Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study

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See **Comment**

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Summary

Background **Although more than 80% of the global burden of cardiovascular disease occurs in low-income and middle-income countries, knowledge of the importance of risk factors is largely derived from developed countries. Therefore, the effect of such factors on risk of coronary heart disease in most regions of the world is unknown.**

Methods **We established a standardised case-control study of acute myocardial infarction in 52 countries, representing every inhabited continent. 15 152 cases and 14 820 controls were enrolled. The relation of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins (Apo), and psychosocial factors to myocardial infarction are reported here. Odds ratios and their 99% CIs for the association of risk factors to myocardial infarction and their population attributable risks (PAR) were calculated.**

Findings **Smoking (odds ratio 2·87 for current *vs* never, PAR 35·7% for current and former *vs* never), raised ApoB/ApoA1 ratio (3·25 for top *vs* lowest quintile, PAR 49·2% for top four quintiles *vs* lowest quintile), history of hypertension (1·91, PAR 17·9%), diabetes (2·37, PAR 9·9%), abdominal obesity (1·12 for top *vs* lowest tertile and 1·62 for middle *vs* lowest tertile, PAR 20·1% for top two tertiles *vs* lowest tertile), psychosocial factors (2·67, PAR 32·5%), daily consumption of fruits and vegetables (0·70, PAR 13·7% for lack of daily consumption), regular alcohol consumption (0·91, PAR 6·7%), and regular physical activity (0·86, PAR 12·2%), were all significantly related to acute myocardial infarction (p<0·0001 for all risk factors and p=0·03 for alcohol). These associations were noted in men and women, old and young, and in all regions of the world. Collectively, these nine risk factors accounted for 90% of the PAR in men and 94% in women.**

Interpretation **Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions. This finding suggests that approaches to prevention can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction.**

Introduction

Worldwide, cardiovascular disease is estimated to be the leading cause of death and loss of disability-adjusted life years.[1] Although age-adjusted cardiovascular death rates have declined in several developed countries in past decades, rates of cardiovascular disease have risen greatly in low-income and middle-income countries,[1,2] with about 80% of the burden now occurring in these countries. Effective prevention needs a global strategy based on knowledge of the importance of risk factors for cardiovascular disease in different geographic regions and among various ethnic groups.

Current knowledge about prevention of coronary heart disease and cardiovascular disease is mainly derived from studies done in populations of European origin.[2] Researchers are unsure to what extent these findings apply worldwide. Some data suggest that risk factors for coronary heart disease vary between populations—eg, lipids are not associated with this disorder in south Asians,[3] and increases in blood pressure might be more important in Chinese people.[4] Even if the association of a risk factor with coronary heart disease is similar across populations, prevalence of this factor might vary, resulting in different population attributable risks (PAR)—eg, serum cholesterol might be lower in Chinese populations.[4] On the other hand, these apparent variations between ethnic populations could be attributable to differences between studies in their design and analysis, information obtained, and small sample sizes.

To clarify whether the effects of risk factors vary in different countries or ethnic groups, a large study undertaken in many countries—representing different regions and ethnic groups and using standardised methods—is needed, with the aim to investigate the relation between risk factors and coronary heart disease. Such a study could also estimate the importance of known risk factors on the PAR for acute myocardial infarction. This aim, however, needs either very large cohort trials or case-control studies with many events—eg, several thousands of cases of myocardial infarction in whom all (or most) currently

known risk factors are measured. We judged the latter most practical.

INTERHEART is a large, international, standardised, case-control study, designed as an initial step to assess the importance of risk factors for coronary heart disease worldwide (slides available at http://www.phri.ca/interheart).[5] We aimed to include about 15 000 cases and a similar number of controls from 52 countries, representing all inhabited continents. Specific objectives are to determine the strength of association between various risk factors and acute myocardial infarction in the overall study population and to ascertain if this association varies by geographic region, ethnic origin, sex, or age. A key secondary objective is to estimate the PAR for risk factors and their combinations in the overall population and in various subgroups. This report focuses on the association of nine easily measured protective or risk factors (smoking, lipids, self-reported hypertension or diabetes, obesity, diet, physical activity, alcohol consumption, and psychosocial factors) to first myocardial infarction.

See http://image.thelancet.com/extras/04art8002web.pdf

Methods

Participants

Study participants were recruited from 262 centres from 52 countries in Asia, Europe, the Middle East, Africa, Australia, North America, and South America (web-table 1; http://image.thelancet.com/extras/04art8001webtable1.pdf). The national coordinator selected centres within every country on the basis of feasibility. To identify first cases of acute myocardial infarction, all patients (irrespective of age) admitted to the coronary care unit or equivalent cardiology ward, presenting within 24 h of symptom onset, were screened. Cases were eligible if they had characteristic symptoms plus electrocardiogram changes indicative of a new myocardial infarction (webappendix 1; http://image.thelancet.com/extras/04art8001webappendix1.pdf).

At least one age-matched (up to 5 years older or younger) and sex-matched control was recruited per case, using specific criteria. Exclusion criteria for controls were identical to those described for cases, with the additional criterion that controls had no previous diagnosis of heart disease or history of exertional chest pain. The overall median interval from recruitment of cases to inclusion of controls was 1·5 months. Hospital-based controls (58%) were individuals who had a wide range of disorders unrelated to known or potential risk factors for acute myocardial infarction and were admitted to the same hospital as the matching case. Community-based controls (36%) were attendants or relatives of a patient from a non-cardiac ward or an unrelated (not first-degree relative) attendant of a cardiac patient. In the remaining controls, 3% were from an undocumented source and 3% were recruited through the WHO MONICA study.[6]

Procedures

Structured questionnaires were administered and physical examinations were undertaken in the same manner in cases and controls. Information about demographic factors, socioeconomic status (education, income), lifestyle (smoking, leisure time, physical activity, and dietary patterns), personal and family history of cardiovascular disease, and risk factors (hypertension, diabetes mellitus) was obtained. Psychosocial factors (depression, locus of control, perceived stress, and life events) were systematically recorded and integrated into one score: details are provided in the accompanying paper.[7] Height, weight, waist and hip circumferences, and heart rate were determined by a standardised protocol. Waist and hip circumferences were measured with a non-stretchable standard tape measure: waist measurements were obtained over the unclothed abdomen at the narrowest point between the costal margin and iliac crest, and hip circumferences over light clothing at the level of the widest diameter around the buttocks. Although blood pressure at the time of examination was recorded in both cases and controls, the levels in cases would be systematically affected by the myocardial infarction and treatments—eg, β blockers, nitrates, and angiotensin-converting-enzyme inhibitors—that could lower blood pressure. Therefore, only self-reported history of hypertension is used in the analysis.

Non-fasting blood samples (20 mL) were drawn from every individual and centrifuged within 2 h of admission, separated into six equal volumes, and frozen immediately at –20°C or –70°C after processing. Centres were instructed to draw blood from cases within 24 h of symptom onset. However, because of delays in patient presentation, especially in some low-income countries, blood samples could only be obtained within 24 h in two-thirds of cases. Samples were shipped in nitrogen vapour tanks by courier from every site to a blood storage site, where they were stored at –160°C in liquid nitrogen (Hamilton, Canada) or at –70°C (India and China). Blood samples from all countries other than China were analysed in Hamilton for total cholesterol, HDL cholesterol, and apolipoproteins B (ApoB) and A1 (ApoA1).

Immunoturbidimetric assays were used to measure apolipoprotein concentrations (Roche/Hitachi 917 analyser with Tina-quant ApoB version 2 and ApoA1 version 2 kits; Roche Diagnostics, Mannheim, Germany). The ApoB method was standardised against the IFCC SP3–07 reference standard[8] and the ApoA1 method against the IFCC SP1–01 reference preparation.[9] The same measurement kits and a Roche/Hitachi 911 analyser were used in Beijing, China. Both laboratories measured the same lot numbers of Precinorm and Precipath controls (Roche Diagnostics) in every run, and in every patient sample analysis run in China, two study patients and two serum reference pool samples (pool A and B) were measured that had previously been analysed

in the central core laboratory in Canada. Because apolipoprotein concentrations are not affected by the fasting status of the individual (unlike calculated LDL), we used the ApoB/ApoA1 ratio as an index of abnormal lipids in the current analysis.[10] Moreover, this ratio was predictive of myocardial infarction in subsets of patients (<12 h, 12–24 h, and >24 h after symptoms) in the present study (data not shown). Detailed information on lipoprotein fractions will be reported separately.

All data were transferred to the Population Health Research Institute, McMaster University, and Hamilton Health Sciences, Canada, where quality-control checks and statistical analyses were done. Data on smoking were missing in 1·1% of participants, hypertension in 0·6%, diabetes in 0·7%, psychosocial variables in 11%, physical activity in 1·1%, diet in 2·1%, and waist and hip measurements in 3·5%. Blood samples were available in 21 508 (79%) of 27 098 cases and controls.

INTERHEART was approved by appropriate regulatory and ethics committees in all participating countries and centres. All participants provided informed consent before taking part in the study.

We defined current smokers as individuals who smoked any tobacco in the previous 12 months and included those who had quit within the past year. Former smokers were defined as those who had quit more than a year earlier. For waist/hip ratio, tertiles were calculated separately for men and women based on the overall control data. The cutoffs used were 0·90 and 0·95 in men and 0·83 and 0·90 in women, to divide participants into thirds. Cutoffs for ApoB/ApoA1 ratios (deciles and quintiles) were derived from all controls (men and women). Region-specific cutoffs did not alter the results. Individuals were judged to be physically active if they were regularly involved in moderate (walking, cycling, or gardening) or strenuous exercise (jogging, football, and vigorous swimming) for 4 h or more a week. Regular alcohol use was defined as consumption three or more times a week. The combined psychosocial index was devised with a combination of the parameter estimates from the completely adjusted multivariate logistic regression model. The score was based on a combination of depression versus none, stress at work or at home (general stress variable) versus none, moderate or severe financial stress versus minimal or none, one or more life events versus none, and a locus of control score in the lower three quartiles versus the top quartile of the distribution.

Statistical analysis

Simple associations were assessed with frequency tables and Pearson's χ^2 tests for two independent proportions. For comparison of prevalence across distinct subgroups—eg, by region, country, or ethnic group—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 factor (<45, 46–55, 56–65, 66–70, >70).[11] Means and medians were calculated to summarise continuous effects and were compared by *t* tests or appropriate non-parametric tests when distributional assumptions were in doubt. When data have been categorised by tertiles, quintiles, or deciles, these were based on the overall control data. For waist/hip ratio, sex-specific cutoffs were used. For protective factors (exercise, diet, and alcohol), the PAR is calculated for the group without the exposure.

The findings presented are for models fitted with unconditional logistic regression, adjusted for the matching criteria, for two reasons. First, unmatched analyses were used because for 14% (1763/12461) of cases of myocardial infarction and 5% (738/14637) of controls, perfect matching was not possible. Undertaking a strict matched analysis would mean relevant loss of information because of the exclusion of these participants. Moreover, when data on a risk factor were missing in a case or control, the entire pair would be excluded from all analyses. Therefore, we widened the age-matching criteria and used frequency matching of cases and controls, using age and sex strata. Second, there was general agreement for key results among the many methods compared (conditional logistic regression, mixed models, and unconditional logistic regression, with adjustment for matching criteria). Estimated odds ratios and CIs calculated with the different methods were within 5% of each other, with a slight attenuation of effect estimates in the unconditional versus conditional models (webtable 2; http://image.thelancet.com/extras/04art8001webtable2.pdf).[11] Hence, findings presented are adjusted for age, sex, geographic region, and potential confounders, and should be interpreted as providing a slight underestimation of effect sizes for most comparisons.

Adjusted odds ratios for combinations of risk factors can be derived from their respective model coefficients in the multivariate logistic model. By summation of model coefficients and taking the antilog (panel) the combined effect of combinations of exposures can be estimated. Estimates of odds ratios and accompanying 99% CIs are presented for every risk factor and their combinations. Statistical analyses and graphics were produced with SAS version 8.2 (SAS, Cary, NC, USA) and S-Plus version 6 (Insightful, Seattle, WA, USA). All statistical tests of hypotheses are two-sided. PARs and 99% CIs were calculated for various risk factors in the study by a method based on unconditional logistic regression.[12] The PARs presented are adjusted for confounders in a similar manner to the corresponding logistic regression models for odds ratio estimates and, where indicated, are stratified by subgroups of interest. PAR estimates were calculated by the interactive risk attributable program software (US National Cancer Institute, 2002).[13]

For a simple dichotomous exposure and disease, and no adjustment for confounding, the usual formula for PAR was used (panel).[12] PAR adjusted for confounding

Panel: **Formulae**

Antilog $e^{(\Sigma\beta_i)}$

PAR $$\frac{Pr(E)(R-1)}{Pr(E)(R-1)+1}$$

where Pr(*E*) is probability of exposure to the risk factor and *R* is the relative risk of the disease in exposed versus unexposed individuals.

PAR adjusted for confounding

$$1-\sum_{i=1}^{I}\sum_{j=1}^{J}\rho_{ij}R_{ij}^{-1}$$

where

$$R_{ij}=\frac{Pr(D=1|X=x_i,C=c_j)}{Pr(D=1|X=x_1,C=c_j)}$$

and

$$\rho_{ij}=Pr\,(X=x_i,C=c_j|D=1)$$

X is the exposure level, C is the confounder level, and D is disease status (D=0, disease is absent; D=1, disease is present).

