Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study

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See Comment page 912

*See Articles page 937

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Summary

Background **Psychosocial factors have been reported to be independently associated with coronary heart disease. However, previous studies have been in mainly North American or European populations. The aim of the present analysis was to investigate the relation of psychosocial factors to risk of myocardial infarction in 24 767 people from 52 countries.**

Methods **We used a case-control design with 11 119 patients with a first myocardial infarction and 13 648 age-matched (up to 5 years older or younger) and sex-matched controls from 262 centres in Asia, Europe, the Middle East, Africa, Australia, and North and South America. Data for demographic factors, education, income, and cardiovascular risk factors were obtained by standardised approaches. Psychosocial stress was assessed by four simple questions about stress at work and at home, financial stress, and major life events in the past year. Additional questions assessed locus of control and presence of depression.**

Findings **People with myocardial infarction (cases) reported higher prevalence of all four stress factors (p<0·0001). Of those cases still working, 23·0% (n=1249) experienced several periods of work stress compared with 17·9% (1324) of controls, and 10·0% (540) experienced permanent work stress during the previous year versus 5·0% (372) of controls. Odds ratios were 1·38 (99% CI 1·19–1·61) for several periods of work stress and 2·14 (1·73–2·64) for permanent stress at work, adjusted for age, sex, geographic region, and smoking. 11·6% (1288) of cases had several periods of stress at home compared with 8·6% (1179) of controls (odds ratio 1·52 [99% CI 1·34–1·72]), and 3·5% (384) of cases reported permanent stress at home versus 1·9% (253) of controls (2·12 [1·68–2·65]). General stress (work, home, or both) was associated with an odds ratio of 1·45 (99% CI 1·30–1·61) for several periods and 2·17 (1·84–2·55) for permanent stress. Severe financial stress was more typical in cases than controls (14·6% [1622] *vs* 12·2% [1659]; odds ratio 1·33 [99% CI 1·19–1·48]). Stressful life events in the past year were also more frequent in cases than controls (16·1% [1790] *vs* 13·0% [1771]; 1·48 [1·33–1·64]), as was depression (24·0% [2673] *vs* 17·6% [2404]; odds ratio 1·55 [1·42–1·69]). These differences were consistent across regions, in different ethnic groups, and in men and women.**

Interpretation **Presence of psychosocial stressors is associated with increased risk of acute myocardial infarction, suggesting that approaches aimed at modifying these factors should be developed.**

Introduction

Popular opinion holds that stress is an important risk factor for coronary heart disease. However, compared with other major risk factors, psychosocial variables such as stress are difficult to define objectively, and stress consists of several different (and inter-related) elements. Therefore, measurement of stress is complex and difficult. Despite this drawback, several constructs within the broad conceptual framework of stress are increasingly regarded as being causally related to coronary heart disease.[1–15]

The concept of stress encompasses several factors, from external stressors such as job stress,[5,8,10,13] adverse life events[7] and financial problems, to potential reactions to stress such as depression,[1–3] vital exhaustion,[15] anxiety,[12,14] psychological distress,[11] and sleeping difficulties. The same construct might not be applicable in different countries and ethnic groups, because cultural influences can vary. Perceived mental stress, measured by response to a single-item question, was associated with increased mortality from coronary disease in a large study of Japanese men and women.[9] Apart from this study,[9] previous investigations have been done in mainly North American or European populations. Thus, limited data are available about psychological variables and coronary heart disease in other countries and ethnic groups. The aim of the INTERHEART study, undertaken in a large number of patients with a first acute myocardial infarction and controls matched for age and sex, was to investigate the associations of several psychosocial stressors with the risk of acute myocardial infarction globally, and in different populations characterised by age, sex, geographic region, and ethnic origin.

Patients and methods

Study population

12 461 incident cases of acute myocardial infarction from 262 centres in 52 countries representing all geographic regions, and 14 637 age-matched, sex-matched, and site-matched controls free of clinical heart disease, took part in the study.[16,17] Centres attempted to recruit consecutive patients. Recruitment was from February, 1999, until March, 2003. Patients admitted to the coronary care unit or equivalent cardiology ward of participating centres were screened to identify incident cases of acute myocardial infarction and enrolled within 24 h. Details of criteria used for the definition of acute myocardial infarction are described in the accompanying paper.[16] At least one control was recruited and matched to every case of acute myocardial infarction by age (up to 5 years older or younger) and sex. Eligible control sources were community-based (visitor or relative of a patient from a non-cardiac ward, or an unrelated visitor of a cardiac patient) or hospital-based.[16]

See Articles page 937

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.

Procedures

We obtained data for demographic factors (country of origin, first language), socioeconomic status (education, occupation, income), lifestyle (tobacco use, physical activity, dietary patterns), personal and family patterns of cardiovascular disease, and risk factors.[16] Staff were trained in study procedures with standard manuals, videotapes, and instructions at meetings or at site visits. Trained staff administered the questionnaire before patients left the hospital. A standard yet simple set of questions that inquired about psychosocial conditions during the previous 12 months was included in the interview. Complete data on psychosocial variables were available for 11 119 cases and 13 648 controls.

We assessed psychological stress with two single-item questions relating to stress at work and home. Stress was defined as feeling irritable, filled with anxiety, or as having sleeping difficulties as a result of conditions at work or at home. Patients were specifically asked to respond about their condition before their acute myocardial infarction. For every question, we asked participants to report how often they had felt stress, using the following response options: 1) never; 2) some periods; 3) several periods; or 4) permanent stress. These two questions are an adaptation of a single question that has been used in multiple studies in Göteborg, Sweden since 1970. For example, in a prospective study of Swedish men,[14] permanent stress, according to this question, was associated with an increased risk of acute myocardial infarction, stroke, and death. Because stress at work and at home were highly intercorrelated, and because only 48·8% (5426) of cases and 54·1% (7387) of controls were currently working, we created a general stress scale that combined stress at work, home, or both and was graded as follows: 1) never experienced stress; 2) experienced some periods at home or at work; 3) experienced several periods at home or at work; 4) experienced permanent stress at home or at work.

