# Physical Activity and Anger or Emotional Upset as Triggers of Acute Myocardial Infarction

## The INTERHEART Study



**BACKGROUND:** Physical exertion, anger, and emotional upset are reported to trigger acute myocardial infarction (AMI). In the INTERHEART study, we explored the triggering association of acute physical activity and anger or emotional upset with AMI to quantify the importance of these potential triggers in a large, international population.

**METHODS:** INTERHEART was a case-control study of first AMI in 52 countries. In this analysis, we included only cases of AMI and used a case-crossover approach to estimate odds ratios for AMI occurring within 1 hour of triggers.

**RESULTS:** Of 12 461 cases of AMI 13.6% (n=1650) engaged in physical activity and 14.4% (n=1752) were angry or emotionally upset in the case period (1 hour before symptom onset). Physical activity in the case period was associated with increased odds of AMI (odds ratio, 2.31; 99% confidence interval [CI], 1.96–2.72) with a population-attributable risk of 7.7% (99% CI, 6.3–8.8). Anger or emotional upset in the case period was associated with an increased odds of AMI (odds ratio, 2.44; 99% CI, 2.06–2.89) with a population-attributable risk of 8.5% (99% CI, 7.0–9.6). There was no effect modification by geographical region, prior cardiovascular disease, cardiovascular risk factor burden, cardiovascular prevention medications, or time of day or day of onset of AMI. Both physical activity and anger or emotional upset in the case period were associated with a further increase in the odds of AMI (odds ratio, 3.05; 99% CI, 2.29–4.07; *P* for interaction <0.001).

**CONCLUSIONS:** Physical exertion and anger or emotional upset are triggers associated with first AMI in all regions of the world, in men and women, and in all age groups, with no significant effect modifiers.

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- myocardial infarction
- precipitating factors

## Clinical Perspective

### What Is New?

- In these analyses of INTERHEART, we confirm previous reports that heavy physical exertion and anger or emotional upset may act as triggers of first acute myocardial infarction, but we also extend findings to all regions of the world.
- We found an interaction between heavy physical exertion and anger or emotional upset with an additive association in participants with exposure to both in the 1 hour before acute myocardial infarction.
- We do not report effect modification by previous cardiovascular disease, cardiovascular risk factor burden, cardiovascular prevention medications, or time and day of onset of symptoms.

### What Are the Clinical Implications?

- Our findings suggest that clinicians should advise patients to minimize exposure to extremes of anger or emotional upset because of the potential risk of triggering acute myocardial infarction.
- Our findings suggest that heavy or vigorous physical exertion (but not any physical activity) may trigger a myocardial infarction.
- Therefore, given the established benefits of regular physical activity over the long term, clinicians should continue to advise patients about the lifelong benefits of exercise.

Cardiovascular disease is the leading cause of death worldwide.[1] The INTERHEART study reported that >90% of the risk of myocardial infarction was attributable to long-term exposure to 9 risk factors.[2] Most long-term exposures (eg, lipids, obesity) are mediated through an intermediate phenotype (atherosclerotic change) rather than trigger acute rupture of atherosclerotic plaque, precipitating an acute myocardial infarction (AMI). Observational studies identified potential external triggers for AMI, including physical exertion and anger or emotional upset.[3,4] However, with few exceptions, the included studies had small sample sizes (n<2000) and were completed primarily in 1 country or geographical region (predominantly Western countries). As with long-term exposure to cardiovascular risk factors, the prevalence of potential triggers of AMI may also vary by geographical region; triggers important in 1 region or ethnic group may be different in others. Large, international studies using standardized methodology are required to determine whether there are variations in the importance of triggering risk factors and to determine other factors that may modify the association. The INTERHEART study provides an opportunity to study the association between these potential external triggers of AMI and effect modifiers in a large, international population.

## METHODS

### Study Population

As previously described, the INTERHEART study was a case-control study of first AMI completed in 262 centers across 52 countries.[2,5] In brief, consecutive cases with first AMI (defined by characteristic symptoms and ischemic ECG changes) were recruited, in addition to at least 1 age- and sex-matched control without a history of heart disease or exertional chest pain. In our primary analyses, we include only the cases of AMI, because the exposure to potential triggers was collected systematically in cases and not in controls.

### Study Procedures

Trained study staff performed a standardized physical examination on participants and administered a structured questionnaire. Participants with AMI (cases) were asked dichotomous questions, "Were you engaged in heavy physical exertion?" and "Were you angry or emotionally upset?" in the 1 hour before the onset of symptoms and during the same hour on the previous day. Control participants were asked, "During the last 24 hours, were you engaged in heavy physical exertion?" and "During the last 24 hours, were you angry or emotionally upset?" Data were also collected on age, ethnicity, diet, physical activity, tobacco use, education, employment, psychosocial factors, and cardiovascular risk factors. Anthropometric measurements (height, weight, waist, and hip circumference) were measured in a standardized manner.[6] Medical history (diabetes mellitus, hypertension, angina, stroke, other vascular disease, and depression) and baseline medications were self-reported. Smoking was categorized as never smoking, former smoking (defined as no smoking within the previous year), or current smoking. Obesity was defined as body mass index of ≥30 kg/m$^2$. Countries were grouped into 10 geographical regions: Western Europe, Central and Eastern Europe, Middle East and Egypt, Africa, South Asia, China and Hong Kong, Southeast Asia and Japan, Australia and New Zealand, South America and Mexico, and North America. Physical activity was categorized as mainly sedentary, mild exercise, or moderate/strenuous activity.[7] Stress was categorized as none or some periods of stress versus several periods or permanent stress.[8] Education was categorized as none, 1 to 8 years, 9 to 12 years, trade school, or college/university.