	Cases (n=12 461)	Controls (n=14 637)
Geographic region		
Western Europe	664	767
Central and eastern Europe	1727	1927
Middle East	1639	1786
Africa	578	789
South Asia	1732	2204
China and Hong Kong	3030	3056
Southeast Asia and Japan	969	1199
Australia and New Zealand	589	681
South America and Mexico	1237	1888
North America	296	340
Ethnic origin		
European	3314	3710
Chinese	3130	3167
South Asian	2171	2573
Other Asian	871	1073
Arab	1306	1479
Latin American	1141	1834
Black African	157	369
Coloured African	311	339
Other	60	93

Table 1: **Distribution of study population**

is also shown in the panel. For variance estimates, the reader is referred to Benichou and Gail[15] since the derivations and formulae are complex. CI calculations were based on this method using a logit transformation approach, apart from when PAR estimates were negative, in which case conventional Wald type CIs were used.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between February, 1999, and March, 2003, 15 152 cases and 14 820 controls were enrolled. 1531 cases were diagnosed as having unstable angina, 260 had insufficient data, 205 did not have coronary artery disease, and 695 had a previous myocardial infarction. For 74 controls data were missing and 109 had previous coronary heart disease. Therefore, 12 461 cases and 14 637 controls are included in the analysis. Table 1 shows the distribution of participants by region and ethnic origin. 9459 cases (76%) and 10 851 controls (74%) were male.

Table 2 shows the median age of presentation of cases. The overall median age of cases with first acute myocardial infarction is about 9 years lower in men than in women in all regions of the world. However, the proportion of male cases was highest in countries with a younger age of presentation of acute myocardial infarction—eg, 85% of cases in south Asia and 86% in the Middle East were male compared with 74% in western Europe, 68% in central and eastern Europe, and 70% in China. Among regions, striking variations were noted in the age of first presentation of acute myocardial infarction, with the youngest patients in south Asia (median age 53 years) and the Middle East (51 years), and the oldest patients in western Europe, China, and Hong Kong (63 years). The highest proportion of cases with first acute myocardial infarction at age 40 years or younger was in men from the Middle East (12·6%), Africa (10·9%), and south Asia (9·7%) and the lowest proportion was in women from China and Hong Kong (1·2%), South America (1·0%), and central and eastern Europe (0·9%).

Overall effect of risk factors

Table 3 provides the overall odds ratios for individual risk factors adjusted for age, sex, smoking status, and region and by multivariate adjustment for all risk factors. All risk factors were significantly ($p<0·0001$) related to acute myocardial infarction, except alcohol, which had a weaker association ($p=0·03$). After multivariate analysis, current smoking and raised ApoB/ApoA1 ratio (top *vs* lowest quintile) were the two strongest risk factors, followed by history of diabetes, hypertension, and psychosocial factors (table 3). Body-mass index was related to risk of myocardial infarction, but this relation was weaker than that of abdominal obesity (waist/hip ratio), with body-mass index becoming non-significant with the inclusion of waist/hip ratio in the multivariate model (data not shown). Before multivariate adjustment, abdominal obesity (top *vs* lowest tertile) doubled the risk of acute myocardial infarction, but the effects were substantially diminished after adjustment for other risk factors, especially apolipoproteins. Daily consumption of fruits or vegetables, moderate or strenuous physical exercise, and consumption of alcohol three or more times per week, were protective (table 3).

	Overall			Men			Women		
	Number	Median age (IQR)	% <40 years (n)	Number	Median age (IQR)	% <40 years (n)	Number	Median age (IQR)	% <40 years (n)
Geographic region									
Western Europe	664	63 (54–72)	2·7 (18)	493	61 (53–70)	2·8 (14)	171	68 (59–76)	2·3 (4)
Central and eastern Europe	1727	62 (52–70)	2·9 (51)	1173	59 (50–68)	3·9 (46)	554	68 (59–74)	0·9 (5)
North America	296	59 (50–71)	4·0 (12)	210	58 (49–68)	3·3 (7)	86	64 (52–75)	5·8 (5)
South America and Mexico	1237	60 (51–70)	3·4 (42)	926	59 (50–68)	4·2 (39)	311	65 (56–73)	1·0 (3)
Australia and New Zealand	589	60 (51–69)	5·3 (31)	464	58 (50–67)	5·6 (26)	125	66 (59–74)	4·0 (5)
Middle East	1639	51 (45–59)	11·2 (184)	1410	50 (44–57)	12·6 (177)	229	57 (50–65)	3·1 (7)
Africa	578	54 (47–62)	9·7 (56)	385	52 (46–61)	10·9 (42)	193	56 (49–65)	7·3 (14)
South Asia	1732	53 (46–61)	8·9 (54)	1480	52 (45–60)	9·7 (143)	252	60 (50–66)	4·4 (11)
China and Hong Kong	3030	63 (53–70)	4·5 (135)	2131	60 (50–68)	5·8 (124)	899	67 (62–72)	1·2 (11)
Southeast Asia and Japan	969	57 (49–65)	7·0 (68)	787	55 (47–64)	8·3 (65)	182	63 (56–68)	1·7 (3)
Ethnic origin									
European	3314	62 (52–71)	3·2 (107)	2371	59 (51–69)	3·8 (89)	943	68 (58–75)	1·9 (18)
Chinese	3130	63 (53–70)	4·4 (139)	2217	60 (50–68)	5·8 (128)	913	67 (61–72)	1·2 (11)
South Asian	2171	52 (45–60)	10·6 (231)	1889	50 (45–60)	11·7 (220)	282	60 (51–66)	3·9 (11)
Other Asian	871	57 (48–65)	7·0 (61)	705	55 (47–64)	8·2 (58)	166	63 (56–68)	1·8 (3)
Arab	1306	53 (46–60)	9·0 (118)	1083	52 (45–59)	10·3 (111)	223	57 (50–65)	3·1 (7)
Latin American	1141	60 (51–69)	3·7 (42)	854	58 (50–67)	4·5 (38)	287	64 (55–72)	1·4 (4)
Black African	157	52 (46–61)	14·0 (22)	98	52 (46–59)	17·4 (17)	59	54 (48–67)	8·5 (5)
Coloured African	311	54 (47–63)	8·7 (27)	196	52 (46–62)	9·7 (19)	115	58 (49–65)	7·0 (8)
Other	60	57 (48–64)	6·7 (4)	46	53 (48–62)	6·5 (3)	14	63 (59–73)	7·1 (1)
Overall	12 461	58 (49–67)	6·0 (751)	9459	56 (48–65)	7·2 (683)	3002	65 (56–72)	2·3 (68)

Table 2: **Median age (years) of presentation of cases**

A strong and graded relation was noted between numbers smoked and risk of myocardial infarction, with the risk increasing at every increment, so that individuals smoking greater than 40 cigarettes per day had an odds ratio of 9·16 (99% CI 6·18–13·58; figure 1). The ApoB/ApoA1 ratio also showed a graded relation with myocardial infarction risk, with no evidence of a threshold, with an odds ratio of 4·73 (99% CI 3·93–5·69) for the top versus the lowest decile of ApoB/ApoA1 ratio (figure 1).

Cumulative effect of risk factors

Figure 2 shows the effect of multiple risk factors on increased risk of myocardial infarction. Together, current smoking, hypertension, and diabetes increased the odds ratio for acute myocardial infarction to 13·01 (99% CI 10·69–15·83) compared to those without these risk factors, and they accounted for 53% of the PAR of acute myocardial infarction. Addition of ApoB/ApoA1 ratio (top *vs* lowest quintile) increased the odds ratio to

	Prevalence		Odds ratio (99% CI) adjusted for age, sex, and smoking (OR 1)	PAR (99% CI)	Odds ratio (99% CI) adjusted additionally for all other risk factors (OR 2)	PAR 2 (99% CI)
	Controls (%)	Cases (%)				
Risk factor						
Current smoking*	26·76	45·17	2·95 (2·72–3·20)	–	2·87 (2·58–3·19)	–
Current and former smoking*	48·12	65·19	2·27 (2·11–2·44)	36·4% (33·9–39·0)	2·04 (1·86–2·25)	35·7% (32·5–39·1)
Diabetes	7·52	18·45	3·08 (2·77–3·42)	12·3% (11·2–13·5)	2·37 (2·07–2·71)	9·9% (8·5–11·5)
Hypertension	21·91	39·02	2·48 (2·30–2·68)	23·4% (21·7–25·1)	1·91 (1·74–2·10)	17·9% (15·7–20·4)
Abdominal obesity (2 *vs* 1)†	33·40	30·21	1·36 (1·24–1·48)	–	1·12 (1·01–1·25)	–
Abdominal obesity (3 *vs* 1)†	33·32	46·31	2·24 (2·06–2·45)	33·7% (30·2–37·4)	1·62 (1·45–1·80)	20·1% (15·3–26·0)
All psychosocial‡	–	–	2·51 (2·15–2·93)	28·8% (22·6–35·8)	2·67 (2·21–3·22)	32·5% (25·1–40·8)
Vegetables and fruit daily*	42·36	35·79	0·70 (0·64–0·77)	12·9% (10·0–16·6)	0·70 (0·62–0·79)	13·7% (9·9–18·6)
Exercise*	19·28	14·27	0·72 (0·65–0·79)	25·5% (20·1–31·8)	0·86 (0·76–0·97)	12·2% (5·5–25·1)
Alcohol intake*	24·45	24·01	0·79 (0·73–0·86)	13·9% (9·3–20·2)	0·91 (0·82–1·02)	6·7% (2·0–20·2)
ApoB/ApoA1 ratio (2 *vs* 1)§	19·99	14·26	1·47 (1·28–1·68)	–	1·42 (1·22–1·65)	–
ApoB/ApoA1 ratio (3 *vs* 1)§	20·02	18·05	2·00 (1·74–2·29)	–	1·84 (1·58–2·13)	–
ApoB/ApoA1 ratio (4 *vs* 1)§	19·99	24·22	2·72 (2·38–3·10)	–	2·41 (2·09–2·79)	–
ApoB/ApoA1 ratio (5 *vs* 1)§	20·00	33·49	3·87 (3·39–4·42)	54·1% (49·6–58·6)	3·25 (2·81–3·76)	49·2% (43·8–54·5)
All above risk factors combined¶	–	–	129·20 (90·24–184·99)	90·4% (88·1–92·4)	129·20 (90·24–184·99)	90·4% (88·1–92·4)

The median waist /hip ratio was 0·93 in cases and 0·91 in controls (p<0·0001), and the median ApoB/ApoA1 ratio was 0·85 in cases and 0·80 in controls (p<0·0001). Percentage of controls with four or five factors positive is 22·2% compared with 29·2% in cases. *PARs for smoking, abdominal obesity, and ApoB/ApoA1 ratio are based on a comparison of all smokers *vs* never, top two tertiles *vs* lowest tertile, and top four quintiles *vs* lowest quintile. For protective factors (diet, exercise, and alcohol), PARs are provided for the group without these factors. †Top two tertiles *vs* lowest tertile. ‡A model-dependent index combining positive exposure to depression, perceived stress at home or work (general stress), low locus of control, and major life events, all referenced against non-exposure for all five factors. §Second, third, fourth, or fifth quintiles *vs* lowest quintile. ¶The model is saturated, so adjusted and unadjusted estimates are identical for all risk factors. The odds ratio of 129·20 is derived from combining all risk factors together, including current and former smoking *vs* never smoking, top two tertiles *vs* lowest tertile of abdominal obesity, and top four quintiles *vs* lowest quintile of ApoB/ApoA1. If, however, the model includes only current smoking *vs* never smoking, the top *vs* lowest tertile for abdominal obesity, and the top *vs* lowest quintile for ApoB/ApoA1, the odds ratio for the combined risk factors increases to 333·7 (99% CI 230·2–483·9).

Table 3: **Risk of acute myocardial infarction associated with risk factors in the overall population**

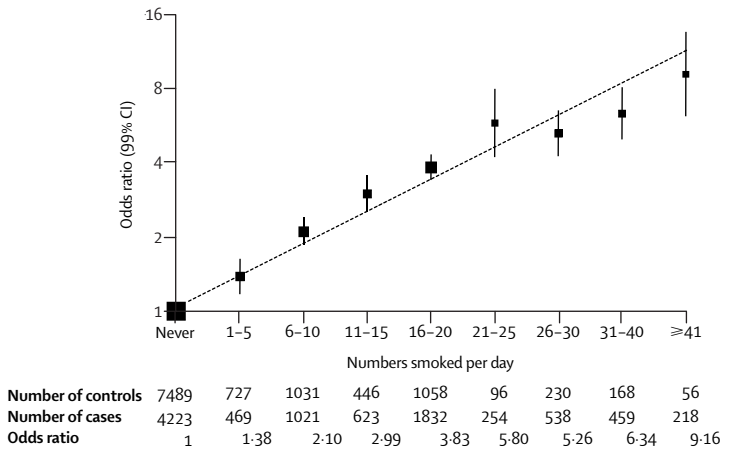


Figure 1: **Odds of myocardial infarction according to number of cigarettes smoked and ApoB/ApoA1 ratio**
Note the doubling scale on the y axis for both figures.

42·3 (33·2–54·0), and the PAR for these four risk factors together (top four quintiles of ApoB/ApoA1 ratio *vs* lowest quintile) was 75·8% (99% CI 72·7–78·6). Addition of abdominal obesity (top two tertiles *vs* lowest tertile) further increased the PAR to 80·2% (77·5–82·7).