See Articles page 937

We defined level of financial stress as: 1) little or none; 2) moderate; or 3) high or severe. Occurrence of major adverse life events was documented by asking participants whether they had experienced any specified life events in the past year—marital separation or divorce, loss of job or retirement, loss of crop or business failure, violence, major intrafamily conflict, major personal injury or illness, death or major illness of a close family member, death of a spouse, or other major stress.

Generalised locus of control—that is, the perceived ability to control life circumstances—was determined by responses to a questionnaire containing six scale items that have been used extensively in studies in eastern Europe.[18] Responses from controls were used to provide a summary score that was divided into quartiles, of which the first quartile represented the lowest and the fourth quartile the highest score.

We assessed depression by asking whether, during the past 12 months, the participant had felt sad, blue, or depressed for 2 weeks or more in a row, and if yes, graded by a set of seven no-yes questions—lose interest in things, feel tired or low on energy, gain or lose weight, trouble falling asleep, trouble concentrating, think of death, feeling worthless—of which five or more positive responses were defined as clinical depression. This questionnaire is an adaptation of the short form DSM-IV CIDI questionnaire for depression.[19]

Standard physical measurements were done in duplicate, by the same examiner, on every participant: height, weight, and waist and hip circumference. Waist and hip circumferences were measured with a non-stretchable standard tape measure. We recorded relevant items, including history of tobacco use, diabetes, family history, physical activity, and patterns of alcohol and food consumption. In 292 controls, we readministered the questionnaire after a median interval of 409 days. The weighted κ statistic was 0·53 for global stress, 0·66 for financial stress, 0·43 for life events, 0·60 for locus of control, and 0·44 for depression.

Statistical analysis

Details of statistical analysis are provided in the accompanying paper.[16] Briefly, we accounted for the potential differences in age structure of the populations (subdivided by region or ethnic origin) by direct standardisation of the frequencies to the overall INTERHEART age distribution, using a five-level age stratification factor (<45, 45–55, 56–65, 66–70, >70).[20] We calculated means and medians to summarise continuous effects and compared them with *t* tests, or

Region	Number	Case (%)	Control (%)	Odds ratio (99% CI)
Overall	24 767	27·3	20·1	1·55 (1·42–1·68)
Western Europe	1375	39·7	29·5	1·70 (1·23–2·34)
Central and eastern Europe	3473	26·6	23·7	1·11 (0·89–1·37)
Middle East	2892	30·2	23·0	1·27 (1·01–1·58)
Africa	1259	29·5	21·7	1·51 (1·07–2·12)
South Asia	3300	25·9	17·4	1·59 (1·28–1·98)
China and Hong Kong	5894	15·6	7·7	2·10 (1·66–2·67)
Southeast Asia	1921	29·8	24·2	1·27 (0·96–1·67)
Australia and New Zealand	1255	42·9	31·3	1·82 (1·32–2·51)
South America and Mexico	2783	40·2	24·6	2·01 (1·6–2·52)
North America	615	43·8	35·3	1·65 (1·05–2·59)
Ethnic group				
Overall	24767	27·3	20·1	1·55 (1·42–1·68)
European	6737	34·1	27·3	1·37 (1·18–1·59)
Chinese	6034	15·7	7·9	2·08 (1·64–2·62)
South Asian	3825	25·3	17·5	1·51 (1·23–1·85)
Other Asian	1770	30·6	25·5	1·25 (0·94–1·66)
Arab	2538	31·5	23·4	1·31 (1·03–1·66)
Latin American	2652	39·7	24·7	2·03 (1·60–2·56)
Black African	471	33·8	23·9	1·64 (0·91–2·95)
Coloured African	601	29·5	16·6	2·09 (1·25–3·50)

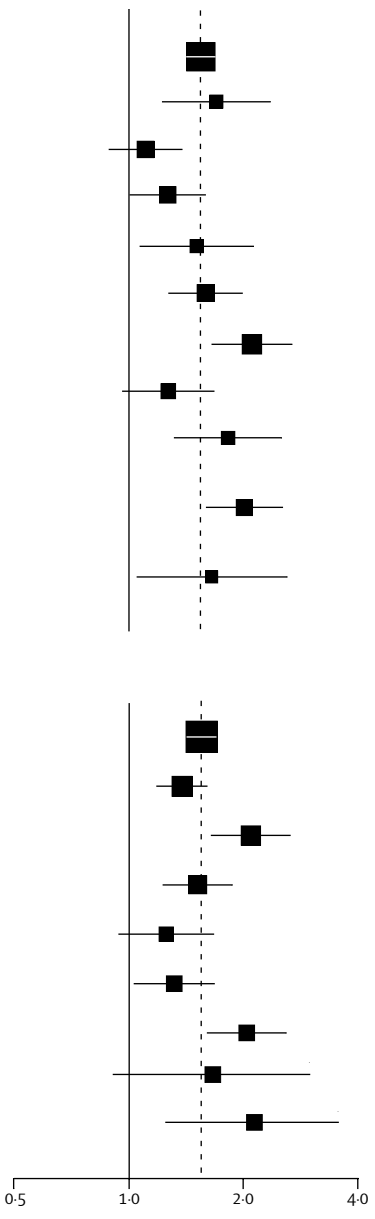

Figure 1: **Moderate or severe general stress in cases and controls by geographic region and ethnic origin**
Percentages and controls are age adjusted. Odds ratios are adjusted for geographic region, age, sex, and smoking.

appropriate non-parametric tests when distributional assumptions were in doubt. When testing for associations between stress subgroups, linear regression was used for continuous variables and the Cochran-Armitage trend test for frequencies. The findings presented are for models fitted with unconditional logistic regression, adjusted for age, sex, geographic region, and potential confounders.