All data were transferred to the Population Health Research Institute, McMaster University and Hamilton Health Sciences (Hamilton, ON, Canada). Ethics and regulatory committees in participating countries and centers approved the study protocol, and all participants gave informed consent before study involvement.

### Statistical Analysis

Categorical variables are presented as percentage (number) and continuous variables as mean (SD) or median (25th–75th percentiles), as appropriate. A case-crossover approach was used for these analyses[9] in which each participant acts as





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his/her own control. The case period was defined as the 1 hour before the onset of symptoms of AMI, and the control period was defined as the same 1-hour period on the day before the onset of symptoms. Conditional logistic regression was used to estimate odds ratios and 99% confidence intervals (CIs) for physical exertion and anger or emotional upset within the case period compared with the control period. Because each participant acts as his or her own control, multivariable adjustment for baseline confounding factors was not required, but we did adjust for the other triggering event, because it varied with time, and the interaction between both triggers was significant ($P<0.001$). Population-attributable risk was calculated[10] from the proportion of participants with exposure to potential triggers in the case and control periods; 99% CIs are also reported. The Breslow-Day test of homogeneity was used to ensure that the conditional relationship between potential triggers and AMI was consistent by time and day of onset of AMI.[11]

Analyses were stratified by the following prespecified subgroups: age (<45, 45–65, >65 years), sex, smoking, diabetes mellitus, hypertension, obesity, angina, stroke, and INTERHEART risk score. For physical exertion only, subgroup analyses were also stratified by baseline level of physical activity. For anger or emotional upset only, subgroup analyses were also stratified by baseline level of chronic stress, depression, and level of education. We explored for differences in the observed associations by medications commonly used for the prevention of cardiovascular disease[12] (aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and cholesterol-lowering therapies), geographical region, and the time of day and day of the week of onset of AMI. As sensitivity analyses, we first excluded participants with exposure to alcohol in the 24 hours before AMI.[13] Second, we included the controls from INTERHEART (ie, participants without AMI) and completed a case-control analysis using conditional logistic regression, adjusting for the other trigger, the interaction term between triggers, age, sex, education, and the primary modifiable risk factors previously identified from INTERHEART (lipids, smoking, hypertension, diabetes mellitus, abdominal obesity, psychosocial factors, fruit and vegetable intake, alcohol, physical activity).[2]

Differential effects between subgroups were considered to be significant if the interaction term between the subgroup and the exposure was statistically significant; to address multiple testing, a value of $P<0.01$ was considered statistically significant. All statistical analyses were performed with Stata/MP 13.1 for Mac except population-attributable risk, for which R version 3.3.1 for Mac was used.

## RESULTS

Of the 12 461 included patients with AMI, the mean age was 58.1 years (SD, 12.2 years), 75.9% (n=9459) were male, and there was representation from multiple ethnicities (online-only Data Supplement Table I).

### Physical Exertion as a Trigger

Physical exertion was reported by 13.6% (n=1650) of participants during the case period and 9.1% (n=1111) during the control period. There were no significant differences between those who reported physical exertion in the case period and those who did not ($P>0.01$ for all; Table II in the online-only Data Supplement). Compared with the control period, the adjusted odds of AMI associated with physical exertion occurring during the case period was 2.31 (99% CI, 1.96–2.72) with a population-attributable risk of 7.7% (99% CI, 6.3–8.8; Figure 1). There was no statistically significant effect modification (all $P>0.01$) on analyses stratified by age group, sex, smoking, diabetes mellitus, hypertension, obesity, angina, stroke INTERHEART risk score, or baseline physical activity.

### Anger or Emotional Upset as a Trigger

Anger or emotional upset was reported by 14.4% (n=1746) of participants during the case period and 9.9% (n=1210) during the control period. There were no significant differences between those who reported anger or emotional upset in the case period and those who did not ($P>0.01$ for all; Table III in the online-only Data Supplement). Compared with the control period, the adjusted odds of AMI associated with anger or emotional upset occurring during the case period was 2.44 (99% CI, 2.06–2.89) with a population-attributable risk of 8.5% (99% CI, 7.0–9.6; Figure 2). There was no statistically significant effect modification (all $P>0.01$) on analyses stratified by age group, sex, smoking, diabetes mellitus, hypertension, obesity, angina, stroke, INTERHEART risk score, levels of stress, depression, or level of education.

### Effects of Both Triggers

Compared with exposure to neither trigger during the control period, the adjusted odds of AMI associated with exposure to both physical exertion and anger or emotional upset occurring during the case period was 3.05 (99% CI, 2.29–4.07; $P$ for interaction <0.001).

### Effect Modification by Cardiovascular Medications

There was no statistically significant effect modification for physical exertion or anger or emotional upset on analyses stratified by cardiovascular prevention medications before AMI, including aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and cholesterol-lowering therapy (Figure 3).