Figure 3 shows the effects of multiple risk factors on reduced risk of acute myocardial infarction associated with healthy lifestyles. Daily consumption of fruit and vegetables and regular physical activity conferred an odds ratio of 0·60 (99% CI 0·51–0·71). Further, if an individual avoided smoking, the odds ratio would be 0·21 (0·17–0·25; figure 3), suggesting that modification of these aspects of lifestyle could potentially reduce the risk of an acute myocardial infarction by more than three-quarters compared with a smoker with a poor lifestyle.

Incorporation of all nine independent risk factors (current or former smoking, history of diabetes or hypertension, abdominal obesity, combined psychosocial stressors, irregular consumption of fruits and vegetables, no alcohol intake, avoidance of any regular exercise, and raised plasma lipids) indicates an odds ratio of 129·20 (99% CI 90·24–184·99; table 3), compared with not having any of these risk factors. Substituting the odds ratios for current smoking, the extremes of abdominal obesity (top *vs* lowest tertile) and ApoB/ApoA1 ratio (top *vs* lowest quintile) increases the combined effect of all nine risk factors to 333·7 (99% CI 230·2–483·9; figure 2). This represents a PAR of 90·4% (99% CI 88·1–92·4), suggesting that these risk factors account for most of the risk of acute myocardial infarction in our study population. In view of the overlap in the effect of the nine risk factors, most of the PAR could be accounted for by a combination of various risk factors, as long as they included smoking and the ApoB/ApoA1 ratio (PAR for their combination is 66·8% [99% CI 62·8–70·6]). The estimate of the combined effect of all nine risk factors is derived from a model, since very few individuals had zero risk factors or all nine risk factors. However, confidence that the majority of risk is indeed accounted for by these risk factors is lent support by the fact that of the 18 708 individuals with complete data on all risk factors, 43 controls and 24 cases had no risk factors and 49 cases and 11 controls had eight or more. Also, just five risk factors (smoking, lipids, hypertension, diabetes, and obesity), which a large proportion of individuals had, accounted for about 80% of the PAR.

Risk in men and women

Figure 4 presents odds ratios and PARs for risk of acute myocardial infarction in men and women. Similar odds ratios were recorded in women and men for the association of acute myocardial infarction with smoking, raised lipids, abdominal obesity, composite of psychosocial variables, and vegetable and fruit consumption. However, the increased risk associated with hypertension and diabetes, and the protective effect of exercise and alcohol, seemed to be greater in women then in men (figure 4).

Table 4 also shows PARs by sex for the various risk factors, adjusted for age and region only and the fully adjusted model. In men, smoking was associated with 42·7% of the PAR for acute myocardial infarction compared with 14·8% in women in the fully adjusted model. Abnormal lipids had the highest PAR in both men (49·5%) and women (47·1%), with high contributions from psychosocial risk factors (28·8% *vs* 45·2%) and abdominal obesity (19·7% *vs* 18·7%). Hypertension contributed to PAR in women to a greater extent (29·0%) compared with men (14·9%), partly because of a higher prevalence of hypertension in women who were about a decade older. Collectively, all nine risk factors accounted for 90% of the PAR in men and 94% in women (table 4).

Risk by age

Smoking, adverse lipid profile, hypertension, and diabetes had a greater relative effect on risk of acute myocardial infarction in younger than older individuals (table 5). Overall, abnormal lipids was the most important risk factor with respect to PAR in both young and old individuals (table 5). Collectively, the nine risk factors accounted for a significantly greater (p<0·0001) PAR in younger than older individuals; these patterns were consistent in males and females.

Regional and ethnic variations in importance of risk factors

When the odds ratio (adjusted for age, sex, smoking, and geographic region) for association of acute myocardial infarction with a risk factor is around 2 or more, eg, for smoking, lipids, hypertension, diabetes, abdominal obesity, and the combined psychosocial index, subgroup analyses are likely to be fairly robust. We recorded a clear, significant, and consistent excess risk of acute myocardial infarction associated with these risk factors in most regions of the world and in every ethnic group (figures 5–10). By contrast, when odds ratios were weaker (0·70–1·50; alcohol consumption, exercise, or diet), greater variability was noted across regions (data not shown). This apparent variability could be attributable to chance, because subgroup analyses are likely to be less reliable when smaller overall differences are subdivided across multiple subsets of the populations. Similar results were noted for analyses across various subgroups defined by ethnic origin, with consistent and clear excess risks being reported for tobacco use, abnormal lipids, history of hypertension, diabetes, and abdominal obesity (data not shown).

Population attributable risk by geographic region

Table 4 also presents overall PARs and values by sex across different geographic regions. In all regions, the nine risk factors account for between three-quarters and virtually all the PAR for acute myocardial infarction. The relative importance of every risk factor varied, and was largely related to its prevalence. However, raised lipids, smoking, and psychosocial factors were the most important risk factors in all regions in the world. It is noteworthy that in western Europe, North America, and Australia and New Zealand (representing high-income countries) and southeast Asia (mostly middle-income countries), abdominal obesity was associated with a PAR greater than that associated with smoking. A similar pattern was seen for Africa, but most of our data are drawn from South Africa, which is a middle-income country. However, obesity was less important in other parts of the world, where it is less prevalent. For example, obesity accounted for only 5·5% of the PAR in China compared with 35·8% for smoking (where 41% of male and 4% of female controls smoked). Subdividing the population by ethnic origin, these nine risk factors accounted for a very high proportion of the PAR in every ethnic group (Europeans, 86%; Chinese, 90%; south Asians, 92%; black Africans, 92%; Arabs, 93%; and Latin Americans, 90%).

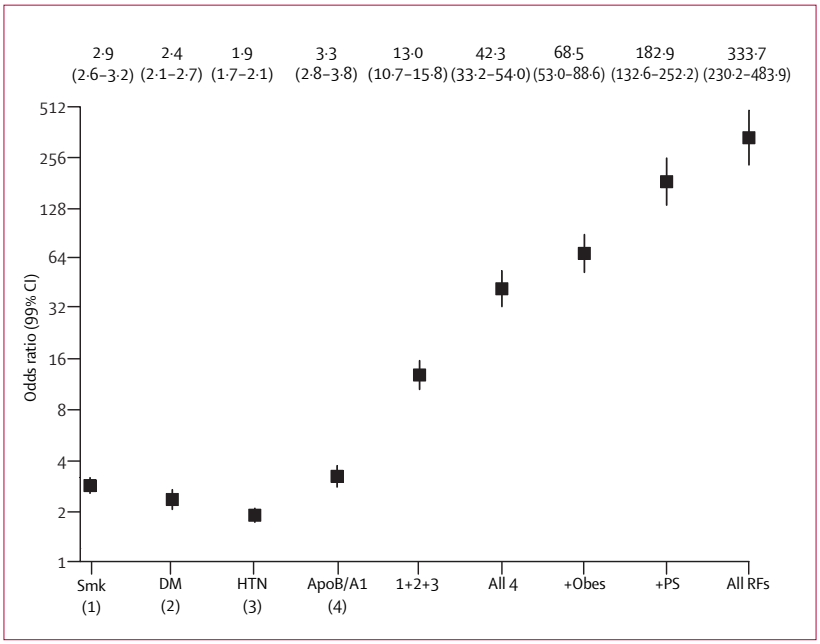


Figure 2: **Risk of acute myocardial infarction associated with exposure to multiple risk factors**
Smk=smoking. DM=diabetes mellitus. HTN=hypertension. Obes=abdominal obesity. PS=psychosocial. RF=risk factors. Note the doubling scale on the y axis. The odds ratios are based on current *vs* never smoking, top *vs* lowest tertile for abdominal obesity, and top *vs* lowest quintile for ApoB/ApoA1. If these three are substituted by current and former smoking, top two tertiles for abdominal obesity and top four quintiles for ApoB/ApoA1, then the odds ratio for the combined risk factor is 129·20 (99% CI 90·24–184·99).

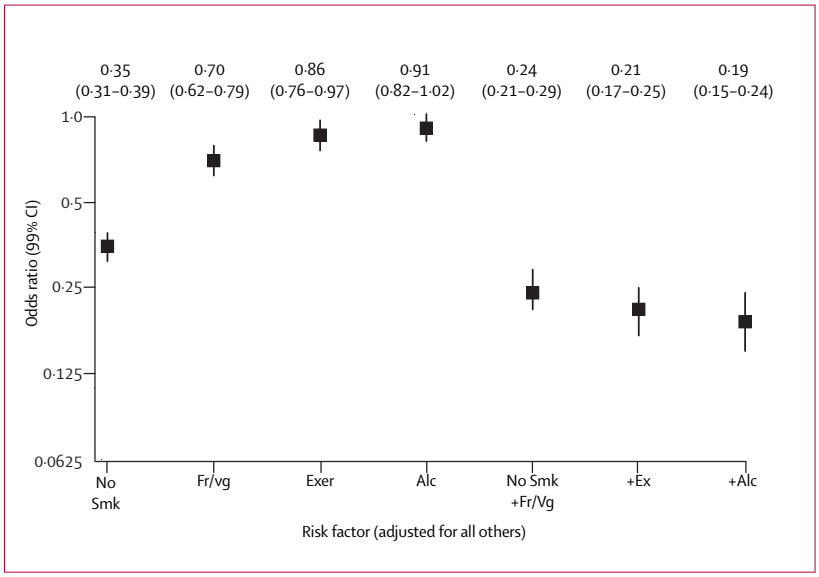


Figure 3: **Reduced risk of acute myocardial infarction associated with various risk factors**
Smk=smoking. Fr/vg=fruits and vegetables. Exer=exercise. Alc=alcohol. Note the doubling scale on the y axis. Odds ratios are adjusted for all risk factors.

Risk factor	Sex	Control (%)	Case (%)	Odds ratio (99% CI)	PAR (99% CI)
Current smoking	F	9·3	20·1	2·86 (2·36–3·48)	15·8% (12·9–19·3)
	M	33·0	53·1	3·05 (2·78–3·33)	44·0% (40·9–47·2)
Diabetes	F	7·9	25·5	4·26 (3·51–5·18)	19·1% (16·8–21·7)
	M	7·4	16·2	2·67 (2·36–3·02)	10·1% (8·9–11·4)
Hypertension	F	28·3	53·0	2·95 (2·57–3·39)	35·8% (32·1–39·6)
	M	19·7	34·6	2·32 (2·12–2·53)	19·5% (17·7–21·5)
Abdominal obesity	F	33·3	45·6	2·26 (1·90–2·68)	35·9% (28·9–43·6)
	M	33·3	46·5	2·24 (2·03–2·47)	32·1% (28·0–36·5)
Psychosocial index	F	–	–	3·49 (2·41–5·04)	40·0% (28·6–52·6)
	M	–	–	2·58 (2·11–3·14)	25·3% (18·2–34·0)
Fruits/veg	F	50·3	39·4	0·58 (0·48–0·71)	17·8% (12·9–24·1)
	M	39·6	34·7	0·74 (0·66–0·83)	10·3% (6·9–15·2)
Exercise	F	16·5	9·3	0·48 (0·39–0·59)	37·3% (26·1–50·0)
	M	20·3	15·8	0·77 (0·69–0·85)	22·9% (16·9–30·2)
Alcohol	F	11·2	6·3	0·41 (0·32–0·53)	46·9% (34·3–60·0)
	M	29·1	29·6	0·88 (0·81–0·96)	10·5% (6·1–17·5)
ApoB/ApoA1 ratio	F	14·1	27·0	4·42 (3·43–5·70)	52·1% (44·0–60·2)
	M	21·9	35·5	3·76 (3·23–4·38)	53·8% (48·3–59·2)

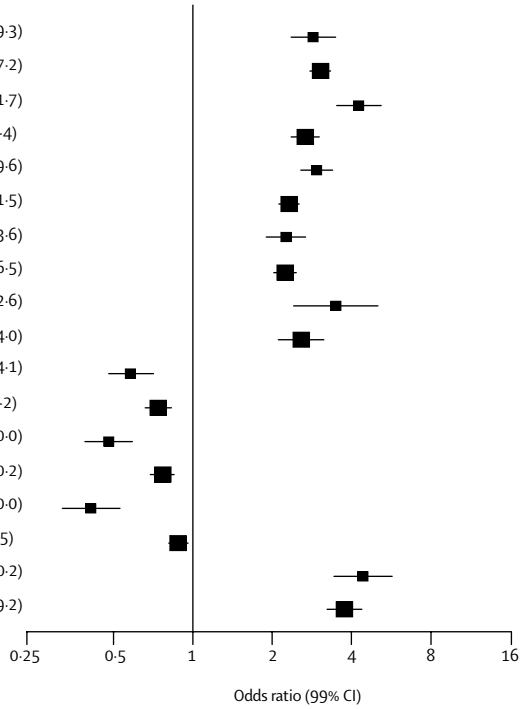


Figure 4: **Association of risk factors with acute myocardial infarction in men and women after adjustment for age, sex, and geographic region**
For this and subsequent figures, the odds ratios are plotted on a doubling scale. Prevalence cannot be calculated for psychosocial factors because it is derived from a model.

Consistency of results

Subgroup analyses with both types of controls (hospital-based and community-based) showed consistent odds ratios for current smoking (hospital-based 3·1 *vs* community-based 2·8), for the top quintile versus lowest quintile of lipids (4·2 *vs* 3·9), for diabetes (2·7 *vs* 3·4), for hypertension (2·1 *vs* 3·0), for abdominal obesity (1·7 *vs* 1·9), for psychosocial factors (1·6 *vs* 1·5), for consumption of fruits (0·78 *vs* 0·93) and vegetables (0·78 *vs* 0·83), for regular physical activity (0·79 *vs* 0·79), and for alcohol use (0·79 *vs* 0·86).

