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Does Heavy Physical Exertion Trigger Myocardial Infarction?

A Case-Crossover Analysis Nested in a Population-based Case-referent Study

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To study possible triggering of first events of acute myocardial infarction by heavy physical exertion, the authors conducted a case-crossover analysis (1993–1994) within a population-based case-referent study in Stockholm County, Sweden (the Stockholm Heart Epidemiology Program). Interviews were carried out with 699 myocardial infarction patients after onset of the disease. These cases represented 47 percent of all cases in the study base, and 70 percent of all nonfatal cases. The relative risk from vigorous exertion was 6.1 (95% confidence interval: 4.2, 9.0). The rate difference was 1.5 per million person-hours, and the attributable proportion was 5.7 percent. The risk was modified by physical fitness, with an increased risk being seen among sedentary subjects as in earlier studies, but the data also suggested a U-shaped association. In addition, the trigger effect was modified by socioeconomic status. Premonitory symptoms were common, and this implies risks of reverse causation bias and misclassification of case exposure information that require methodological consideration. Different techniques (the use of the usual-frequency type of control information, a pair-matched analysis, and a standard case-referent analysis) were applied to overcome the threat of misclassification of control exposure information. A case-crossover analysis in a random sample of healthy subjects resulted in a relative risk close to unity, as expected. *Am J Epidemiol* 2000;151:459–67.

case-control studies; cross-over studies; myocardial infarction; physical exertion; physical fitness

The first two studies to apply the new case-crossover design (1) to analyses of whether heavy physical exertion triggers the onset of acute myocardial infarction both obtained results that supported the hypothesis (2, 3). In the US study (2), the relative risk of myocardial infarction within 1 hour after heavy exertion was 5.9 (95 percent confidence interval (CI): 4.6, 7.7), and in the German study (3) it was 2.1 (95 percent CI: 1.6, 3.1). In both studies, the effect was modified by frequency of regular physical exercise, with sedentary persons being at the highest risk.

We recently carried out a third independent case-crossover study on exertion and myocardial infarction. Our main objective was to examine the case-crossover method and to look for sources of bias and other weaknesses that could refute the earlier findings. Because this study was nested within a population-based case-referent study, comparisons with standard epidemiologic techniques were possible. To test the new design further, we carried out a case-crossover analysis using information from a random sample of the population. If the case-crossover design is valid, healthy subjects should not have an excess risk of being sampled in a moment of exposure to physical exertion. Our second objective was to analyze how the trigger effect is modified by physical fitness. Information on regular exercise was available from the questionnaire used in the case-referent study. Therefore, we did not have to rely solely on usual trigger frequency as the indicator of physical fitness, as was the case in the earlier studies.

MATERIALS AND METHODS

Study population

The Swedish Onset Study is part of the Stockholm Heart Epidemiology Program (SHEEP), a population-based case-referent study of causes of myocardial infarction. Cases, defined as persons with first events of myocardial infarction, were recruited from all 10 emergency hospitals in the region through a special organization and from continuous screening of death

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Abbreviations: CI, confidence interval; MET(s), metabolic equivalent(s); SHEEP, Stockholm Heart Epidemiology Program.

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certificates by Statistics Sweden. A small number of missed cases were identified later through the computerized hospital discharge register and were then included. All cases of hospitalized myocardial infarction were diagnosed according to standardized criteria using information on symptoms, electrocardiograms, and enzyme levels. The study base included all Swedish citizens aged 45–70 years who had not had a myocardial infarction previously and were living in Stockholm County. Cases were included at the time of disease incidence. At the same time, one referent subject per case was randomly selected from the study base after stratification for age, sex, and hospital catchment area.

The cases in the Onset portion of the SHEEP Study were identified between April 1993 and December 1994 in the coronary care units of the departments of internal medicine at nine of the 10 regional hospitals. Because all of these hospitals have geographically defined catchment areas, the Swedish Onset Study was still population-based. The total number of fatal and nonfatal cases in these areas during the study period was 1,489; 699 patients were interviewed. After exclusion of patients with unreliable information on time of onset or with a high percentage of absent or clearly inaccurate answers, 660 cases remained (figure 1). Female referents were recruited throughout the entire study period, but the recruitment of male referents ended in January 1994. All referents of patients interviewed were asked to participate in a telephone interview on trigger exposures; 367 of the 383 referents who were eligible agreed (96 percent). Characteristics of the study populations are shown in table 1.