Relative risk estimates are reported as odds ratios and accompanying 99% CIs. We produced statistical analyses and graphics 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. Population attributable risks (PARs)—ie, the proportion of all cases attributable to the relevant factor if causality were proven—and 99% CIs were calculated for various risk factors in the study, using the methods of Benichou and Gail.[21] The PARs presented are adjusted for confounders in a similar fashion to the corresponding logistic regression models for odds ratio estimates. PAR estimates

Region	Number	Case (%)	Control (%)	Odds ratio (99% CI)
Overall	24767	24·1	17·6	1·55 (1·42–1·69)
Western Europe	1375	28·4	22·9	1·20 (0·87–1·66)
Central and eastern Europe	3473	17·3	15·7	1·04 (0·82–1·33)
Middle East	2892	24·5	15·2	1·95 (1·51–2·52)
Africa	1259	30·3	19·7	1·69 (1·20– 2·39)
South Asia	3300	30·0	19·0	1·62 (1·3–2·02)
China and Hong Kong	5894	20·4	9·7	2·38 (1·94–2·92)
Asia	1921	19·4	12·3	1·70 (1·21–2·39)
Australia and New Zealand	1255	25·6	22·1	1·18 (0·82–1·69)
South America and Mexico	2783	34·9	30·2	1·20 (0·96–1·50)
North America	615	23·7	19·3	1·37 (0·80–2·35)
Ethnic group				
Overall	24767	24·1	17·6	1·55 (1·42–1·69)
European	6737	22·1	18·6	1·16 (0·98–1·36)
Chinese	6034	20·2	9·6	2·38 (1·95– 2·92)
South Asian	3825	29·5	18·4	1·64 (1·34–2·02)
Other Asian	1770	20·1	13·5	1·59 (1·13–2·25)
Arab	2538	25·5	15·7	2·03 (1·55–2·65)
Latin American	2652	34·5	29·8	1·21 (0·96–1·52)
Black African	471	35·2	21·9	1·63 (0·91–2·93)
Coloured African	601	26·9	17·8	1·72 (1·03–2·88)

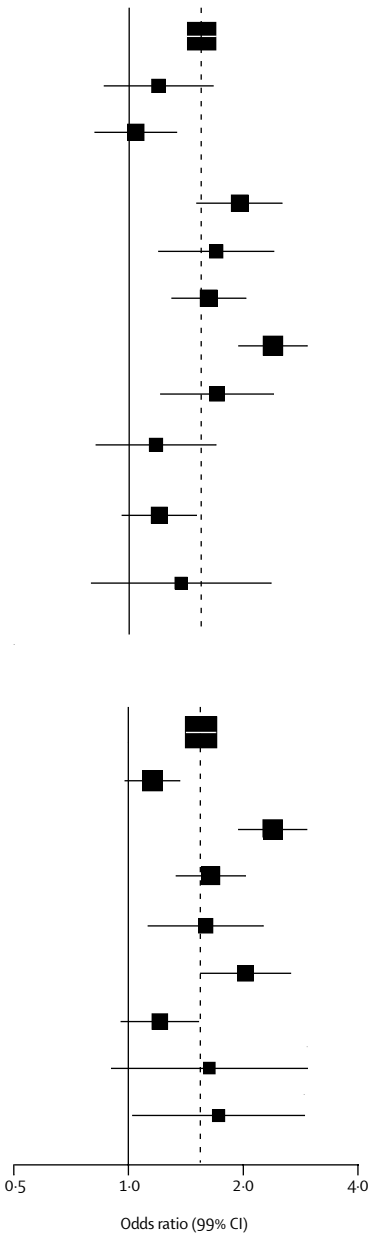

Figure 2: **Depression in cases and controls by geographic region and ethnic origin**
Percentages of cases and controls are age adjusted. Odds ratios are adjusted for geographic region, age, sex, and smoking.

were calculated with the Interactive Risk Attributable Program software (US National Cancer Institute, 2002).[22]

Role of the funding source

The sponsor 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 data and had final responsibility for the decision to submit for publication.

Results

The mean age of cases was 58·2 years (SD 12·2) and of controls 57·1 years (12·1); 24·2% (2686) of cases and 26·5% (3619) of controls were women. Figure 1 outlines the distribution of cases and controls by region and ethnic origin and provides the odds ratios associated with high general stress. We defined high general stress as several periods of or permanent stress, at work, home, or both. Figure 2 shows corresponding data for

depressive mood, which we defined as feeling sad, blue, or depressed for 2 weeks or more in a row during the past 12 months.

Table 1 presents analyses among controls by general stress score. Individuals with high general stress were younger, heavier, and more usually smokers, had a slightly lower waist/hip ratio, and were less likely to have low income and low education. Strong associations were noted between perceived general stress and financial stress, having had two or more life events, depression, and low control. Inter-relations between the different psychosocial variables were very similar among cases and controls.

Half the study population (5426 cases [48·8%] and 7387 controls [54·1%]) were working outside the home. Higher ratings for work stress were more usual in cases than controls (table 2). For example, during the previous year, just over a third more cases experienced several periods of work stress compared with controls (odds ratio 1·38 [99% CI 1·19–1·61]), and permanent work stress was experienced by twice as many cases than controls (2·14 [1·73–2·64]), after adjustment for age, sex, geographic region, and smoking. The PAR among those working was 9% (99% CI 1–18). Further adjustment for education and income, hypertension, diabetes, level of physical activity, waist/hip ratio, dietary patterns, alcohol, or raised plasma lipids did not alter these results to a significant degree. Therefore, we report results from the most parsimonious model.