583 cases of acute myocardial infarction subsequently died in hospital. Odds ratios for fatal myocardial infarction associated with various risk factors were similar to those overall—smoking (2·1 for fatal myocardial infarction *vs* 3·0 overall), diabetes (4·0 *vs* 3·1), hypertension (2·4 *vs* 2·5), abdominal obesity (1·5 *vs* 2·2), and lipids (2·6 *vs* 3·9).

Family history

Family history of coronary heart disease was associated with an odds ratio of 1·55 (99% CI 1·44–1·67), adjusted for age, sex, smoking, and geographic region. Adjustments for the nine previously described risk factors slightly reduced the odds ratio to 1·45 (1·31–1·60). The PAR was 12·0% (99% CI 9·2%–15·1%), which fell to 9·8% (7·6–12·5) after full adjustment. However, when family history is added to the information from other nine risk factors, the overall PAR rose from 90·4% to only 91·4%, indicating that although family history is an independent risk factor for myocardial infarction, most of the associated risk burden can be accounted for through the other risk factors studied. Family history seemed to be slightly more important in young (PAR 14·8% [11·7–18·5]) compared with old individuals (10·4% [8·3–13·0]).

Repeat measures

Repeat measures of risk factors were made in 279 controls at a median interval of 409 days. The agreement rates for smoking (Cohen's kappa[16] κ=0·94), history of diabetes (κ=0·90), ApoB/ApoA1 (intraclass correlation=0·74), hypertension (κ=0·82), depression (κ=0·44), abdominal obesity (intraclass correlation=0·68), regular physical activity (κ=0·56), and consumption of fruits (κ=0·66), vegetables (κ=0·52), and alcohol (κ=0·52) were high to moderate. These data suggest that the association of myocardial infarction with smoking and diabetes is closer to the real effect, whereas the association of other risk factors measured with greater variability are probably underestimates due to regression-dilution bias.[17]

Region	Lifestyle factors					Other risk factors					
	Smoking (%)	Fruits and vegetables (%)	Exercise (%)	Alcohol (%)	All lifestyles (%)	Hypertension (%)	Diabetes (%)	Abdominal obesity (%)	All psychosocial (%)	Lipids (%)	All nine risk factors (%)
Men											
Western Europe	39·0	13·3	37·7	14·1	69·6	20·5	12·8	68·6	23·7	36·7	92·0
Central and eastern Europe	40·4	7·6	−0·4	10·4	48·9	15·9	5·8	31·7	−0·9	38·7	71·9
Middle East	51·4	5·8	1·9	−2·7	50·7	5·8	13·1	23·9	37·2	72·7	94·8
Africa	45·2	−4·4	15·9	24·1	63·7	26·8	11·6	60·4	33·8	73·7	97·9
South Asia	42·0	16·0	25·5	−5·7	58·1	17·8	10·5	36·0	13·9	60·2	88·4
China	45·3	15·1	16·6	4·2	63·7	19·9	7·9	4·9	32·0	41·3	88·8
Southeast Asia and Japan	39·2	8·5	31·4	24·6	69·6	34·3	19·1	57·9	26·9	68·7	93·7
Australia and New Zealand	46·1	8·0	20·6	11·2	61·0	18·3	5·6	49·5	31·6	48·7	87·5
South America	42·4	7·1	27·6	−7·4	57·7	28·1	9·7	35·2	36·1	41·6	86·1
North America	30·9	22·4	24·7	6·6	53·9	13·9	6·1	64·7	63·7	60·0	100
Overall 1	44·0	10·3	22·9	10·5	63·8	19·5	10·1	32·1	25·3	53·8	89·8*
Overall 2	42·7	11·7	9·3	5·1	56·5	14·9	8·0	19·7	28·8	49·5	89·8*
Women											
West Europe	11·1	8·4	38·3	34·2	65·2	25·9	21·0	50·6	67·1	47·9	97·1
Central and eastern Europe	13·1	12·8	42·7	29·9	65·4	42·7	15·7	20·0	15·0	26·8	86·1
Middle East	8·1	15·9	39·1	59·0	80·3	30·1	30·3	38·9	77·4	63·3	99·4
Africa	27·6	21·0	−37·9	28·8	61·2	35·1	27·5	54·6	54·9	74·6	93·3
South Asia	7·1	30·6	45·0	26·0	59·8	28·9	20·5	48·7	29·2	52·1	99·3
China	12·5	23·6	33·5	35·8	78·6	27·6	15·0	6·3	43·2	48·3	93·6
Southeast Asia and Japan	14·8	19·9	32·8	69·5	84·5	56·3	29·2	58·0	27·0	64·5	96·5
Australia and New Zealand	40·7	15·8	33·6	47·4	80·0	37·0	11·7	67·2	17·2	14·9	†
South America	25·8	5·9	27·4	44·1	71·8	47·9	22·2	63·0	37·8	59·3	96·1
North America	25·3	12·8	27·2	73·3	86·9	30·2	12·4	44·5	32·7	32·2	†
Overall 1	15·8	17·8	37·3	46·9	75·0	35·8	19·1	35·9	40·0	52·1	94·1*
Overall 2	14·8	19·1	27·1	22·1	60·6	29·0	16·1	18·7	45·2	47·1	94·1*
Men and women											
West Europe	29·3	12·4	38·4	18·7	67·6	21·9	15·0	63·4	38·9	44·6	93·9
Central and eastern Europe	30·2	10·2	11·3	12·9	49·6	24·5	9·1	28·0	4·9	35·0	72·5
Middle East	45·5	7·3	4·2	−1·0	47·6	9·2	15·5	25·9	41·6	70·5	95·0
Africa	38·9	4·8	10·1	26·6	63·4	29·6	16·7	58·4	40·0	74·1	97·4
South Asia	37·4	18·3	27·1	−5·5	56·6	19·3	11·8	37·7	15·9	58·7	89·4
China	35·9	18·0	20·3	5·7	62·3	22·1	10·0	5·5	35·4	43·8	89·9
Southeast Asia and Japan	36·2	11·2	31·4	27·9	69·9	38·4	21·0	58·0	26·7	67·7	93·7
Australia and New Zealand	44·8	11·1	23·8	18·6	66·0	22·6	7·2	61·3	28·9	43·4	89·5
South America	38·3	6·6	27·6	−3·7	56·6	32·7	12·7	45·5	35·6	47·6	89·4
North America	26·1	19·8	25·6	25·5	59·9	19·0	8·0	59·5	51·4	50·5	98·7
Overall 1	36·4	12·9	25·5	13·9	62·9	23·4	12·3	33·7	28·8	54·1	90·4*
Overall 2	35·7	13·7	12·2	6·7	54·6	17·9	9·9	20·1	32·5	49·2	90·4*

PAR estimates in women in some countries are based on small numbers and so they are less reliable . Overall 1= adjusted for age, sex, and smoking, Overall 2=adjusted for all risk factors. An extended version of this table with 99% CIs is shown in webtable 3 (http://image.thelancet.com/extras/04art8001webtable3.pdf). *Saturated model, no difference between adjusted and unadjusted models. †Non-estimatable.

Table 4: **PARs associated with nine risk factors in men and women by geographic region**

Discussion

Our study shows that nine easily measured and potentially modifiable risk factors account for an overwhelmingly large (over 90%) proportion of the risk of an initial acute myocardial infarction. The effect of these risk factors is consistent in men and women, across different geographic regions, and by ethnic group, making the study applicable worldwide. The effect of the risk factors is particularly striking in young men (PAR about 93%) and women (about 96%), indicating that most premature myocardial infarction is preventable. Worldwide, the two most important risk factors are smoking and abnormal lipids. Together they account for about two-thirds of the PAR of an acute myocardial infarction. Psychosocial factors, abdominal obesity, diabetes, and hypertension were the next most important risk factors in men and women, but their relative effect varied in different regions of the world. The usual measure of obesity (body-mass index) showed a modest relation with acute myocardial infarction but was not significant when abdominal obesity was included in the analysis.

Both smoking and apolipoproteins showed a graded relation with the odds of a myocardial infarction, without either a threshold or a plateau in the dose response. In particular, smoking even five cigarettes per day increased risk. This finding suggests that there is no safe level of smoking and that if quitting is not possible, the risk of myocardial infarction associated with smoking could be significantly reduced by a reduction in the numbers smoked. The graded relation between ApoB/ApoA1 ratio across the deciles is consistent with findings of a Swedish study[10] and shows that most populations in the world (at least

	Both sexes		Men		Women	
	Young	Old	≤55 years	>55 years	≤65 years	> 65 years
Odds ratios for relative effect of risk factors (99% CI)						
Lifestyle factors						
Smoking	3·33 (2·86–3·87)	2·44* (2·10–2·84)	3·33 (2·80–3·95)	2·52 (2·15–2·96)	4·49 (3·11–6·47)	2·14 (1·35–3·39)
Fruit and vegetables	0·69 (0·58–0·81)	0·72 (0·61–0·85)	0·72 (0·59–0·88)	0·77 (0·64–0·93)	0·62 (0·44–0·87)	0·55 (0·38–0·80)
Exercise	0·95 (0·79–1·14)	0·79 (0·66–0·94)	1·02 (0·83–1·25)	0·79 (0·66–0·96)	0·74 (0·49–1·10)	0·75 (0·46–1·22)
Alcohol	1·00 (0·85–1·17)	0·85 (0·73–1·00)	1·03 (0·87–1·23)	0·86 (0·73–1·01)	0·74 (0·41–1·31)	0·83 (0·49–1·42)
All four lifestyle factors	0·20 (0·14–0·27)	0·20† (0·15–0·27)	0·23 (0·16–0·33)	0·21 (0·15–0·29)	0·07 (0·03–0·18)	0·16 (0·06–0·41)
Hypertension	2·24 (1·93–2·60)	1·72 (1·52–1·95)	1·99 (1·66–2·39)	1·72 (1·49–1·98)	2·94 (2·25–3·85)	1·82 (1·39–2·38)
Diabetes	2·96 (2·40–3·64)	2·05* (1·71–2·45)	2·66 (2·04–3·46)	1·93 (1·58–2·37)	3·53 (2·49–5·01)	2·59 (1·78–3·78)
Abdominal obesity	1·79 (1·52–2·09)	1·50 (1·29–1·74)	1·83 (1·52–2·20)	1·54 (1·30–1·83)	1·58 (1·14–2·20)	1·22 (0·88–1·70)
Psychosocial	2·87 (2·19–3·77)	2·43 (1·86–3·18)	2·62 (1·91–3·60)	2·45 (1·82–3·29)	3·92 (2·26–6·79)	2·31 (1·22–4·39)
High ApoB/ApoA1 ratio	4·35 (3·49–5·42)	2·50* (2·05–3·05)	4·16 (3·19–5·42)	2·51 (2·00–3·15)	4·83 (3·19–7·32)	2·48 (1·60–3·83)
All risk factors other than smoking	101·86 (61·22–169·46)	43·24* (26·96–69·37)	59·06 (32·25–108·14)	38·88 (22·95–65·86)	473·43 (158·34–1415·5)	67·49 (21·39–212·90)
All nine risk factors including smoking‡	216·47 (126·67–369·94)	81·99* (50·02–134·40)	129·19 (68·60–243·28)	76·25 (44·07–131·93)	1100·6§ (342·72–3534·2)	111·45 (32·59–381·12)
Population attributable risks (99% CI)						
Lifestyle factors						
Smoking	40·7% (35·9 to 45·7)	33·1% (28·9 to 37·6)	52·0% (44·9 to 59·0)	39·0% (34·0 to 44·1)	20·8% (15·7 to 26·9)	8·2% (4·1 to 15·7)
Fruit and vegetables	16·9% (10·8 to 25·3)	11·9% (7·4 to 18·4)	15·7% (8·3 to 27·8)	10·1% (5·3 to 18·2)	18·4% (10·0 to 31·5)	18·7% (10·0 to 32·1)
Exercise	7·5% (0·7 to 46·9)	13·4% (5·4 to 29·7)	0·1% (0·0 to 100·0)	12·5% (4·4 to 30·6)	24·6% (6·8 to 59·2)	23·6% (4·3 to 67·8)
Alcohol	−4·1% (−19·8 to 11·6)	11·1% (4·7 to 23·9)	−9·1% (−25·1 to 6·9)	10·5% (4·3 to 23·6)	24·9% (3·3 to 76·3)	14·6% (0·5 to 84·6)
All four lifestyle factors	52·1% (39·5 to 64·4)	54·8% (46·2 to 63·1)	55·8% (42·1 to 68·7)	57·1% (48·4 to 65·4)	63·3% (36·8 to 83·6)	51·5% (21·7 to 80·3)
Hypertension	19·2% (16·0 to 22·8)	17·0% (14·0 to 20·5)	12·8% (9·4 to 17·1)	15·7% (12·7 to 19·4)	31·9% (25·7 to 38·6)	25·4% (17·1 to 35·8)
Diabetes	12·4% (10·3 to 14·9)	8·6% (6·9 to 10·7)	8·7% (6·6 to 11·5)	7·8% (6·0 to 10·1)	19·3% (15·1 to 24·5)	13·0% (8·9 to 18·5)
Abdominal obesity	24·8% (17·2 to 34·5)	18·1% (12·2 to 26·0)	23·4% (14·4 to 35·7)	18·3% (11·9 to 27·0)	24·9% (12·4 to 43·7)	11·8% (2·1 to 46·1)
Psychosocial	43·5% (32·2 to 55·6)	25·2% (16·0 to 37·2)	39·7% (25·4 to 56·0)	23·7% (13·9 to 37·4)	53·0% (35·4 to 69·9)	30·6% (10·6 to 62·1)
High ApoB/ApoA·1 ratio	58·9% (50·9 to 66·5)	43·6% (36·6 to 50·8)	59·7% (48·6 to 70·0)	45·3% (37·5 to 53·3)	56·1% (43·7 to 67·7)	36·3% (21·8 to 53·8)
All risk factors other than smoking	89·4% (84·7 to 92·7)	81·7% (76·4 to 86·1)	85·6% (77·7 to 91·0)	80·8% (74·8 to 85·7)	95·5% (90·0 to 98·0)	86·4% (70·8 to 94·3)
All nine risk factors including smoking	93·8% (90·9 to 95·8)	87·9% (84·1 to 90·8)	93·1% (88·9 to 95·8)	88·3% (84·4 to 91·4)	96·5% (92·0 to 98·5)	87·7% (73·1 to 94·9)

*p<0·001 are only provided for the overall comparison. †These values differ slightly but appear similar because of rounding. ‡Based on combining current and former smokers *vs* never smokers, top two tertiles *vs* lowest tertile for abdominal obesity, and top four quintiles *vs* lowest quintile for ApoB/ApoA1 ratio. If, however, extreme exposures (current *vs* never, top *vs* lowest tertile for abdominal obesity, and top *vs* lowest quintile for ApoB/ApoA1 ratio) were included, the odds ratios for all risk factors for the young group increases to 756·0 and in the old group to 160·8. §Unstable estimate, should be interpreted cautiously.