Interview

Cases were interviewed during their hospital stay or shortly afterwards. The median interval between the onset of myocardial infarction and the interview was 15 days. The interviews were carried out by 28 nurses who had received preparatory training during at least three evening classes. Meetings for discussion of methodological problems were held regularly during the study period. The interviewers were not informed about our assumptions on the length of induction periods, and they were asked to pay equal attention to each of the 26 1-hour intervals before disease onset. The median duration of the interview was 90 minutes. The telephone interviews with referents took approximately 15 minutes and were conducted by specially trained administrative staff.

In the case interview, detailed information was first obtained on all episodes of pain (clock time, type, duration, etc.), other symptoms, and circumstances during the 4 days before the myocardial infarction to determine the precise time of disease onset. The interviewers were also instructed to distinguish between premonitory symptoms of disease onset and symptoms of ordinary angina pectoris. Then, for various hypothetical triggers, there were questions on the time of the last exposure before myocardial infarction, the usual frequency and duration of trigger occurrences during the previous year, and the intensity and timing of trigger events during the 26 hours before the onset of myocardial infarction. We used the questionnaire from the US study (2), with slight modifications. The degree of physical exertion was quantified on a scale

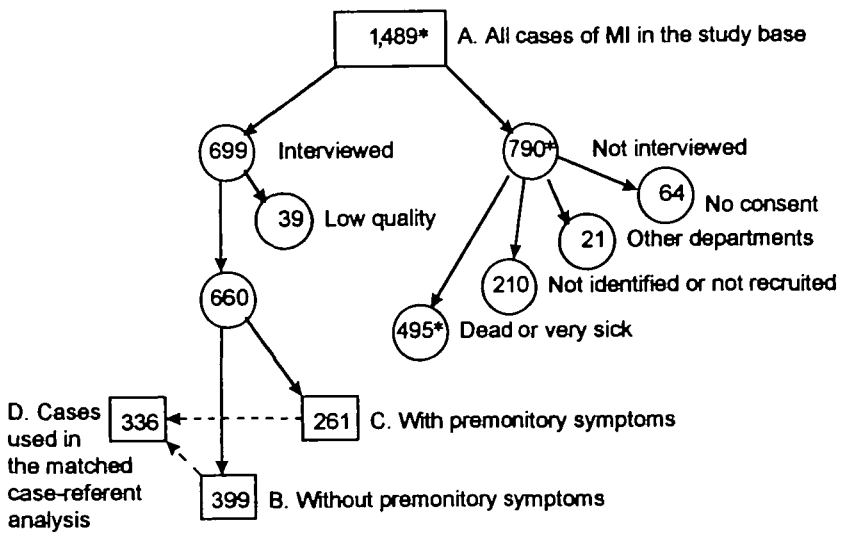

FIGURE 1. Distribution of cases in a study of triggering of myocardial infarction (MI) by physical exertion, Stockholm Heart Epidemiology Program (SHEEP), 1993–1994. Characteristics of the subjects in the squares are given in table 1. (*These data include 223 subjects who represent an estimate of the number of male fatal cases in 1994. This category was not identified in the SHEEP Study.)