### Effect Modification by Geographical Region and Timing of AMI

There was no effect modification by geographical region for either trigger (Figure 4). The conditional relationship between physical exertion and AMI was consistent by time of onset ($P$ for homogeneity=0.08) and day of onset (P for homogeneity=0.95). Similarly, the conditional

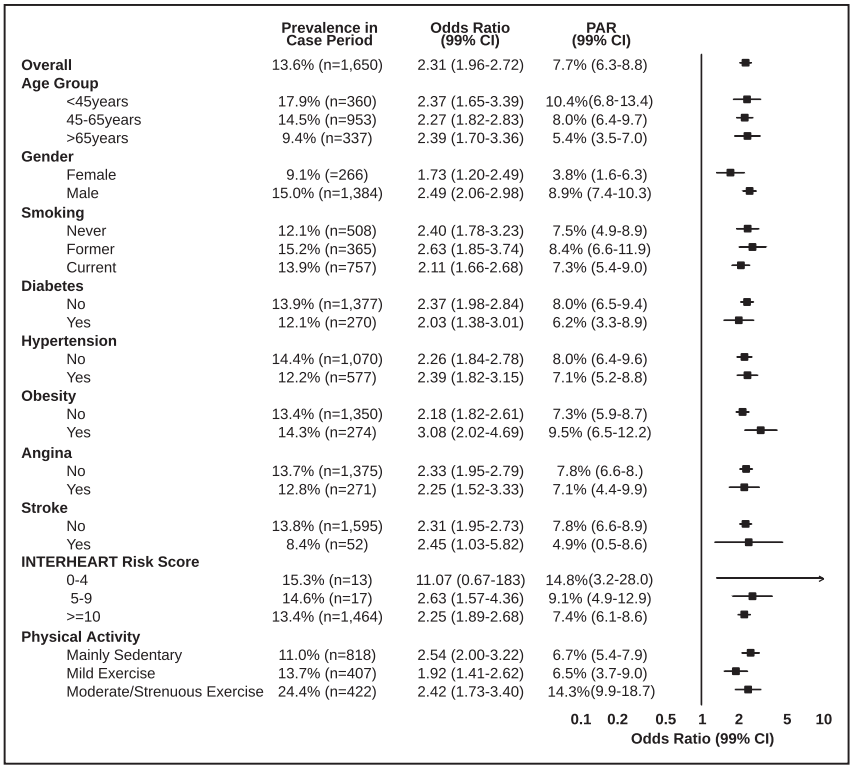


**Figure 1. Physical exertion as a trigger of acute myocardial infarction.** No significant subgroup effects (all *P* for interaction >0.01). CI indicates confidence interval; and PAR, population-attributable risk.

relationship between anger or emotional upset and AMI was consistent by time of onset (*P* for homogeneity=0.17) and day of onset (P for homogeneity=0.99). The odds of AMI occurring with either trigger tended to be highest between 6 PM and midnight and lowest between midnight and 6 AM.

## Sensitivity Analyses

There was no material change in the observed associations with the exclusion of participants with exposure to alcohol in the 24 hours before AMI for physical exertion (*P* for interaction=0.091) or anger or emotional upset (*P* for interaction=0.690). Heavy physical exertion was reported by 6.0% (790 of 13071) of INTERHEART controls, and anger or emotional upset was reported by 7.2 (945 of 13071). Compared with INTERHEART controls the adjusted odds of AMI associated with physical exertion in cases was 3.08 (99% CI, 2.50–3.81). The adjusted odds of AMI associated with anger or emotional upset in cases was 2.41 (99% CI, 1.99–2.92).

# DISCUSSION

In this large, international study, we report that heavy physical exertion and anger or emotional upset occurring in the 1 hour before first AMI are common (reported by 1 in 7 cases) and confirm that both exposures may act as external triggers for AMI. We extend previous findings that physical exertion and anger or emotional may act as external triggers for AMI[14–21] to a large, international population (Figure 4). It is important to note that we found no significant regional differences in the observed association, despite differences in prevalence of exposure to the triggers. In addition, we report an additive effect of both physical exertion and anger or emotional upset in the case period.

Physical exertion and emotions (including anger and emotional upset) are reported to cause sympathetic activation,[14] catecholamine secretion,[22] systemic vasoconstriction, and increase heart rate and blood pressure, thereby modifying myocardial oxygen demand,[23–26] which may precipitate the rupture of an already vulnerable atherosclerotic plaque.[27] Therefore, it is not surprising that we identified an additive effect of both physical exertion and anger or emotional upset in the case period (odds ratio, 3.05; 99% CI, 2.29–4.07; *P* for interaction <0.001). Other potential triggers, including viewing stressful sporting events[28,29] and ecological events such as earthquakes,[30–32] have been implicated for similar reasons. These findings led to recommendations that the link between triggering events and their pathophysiological consequences may be reduced through the use of aspirin, β-blockers, statins, or angiotensin-converting enzyme inhibitors.[33] However, we report no effect modification by cardiovascular prevention medication for AMI associated with physical exertion or anger or emotional upset. Therefore, our report highlights difficulties with primary prevention of AMI associated with external triggering events.[33]

Exposure to external triggers is common and clearly does not always lead to AMI, and it is likely that external