Table 5: **Importance of risk factors in young and old individuals**

urban) have lipid abnormalities, which increase the risk of myocardial infarction. Since ApoB/ApoA1 ratio was the most important risk factor in all geographic regions in our study, a substantial modification of its population distribution is important for worldwide reduction of myocardial infarction. This act will probably need a concerted effort, including both population-based strategies to shift the distribution and treatments targeted at people with the greatest abnormalities.

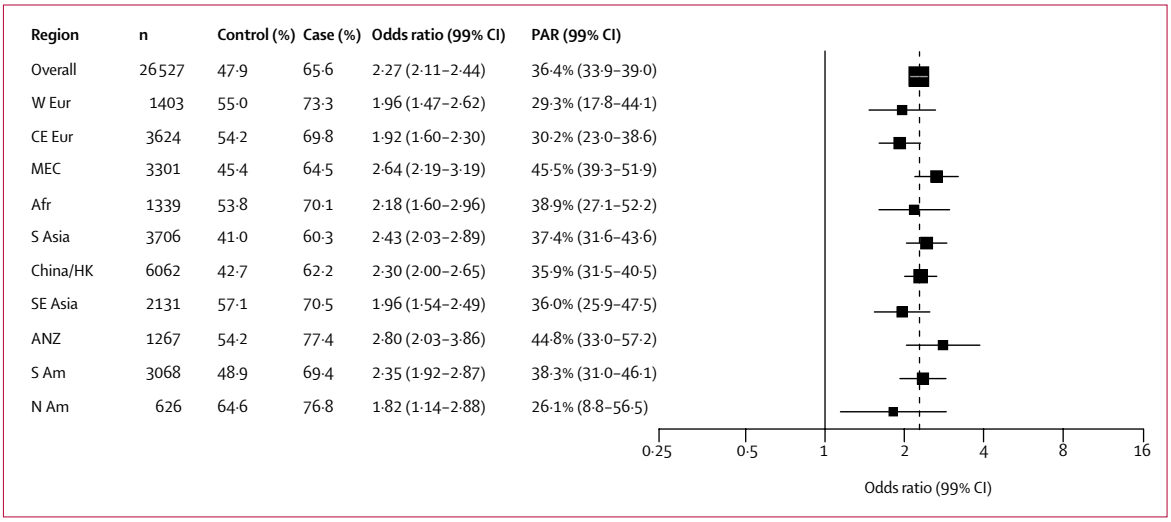


Figure 5: **Risk of acute myocardial infarction associated with current or former smoking, overall and by region after adjustment for age and sex**
W Eur=western Europe. CE Eur=central and eastern Europe. MEC=Middle East Crescent. Afr=Africa. S=South. HK=Hong Kong. SE=southeast. ANZ=Australia and New Zealand. N=North. Am=America.

Region	n	Control (%)	Case (%)	Odds ratio (99% CI)	PAR (99% CI)
Overall	21408	20·0	33·5	3·87 (3·39–4·42)	54·1% (49·6–58·6)
W Eur	1047	13·8	29·4	3·76 (2·10–6·74)	44·6% (23·5–67·8)
CE Eur	2618	20·3	29·4	2·20 (1·52–3·18)	35·0% (19·2–54·9)
MEC	3291	29·9	49·6	5·33 (3·48–8·18)	70·5% (57·8–80·7)
Afr	1037	18·0	39·0	7·93 (4·32–14·58)	74·1% (59·7–84·6)
S Asia	2820	27·7	42·7	3·81 (2·49–5·83)	58·7% (42·7–73·1)
China/HK	5400	7·3	14·3	3·43 (2·61–4·51)	43·8% (36·7–51·2)
SE Asia	1858	22·7	48·0	6·22 (3·71–10·41)	67·7% (52·0–80·2)
ANZ	487	13·8	26·8	3·97 (1·71–9·22)	43·4% (16·0–75·6)
S Am	2644	27·1	40·6	2·79 (1·85–4·23)	47·6% (29·6–66·2)
N Am	206	12·4	28·8	4·75 (1·34–16·86)	50·5% (18·2–82·4)

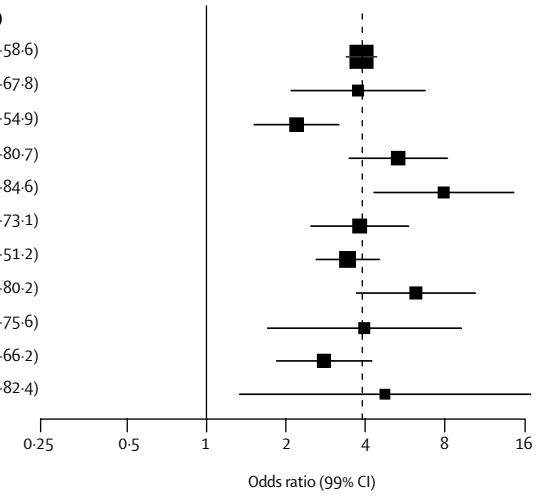


Figure 6: **Risk of acute myocardial infarction associated with ApoB/ApoA1 ratio (top *vs* lowest quintile), overall and by region after adjustment for age, sex, and smoking**
PAR is for the top four quintiles versus the lowest quintile.

Our data show that risks associated with the major risk factors (odds ratio of about 2 or greater on univariate analyses, such as smoking, abnormal lipids, psychosocial factors, hypertension, diabetes, and abdominal obesity) were consistently adverse in all regions of the world and in all ethnic groups. In particular, the odds ratios for these risk factors were qualitatively similar (although some quantitative differences were apparent), despite variations in prevalence for every risk factor in controls derived from different subpopulations. However, as expected, the PAR is affected both by the prevalence of the risk factor and the odds ratio. We are unaware of any other large study that has assessed whether risk factors have a similar or differing effect in many ethnic groups.

Our finding that most risk factors have directionally similar odds ratios in ethnic groups and countries differs from inferences reached by comparison of results of different studies, which used other methods.[3,4] Some of these researchers suggested that the effects of the major risk factors could vary qualitatively in different regions and ethnic groups, possibly because of inconsistent methodologies, differences in criteria used to recruit participants, variations in information obtained, and a fairly modest number of events in each study, thereby leading to imprecise estimates of risk that could have been exaggerated or diluted by the play of chance. Since we had more than 800 cases of acute myocardial infarction within every major ethnic group (other than black or coloured Africans), our results within most

Region	n	Control (%)	Case (%)	Odds ratio (99% CI)	PAR (99% CI)
Overall	26916	22·3	38·6	2·48 (2·30–2·68)	23·4% (21·7–25·1)
W Eur	1425	16·4	33·0	2·22 (1·62–3·05)	21·9% (15·6–30·0)
CE Eur	3636	32·7	46·0	2·11 (1·76–2·53)	24·5% (19·2–30·6)
MEC	3404	20·2	25·9	1·84 (1·45–2·33)	9·2% (5·7–14·4)
Afr	1355	21·6	43·4	3·34 (2·40–4·65)	29·6% (22·8–37·3)
S Asia	3881	13·8	31·1	2·89 (2·31–3·60)	19·3% (15·7–23·4)
China/HK	6075	21·1	37·3	2·41 (2·06–2·80)	22·1% (18·7–26·0)
SE Asia	2141	15·3	46·8	5·63 (4·26–7·45)	38·4% (33·3–43·6)
ANZ	1269	22·0	37·8	1·94 (1·40–2·68)	22·6% (15·6–31·6)
S Am	3100	27·7	49·3	2·48 (2·03–3·04)	32·7% (27·2–38·8)
N Am	630	28·6	38·8	1·58(1·01–2·47)	19·0% (9·2–35·2)

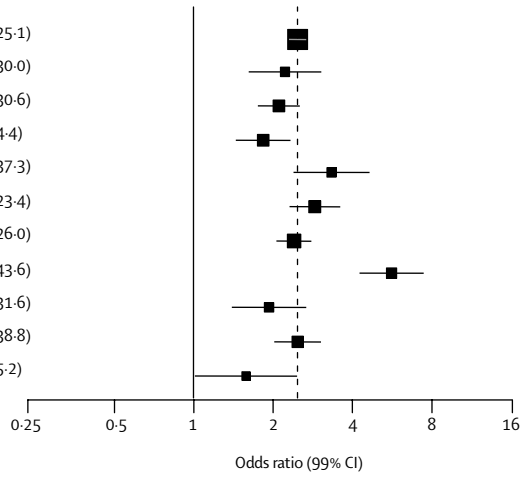
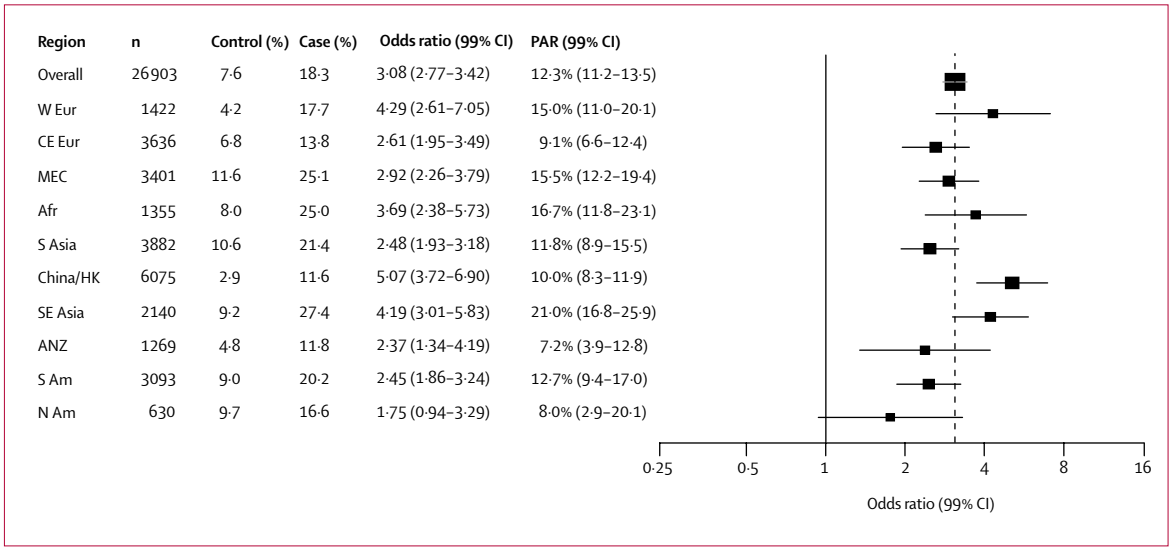


Figure 7: **Risk of acute myocardial infarction associated with self-reported hypertension, overall and by region after adjustment for age, sex, and smoking**