TABLE 1. Characteristics (%) of the study populations in a study of myocardial infarction triggered by physical exertion, Stockholm County, Sweden, 1993–1994

Characteristic	Study population*				
	A (n = 1,268)	B (n = 399)	C (n = 261)	D (n = 336)	E (n = 369)
Demographic factors					
Age 45–60 years†	43	49	50	48	49
Male sex	68	78	75	56	57
Socioeconomic group					
Manual worker	31	30	27	32	28
Nonmanual worker, low grade	19	18	15	17	23
Nonmanual worker, high and middle grades	40	42	46	42	42
Self-employed	10	11	12	8	7
Smoking status					
Never smoker	19	22	23	24	42
Ex-smoker	20	26	26	24	31
Current smoker	61	52	51	52	27
Medical history					
Hypertension	38	35	36	35	29
Obesity	36	37	40	38	28
Diabetes mellitus	24	25	28	26	11

* The letters A–D refer to study populations depicted in figure 1: A, all cases; B, all interviewed cases with high quality information who did not report premonitory symptoms; C, all interviewed cases with high quality information who reported premonitory symptoms; D, all cases of the pairs in the case-referent study; E, all interviewed referents who were used in the referent case-crossover study.

† The rest of the subjects were aged 61–70 years.

of 1–8 metabolic equivalents (METs). One MET is defined as the amount of energy expended per minute by a subject sitting quietly; it is equivalent to 3.5 ml of oxygen uptake per kilogram of body weight per minute by a 70-kg adult. The MET scale was presented to the study subject along with several examples of typical activities on each level. This list of activities has been published elsewhere (2, 4). The subject was then asked questions about the latest exposure, usual frequency of exposure, etc., by level, starting with the highest level. Heavy exertion was defined as a peak exertion level of at least 6 METs, and was described as vigorous exertion leading to panting and overheating.

The referents were questioned about episodes of exertion before a certain point in time. This fictitious time of myocardial infarction was the same as that of the corresponding case with regard to time of day and day of the week, but not month or season. The most recent time before the referent interview that matched these criteria was chosen. Questions on physical exertion were not posed level by level. Instead, the interviewer established the 6-MET limit with information on physiologic responses and examples of typical activities. Information on the latest exposure, usual frequency of exposure, and exposure during the 26-hour interval preceding disease onset was then obtained.

Comprehensive information on common cardiovascular disease risk factors was available from the postal questionnaire of the SHEEP Study. The response rate was 91 percent among cases already interviewed in the Onset portion of the study. Physical fitness was determined from answers to the question, "How much did you exercise earlier?", which was repeated for each 10-year period of adult life. Possible answers were "very little exercise," "sporadic walks," "occasional exercise," and "regular exercise (at least once a week)." Socioeconomic status was determined from occupational job titles in the questionnaire database. Smoking status, hypertension (systolic pressure ≥170 mmHg or diastolic pressure ≥95 mmHg), obesity (body mass index >27), and regular medication use were determined from questionnaire information and from measurements made at the SHEEP health examination.

Study design

Four analytic strategies were applied: 1) a case-crossover analysis (analysis I) carried out among the cases using the usual-frequency type of referent information (the usual-frequency study); 2) a case-crossover analysis (analysis II) carried out among the cases using the pair-matched type of referent infor-

mation (the pair-matched study); 3) a matched case-referent study (analysis III) with referents sampled from the population; and 4) a case-crossover analysis (analysis IV) carried out among the referents using the usual-frequency type of referent information (the referent study).

In the usual-frequency (analysis I) and referent (analysis IV) studies, the estimates of relative risk were calculated from the ratio of the observed exposure odds to the expected exposure odds. The observed exposure odds (either 1 or 0) were based on the observed frequency of heavy physical exertion during the hazard period before onset. The expected exposure odds were based on the subjects' usual annual frequency of heavy exertion. These trigger exposures were assumed to be discrete events, and their effect periods were assumed not to overlap. The probability (p) of sampling an exposed hazard period of a given duration (H) from the previous year's person-time was then calculated from the formula $p = n(D + H)/T$, where n = annual frequency of exertion, D = average duration of exertion each time, and T = total time—that is, the full year expressed in the same units as D and H (see Maclure (1), appendix). For example, if H is close to 0, then ongoing trigger exposure at the onset of myocardial infarction is required for the case to be exposed, and the expected exposure odds are then based on only the sum of trigger-exposed person-time in the previous year. The relative risk refers to the risk of having a myocardial infarction during a period of heavy exertion as compared with the risk during periods of lighter exertion or no exertion.