Compared with controls, cases also reported more frequent periods of stress at home during the previous 12 months (table 2). For example, more cases than controls experienced several periods of stress (odds ratio 1·52 [1·34–1·72]), whereas twice as many cases reported permanent stress at home compared with controls (2·12 [1·68–2·65]). The PAR for stress at home was 8% (4–12). Reports of severe financial stress were also more typical in cases than controls (adjusted odds ratio 1·33 [1·19–1·48]; table 2). The PAR for financial stress was 11% (7–14). Two or more stressful life events were reported by about a half more cases compared with controls (odds ratio 1·48 [1·33–1·64]; PAR 10% [8–13]; table 2). Of these events, business failure (1·60 [1·42–1·80]) and major intra-family conflict (1·55 [1·41–1·70]) had the highest risks, whereas job loss (1·36 [1·22–1·52]), death of spouse (1·37 [1·11–1·69]) and violence (1·31 [1·13–1·53]), although still significant, were associated with lower risk. Divorce, injury, and death of other family members were similar among cases and controls.

High locus of control was a significant protective factor. After adjustment for age, sex, geographic region and smoking, the odds ratio was 0·72 (99% CI 0·65–0·79) for the second highest quartile of the population relative to those in the lowest quartile for locus of control, and 0·68 (0·61–0·76) for the highest relative to the lowest quartile (table 2). However, after full adjustment for all risk factors, the apparent effect was substantially attenuated, with an estimated odds ratio of 0·75 (0·65–0·86) in the fourth quartile relative to the first. The PAR for low locus of control was 16% (10–22).

More cases than controls reported feeling sad, blue, or depressed for more than 2 weeks or more in a row (odds ratio 1·55 [1·42–1·69]; table 2), and this difference did not change substantially after adjustment for other factors. No relation was reported between number of items with positive responses for the depression question and risk of acute myocardial infarction. The PAR associated with sadness and depression was 9% (7–10).

The general stress measure—combining work and home stress—was associated with an odds ratio of 1·45 (1·30–1·61) for several periods and 2·17 (1·84–2·55) for permanent stress (table 2). Adding financial stress, locus of control, life events, and reports of feeling sad, either as single elements or in combination with this scale, did not improve its discriminatory power. For general stress, the PAR was 12% (7–17); however, combining any exposure to general stress, financial stress, stressful life events, depression, and low locus of control, a PAR of 29% (22–35) was estimated after adjustment for age, sex, geographic region, and smoking. Further adjustment for all risk factors as above changed the PAR estimate to 33% (25–41).

	Never (n=3688)	Some (n=7193)	Several (n=2183)	Permanent (n=584)	p*
Risk factor					
Age (years)	60·7 (12·01)	56·7 (12·0)	53·6 (11·4)	52·5 (10·6)	<0·0001
Body-mass index (kg/m²)	25·7 (4·0)	25·8 (4·1)	26·0 (4·3)	26·6 (4·5)	<0·0001
Waist/hip ratio	0·918 (0·082)	0·906 (0·084)	0·906 (0·082)	0·912 (0·085)	<0·0001
Systolic blood pressure (mm Hg)	131 (18)	129 (17)	128 (17)	128 (18)	<0·0001
Serum cholesterol (mmol/L)	5·03 (1·31)	5·04 (1·22)	5·22 (1·22)	5·32 (1·17)	<0·0001
Serum triglyceride (mmol/L)	1·90 (1·29)	1·96 (1·35)	2·05 (1·65)	2·03 (1·32)	0·0003
Serum HDL (mmol/L)	1·08 (0·38)	1·07 (0·38)	1·08 (0·41)	1·11 (0·40)	0·67
ApoB/ApoA1 ratio	0·790 (0·374)	0·791 (0·326)	0·806 (0·327)	0·800 (0·243)	0·16
Smoking	25·6% (943)	27·2% (1952)	30·2% (658)	34·0% (197)	<0·0001
Sedentary leisure time physical activity	52·3% (1927)	55·1% (3963)	51·8% (1131)	49·9% (291)	0·48
Diabetes	7·9% (291)	7·0% (503)	7·2% (157)	7·2% (42)	0·28
Hypertension	24·0% (885)	21·7% (1559)	20·1% (438)	23·1% (135)	0·006
Income					
Lowest two-fifths	52·3% (1901)	49·2% (3494)	46·7% (1001)	44·1% (254)	<0·0001
Education					
Fewer than 8 years	44·5% (1639)	37·5% (2693)	30·5% (666)	26·7% (156)	
College or university	29·6% (1093)	36·2% (2605)	48·2% (1052)	49·5% (289)	<0·0001
Other psychosocial variables					
High or severe financial stress	4·8% (177)	11·6% (832)	21·7% (473)	30·3% (177)	<0·0001
Two or more events	7·2% (266)	10·7% (771)	25·0% (546)	32·2% (188)	<0·0001
Depression	10·1% (374)	15·7% (1132)	29·4% (642)	43·8% (256)	<0·0001
Low locus of control	16·0% (590)	18·7% (1343)	22·7% (496)	32·5% (190)	<0·0001

Data are mean (SD) or percentage of controls (n). Missing data for smoking in 46 controls, diabetes in nine, hypertension in eight, physical activity in eight, income in 192, and education in five. Spearman correlation coefficients (cases/controls) between global stress and financial stress 30·0/25·7, two or more life events 26·2/22·2, depression 22·7/19·5, locus of control −12·1/−5·6. *Test for trend.