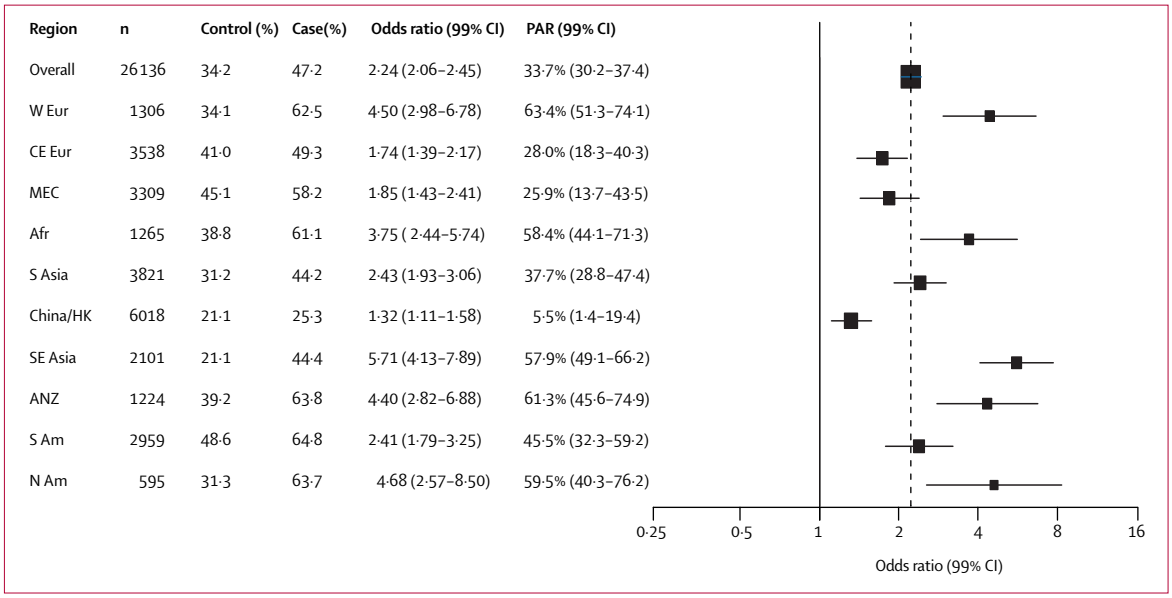


Region	n	Control (%)	Case (%)	Odds ratio (99% CI)	PAR (99% CI)
Overall	26903	7·6	18·3	3·08 (2·77–3·42)	12·3% (11·2–13·5)
W Eur	1422	4·2	17·7	4·29 (2·61–7·05)	15·0% (11·0–20·1)
CE Eur	3636	6·8	13·8	2·61 (1·95–3·49)	9·1% (6·6–12·4)
MEC	3401	11·6	25·1	2·92 (2·26–3·79)	15·5% (12·2–19·4)
Afr	1355	8·0	25·0	3·69 (2·38–5·73)	16·7% (11·8–23·1)
S Asia	3882	10·6	21·4	2·48 (1·93–3·18)	11·8% (8·9–15·5)
China/HK	6075	2·9	11·6	5·07 (3·72–6·90)	10·0% (8·3–11·9)
SE Asia	2140	9·2	27·4	4·19 (3·01–5·83)	21·0% (16·8–25·9)
ANZ	1269	4·8	11·8	2·37 (1·34–4·19)	7·2% (3·9–12·8)
S Am	3093	9·0	20·2	2·45 (1·86–3·24)	12·7% (9·4–17·0)
N Am	630	9·7	16·6	1·75 (0·94–3·29)	8·0% (2·9–20·1)

Figure 8: **Risk of acute myocardial infarction associated with self-reported diabetes, overall and by region after adjusting for age, sex, and smoking**

ethnic groups are statistically robust. The number of cases of myocardial infarction in this study within every region or ethnic group is larger than in most previous studies, especially in those of non-European origin.

The prevalence of several risk factors varied substantially, especially when subdivided by sex. For example, smoking in female controls worldwide has a prevalence of only 9·25% compared with 33% in male controls. As a result, despite similar odds ratios in women and men, the PAR attributable to smoking varied greatly (16% in women and 44% in men). These data suggest that the overall approach to prevention of coronary heart disease could be similar worldwide, but with varying emphasis in different subgroups (eg, sex and geographic region) on the basis of the prevalence of individual risk factors and economic and cultural factors. The above data also suggest that smoking cessation is very important in most male populations worldwide and in women in North and South America, western Europe, and Australia and New Zealand. By contrast, quitting smoking is currently less important for reducing acute myocardial infarction in women in most other geographic regions. However, if women in these countries start smoking they are likely to have a



Region	n	Control (%)	Case(%)	Odds ratio (99% CI)	PAR (99% CI)
Overall	26136	34·2	47·2	2·24 (2·06–2·45)	33·7% (30·2–37·4)
W Eur	1306	34·1	62·5	4·50 (2·98–6·78)	63·4% (51·3–74·1)
CE Eur	3538	41·0	49·3	1·74 (1·39–2·17)	28·0% (18·3–40·3)
MEC	3309	45·1	58·2	1·85 (1·43–2·41)	25·9% (13·7–43·5)
Afr	1265	38·8	61·1	3·75 (2·44–5·74)	58·4% (44·1–71·3)
S Asia	3821	31·2	44·2	2·43 (1·93–3·06)	37·7% (28·8–47·4)
China/HK	6018	21·1	25·3	1·32 (1·11–1·58)	5·5% (1·4–19·4)
SE Asia	2101	21·1	44·4	5·71 (4·13–7·89)	57·9% (49·1–66·2)
ANZ	1224	39·2	63·8	4·40 (2·82–6·88)	61·3% (45·6–74·9)
S Am	2959	48·6	64·8	2·41 (1·79–3·25)	45·5% (32·3–59·2)
N Am	595	31·3	63·7	4·68 (2·57–8·50)	59·5% (40·3–76·2)

Figure 9: **Risk of acute myocardial infarction associated with abdominal obesity measured as waist/hip ratio (upper tertile *vs* lowest tertile), overall and by region after adjusting for age, sex, and smoking**
PARs are for top two tertiles *vs* lowest tertile.

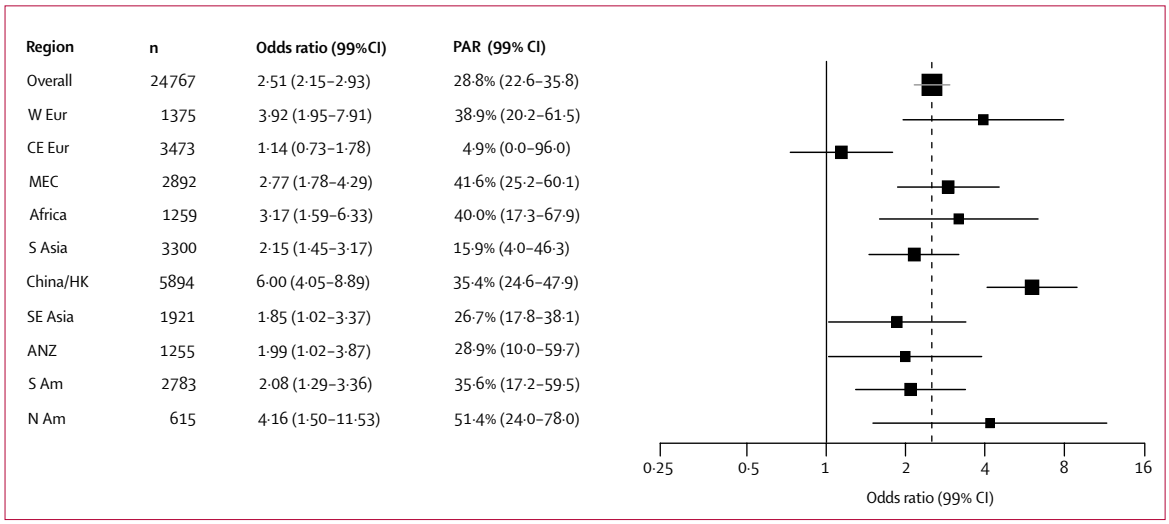


Figure 10: **Risk of acute myocardial infarction associated with the composite psychosocial index, overall and by region**

substantial increase in rates of acute myocardial infarction attributable to smoking.

Hypertension and diabetes were associated with a greater odds ratio and PAR in women compared with men, but women with these factors were about a decade older than men. Further, the protective effects of exercise and alcohol consumption also seemed greater in women than in men. While the amplified effect of diabetes in women has been reported before,[18] we are not aware of similar data about the other three factors. Thus, even though significant interactions were noted between these risk factors and sex for the odds of myocardial infarction, it would be prudent to seek independent confirmation.

Known risk factors (generally smoking, hypertension, raised lipids, and diabetes) have sometimes been claimed to account for only about half the risk of a myocardial infarction. The origins of this claim are unclear.[19] Our analysis, which is based on traditional and some newly described risk factors, suggests that more than 90% of the risk of an acute myocardial infarction in a population can be predicted by the risk factors included in our study. Findings of several previous studies—in which fewer risk factors were measured (most large studies have not included apolipoproteins, psychosocial factors or abdominal obesity)—lend support to our observations. Stamler and colleagues[20] studied five US cohorts and categorised individuals on the basis of the presence of five factors (abnormal electrocardiogram, diabetes, smoking, cholesterol, and blood pressure). Those without any of these risk factors were judged to be in the low-risk category and had an 80–90% lower risk of coronary heart disease in every cohort compared with the rest of the population. Similar results were also reported in an analysis of the Göteborg population, in which individuals with low blood pressure and a low amount of cholesterol, who were also non-smokers, had an age-adjusted relative risk of 0·09, which was much lower that for than the average population (relative risk 1·0) in the study.[21]

The importance of modifying risk factors is lent support by data from randomised trials—eg, blood-pressure lowering,[22] lipid lowering,[23] dietary modification[24]—or persuasive evidence of causality from observational studies[25] (eg, smoking cessation).[26] Some investigators have suggested that a pill that combines a statin, antihypertensive drugs, and aspirin, together with avoidance of smoking, could potentially reduce the risk of myocardial infarction by more than 80% to 90%.[27] These studies, along with INTERHEART, suggest that one of the major emphases in research should be to understand why currently known risk factors develop in some individuals and populations, and to identify approaches to prevent their development or reduce them. For example, understanding the mechanisms by which societal factors affect development of risk factors (urbanisation, food and tobacco policies, shifts in occupation from energy expending jobs to sedentary ones, and urban structure, etc) could lead to new approaches to prevent development of risk factors (primordial prevention),[4] which in turn could reduce coronary heart disease substantially.

Although the odds ratio for an acute myocardial infarction in people with a family history was about 1·5, the PAR rose from 90% with the nine potentially modifiable risk factors to 91% with the addition of family history. This finding suggests that a large part of the effect of family history might be mediated through known risk factors, which could be affected by both shared lifestyles and genetic factors rather than through independent pathways. Therefore, the main challenge in the next few decades will be a combination of discovering more effective strategies to substantially alter or prevent development of known risk factors by understanding the societal, environmental, and biological causes of the development of these factors.

One of the most important risk factors for acute myocardial infarction in our study was smoking, which accounts for about 36% of the PAR of acute myocardial infarction worldwide (and about 44% in men). Regular consumption of fruits and vegetables was associated with a 30% relative risk reduction. Thus, eating fruit and vegetables, taking exercise, and avoiding smoking could lead to about 80% lower relative risk for myocardial infarction. Our results are similar to the findings of the US Nurses Health Study,[28] which also indicated that lifestyle modification could potentially avoid more than three-quarters of the risks of coronary heart disease and strokes in women. These conclusions are also lent support by the results of the Lyon Heart Study,[24] which suggested that dietary modification by itself reduced the risk of coronary heart disease by about half in patients with coronary disease. Our data suggest that lifestyle modification is of substantial importance in both men and women, at all ages, in individuals from all geographic regions of the world, and in those belonging to all major ethnic groups. Therefore, smoking avoidance, increased consumption of fruits and vegetables, and moderate activity (along with lipid lowering) should be the cornerstone of prevention of coronary heart disease in all populations worldwide.

We also recorded an additional protective effect of moderate alcohol consumption (PAR 7%). The effect seemed to be surprisingly large in women, in whom absence of regular alcohol consumption accounted for about 22% of PAR, but with wide confidence limits (–4·9 to 60·8). This finding suggests that the best estimate of PAR attributable to alcohol consumption in women is probably closer to the overall estimate of 7%. Promotion of the consumption of moderate alcohol to prevent myocardial infarction might also not be acceptable to many populations, for cultural or religious reasons, and might increase the proportion of heavy drinkers and thereby enhance the risk of other diseases such as strokes, some cancers, cirrhosis of the liver, or injuries. The overall PAR without alcohol included in the model is 89·7%; adding alcohol increases it by less than 1% because of the substantial overlap in contributions of other risk factors. Therefore, advice about alcohol use could be best customised to individuals depending on their social, cultural, and religious backgrounds and the overall effect on their health.

Our study has several potential limitations. First, a case-control design is potentially open to confounding if there is differential ascertainment of risk factors between cases and controls. We minimised this factor by using standardised methods for data collection in both cases and controls. The inclusion of incident (first) acute myocardial infarction cases reduces the possibility that individuals with previous cardiovascular disease might have substantially altered lifestyles or risk factor levels before this event. Further, the odds ratios associated with all major risk factors—eg, smoking, lipids, diabetes, and hypertension—in INTERHEART is similar to that reported in other cohort studies in western populations. We attempted to minimise biases in the selection of controls by excluding individuals in whom the risk factors that we were interested in studying were implicated as being protective or harmful. Reanalysis of our data by the two types of controls—hospital-based and community-based—did not alter our results. Our results are qualitatively similar for most risk factors in all regions of the world, providing internal replication. Any selection biases are unlikely to have been similarly prevalent across a large number of centres in 52 countries. Therefore, we think that there is little material bias in our results because of the use of a case-control study design.

Second, whereas some of the risk factors were ascertained or measured with high accuracy (eg, smoking), others (eg, history of diabetes or hypertension) were based on history and therefore ascertained with some error. The actual blood pressure value after a myocardial infarction is potentially confounded because it might have fallen in some patients because of the infarction itself or as a result of the drugs used in the management of the acute phase. Similarly, glucose concentrations rise with acute myocardial infarction (stress hyperglycaemia) and are therefore not an indication of earlier levels. We obtained blood samples for HbA1c but these are yet to be analysed. Therefore, our approach to diagnosis of hypertension or diabetes might have led to misclassification in some individuals with respect to their risk-factor status. These misclassifications would tend to underestimate the real relation between these risk factors and outcomes. Analysis of our control group data indicates a relation between the reported prevalence of hypertension in every centre and measured blood pressure in controls (data not shown), suggesting that there is some validity in using self-reports of hypertension as a surrogate for measured blood pressure. However, the absence of available blood pressure and glucose values could have underestimated their importance.