An estimate of the length of the maximum hazard period is the maximum recovery time—the time during which the risk is still increased after the end of a brief episode of heavy exertion. To determine the length of this interval, we calculated relative risks after determining whether or not cases had been exposed during each consecutive 15-minute or 1-hour period before the onset of myocardial infarction. Control for subsequent exposure was done by restriction. The maximum time examined was 4 hours before myocardial infarction. The estimates of each case's probability of exposure during the interval were based on annual frequency of trigger exposure and total hazard periods of either 15 or 60 minutes.

In the pair-matched study (analysis II), the hazard period 1 hour before onset was compared with the actual level of exertion in the comparable hour 1 full day earlier—that is, the period from 25 hours before onset to 24 hours before onset. In the case-referent study (analysis III), the referents were considered exposed or unexposed according to their physical exertion during the 1 hour before their fictitious time of onset. In the referent study (analysis IV), the referent's exposure status 1 hour before the fictitious onset was regarded as "case" information and answers to questions on usual frequency supplied the "control" information.

The onset of disease was defined as the time of appearance of a typical pain that was timed with other diagnostic criteria. Each case was then classified as exposed or unexposed ("concurrent" and "nonconcurrent" with exposure are alternative expressions (1)) during a hazard period before the onset of disease.

Statistical analysis

In the usual-frequency (analysis I), pair-matched (analysis II), and referent (analysis IV) studies, case and referent data were matched individually. Methods for analyzing stratified data were applied, with the individual patient used as the stratifying variable (1, 5). In the usual-frequency (analysis I) and referent (analysis IV) studies, standard Mantel-Haenszel methods for follow-up studies with sparse data in each stratum were used (1, 6). The pair-matched (analysis II) and case-referent (analysis III) studies were analyzed as matched case-referent studies with the use of conditional logistic regression (1, 5). Modification of the relative risk by various factors was assessed by comparing relative risks in subgroups defined by different levels of the potential effect modifier. Subgroups were compared using the χ^2 test for homogeneity (5). All calculations were carried out with SAS (version 6.11; SAS Institute, Cary, North Carolina) and Excel 7.0.

RESULTS

When using all available cases and a hazard period of 1 hour as Mittleman et al. (2) did, we found that 42 patients (6.4 percent) had been engaged in heavy physical exertion during the hour before the onset of myocardial infarction. The relative risks of 3.3 in our study (table 2) and 5.9 in the US study (2) are directly comparable. However, these effect estimates depend on the choice of hazard period, as well as potential bias in the group of patients that had premonitory symptoms before disease onset.

A large group of patients (40 percent) reported having symptoms before the onset of diagnostic pain that they and the interviewer afterwards thought might have been a part of the disease process. In 79 percent of these subjects, the premonitory symptoms contained at least one episode of chest pain. Table 3 shows that the relative risk in the group reporting premonitory symptoms was close to unity. The relative risk for those without premonitory symptoms was 6.1. It was not possible to carry out corresponding pair-matched

TABLE 2. Relative risk of myocardial infarction within 1 hour after exposure to physical exertion, Stockholm County, Sweden, 1993–1994

Study design	No. of subjects	No. of exposed cases	Relative risk	95% confidence interval
Case-crossover (usual frequency)	660	42*	3.3	2.4, 4.5
Case-crossover† (pair-matched)	660	42	4.2	2.0, 8.7
Case-referent‡ (matched)	336 × 2	22	4.7§	0.9, 23.6

* In 32 patients (76 percent), exertion was ongoing when the symptoms of disease began.

† There were 38 patients who reported heavy exertion only during the 1-hour hazard period, as compared with nine who reported heavy exertion only during the control period (24 hours earlier). Four subjects reported heavy exertion during both time periods.

‡ There were 21 discordant pairs with only the case exposed, four discordant pairs with only the referent exposed, and one concordant pair with both members exposed.

§ Subjects were matched according to age, sex, and hospital catchment area. Data were adjusted for smoking and trigger frequency. Nonadjusted estimate: relative risk = 5.2 (95% confidence interval: 1.8, 15.3).

(analysis II) and case-referent (analysis III) analyses in this group, because there was too little information.