Table 1: **Cardiovascular risk factors, income, education, and other psychosocial variables in controls (both working and non-working) by general stress score**

	Number of cases (%)	Number of controls (%)	Odds ratio (99% CI)	PAR (99% CI)
Stress at work (n=12 813)				
Never	1138 (21·0%)	1768 (23·9%)	1	
Some of the time	2499 (46·1%)	3923 (53·1%)	0·95 (0·84–1·08)	
Several periods	1249 (23·0%)	1324 (17·9%)	1·38 (1·19–1·61)	
Permanent	540 (10·0%)	372 (5·0%)	2·14 (1·73–2·64)	9% (1–18)
Stress at home (n=24 767)				
Never	4086 (36·8%)	5343 (39·2%)	1	
Some of the time	5361 (48·2%)	6873 (50·4%)	1·05 (0·97–1·13)	
Several periods	1288 (11·6%)	1179 (8·6%)	1·52 (1·34–1·72)	
Permanent	384 (3·5%)	253 (1·9%)	2·12 (1·68–2·65)	8% (4–12)
General stress* (n=24 767)				
Never	2777 (25·0%)	3688 (27·0%)	1	
Some period, home or work	5352 (48·1%)	7193 (52·7%)	1·05 (0·96–1·14)	
Several periods, home or work	2139 (19·2%)	2183 (16·0%)	1·45 (1·30–1·61)	
Permanent, home or work	851 (7·7%)	584 (4·3%)	2·17 (1·84–2·55)	12% (7–17)
Financial stress (n=24 767)				
Little or none	4872 (43·8%)	6628 (48·6%)	1	
Moderate	4625 (41·6%)	5361 (39·3%)	1·19 (1·11–1·29)	
Severe	1622 (14·6%)	1659 (12·2%)	1·33 (1·19–1·48)	11% (7–14)
Stressful life events (n=24 767)				
None	6425 (57·8%)	8528 (62·5%)	1	
1	2904 (26·1%)	3349 (24·5%)	1·23 (1·13–1·34)	
2 or more	1790 (16·1%)	1771 (13·0%)	1·48 (1·33–1·64)	10% (8–13)
Locus of control (n=24 767)				
Q1	2620 (23·6%)	2619 (19·2%)	1	
Q2	2938 (26·4%)	3265 (23·9%)	0·89 (0·80–0·98)	
Q3	3614 (32·5%)	4839 (35·5%)	0·72 (0·65–0·79)	
Q4	1947 (17·5%)	2925 (21·4%)	0·68 (0·61–0·76)	16% (10–22)
Feeling depressed† (n=24 767)				
No	8446 (76·0%)	11244 (82·4%)	1	
Yes	2673 (24·0%)	2404 (17·6%)	1·55 (1·42–1·69)	9% (7–10)
Depression (n=24 767)				
Not depressed	8446 (76·0%)	11244 (82·4%)	1	
0–1 items	346 (3·1%)	298 (2·2%)	1·50 (1·21–1·86)	
2–4 items	1369 (12·3%)	1145 (8·4%)	1·65 (1·47–1·85)	
5 or more items	958 (8·6%)	961 (7·0%)	1·44 (1·27–1·65)	

All associations are significant at p<0·0001. Q=quartile, where Q1 is lowest locus. *Includes both working and non-working participants. †Felt sad, blue, or depressed for more than 2 consecutive weeks in past year.

Table 2: **Psychosocial risk factors in cases and controls**

Separate analyses in men and women showed that, by contrast to men, work stress did not seem to be associated with acute myocardial infarction in women (p=0·006, for interaction; table 3). However, this apparent interaction should be interpreted cautiously because several subgroup analyses were done. For all other factors, effects among women were similar to those seen among men, with no significant heterogeneity. A separate analysis in the 435 patients who died while still in hospital showed the same relation with stress as the total population of patients with acute myocardial infarction (not shown).

Table 4 presents results of the effect of general stress in various subgroups stratified by age, smoking, income, and education. The association with acute myocardial infarction did not differ greatly by any of these factors. Permanent stress was less prevalent in older versus younger participants, but no significant interaction was recorded between age and stress (p=0·13). The effect of general stress was similar across different strata defined by age, income, or education and among smokers and non-smokers. Table 5 describes the combined effects of general stress and depression, and of general stress and locus of control.

The prevalence of moderate or severe general stress ranged from 7·7% among controls in China to 35·3% in North America (figure 1). Despite this difference, stress was more common among cases than controls in all geographic regions, with odds ratios varying between 1·3 and 2·1, with the exception of central and eastern Europe, where the difference in rates of stress between cases and controls seemed to be only minor. Almost all ethnic groups were characterised by more general stress in cases than controls (figure 1). Although the prevalence of sadness and depression also varied between regions and various ethnic groups (figure 2), it was related to acute myocardial infarction in various subgroups examined.

Discussion

Our study shows that several elements reflecting psychosocial stress are associated with increased risk of acute myocardial infarction. These factors include those that are subjective and perceived by the patients, such as stress, defined as tension or anxiety due to external influences. Some of these measures—eg, locus of control or depression—are not generally perceived by lay people to be stressors. Further, discrete external events (eg, major life events), which are less subjective and less likely to be subject to any biases, were also more frequent in cases than controls. The effect of stress is independent of socioeconomic status and smoking, and is by and large consistent across geographic regions, in different age groups, and in men and women. The excess risk of acute myocardial infarction associated with high levels of stress was still significant after adjusting for other cardiovascular risk factors.

During the past two decades, considerable evidence has accumulated with respect to the association of markers of stress and other psychosocial factors with coronary disease.[4,23] However, compared with many other biological and lifestyle risk factors, stress is a more difficult construct in that no consensus exists with respect to either definition or measurement. Further, stress is inevitably a subjective measurement, and hence is potentially open to biases and confounding. Nevertheless, the strong relation between self-reported stress and other more objective markers, such as life events or depression, and constructs such as locus of control (which is not associated by lay people as being related to stress) suggests face validity for the measures used in the study.