Third, the correlations between repeated measures of several variables (eg, diet or physical activity) many months apart is only moderate. Methods to correct for measurement error and regression dilution bias for one risk factor have been described;[17] however, we are not aware of methods that adjust for several risk factors simultaneously. However, if correction for regression-dilution bias could have been made it could further increase the odds ratios for most risk factors, which in turn would increase the overall PAR accounted for by the nine risk factors that we measured. This outcome means that the nine risk factors measured in this study probably account for virtually all the PAR for myocardial infarction in the population included in this study.

Fourth, our data are based on hospital-based patients with acute myocardial infarction and matched controls (mainly from urban areas) and are therefore unlikely to

reflect the population prevalence of risk factors in an entire country or region. This fact could potentially have an effect on our estimates of PAR. However, the key to ensuring internal validity of the study is to recruit cases and controls from the same population, which has been our emphasis. Therefore, our estimates of PAR should be regarded as providing reliable information about the specific population enrolled into our study. Nevertheless, when data are available from several countries (eg, for smoking), the rates in controls in INTERHEART closely match published reports for similar age-groups and sexes. As a result, our overall conclusions that the risk factors measured in this study account for most of the risk of acute myocardial infarction is probably broadly applicable. In view of the consistency of our data, the odds ratios from the present study could be applied to other populations and their PAR can then be derived by using population-specific prevalence rates of specific risk factors.

Fifth, although the effects of individual risk factors and combinations of four or five of them are reasonably robust, our estimates of the effect of all nine is model-dependent because very few individuals have eight or nine risk factors or, conversely, none. However, crude examination of the extremes of risk-factor distribution, and the fact that just five risk factors (smoking, lipids, hypertension, diabetes, and obesity) for which we have a sizeable number of individuals predicts about 80% of the PAR, suggests that our model-based estimates are reasonably valid.

Our study has several strengths. First, the case-control study has several advantages over other designs, especially a cohort study. It allows efficient enrolment of large numbers of cases and hence greater statistical power, rapid and cost-effective study conduct, and enhances the ability to recruit a large number of cases occurring at young ages, in whom disease association might be stronger. Second, our study included several risk factors that have previously not been assessed with conventional risk factors, including apolipoproteins (ApoB/A1 ratio), which might be the best marker of the balance of atherogenic and antiatherogenic particles,10 psychosocial factors,7 and measures of abdominal obesity, all of which have added substantial information to the other commonly studied risk factors. Third, the large size of the study provides high power and precision in estimates both overall and in subgroups. Fourth, the inclusion of large numbers of individuals from all regions of the world and multiple ethnic groups makes our study results broadly applicable.

In conclusion, our study has shown that nine easily measured risk factors are associated with more than 90% of the risk of an acute myocardial infarction in this large global case-control study. These results are consistent across all geographic regions and ethnic groups of the world, men and women, and young and old. Although priorities can differ between geographic regions because of variations in prevalence of risk factors and disease and economic circumstances, our results suggest that approaches to prevention of coronary artery disease can be based on similar principles throughout the world. Therefore, modification of currently known risk factors has the potential to prevent most premature cases of myocardial infarction worldwide.

Contributors

S Yusuf initiated the INTERHEART study, supervised its conduct and data analysis and had primary responsibility for writing this paper. S Ôunpuu coordinated the worldwide study and reviewed and commented on drafts. S Hawken did all data analyses and reviewed and commented on drafts. All other authors coordinated the study in their respective countries and provided comments on drafts of the manuscript.

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Conflict of interest statement

We declare that we have no conflict of interest.

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Webappendix 1: Criteria for recruitment of cases and controls

Cases

Definition of acute myocardial infarction: clinical symptoms and electrocardiogram showing substantial changes such as new pathological Q waves or 1 mm ST elevation in any two or more contiguous limb leads, or a new left bundle branch block or new persistent ST-T wave changes diagnostic of a non-Q wave myocardial infarction, or raised concentration of troponin. Criteria for subsequent confirmation include substantially raised concentration of enzyme (>2 times normal) or evolution of electrocardiogram changes.

Exclusion criteria: cardiogenic shock, a significant chronic medical illness (eg, liver, untreated hyperthyroidism or hypothyroidism, renal disease or malignant disease, or who were pregnant) because these conditions might change lifestyle or alter the risk factors for acute myocardial infarction; failure to provide informed consent.

Controls

Inclusion criteria

First control per case:

Visitor or relative of a patient from a non-cardiac ward, or an unrelated (not first-degree relative) visitor of a cardiac patient.

Second control per case:

a) Preferred:

Patients attending the hospital or outpatients clinic for the following reasons:

- 2.1 refraction and cataracts
- 2.2 physical check-up
- 2.3 routine Papanicolaou smear
- 2.4 routine breast examination
- 2.5 elective minor surgery for conditions that are not obviously related to coronary heart disease or its risk factors
- 2.6 elective orthopaedic surgery

b) Acceptable:

Patients attending the hospital or outpatients clinic for the following reasons:

- 3.1 outpatient fractures
- 3.2 arthritic complaints
- 3.3 plastic surgery
- 3.4 haemorrhoids, hernias, hydroceles
- 3.5 routine colon cancer screening
- 3.6 endoscopy
- 3.7 minor dermatological disorders

Exclusion criteria for controls were identical to those described for cases, with the additional criterion that controls had no previous diagnosis of heart disease or history of exertional chest pain.

Webappendix 2: Funding

The INTERHEART study was funded by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario, the International Clinical Epidemiology Network (INCLEN), and through unrestricted grants from several pharmaceutical companies [with major contributions from Astra Zeneca, Novartis, Hoechst Marion Roussel (now Aventis), Knoll Pharmaceuticals (now Abbott), Bristol-Myers Squibb and Sanofi-Sythelabo], and additionally by various national bodies in different countries: *Chile*—Universidad de la Frontera, Sociedad Chilena de Cardiologia Filial Sur; *Colombia*—Colciencias, Ministerio de Salud; *Croatia*—Croatian Ministry of Science and Technology; *Guatemala*—Liga Guatemalteca del Corazon; *Hungary*—Astra Hassle, National Health Science Council, George Gabor Foundation; *Iran*—Iran Ministry of Health; *Italy*—Boehringer Ingelheim; *Japan*—Sankyo Pharmaceutical, Banyu Pharmaceutical, Astra Japan; *Kuwait*—Endowment Fund for Health Development in Kuwait; *Pakistan*—ATCO Laboratories; *Philippines*—Philippine Council for Health Research and Development, Pfizer Philippines Foundation, Astra Pharmacetuicals and the Astra Fund for Clinical Research and Continuing Medical Education, Pharmacia and Upjohn; *Poland*—Foundation PROCLINICA, State Committee for Scientific Research; *Singapore*—Singapore National Heart Association; *South Africa*—MRC South Africa, Warner-Parke-Davis Pharmaceuticals, Aventis; *Sweden*—Grant from the Swedish State under LUA Agreement, Swedish Heart and Lung Foundation; *Thailand*—The Heart Association of Thailand, Thailand Research Fund; *USA*—King Pharma.

Region/Country	Cases	Controls
Western Europe		
Germany	45	56
Italy	187	165
Netherlands	17	4
Portugal	8	5
Spain	130	128
Sweden	247	403
UK	30	6
Subtotal	664	767
Central Europe		
Croatia	263	264
Czech Republic	16	25
Greece	51	29
Hungary	179	198
Poland	1030	1008
Russia	188	403
Subtotal	1727	1927
North America		
Canada	221	243
USA	75	97
Subtotal	296	340
South America		
Argentina	234	178
Brazil	313	364
Chile	322	672
Colombia	275	550
Guatemala	85	107
Mexico	8	17
Subtotal	1237	1888
Australia and New Zealand		
Australia	572	625
New Zealand	17	56
Subtotal	589	681
Middle East		
Bahrain	52	43
Egypt	595	509
Kuwait	247	458
Iran	252	254
Israel	12	12
Qatar	95	43
Oman	98	179
United Arab Emirates	288	288
Subtotal	1639	1786
Africa		
Benin	4	8
Botswana	16	30
Cameroon	17	19
Kenya	27	48
Mozambique	16	20
Nigeria	7	7
Seychelles	1	2
South Africa	473	644
Zimbabwe	17	11
Subtotal	578	789
South Asia		
Bangladesh	228	238
India	470	940
Nepal	244	239
Pakistan	637	655
Sri Lanka	153	132
Subtotal	1732	2204
China		
China	2909	2947
Hong Kong	121	109
Subtotal	3030	3056
Other Asia		
Japan	91	162
Malaysia	79	43
Philippines	364	424
Singapore	192	195
Thailand	243	375
Subtotal	969	1199
Overall	12 461	14 637

Webtable 1: **Numbers of cases and controls by country, region, and overall**

	Matched*	Unmatched†
Smoking		
Former	1·55 (1·39–1·72)	1·52 (1·37–1·67)
Current	3·04 (2·76–3·34)	2·93 (2·69–3·19)
Diabetes	3·10 (2·75–3·50)	3·06 (2·74–3·41)
Hypertension	2·55 (2·33–2·78)	2·44 (2·25–2·64)
Waist/hip ratio		
Middle *vs* lowest tertile	1·41 (1·28–1·57)	1·32 (1·20–1·44)
Top *vs* lowest tertile	2·26 (2·03–2·51)	2·11 (1·92–2·31)
Exercise	0·75 (0·67–0·84)	0·73 (0·66–0·81)
Psychosocial (depression)	1·63 (1·47–1·80)	1·56 (1·42–1·70)
Global stress		
Some periods	0·97 (0·88–1·07)	1·02 (0·93–1·11)
Several periods	1·38 (1·22–1·56)	1·40 (1·26–1·57)
Permanent periods	2·17 (1·81–2·60)	2·13 (1·81–2·52)
Daily vegetables	0·79 (0·72–0·86)	0·78 (0·72–0·84)
Daily fruits	0·82 (0·76–0·89)	0·85 (0·79–0·91)
Alcohol intake	0·81 (0·73–0·90)	0·82 (0·75–0·90)
ApoB/ApoA1 (top *vs* lowest quintile)	4·43 (3·78–5·19)	3·96 (3·45–4·55)

*Matched models included additional adjustment for smoking status for all models where smoking was not the risk factor of focus. †Unmatched models included adjustment for age, sex, region, and smoking (where smoking was not the risk factor of focus). The matched analysis data subset was used in the unmatched analyses for direct comparability.

Webtable 2: **Comparison of results of matched and unmatched analyses**

Webtable 3: PARs associated with nine risk factors in men and women by geographic region

(a) Men

	LIFESTYLE FACTORS					OTHER RISK FACTORS					
Region	Smoke %	Fr/vg %	Exer %	Alcohol %	All LS %	HTN %	Diabetes %	Abd Obes %	All PS %	Lipids %	All 9 RF
W. Europe	39.0 (24.4,55.9)	13.3 (4.8, 31.5)	37.7 (26.7, 50.0)	14.1 (6.1, 29.1)	69.6 (56.4, 80.2)	20.5 (13.5, 29.9)	12.8 (8.5, 18.8)	68.6 (54.1, 80.2)	23.7 (5.0, 64.7)	36.7 (10.7, 73.8)	92.0 (75.8, 97.7)
E/C. Europe	40.4 (30.1, 51.6)	7.6 (1.3, 34.2)	-0.4 (-18.6, 17.8)	10.4 (3.3, 28.6)	48.9 (33.4, 64.7)	15.9 (10.1, 24.1)	5.8 (3.3, 10.0)	31.7 (19.5, 47.0)	-0.9 (-37.8, 36.0)	38.7 (20.0, 61.4)	71.9 (47.5, 87.8)
Middle East	51.4 (44.2, 58.6)	5.8 (0.7, 34.1)	1.9 (0.0, 100.0)	-2.7 (-44.4, 39.0)	50.7 (26.4, 74.6)	5.8 (2.6, 12.3)	13.1 (9.7, 17.3)	23.9 (11.4, 43.4)	37.2 (19.5, 59.1)	72.7 (58.8, 83.2)	94.8 (87.1, 98.0)
Africa	45.2 (28.9, 62.6)	-4.4 (-26.6, 17.8)	15.9 (1.9, 64.9)	24.1 (9.9, 48.1)	63.7 (40.7, 81.8)	26.8 (19.5, 35.6)	11.6 (6.7, 19.2)	60.4 (44.0, 74.8)	33.8 (9.7, 70.8)	73.7 (55.2, 86.4)	97.9 (91.2, 99.5)
S. Asia	42.0 (35.3, 49.0)	16.0 (6.5, 34.4)	25.5 (6.9, 61.1)	-5.7 (-31.1, 19.7)	58.1 (38.0, 75.8)	17.8 (14.0, 22.2)	10.5 (7.5, 14.4)	36.0 (26.6, 46.6)	13.9 (2.4, 51.5)	60.2 (42.5, 75.6)	88.4 (73.7, 95.4)
China	45.3 (39.2, 51.5)	15.1 (8.5, 25.4)	16.6 (4.2, 47.7)	4.2 (0.3, 42.6)	63.7 (51.2, 74.5)	19.9 (16.0, 24.4)	7.9 (6.1, 10.0)	4.9 (1.0, 20.8)	32.0 (19.5, 47.9)	41.3 (32.4, 50.7)	88.8 (81.9, 93.3)
S.E. Asia	39.2 (26.4, 53.6)	8.5 (1.6, 34.3)	31.4 (15.4, 53.7)	24.6 (13.0, 41.6)	69.6 (54.8, 81.2)	34.3 (28.8, 40.2)	19.1 (14.6, 24.6)	57.9 (48.3, 66.9)	26.9 (17.2, 39.5)	68.7 (51.2, 82.1)	93.7 (83.0, 97.8)
Australia/NZ	46.1 (31.7, 61.2)	8.0 (1.2, 37.8)	20.6 (10.0, 37.8)	11.2 (3.7, 29.1)	61.0 (45.7, 74.4)	18.3 (10.9, 29.2)	5.6 (2.3, 13.2)	49.5 (26.6, 72.6)	31.6 (10.8, 63.8)	48.7 (17.5, 80.9)	87.5 (59.0, 97.2)
S. America	42.4 (33.2, 52.2)	7.1 (1.3, 31.1)	27.6 (14.0, 47.3)	-7.4 (-27.2, 12.4)	57.7 (41.2, 72.6)	28.1 (22.0, 35.1)	9.7 (6.3, 14.7)	35.2 (18.9, 55.9)	36.1 (15.6, 63.4)	41.6 (20.2, 66.6)	86.1 (67.9, 94.8)
N. America	30.9 (8.5, 68.1)	22.4 (8.9, 46.0)	24.7 (9.2, 51.3)	6.6 (0.1, 87.0)	53.9 (25.8, 79.7)	13.9 (4.4, 36.2)	6.1 (1.2, 25.4)	64.7 (38.0, 84.6)	63.7 (36.0, 84.5)	60.0 (22.2, 88.8)	100.0 (97.0, 100.0)
Overall 1	44.0 (40.9, 47.2)	10.3 (6.9, 15.2)	22.9 (16.9, 30.2)	10.5 (6.1, 17.5)	63.8 (59.0, 68.3)	19.5 (17.7, 21.5)	10.1 (8.9, 11.4)	32.1 (28.0, 36.5)	25.3 (18.2, 34.0)	53.8 (48.3, 59.2)	89.8* (86.9, 92.1)
Overall 2	42.7 (38.6, 46.9)	11.7 (7.4, 18.0)	9.3 (2.9, 26.3)	5.1 (1.0, 21.4)	56.5 (49.1, 63.6)	14.9 (12.4, 17.7)	8.0 (6.5, 9.8)	19.7 (14.3, 26.6)	28.8 (20.4, 39.0)	49.5 (43.0, 55.9)	89.8* (86.9, 92.1)