The relative risk among persons with ongoing exposure was 6.1 (table 3). Table 4 shows that during the first 15 minutes after exposure, there was a much lower but still increased relative risk of 1.9 (95 percent CI: 0.5, 7.1). In each of the next two quarters of an hour, the risk was almost identical, with confidence intervals of similar range. There was no increase in risk beyond 45 minutes after the end of exertion. When the full hour after trigger exposure was considered, the relative risk was 1.8 (95 percent CI: 0.8, 3.9) and the confidence interval included 1. Our conclusion is that the risk is increased during heavy exertion and that a slightly increased risk during the first 45 minutes afterwards is suggested but not verified.

The trigger effect was modified by social status, and the risk was smaller in higher socioeconomic status groups (table 5). The self-employed group comprised mainly self-employed manual workers and some small-scale entrepreneurs. There was also effect modification due to physical fitness. The risk was clearly increased among sedentary subjects. When usual trigger frequency was used as an indicator of fitness, there was a dose-response relationship, with the most fit persons having the lowest risk, similar to what has been reported previously. However, this finding was not reproduced when fitness was determined from a direct question on exercise habits. Instead, a U-shaped relation was suggested. No significant effect modification was found from age, sex, smoking status, hypertension, diabetes, obesity, or regular use of beta blockers. Effect modification from aspirin could not be tested, since only a few patients (7 percent) had been using it regularly before their first myocardial infarction.

In the referent study (analysis IV), the fictitious time of myocardial infarction was random for the referents, although it followed the pattern of the true cases. It was not influenced by the referent's level of physical exertion. The comparison between the observed odds of concurrent exposure and the expected odds based on usual frequency should therefore have resulted in an odds ratio close to 1. There was no information on usual average duration of exposure to heavy exertion from the referents. Instead, we tested different assumptions when calculating exposed person-time in the previous year. When assuming a duration of 1 hour, which is close to the median duration reported by the cases, and no carry-over effect, the relative risk is 1.2 (95 percent CI: 0.5, 2.9). Assuming longer durations and hazard periods lowers the relative risk. Assuming a total average duration (hazard period included) of only 30 minutes leads to a relative risk estimate of 2.6 (95 percent CI: 1.1, 6.1).

TABLE 3. Relative risk of myocardial infarction from exposure to physical exertion as a potential trigger among patients without and with premonitory symptoms, with two relevant choices of recovery time, Stockholm County, Sweden, 1993–1994

Length of recovery time (minutes)	Patients without premonitory symptoms (n = 399)			Patients with premonitory symptoms (n = 261)			All patients (n = 660)		
	No.*	Relative risk	95% confidence interval	No.*	Relative risk	95% confidence interval	No.*	Relative risk	95% confidence interval
0†	27	6.1	4.2, 9.0	5	1.5	0.7, 3.4	32	4.1	2.9, 5.8
≤45	33	5.3	3.6, 7.6	7	1.3	0.7, 2.7	40	3.4	2.5, 4.7

* No. = number of concurrent/exposed cases.

† Only patients with *ongoing* physical exertion (≥6 metabolic equivalents) at disease onset were regarded as exposed cases.

TABLE 4. Relative risk of myocardial infarction from exposure to physical exertion as a potential trigger during recovery periods of different lengths, among patients without premonitory symptoms and among all patients, Stockholm County, Sweden, 1993–1994

	Patients without premonitory symptoms				All patients			
	No. of cases*	No. exposed†	Relative risk	95% confidence interval	No. of cases*	No. exposed†	Relative risk	95% confidence interval
Recovery period (minutes)								
>0–≤15	372	2	1.9	0.5, 7.1	628	4	1.9	0.7, 4.7
>15–≤30	370	2	1.9	0.5, 7.4	624	2	0.9	0.2, 3.5
>30–≤45	368	2	2.0	0.5, 7.3	622	2	0.9	0.3, 3.5
>45–≤60	366	0			620	2	0.9	0.3, 3.6
>60–≤75	366	1	1.0	0.2, 6.3	618	2	1.0	0.3, 3.5
>75–≤90	365	0			616	0		
>90–≤105	365	0			616	0		
>105–≤120	365	1	1.0	0.2, 6.2	616	1	0.5	0.1, 3.0
Recovery period (hours)								
>0–≤1	372	6	1.8	0.8, 3.9	628	10	1.5	0.8, 2.7
>1–≤2	366	2	0.6	0.2, 2.3	618	3	0.5	0.2, 1.3
>2–≤3	364	4	1.2	0.5, 3.1	615	5	0.8	0.3, 1.8
>3–≤4	360	0			610	0		