To date, most studies have dealt with stress at work, with stress outside the workplace receiving less attention. Both cross-sectional and prospective studies have shown a positive association between level of work stress and disease.[8,10,13] Number of work stressors has been associated with increased cardiovascular mortality

	Men			Women			
	Cases (%)	Controls (%)	Odds ratio (99% CI)	Cases (%)	Controls (%)	Odds ratio (99% CI)	p*
Stress at work							
Never	993 (20·3)	1504 (24·1)	1	145 (26·7)	264 (23·3)	1	
Some of the time	2265 (46·4)	3315 (53·0)	1·00 (0·88–1·15)	234 (43·0)	608 (53·6)	0·68 (0·48–0·96)	
Several periods	1125 (23·0)	1117 (17·9)	1·45 (1·23–1·70)	124 (22·8)	207 (18·2)	1·02 (0·68–1· 54)	
Permanent	499 (10·2)	316 (5·1)	2·34 (1·86–2·93)	41 (7·5)	56 (4·9)	1·11 (0·60–2·06)	0·006
Stress at home							
Never	3314 (39·3)	4171 (41·6)	1	772 (28·7)	1172 (32·4)	1	
Some of the time	4008 (47·5)	5005 (49·9)	1·01 (0·93–1·10)	1353 (50·4)	1868 (51·6)	1·16 (0·99–1·35)	
Several periods	862 (10·2)	718 (7·2)	1·53 (1·32–1·78)	426 (15·9)	461 (12·7)	1·53 (1·23–1·90)	
Permanent	249 (3·0)	135 (1·4)	2·36 (1·75–3·17)	135 (5·0)	118 (3·3)	1·88 (1·31–2·69)	0·12
General stress†							
Never	2074 (24·6)	2682 (26·7)	1	703 (26·2)	1006 (27·8)	1	
Some period, home or work	4024 (47·7)	5322 (53·1)	1·02 (0·93–1·13)	1328 (49·4)	1871 (51·7)	1·10 (0·94–1·30)	
Several periods, home or work	1654 (19·6)	1601 (16·0)	1·46 (1·29–1·66)	485 (18·1)	582 (16·1)	1·40 (1·13–1·73)	
Permanent, home or work	681 (8·1)	424 (4·2)	2·32 (1·93–2·80)	170 (6·3)	160 (4·4)	1·74 (1·25–2·40)	0·091
Financial stress							
Little or none	3707 (44·0)	4921 (49·1)	1	1165 (43·4)	1707 (47·2)	1	
Moderate	3495 (41·4)	3918 (39·1)	1·19 (1·09–1·29)	1130 (42·1)	1443 (39·9)	1·22 (1·05–1·41)	
Severe	1231 (14·6)	1190 (11·9)	1·33 (1·17–1·50)	391 (14·6)	469 (13·0)	1·33 (1·08–1·64)	0·74
Stressful life events							
None	4857 (57·6)	6242 (62·2)	1	1568 (58·4)	2286 (63·2)	1	
1	2186 (25·9)	2483 (24·8)	1·21 (1·10–1·33)	718 (26·7)	866 (23·9)	1·30 (1·11–1·52)	
2 or more	1390 (16·5)	1304 (13·0)	1·51 (1·34–1·70)	400 (14·9)	467 (12·9)	1·37 (1·12–1·68)	0·17
Locus of control							
Q1	1843 (21·9)	1780 (17·8)	1	777 (28·9)	839 (23·2)	1	
Q2	2130 (25·3)	2304 (23·0)	0·89 (0·79–1·00)	808 (30·1)	961 (26·6)	0·89 (0·74–1·07)	
Q3	2835 (33·6)	3668 (36·6)	0·73 (0·65–0·81)	779 (29·0)	1171 (32·4)	0·71 (0·60–0·85)	
Q4	1625 (19·3)	2277 (22·7)	0·72 (0·63–0·82)	322 (12·0)	648 (17·9)	0·55 (0·44–0·69)	0·019
Feeling depressed in past 2 weeks							
No	6532 (77·5)	8387 (83·6)	1	1914 (71·3)	2857 (78·9)	1	
Yes	1901 (22·5)	1642 (16·4)	1·53 (1·38–1·69)	772 (28·7)	762 (21·1)	1·60 (1·37–1·88)	0·17

*Interaction with sex. †Includes both working and non-working participants.

Table 3: **Psychosocial risk factors in cases and controls by sex**

in the Multiple Risk Factor Intervention Trial.[8] During a 9-year follow-up period of 12 336 men, those with three or more work stressors had an increased risk of cardiovascular death (relative risk 1·26 [95% CI 1·07–1·48]), and the experience of divorce also increased risk (1·37 [1·09–1·72]) relative to those who remained married or single). In one prospective study of women with coronary heart disease,[24] level of marital stress, according to the Stockholm Marital Stress Scale, was associated with a higher risk of recurrent events. By contrast, data from a large North American study of nurses[25] showed no association between a measure of work strain and subsequent coronary heart disease. However, this study had low power (only 146 events) and in view of the homogeneity of the population studied (all nurses) there might have been little variation in the distribution of stress levels.

Other general measures of stress have also been used. In a prospective survey of middle-aged Swedish men,[14] self-reported permanent stress over a defined period in the recent past (as measured by a single-item question similar to that used in INTERHEART) was associated with an increased risk of incident coronary heart disease (odds ratio 1·5 [95% CI 1·2–1·9], after adjustment for conventional coronary risk factors) during the 12-year follow-up. Similar results were noted in a large prospective study involving 281 cases in 73 424 Japanese men and women,[9] which reported an association between perceived mental stress and coronary heart disease mortality. The consistency of results that has been reported across multiple studies using different study designs and approaches provide a body of evidence that supports an association between various types of stress and coronary disease. In view of the large number of cases in the study, INTERHEART provides robust results, even in subgroups. Furthermore, the effect of stress on acute myocardial infarction in the present study was by and large consistent across different geographic regions, in different ethnic groups, in men and women, and at all ages.