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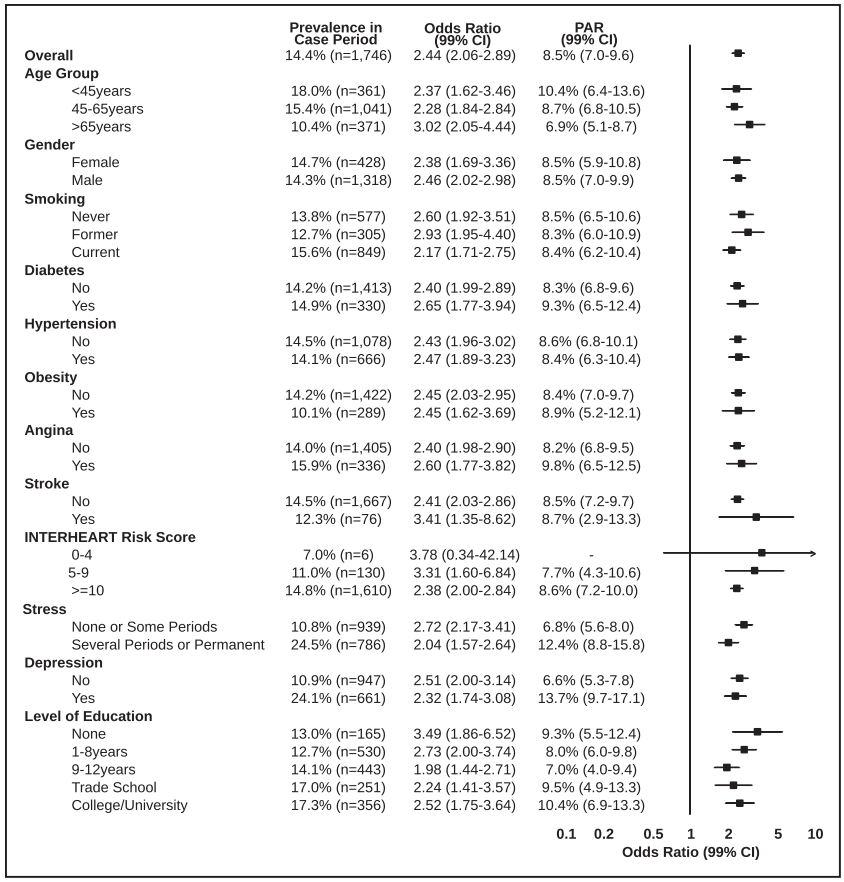


**Figure 2. Anger or emotional upset as a trigger of acute myocardial infarction.**
No significant subgroup effects (all *P* for interaction >0.01). CI indicates confidence interval; and PAR, population-attributable risk.

triggering events precipitate AMI only in the setting of biologically active plaques that may be particularly vulnerable to plaque erosion,[34] which vary significantly between individuals. The case-crossover design is a powerful approach to study potential external triggers for AMI and effect modification because each individual serves as his or her own control, thereby controlling for many potential confounders.[35–37] We report no significant effect modifications for either trigger, unlike previous reports of increased odds of AMI in men with physical exertion[3] or increased odds of AMI in those with the lowest baseline levels of stress.[15]

Regular physical activity is known to play a role in the long-term prevention of cardiovascular disease,[38] and previous studies report the greatest magnitude of association between physical activity as a trigger of AMI in sedentary individuals.[9,39] However, although vigorous physical exertion may act as a trigger of AMI, we did not find any effect modification in the association by baseline level of physical activity. Importantly, our findings suggest that heavy physical exertion may be a trigger for AMI, rather than any physical activity, because the INTERHEART controls were more habitually active. Therefore, clinicians should

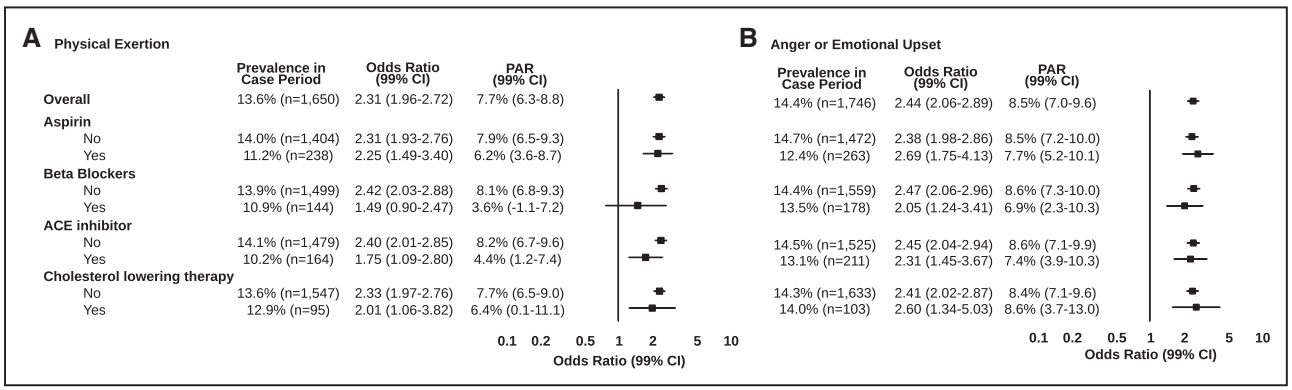


**Figure 3. Effect modification by cardiovascular medications.**
No significant subgroup effects (all *P* for interaction >0.01). ACE indicates angiotensin-converting enzyme; CI, confidence interval; and PAR, population-attributable risk.