* Number of cases in the analysis.
† Number of concurrent/exposed cases.

DISCUSSION

In this study, we found a sixfold increase in risk of a first myocardial infarction shortly after the beginning of exposure to physical exertion that leads to panting and overheating. As in the two earlier case-crossover studies (2, 3), this risk seems to be modified by physical fitness, although the relation might not be linear as in earlier reports if more valid indicators were used. The results suggest the possibility of a U-shaped relation. However, there are also problems with misclassi-

TABLE 5. Relative risk of onset of myocardial infarction during exposure to heavy physical exertion, according to patients' characteristics, Stockholm County, Sweden, 1993–1994

Characteristic	No. of cases	No. exposed	Relative risk	95% confidence interval	*p* value
All patients	399	27	6.1	4.2, 9.0	
Heavy physical exertion* (times/week)					
<1	284	10	100.7	52.7, 192.4	
1–2	49	4	6.9	2.5, 18.5	<0.001
>2–4	22	2	3.7	0.9, 14.9	
>4	44	11	3.3	1.9, 6.2	
Exercise†					
Very little	42	2	54.7	13.7, 218.4	
Sporadic walks	135	5	4.6	1.7, 12.5	<0.001
Occasional exercise	63	3	2.3	0.9, 6.0	
Regular exercise	102	15	12.1	6.8, 21.4	
Socioeconomic group					
Manual worker	103	10	10.5	5.3, 20.5	
Nonmanual worker, low grade	63	2	5.8	1.3, 25.4	
Nonmanual worker, high and middle grades	146	10	4.8	2.5, 9.1	0.026
Self-employed	38	5	25.8	10.3, 64.8	

* Based on usual frequency of trigger exposure reported in the case-crossover interview.
† Based on answers to a question on average level of exercise during preceding years in the questionnaire of the case-referent study. Information was for missing 14 percent of the patients. The overall relative risk in this subset of the patients (n = 342) was 6.8 (95% confidence interval: 4.5, 10.2).

fication of usual trigger frequency—problems that are probably common to all studies undertaken so far.

It is important to restrict the analysis to the subset of cases who do not report any premonitory symptoms, for two reasons. First, there may be a reverse causation bias in that premonitory symptoms make a subject less eager than usual to engage in physical exertion. Second, it is possible that a premonitory symptom signals an important biologic event such as plaque rupture or the beginning of thrombosis. If exertion has its influence at this step in the causal process, the choice of diagnostic pain as the time of onset leads to misclassification of case exposure in these subjects. The empirical evidence supports these arguments. Nevertheless, we analyzed both groups, and although we have focused on the results from the restricted group, the conclusions would not be different if all cases were considered. In future studies, the triggers of strictly identified and defined premonitory symptoms should be analyzed, since this may reveal further details regarding the causal mechanisms. According to our interviews, symptoms and signs often appear before the diagnostic chest pain and are usually not paid attention to in clinical practice.

Mittleman et al. (2) reported an induction period of 1 hour or less and used a hazard period of 1 hour. The choice of hazard period should be guided by the recovery time, i.e., how long the trigger effect carries over into unexposed person-time. Mittleman et al. (2) never reported separate effect estimates for persons with ongoing trigger exposure and those without it but still exposed within 1 hour before myocardial infarction onset. Our findings suggest a rather rapid decrease in risk after termination of trigger exposure. Accordingly, shorter hazard periods should be preferred if there is information in such detail as to support their use.