(b) Women

Region	LIFESTYLE FACTORS					OTHER RISK FACTORS					All 9 RF
	Smoke %	Fr/vg %	Exer %	Alcohol %	All LS %	HTN %	Diabetes %	Abd Obes %	All PS %	Lipids %	
W. Europe	11.1 (1.8, 45.5)	8.4 (0.9, 48.8)	38.3 (16.8, 65.6)	34.2 (14.1, 62.1)	65.2 (40.9, 83.6)	25.9 (13.7, 43.6)	21.0 (12.9, 32.1)	50.6 (29.1, 71.9)	67.1 (38.9, 86.7)	47.9 (20.3, 76.8)	97.1 (84.8, 99.5)
E/C. Europe	13.1 (6.8, 23.8)	12.8 (3.6, 36.4)	42.7 (22.7, 65.4)	29.9 (7.8, 68.2)	65.4 (41.0, 83.7)	42.7 (33.3, 52.7)	15.7 (10.7, 22.4)	20.0 (7.3, 44.2)	15.0 (0.4, 88.2)	26.8 (5.9, 68.2)	86.1 (54.8, 96.9)
Middle East	8.1 (3.6, 17.3)	15.9 (3.2, 51.7)	39.1 (1.5, 96.4)	59.0 (1.9, 99.1)	80.3 (9.6, 99.4)	30.1 (19.1, 43.9)	30.3 (20.6,42.2)	38.9 (9.2, 80.0)	77.4 (41.5, 94.3)	63.3 (32.0, 86.3)	99.4 (82.6, 100.0)
Africa	27.6 (13.8,47.6)	21.0 (6.6, 49.8)	-37.9 (-165, 89.6)	28.8 (0.9, 94.5)	61.2 (11.0, 95.3)	35.1 (21.9, 51.0)	27.5 (17.8, 40.0)	54.6 (28.5, 78.4)	54.9 (17.4, 87.6)	74.6 (49.1, 90.0)	93.3 (16.4, 99.9)
S. Asia	7.1 (2.7, 17.3)	30.6 (10.4,62.6)	45.0 (4.2,93.9)	26.0 (0.0, 100.0)	59.8 (1.5, 99.3)	28.9 (19.6, 40.3)	20.5 (12.4, 32.0)	48.7 (24.1, 74.0)	29.2 (4.3, 79.2)	52.1 (19.0, 83.5)	99.3 (82.8, 100.0)
China	12.5 (8.7, 17.7)	23.6 (14.8, 35.4)	33.5 (9.0, 71.9)	35.8 (5.8, 83.5)	78.6 (48.5, 93.5)	27.6 (21.1, 35.2)	15.0 (11.6, 19.0)	6.3 (0.3, 61.0)	43.2 (24.6, 64.0)	48.3 (36.9, 59.9)	93.6 (76.9, 98.4)
S.E. Asia	14.8 (6.9, 28.9)	19.9 (6.2, 48.2)	32.8 (3.4, 87.0)	69.5 (16.1, 96.4)	84.5 (33.7, 98.3)	56.3 (44.3, 67.6)	29.2 (19.4, 41.4)	58.0 (36.2, 77.0)	27.0 (9.7, 55.9)	64.5 (29.5, 88.7)	96.5 (55.5, 99.8)
Australia/NZ	40.7 (23.3,60.8)	15.8 (4.7, 41.8)	33.6 (14.9, 59.4)	47.4 (26.9, 68.8)	80.0 (61.9, 90.8)	37.0 (21.8, 55.2)	11.7 (5.5, 23.3)	67.2 (45.8, 83.2)	17.2 (0.2, 95.9)	14.9 (0.0, 99.6)	non.est.
S. America	25.8 (16.3,38.2)	5.9 (0.3, 56.3)	27.4 (5.1, 72.7)	44.1 (8.1, 87.6)	71.8 (34.3, 92.5)	47.9 (36.4, 59.6)	22.2 (14.9, 31.7)	63.0 (43.7, 78.9)	37.8 (8.7, 79.6)	59.3 (30.5, 82.9)	96.1 (79.8, 99.4)
N. America	25.3 (5.6, 65.8)	12.8 (1.2, 64.1)	27.2 (5.1, 72.0)	73.3 (42.7, 91.0)	86.9 (58.9, 96.9)	30.2 (11.2, 59.6)	12.4 (3.8, 33.6)	44.5 (19.0, 73.1)	32.7 (0.8, 96.7)	32.2 (1.1, 95.1)	non.est
Overall 1	15.8 (12.9,19.3)	17.8 (12.9, 24.1)	37.3 (26.1, 50.0)	46.9 (34.3, 60.0)	75.0 (66.0, 82.2)	35.8 (32.1, 39.6)	19.1 (16.8, 21.7)	35.9 (28.9, 43.6)	40.0 (28.6, 52.6)	52.1 (44.0, 60.2)	94.1 (89.6, 96.7)*
Overall 2	14.8 (11.2,19.2)	19.1 (12.7, 27.8)	27.1 (11.7, 51.0)	22.1 (−4.9, 60.8)	60.6 (41.3, 77.1)	29.0 (23.8, 34.7)	16.1 (13.0, 19.8)	18.7 (9.3, 33.9)	45.2 (31.2, 59.9)	47.1 (37.4, 57.0)	94.1 (89.6, 96.7)

The PAR estimates in women in some countries is based on small numbers and so it is less reliable .
Smoke=Smoking, FR=Fruits, Vg=Vegetables, Exer=Exercise, LS=Lifestyle, HTN=Hypertension, Abd Obes=Abdominal Obesity, PS=Psychosocial, W=Western, E/C=Eastern, Central, S=South, NZ=New Zealand, N=North, Overall 1=Only adjusted for age, sex, and smoking, Overall 2=Additionally adjusted for all other risk factors
SE Asia includes Japan
*Saturated model, no difference between adjusted and unadjusted models

(c) Men and women

	LIFESTYLE FACTORS					OTHER RISK FACTORS					All 9 RF
Region	Smoke	Fr/vg	Exer	Alcohol	All LS	HTN	Diabetes	Abd Obes	All PS	Lipids	
	%	%	%	%	%	%	%	%	%	%	
W. Europe	29.3 (17.8,44.1)	12.4 (5.2, 26.9)	38.4 (28.3, 49.6)	18.7 (10.3, 31.6)	67.6 (56.1, 77.3)	21.9 (15.6, 30.0)	15.0 (11.0, 20.1)	63.4 (51.3, 74.1)	38.9 (20.2, 61.5)	44.6 (23.5, 67.8)	93.9 (84.6, 97.7)
E/C. Europe	30.2 (23.0,38.6)	10.2 (3.8, 24.8)	11.3 (2.9, 35.3)	12.9 (4.8, 30.4)	49.6 (36.5, 62.7)	24.5 (19.2, 30.6)	9.1 (6.6, 12.4)	28.0 (18.3, 40.3)	4.9 (0.0, 96.0)	35.0 (19.2, 54.9)	72.5 (53.0,86.0)
Middle East	45.5 (39.3,51.9)	7.3 (1.7, 26.8)	4.2 (0.0, 98.0)	-1.0 (-41.7, 39.7)	47.6 (23.3, 73.1)	9.2 (5.7, 14.4)	15.5 (12.2, 19.4)	25.9 (13.7, 43.5)	41.6 (25.2, 60.1)	70.5 (57.8, 80.7)	95.0 (88.2, 98.0)
Africa	38.9 (27.1,52.2)	4.8 (0.2, 62.5)	10.1 (0.3, 78.3)	26.6 (11.4, 50.5)	63.4 (42.9, 80.0)	29.6 (22.8, 37.3)	16.7 (11.8, 23.1)	58.4 (44.1, 71.3)	40.0 (17.3, 67.9)	74.1 (59.7, 84.6)	97.4 (90.7, 99.3)
S. Asia	37.4 (31.6,43.6)	18.3 (9.0,33.8)	27.1 (8.7, 59.4)	-5.5 (-31.2, 20.2)	56.6 (36.8, 74.4)	19.3 (15.7, 23.4)	11.8 (8.9, 15.5)	37.7 (28.8, 47.4)	15.9 (4.0, 46.3)	58.7 (42.7, 73.1)	89.4 (76.9, 95.5)
China	35.9 (31.5,40.5)	18.0 (12.3, 25.4)	20.3 (7.5, 44.2)	5.7 (0.6, 38.3)	62.3 (50.4, 72.9)	221 (18.7, 26.0)	10.0 (8.3, 11.9)	5.5 (1.4, 19.4)	35.4 (24.6, 47.9)	43.8 (36.7, 51.2)	89.9 (84.3, 93.6)
S.E. Asia	36.0 (25.9,47.5)	11.2 (3.9, 28.4)	31.8 (16.3,52.8)	27.7 (15.6, 44.4)	69.9 (56.4, 80.7)	38.4 (33.3, 43.6)	21.0 (16.8, 25.9)	57.9 (49.1, 66.2)	26.7 (17.8, 38.1)	67.7 (52.0, 80.2)	93.7 (84.6, 97.5)
Australia/NZ	44.8 (33.0,57.2)	11.1 (3.8, 28.3)	23.8 (14.0,37.5)	18.6 (10.3, 31.4)	66.0 (54.3, 76.1)	22.6 (15.6, 31.6)	7.2 (3.9, 12.8)	61.3 (45.6, 74.9)	28.9 (10.0, 59.7)	43.4 (16.0, 75.6)	89.5 (68.1, 97.2)
S. America	38.3 (31.0,46.1)	6.6 (1.4, 25.6)	27.6 (14.7, 45.6)	-3.7 (-23.7, 16.3)	56.6 (41.3, 70.7)	32.7 (27.2, 38.8)	12.7 (9.4, 17.0)	45.5 (32.3, 59.5)	35.6 (17.2, 59.5)	47.6 (29.6, 66.2)	89.4 (78.2, 95.2)
N. America	26.1 (8.8,56.5)	19.8 (8.5, 39.6)	25.6 (11.3, 48.1)	25.5 (10.3, 50.6)	59.9 (37.8, 78.6)	19.0 (9.2, 35.2)	8.0 (2.9, 20.1)	59.5 (40.3, 76.2)	51.4 (24.0, 78.0)	50.5 (18.2, 82.4)	98.7 (83.9, 99.9)
Overall 1	36.4 (33.9,39.0)	12.9 (10.6, 16.6)	25.5 (20.1, 31.8)	13.9 (9.3, 20.2)	62.9 (58.5, 67.1)	23.4 (21.7, 25.1)	12.3 (11.2, 13.5)	33.7 (30.2, 37.4)	28.8 (22.6, 35.8)	54.1 (49.6, 58.6)	90.4* (88.1, 92.4)
Overall 2	35.7 (32.5,39.1)	13.7 (9.9, 18.6)	12.2 (5.5, 25.1)	6.7 (2.0, 20.2)	54.6 (47.6, 61.4)	17.9 (15.7, 20.4)	9.9 (8.5, 11.5)	20.1 (15.3, 26.0)	32.5 (25.1, 40.8)	49.2 (43.8, 54.5)	90.4* (88.1, 92.4)