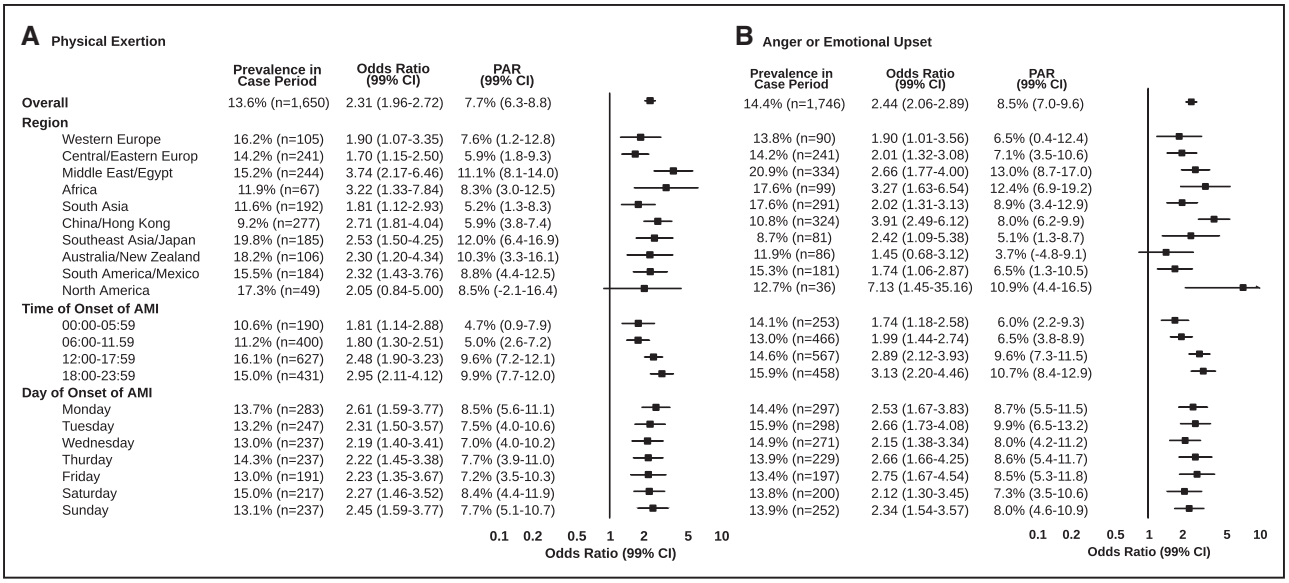


**Figure 4. Effect modification by region and time and day of onset of acute myocardial infarction (AMI).** No significant subgroup effects (*P* for interaction by region >0.01 and all *P* for homogeneity for time and day of onset >0.01). CI indicates confidence interval; and PAR, population-attributable risk.

continue to recommend regular physical activity, while highlighting that short-term intense physical activity may carry a risk of triggering AMI.

Although long-term exposure to established cardiovascular risk factors (eg, lipids, diabetes mellitus) is associated with 90% of the population-attributable risk of AMI,[40] they do not modify the association between triggering risk factors and AMI.[41] We report no effect modification by previous cardiovascular disease, risk factors, or INTEHEART risk score. We confirm previous reports that cardiovascular events are more common earlier in the day,[22] because the majority of cases of AMI occurred between 6 AM and 6 PM. Similarly, we report no significant difference in associations with triggering events throughout the day,[39,42] although there was a tendency toward the greatest magnitude of association for either trigger between 6 PM and midnight. In addition, we found no effect modification by day of onset of AMI for either trigger, suggesting that these triggers do not appear to be triggered by work-related activity. Taken together, these results from INTERHEART suggest that further research is needed to identify those most vulnerable to the effects of external triggers through risk stratification.

The main strengths of this study include the large, international nature of the cohort with first AMI and the ability to explore the role of effect modifiers because of the sample size. INTERHEART includes large numbers of individuals from all regions of the world and multiple ethnicities, making the results broadly applicable, unlike previous studies of potential triggers that were performed primarily in 1 country or region.[9,16,18–21,39,43–47] INTERHEART also includes only participants with first AMI, thereby reducing the possibility that altered lifestyles or risk factors resulting from previous AMI would affect our estimates. In addition, sensitivity analyses including the controls from INTERHEART using multivariable-adjusted conditional logistic regression yielded similar associations. Consistent with previous studies, we defined the case period as the 1 hour immediately preceding the onset of symptoms of AMI because the risk of AMI associated with external triggers decreases significantly with time after exposure.[47] In addition, although it is plausible that the effect of external triggers may last longer than 1 hour, this would bias toward the null because the effect of exposure earlier than 1 hour before AMI would be not counted in the effect of the exposure in the case period. Although no previous studies report emotional upset as a trigger for MI, negative emotion,[17] acute depression,[48] and work-related stress[49] are reported as triggers for AMI, similar to our findings.