Depression has been associated with an increased risk of coronary heart disease in both men and women.[1–3] In the present study, we showed that feeling sad, blue, or depressed for 2 weeks or more in a row was associated with acute myocardial infarction across different populations and across groups of people with different ethnic origins. A meta-analysis of 11 studies concluded that depression predicts the development of coronary heart disease in initially healthy people (odds ratio 1·64 [95% CI 1·29–2·08]).[26] Sensitivity analysis showed that

	Cases (%)	Controls (%)	Odds ratio (99% CI)	Cases (%)	Controls (%)	Odds ratio (99% CI)	Cases	Controls (%)	Odds ratio (%) (99% CI)
Age (years)	**<56**			**56–64**			**>64**		
General stress									
Never	782 (16·2)	1179 (18·7)	1	794 (26·5)	1106 (29·7)	1	1201 (36·4)	1403 (38·8)	1
Some period, home or work	2224 (46·2)	3436 (54·5)	0·98 (0·85–1·13)	1502 (50·0)	1956 (52·6)	1·11 (0·95–1·30)	1626 (49·3)	1801 (49·8)	1·07 (0·94–1·23)
Several periods, home or work	1263 (26·2)	1301 (20·6)	1·49 (1·26–1·76)	500 (16·7)	537 (14·4)	1·37 (1·11–1·69)	376 (11·4)	345 (9·5)	1·37 (1·10–1·71)
Permanent, home or work	548 (11·4)	391 (6·2)	2·10 (1·69–2·62)	206 (6·9)	122 (3·3)	2·50 (1·80–3·47)	97 (2·9)	71 (2·0)	1·82 (1·19–2·78)
Smoking	**Never**			**Former**			**Current**		
General stress									
Never	1062 (28·0)	1919 (27·5)	1	641 (28·9)	816 (28·4)	1	1047 (21·0)	897 (24·9)	1
Some period, home or work	1909 (50·3)	3789 (54·3)	1·01 (0·89–1·14)	1017 (45·9)	1429 (49·7)	1·01 (0·84–1·20)	2369 (47·6)	1888 (52·4)	1·12 (0·97–1·30)
Several periods, home or work	618 (16·3)	1017 (14·6)	1·41 (1·19–1·67)	391 (17·6)	499 (17·4)	1·25 (0·99–1·57)	1099 (22·1)	629 (17·5)	1·65 (1·37–1·98)
Permanent, home or work	208 (5·5)	251 (3·6)	2·07 (1·59–2·71)	169 (7·6)	132 (4·6)	2·17 (1·54–3·04)	465 (9·3)	189 (5·3)	2·33 (1·79–3·02)
Income	**1–2 (low)**			**3**			**4–5 (high)**		
General stress									
Never	1424 (25·0)	1901 (28·6)	1	541 (22·7)	729 (26·3)	1	779 (27·0)	1007 (25·0)	1
Some period, home or work	2802 (49·1)	3494 (52·5)	1·13 (1·00–1·27)	1248 (52·3)	1562 (56·4)	1·09 (0·91–1·31)	1248 (43·2)	2043 (50·6)	0·88 (0·75–1·04)
Several periods, home or work	1071 (18·8)	1001 (15·1)	1·52 (1·30–1·77)	444 (18·6)	384 (13·9)	1·74 (1·36–2·21)	586 (20·3)	759 (18·8)	1·21 (1·00–1·48)
Permanent, home or work	410 (7·2)	254 (3·8)	2·40 (1·90–3·04)	154 (6·5)	97 (3·5)	2·23 (1·52–3·28)	274 (9·5)	225 (5·6)	1·91 (1·45–2·52)
Education	**<8 years**			**9–12 years**			**Trade/college/university**		
General stress									
Never	1387 (28·1)	1639 (31·8)	1	711 (24·2)	955 (27·7)	1	679 (20·9)	1093 (21·7)	1
Some period homework	2483 (50·4)	2693 (52·3)	1·11 (1·01–1·22)	1435 (48·9)	1891 (54·8)	1·07 (0·94–1·21)	1432 (44·0)	2605 (51·7)	0·94 (0·83–1·06)
Several periods	798 (16·2)	666 (12·9)	1.53 (1·34–1·75	548 (18·7)	465 (13·5)	1·72 (1·46–2·03)	793 (24·4)	1052 (20·9)	1·28 (1·11–1·47)
Perrnanent home or work	262 (5·3)	156 (3·0)	2.23 (1·79–2·79)	240 (8·2)	139 (4·0)	2·53 (1·99–3·22)	348 (10·7)	289 (5·7)	2·02 (1·67–2·45)

Table 4: **General stress by age, smoking, income, and education in cases and controls**

clinical depression was a stronger predictor than depressive mood. Contrary to the findings in this meta-analysis, we did not find a so-called dose-response relation, because the risk of a myocardial infarction was similarly increased irrespective of the number of items in the depression scale that were positive. The prevalence of clinical depression among the controls in our study (7·0%) was comparable with estimates of mood disorders worldwide,[27] but lower than that for depressive mood (17·6%). This difference between studies suggests that those who were classified as being depressed in our study include some individuals with true clinical depression and some with a less specific reaction to stressors, which could account for the similarity of findings for depressive mood and stress.

Few studies have investigated the effect of external influences like financial stress or life events on risk of coronary disease. Findings of a case-control study[13] showed that experience of one life event or more during the year preceding an acute myocardial infarction, and dissatisfaction with one's financial situation, was twice as common in cases than controls among men, but no significant relation was found among women. However, the lack of effect in women in the above study[13] might have been because it contained few women. Our study, which includes 2686 female cases and 3619 female controls, shows consistent relations in both men and women. In a Danish registry-based study,[7] an extreme external stressor, such as the death of a child, was shown to be associated with increased risk of future acute myocardial infarction; this finding is consistent with the present study, in which business failure, major intrafamily conflict, job loss, death of spouse, and violence were associated with increased risk.

