase has been shown, with those most exposed experiencing an almost 60% increase in risk.[39] Our data also show that individuals with the highest level of exposure to SHS had a 62% increase in AMI risk, but the confidence intervals are wide and might be consistent with a smaller 45% increase in odds—which is nevertheless of great public-health importance. Tobacco industry research has shown how the combustion products from cigarettes smouldering at low temperatures are much more toxic than when air is drawn through them,[40] which might explain the risks associated with exposure to SHS.

The focus of any anti-tobacco programme must not only prevent young adults from starting smoking, but also promote quitting in current smokers. The latter are at high risk of developing a major vascular event (or tobacco-related cancer) in the next decade or two. Furthermore, the present findings confirm earlier reports that the association between smoking and disease is asymmetrical; the adverse health effects of exposure can take many years to appear, whereas the benefits of withdrawal appear much more rapidly.[8] Therefore, a strategy to facilitate quitting in current middle-aged smokers is likely to have a substantial health benefit within a relatively short time. But typically, middle and low income countries do not have well developed tobacco control policies and activities. The tobacco industry has expended great efforts to create uncertainty about the harm caused by its product.[41] Consequently, public and political support for implementation of effective tobacco control policies is often low. In general, high income countries have better developed control policies in place at the national and community levels.[2] These policies,[42] and ongoing health education about the diseases caused by smoking, have resulted in reduced acceptance of smoking by the public, especially among those with more education. The INTERHEART data provide support for intensifying tobacco control policies worldwide.

This study has potential limitations. One limitation is that it involved participants who have survived AMI, and by using a case-control design we could not elucidate the relation between tobacco use and risk of AMI in individuals who died in the early phase of the AMI or because of serious complications or co-morbidity. Second, patients with AMI might overreport exposure to tobacco smoke, but other reports suggest that compared with biochemical monitoring with cotinine levels, self reporting in AMI survivors tended to underestimate the prevalence of smoking.[43] In any case, self reporting of tobacco use is thought to be reliable and our results are directionally similar to those of other studies with different designs, such as cohort studies. The relative risk for AMI of about 3·00 for AMI survivors in our study is consistent with the relative total mortality risk of 2·19 for current smokers in the British Doctors study.[8] The findings of excess risk of AMI associated with non-smoking tobacco in our study are consistent with those of of the large US Cancer Prevention Studies[32] and the Swedish Construction Workers study.[33] Furthermore, the risks associated with exposure to SHS are close to those reported by a meta-analysis of 18 previous studies, which indicated that passive smoking increases the risk of coronary heart disease by 1·25.[18]

Tobacco use is one of the most important causes of AMI globally, especially in men. Among smokers, even low levels of smoking (about eight to ten cigarettes per day) increase the risk of AMI two-fold. The excess risk of AMI increases with all forms of tobacco smoking, including inhalation of SHS. Chewing tobacco, which is increasingly being promoted as a safe alternative to smoking, is also harmful, and the risk of AMI is even

higher in those who chew and smoke tobacco. Since the risks of AMI associated with smoking dissipate substantially after smoking cessation, public-health efforts to prevent people from starting the habit, and promote quitting in current smokers, will have a large impact in prevention of AMI worldwide.

Contributors

S Yusuf initiated the INTERHEART study, and supervised its conduct, data analysis, and writing the report. K Teo coordinated the study in Canada, and had the main responsibility for writing this report. S Ounpuu coordinated the project worldwide, and reviewed and commented on drafts. Hawken did the statistical analyses, reviewed and commented on drafts. All other authors coordinated the study in their respective countries and provided comments on drafts of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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