The main limitation of this study is recall bias because participants who experienced AMI may differentially recall the intensity of exposure to either triggering event and participants may recall exposures as more proximate to the MI than it actually was.[50] Using only cases of AMI and the case-crossover approach, in which each participant acts as his or her own control, reduces but does not eliminate the effect of differences in perception between participants. In addition, sensitivity analyses including cases and controls from INTERHEART, adopting the case-control approach, revealed similar associations. Second, INTERHEART uses an observational design, meaning that we cannot establish causation. Third, exposure to potential triggering events was self-reported and objective scales were

not used, as in some previous studies. However, our primary findings are consistent with multiple previous studies, suggesting that our measurements of the exposures are equally valid. Fourth, although standardized methodology was used in all regions, risk factors (including diabetes mellitus and hypertension) were self-reported. However, this would likely result in an underestimation of the prevalence of risk factors and bias estimates toward the null. Fifth, our study includes only patients hospitalized with AMI who may not be representative of all cases of AMI occurring within populations. Similarly, because INTERHEART includes only those patients presenting with first AMI and defined symptoms, these data cannot be applied to the impact of triggering events in a secondary prevention population or in those with atypical AMI.

## CONCLUSIONS

We report that physical exertion and anger or emotional upset are common in the 1 hour before the onset of symptoms of AMI and that either exposure may act as an external trigger for AMI. The greatest magnitude of association was seen in those with both physical exertion and anger or emotional upset in the 1 hour before the onset of symptoms of AMI. We report no differences by geographical region, previous cardiovascular disease, cardiovascular prevention medications, cardiovascular risk factors, and INTERHEART risk score.

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## DISCLOSURES

None.

## AFFILIATIONS

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## FOOTNOTES

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# Physical Activity and Anger or Emotional Upset as Triggers of Acute Myocardial Infarction: The INTERHEART Study

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On behalf of the INTERHEART Investigators

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# SUPPLEMENTAL MATERIAL

## Supplementary Table 1. Characteristics of Cohort

| **Characteristic** | | |
|---|---|---|
| Age, years | | 58.8 (12.2) |
| Sex, % (n) | Male | 75.9% (9,459) |
| | Female | 24.1% (3,002) |
| Ethnicity, % (n) | European | 26.6% (3,314) |
| | Chinese | 25.1% (3,130) |
| | South Asian | 17.4% (2,171) |
| | Other Asian | 7.0% (871) |
| | Arab | 10.5% (1,306) |
| | Latin American or Aboriginal | 9.2% (1,141) |
| | Black African | 1.3% (157) |
| | Coloured African | 2.5% (311) |
| | Other | 0.5% (60) |
| Education, % (n) | None | 10.5% (1,284) |
| | 1-8 years | 34.5% (4,224) |
| | 9-12 years | 26.0% (3,177) |
| | Trade School | 12.1% (1,485) |
| | College or University | 16.9% (2,072) |
| Smoking, % (n) | Never Smoker | 34.8% (4,223) |
| | Former Smoker | 20.0% (2,422) |
| | Current Smoker | 45.2% (5,488) |
| Diabetes, % (n) | | 18.5% (2,269) |
| Hypertension, % (n) | | 39.0% (4,803) |
| Global Stress, %(n) | None/Some periods | 73.0% (8,739) |
| | Several/Permanent | 27.0% (3,227) |
| Obesity, % (n) | | 16.0% (1,934) |

## Supplementary Table 1 (continued). Characteristics of Cohort

| Characteristic | | |
|---|---|---|
| Medications, % (n) | ACE inhibitor | 13.3% (1,645) |
| | Aspirin | 17.5% (2,171) |
| | Beta Blocker | 10.9% (1,351) |
| | Cholesterol-lowering therapy | 6.1% (750) |
| Previous CVD, % (n) | Stroke | 5.1% (621) |
| | Angina | 17.4% (2,137) |
| Physical Activity, % (n) | Mainly Sedentary | 61.2% (7,462) |
| | Mild Exercise | 24.6% (2,995) |
| | Moderate/Strenuous Exercise | 14.3% (1,740) |
| INTERHEART Risk Score, % (n) | 0-4 | 1% (130) |
| | 5-9 | 10.3% (1,280) |
| | >=10 | 88.7% (11,051) |
| Time of Onset of AMI, % (n) | 00:00-05:59 | 14.9% (1,851) |
| | 06:00-11:59 | 29.5% (3,665) |
| | 12:00-17:59 | 31.9% (3,996) |
| | 18:00-23:59 | 23.7% (2,952) |
| Day of Onset of AMI, % (n) | Monday | 17.09% (2,107) |
| | Tuesday | 15.4% (1,912) |
| | Wednesday | 15.1% (1,875) |
| | Thursday | 13.7% (1,704) |
| | Friday | 12.1% (1,503) |
| | Saturday | 11.9% (1,483) |
| | Sunday | 14.9% (1,848) |