Our questionnaires were derived from items that were previously shown in longitudinal studies to predict

	General stress category											
	Never			Some periods, at home or work			Several periods, at home or work			Permanent, at home or work		
	Cases	Controls	Odds ratio (99% CI)	Cases	Controls	Odds ratio (99% CI)	Cases	Controls	Odds ratio (99% CI)	Cases	Controls	Odds ratio (99% CI)
Depression												
No	2359	3314	1·0	4319	6061	0·95 (0·80–1·14)	1333	1541	1·19 (0·97–1·45)	435	328	1·71 (1·32–2·21)
Yes	418	374	1.41 (1·21–1·64)	1033	1132	1·34 (1·07–1·68)	806	642	1·67 (1.33–2·11)	416	256	2·40 (1·83–3·15)
Locus of control												
Q4	619	917	1·0	867	1481	0·96 (0·80–1·15)	327	427	1·22 (1·00–1·49)	134	100	1·78 (1·38–2·30)
Q3	900	1186	1·03 (0·87–1·21)	1896	2693	0·99 (0·78–1·25)	605	780	1·26 (0·98–1·61)	213	180	1·84 (1·36–2·47)
Q2	781	995	1·34 (1·12–1·62)	1434	1676	1·29 (1·00–1·66)	535	480	1·64 (1·26–2·13)	188	114	2·40 (1·76–3·26)
Q1	477	590	1·55 (1·28–1·89)	1155	1343	1·49 (1·15–1·93)	672	496	1·90 (1·46–2·47)	316	190	2·77 (2·05–3·75)

Odds ratios adjusted for age, sex, smoking status, and geographic region.

Table 5: **Odds ratios for combined effect of general stress and depression or locus of control on risk of acute myocardial infarction**

cardiovascular events.[14] Because INTERHEART intended to recruit a large number of cases and controls from 52 countries, our questionnaires had to be simple and brief. The fact that such simple questions are informative across such diverse settings is a particular strength of our study.

Levels of stress, depression, and locus of control reported by INTERHEART controls varied substantially across regions. The differences in rates of these factors could be attributable to variations in interpretation of the questions in different cultures and the extent of social desirability with respect to responses, but this difference would not be expected to affect the comparisons between cases and controls, because both groups of participants were recruited within the same centre in every country. The validity of our conclusions is supported by the excess risk associated with most of the measures we used, and it is consistent in various regions. The odds ratios in various subgroups are essentially in the same direction, and the CIs generally overlap the overall odds ratio for every construct examined. Although we cannot exclude that self-reported stress might be subject to biases by cases spuriously reporting stress more often than controls, this is less likely to be a problem with measures such as low locus of control, life events, or perhaps depression, which are not typically judged to be associated with stress by lay individuals. The coherence of the results across both types of questions increases the plausibility of our findings, and the consistency across various geographic regions adds robustness and internal replication. Although quantification of any potential biases is difficult because of the case-control design we used, the similarity of our overall findings with those from several cohort studies is reassuring.

The present study has two additional potential limitations. First, we did not enrol patients who died before they could be interviewed. However, a separate analysis of the 435 patients who died in INTERHEART showed the same relation with stress as the total population of patients with acute myocardial infarction. Second, the experience of the acute myocardial infarction could theoretically alter a patient's perceptions about recent stress and mood. Even so, previous studies have shown that although perception of risk factor status may change, confirmatory search after the discovery of disease only moderately influences the recollection of symptoms in the month preceding disease.[28] A retrospective design has the advantage of assessing stress during the recent past, whereas longitudinal studies can underestimate the effects of a past period of intense stress owing to the long interval between an interview and the occurrence of an event, nor can they explore the relation of stress in the period just before the myocardial infarction. Also, true levels of stress might vary over time in the same individual. In 292 individuals, repeat measures obtained at an interval of greater than a year indicated a moderate correlation of 0·5 (compared with, for example, 0·7 for apolipoprotein B and 0·9 for smoking). This finding suggests that the effect of an analysis adjusting for variability (eg, regression-dilution bias) could indicate an even stronger relation than that described in the present article. However, adjustment for regression-dilution bias simultaneously across multiple variables is complex, and we are not aware of any study that has done that.

Not all prospective studies have reported a significant relation between psychological stress and ischaemic heart disease.[29–31] The lack of an association could be attributable to low power because of few events[29] in several studies and potential waning of an effect when events arise after measurement of stress.[29–31] Residual confounding of low socioeconomic status has been proposed as a potential explanation.[30] However, in INTERHEART, all associations recorded between psychosocial stress factors and myocardial infarction were unchanged after adjustment for income and education.

The mechanism by which psychosocial factors increase the risk of myocardial infarction is complex. In experimental studies, worsened coronary atherosclerosis[32] and endothelial dysfunction[33] happen in response to social disruption. Several studies have shown links between psychosocial variables and vascular function,[34,35] inflammation,[36] increased blood clotting, and decreased fibrinolysis.[37,38] The exact pathophysiological nature of the influence of psychosocial factors remains to be determined, as does the temporal sequence of events.

In conclusion, our study indicates that psychosocial stressors are related to increased risk of acute myocardial infarction. For severe global stress, the size of the effect was less than that for smoking but comparable with hypertension and abdominal obesity.[16] Our study is unique in having evaluated simultaneously multiple elements of stress, in inclusion of perception of stress and life events, and in objective constructs such as locus of control. In view of the large number of participants and inclusion of multiple populations and ethnic groups, we have shown that the effects of stress on acute myocardial infarction are similar in men and women, in people of various ages, and in all geographic regions of the world that we studied. The PAR for each of the measures ranged from 8% to 16%, and collectively adds up to 33% for all variables. If this effect is truly causal, the importance of psychosocial factors is much more important than commonly recognised, and might contribute to a substantial proportion of acute myocardial infarction.

Contributors

S Yusuf initiated the INTERHEART study and supervised the project, data analysis, and writing of the report. A Rosengren had main responsibility for writing the report. S Hawken did statistical analyses. S Ôunpuu coordinated the project. All other investigators facilitated and supervised the study in their own country and commented on drafts of the report.

Conflict of interest statement

We declare that we have no conflict of interest.

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