**Supplementary Table 2. Comparison of cohort by physical exertion in case period**

| | | No Physical Exertion (n=10,549) | Physical Exertion (n=1,659) |
|---|---|---|---|
| Age Group | <45 years | 82.1% (n=1,654) | 17.9% (n=361) |
| | 45-65 years | 95.5% (n=5,648) | 14.5% (n=959) |
| | >65 years | 90.6% (n=3,247) | 9.4% (n=339) |
| Gender | Female | 90.9% (n=2,655) | 9.1% (n=267) |
| | Male | 85.0% (n=7,894) | 15.0% (n=1,392) |
| Smoking Status | Never Smoker | 87.9% (n=3,693) | 12.1% (n=510) |
| | Former Smoker | 84.8% (n=2,047) | 15.2% (n=367) |
| | Current Smoker | 86.1% (n=4,692) | 13.9% (n=759) |
| Diabetes | No | 86.1% (n=8,569) | 13.9% (n=1,383) |
| | Yes | 87.8% (n=1,959) | 12.2% (n=273) |
| Hypertension | No | 85.5% (n=6,370) | 14.5% (n=1,078) |
| | Yes | 87.8% (n=4,164) | 12.2% (n=578) |
| Obesity | No | 86.5% (n=8,723) | 13.5% (n=1,357) |
| | Yes | 85.8% (n=1,653) | 14.2% (n=274) |
| Angina | No | 86.3% (n=8,678) | 13.7% (n=1,382) |
| | Yes | 87.1% (n=1,847) | 12.9% (n=273) |
| Stroke | No | 86.1% (n=9,961) | 13.9% (n=1,604) |
| | Yes | 91.6% (n=567) | 8.4% (n=52) |
| INTERHEART Risk Score | 0-4 | 83.7% (n=72) | 16.3% (n=14) |
| | 5-9 | 85.3% (n=1,012) | 14.7% (n=175) |
| | >=10 | 86.6% (n=9,465) | 13.4% (n=1,470) |
| Physical Activity | Mainly sedentary | 89.0% (n=6,624) | 11.0% (n=821) |
| | Mild exercise | 86.3% (n=2,583) | 13.7% (n=409) |
| | Moderate or Strenuous Activity | 75.6% (n=1,313) | 24.4% (n=424) |

**Supplementary Table 2 (continued). Comparison of cohort by physical exertion in case period**

| | | No Physical Exertion (n=10,549) | Physical Exertion (n=1,659) |
|---|---|---|---|
| Aspirin | No | 85.9% (n=8,624) | 14.1% (n=1,412) |
| | Yes | 88.8% (n=1,900) | 11.2% (n=239) |
| Beta Blocker | No | 86.1% (n=9,345) | 13.9% (n=1,508) |
| | Yes | 89.1% (n=1,181) | 10.9% (n=144) |
| ACE Inhibitors | No | 85.9% (n=9,076) | 14.1% (n=1,487) |
| | Yes | 89.8% (n=1,449) | 10.2% (n=165) |
| Cholesterol Lowering | No | 86.4% (n=9,882) | 13.6% (n=1,555) |
| | Yes | 87.0% (n=641) | 13.0% (n=96) |
| Region | Western Europe | 84.0% (n=553) | 16.0% (n=105) |
| | Central & Eastern Europe | 85.6% (n=1,455) | 14.4% (n=245) |
| | Middle East & Egypt | 84.8% (n=1,362) | 15.2% (n=244) |
| | Africa | 87.9% (n=496) | 12.1% (n=68) |
| | South Asia | 88.4% (n=1,470) | 11.6% (n=193) |
| | China & Hong Kong | 90.9% (n=2,738) | 9.2% (n=277) |
| | Southeast Asia & Japan | 80.1% (n=750) | 19.9% (n=186) |
| | Australia & New Zealand | 81.8% (n=480) | 18.2% (n=107) |
| | South America & Mexico | 84.5% (n=1,008) | 15.5% (n=185) |
| | North America | 82.9% (n=237) | 17.1% (n=49) |
| Time of Onset | 00:00 – 06:00 | 89.4% (n=1,614) | 10.6% (n=191) |
| | 06:00 – 12:00 | 88.8% (n=3,192) | 11.2% (n=401) |
| | 12:00 – 18:00 | 83.8% (n=3,266) | 16.2% (n=630) |
| | 18:00 – 24:00 | 85.0% (n=2,458) | 15.0% (n=435) |

**Supplementary Table 2 (continued). Comparison of cohort by physical exertion in case period**

| | | **No Physical Exertion (n=10,549)** | **Physical Exertion (n=1,659)** |
|---|---|---|---|
| Day of Onset | Monday | 86.2% (n=1,783) | 13.8% (n=285) |
| | Tuesday | 86.8% (n=1,630) | 13.2% (n=247) |
| | Wednesday | 87.0% (n=1,593) | 13.0% (n=238) |
| | Thursday | 85.7% (n=1,423) | 14.3% (n=237) |
| | Friday | 86.9% (n=1,282) | 13.1% (n=193) |
| | Saturday | 85.0% (n=1,236) | 15.0% (n=219) |
| | Sunday | 86.9% (n=1,581) | 13.1% (n=239) |

**Supplementary Table 3. Comparison of cohort by anger or emotional upset in case period**

| | | No Anger or Emotional Upset (n=10,549) | Anger or Emotional Upset (n=1,659) |
|---|---|---|---|
| Age Group | <45 years | 82.0% (n=1,652) | 18.0% (n=363) |
| | 45-65 years | 84.6% (n=5,579) | 15.4% (n=1,018) |
| | >65 years | 89.7% (n=3,213) | 10.3% (n=371) |
| Gender | Female | 85.4% (n=2,493) | 14.6% (n=428) |
| | Male | 85.7% (n=7,951) | 14.3% (n=1,324) |
| Smoking Status | Never Smoker | 86.2% (n=3,619) | 13.8% (n=581) |
| | Former Smoker | 87.3% (n=2,105) | 12.7% (n=306) |
| | Current Smoker | 84.4% (n=4,598) | 15.6% (n=849) |
| Diabetes | No | 85.8% (n=8,527) | 14.2% (n=1,417) |
| | Yes | 85.1% (n=1,897) | 14.9% (n=332) |
| Hypertension | No | 85.5% (n=6,356) | 14.5% (n=1,082) |
| | Yes | 85.9% (n=4,072) | 14.1% (n=668) |
| Obesity | No | 85.8% (n=8,648) | 14.2% (n=1,427) |
| | Yes | 84.9% (n=1,635) | 15.1% (n=290) |
| Angina | No | 86.0% (n=8,641) | 14.0% (n=1,410) |
| | Yes | 84.1% (n=1,781) | 15.9% (n=337) |
| Stroke | No | 85.5% (n=9,882) | 14.5% (n=1,673) |
| | Yes | 87.7% (n=542) | 12.3% (n=76) |
| INTERHEART Risk Score | 0-4 | 93.0% (n=80) | 7.0% (n=6) |
| | 5-9 | 89.0% (n=1,054) | 11.1% (n=131) |
| | >=10 | 85.2% (n=9,310) | 14.8% (n=1,615) |
| Global Stress | None / Some Periods | 89.2% (n=7,770) | 10.8% (n=942) |
| | Several Periods / Permanent | 75.5% (n=2,430) | 24.5% (n=788) |

**Supplementary Table 3 (continued). Comparison of cohort by anger or emotional upset in case period**

| | | No Anger or Emotional Upset (n=10,549) | Anger or Emotional Upset (n=1,659) |
|---|---|---|---|
| Depression | No | 89.1% (n=7,732) | 10.9% (n=950) |
| | Yes | 75.9% (n=2,083) | 24.1% (n=663) |
| Education | None | 87.0% (n=1,107) | 13.0% (n=166) |
| | 1-8 Years | 87.4% (n=3,675) | 12.6% (n=530) |
| | 9-12 Years | 85.6% (n=2,712) | 14.2% (n=447) |
| | Trade School | 83.0% (n=1,227) | 17.0% (n=252) |
| | College or University | 82.7% (n=1,704) | 17.3% (n=356) |
| Aspirin | No | 85.3% (n=8,547) | 14.7% (n=1,477) |
| | Yes | 87.7% (n=1,875) | 12.3% (n=264) |
| Beta Blocker | No | 85.6% (n=9,276) | 14.4% (n=1,564) |
| | Yes | 86.5% (n=1,147) | 13.5% (n=179) |
| ACE Inhibitors | No | 85.5% (n=9,020) | 14.5% (n=1,531) |
| | Yes | 86.9% (n=1,403) | 13.1% (n=211) |
| Cholesterol Lowering | No | 85.7% (n=9,788) | 14.3% (n=1,638) |
| | Yes | 85.9% (n=633) | 14.1% (n=104) |

**Supplementary Table 3 (continued). Comparison of cohort by anger or emotional upset in case period**

| | | No Anger or Emotional Upset (n=10,549) | Anger or Emotional Upset (n=1,659) |
|---|---|---|---|
| Region | Western Europe | 86.3% (n=568) | 13.7% (n=90) |
| | Central & Eastern Europe | 85.8% (n=1,457) | 14.2% (n=241) |
| | Middle East & Egypt | 79.1% (n=1,270) | 20.9% (n=335) |
| | Africa | 82.1% (n=463) | 17.9% (n=101) |
| | South Asia | 82.4% (n=1,368) | 17.6% (n=293) |
| | China & Hong Kong | 89.2% (n=2,688) | 10.8% (n=324) |
| | Southeast Asia & Japan | 91.2% (n=953) | 8.8% (n=82) |
| | Australia & New Zealand | 88.3% (n=518) | 11.8% (n=69) |
| | South America & Mexico | 84.8% (n=1,010) | 15.2% (n=181) |
| | North America | 87.4% (n=249) | 12.6% (n=36) |
| Time of Onset | 00:00 – 06:00 | 85.8% (n=1,546) | 14.2% (n=255) |
| | 06:00 – 12:00 | 87.0% (n=3,124) | 13.0% (n=468) |
| | 12:00 – 18:00 | 85.4% (n=3,322) | 14.6% (n=569) |
| | 18:00 – 24:00 | 84.2% (n=2,433) | 15.8% (n=458) |
| Day of Week of Onset | Monday | 85.6% (n=1,767) | 14.4% (n=297) |
| | Tuesday | 84.0% (n=1,579) | 16.0% (n=300) |
| | Wednesday | 85.1% (n=1,558) | 14.9% (n=272) |
| | Thursday | 86.1% (n=1,425) | 13.9% (n=229) |
| | Friday | 86.6% (n=1,276) | 13.4% (n=198) |
| | Saturday | 86.2% (n=1,254) | 13.8% (n=201) |
| | Sunday | 86.1% (n=1,565) | 13.9% (n=253) |