The Swedish Onset Study was population-based by design and ambition. Although we had questionnaire information on common risk factors from 78 percent of all identified cases in the SHEEP Study, we managed to interview only 47 percent of the case patients (70 percent of the nonfatal cases). Because of the self-matching procedure, there was no control subject selection bias, and since there did not seem to be much effect modification from most standard risk factors, the results should be generalizable to the total population, not only to some identifiable high risk groups. There is still the possibility of case selection, with survival bias being the most obvious. However, because heavy exertion often takes place outdoors in areas where the chances of instant detection and rapid transport are comparatively smaller and the risk of sudden death is therefore increased, any survival bias in the study should have conferred a risk estimate that was too low. There are no reasons to believe that recruitment and participation of nonfatal cases should depend on recent trigger exposure. Case selection that is dependent on usual frequency of trigger exposure only concerns exposure opportunity (7), and it does not lead to bias. In analogy to distinctions made concerning sources of confounding, this phenomenon could also be called between-individual control-time selection bias.

Another control-time selection problem has not been discussed before but must be considered a possible source of bias, and we suggest that it be called within-individual control-time selection bias. A special case exists where a subject is experiencing a steady upward (or downward) trend in trigger frequency. If usual frequency is reported as the average frequency over a longer period, it does not reflect the probability of exposure at the time of disease onset, and the relative risk will be biased towards infinity (or zero). This was mentioned by Greenland (8) in his discussion of the case-time-control design (9); he called it "selection confounding." However, within-individual control-selection bias may also arise from cyclic patterns in trigger exposure, such as circadian, workday-versus-weekend, or seasonal variations. For example, if there are seasonal differences in trigger frequency, it would be preferable to have usual-frequency data relevant to the season of the time of onset. If this information is not available, having to rely on a yearly average implies a bias in each case's contribution to the common effect estimate. However, a peculiar feature of case-crossover analysis is that all of these individually biased contributions cancel out as long as there is not an unequal selection (in relation to the true incidence rates) of cases from the different phases of the trigger variation. The instruction given to the case patients was that the usual-frequency information should apply to the last full year. Because the data collection started in April and ended in December 1½ years later, we had artificially created a seasonal variation in incidence, with fewer cases in the first 4 months of the year. There was also a higher relative risk if the analysis was confined to cases included during these 4 months. This may have been due to a higher true frequency of usual trigger activities in this period that was not reflected in the reported annual average, but we had no information on the true frequency. To estimate the magnitude of this potential within-individual control-selection bias, we repeated the main analysis of the study using only subjects from 1 full year. However, the relative risk changed only from 6.1 to 6.2.

The self-matching in the case-crossover design eliminates confounding due to risk factors with long induc-

tion periods, and since concurrent exposure to other potential triggers among cases exposed to heavy exertion was extremely rare, within-individual confounding was also not a problem. Both the incidence of myocardial infarction and the occurrence of heavy exertion have circadian variations, and therefore there may have been confounding by time of day (4). Control for this type of confounding is inherent in the pair-matched analysis (analysis II), and the similarity in relative risks between different analytic strategies is reassuring. In an attempt to control for this in the usual-frequency study (analysis I), we restricted the analysis to cases with onsets between 7:00 a.m. and 11:00 p.m. and to usual frequencies based only on trigger events occurring within those time limits. The relative risk increased only slightly from 6.1 (see table 3) to 6.5 (95 percent CI: 4.3, 10.0). We further tried to stratify by smaller segments of the time of day, but this failed because the quality of the data was too low. In the German study (3), a restriction was made in the base time for the usual frequency but not for the incidence of cases, and this should lead to a lowered relative risk. In the case-referent analysis, the investigators did not adjust for trigger frequency, which would have the same influence, and therefore it is probable that the relative risk of 2.1 reported underestimates the true relative risk.

Misclassification of case status, time of disease onset, and case exposure information was discussed above. However, the real challenge to the case-crossover design is the threat of misclassification of referent exposure information, especially the usual-frequency type (10). The reader should appreciate the difficulties involved in integrating various forms of activity with the same intensities in terms of breathing and body heating into two single measures of "usual frequency" and "usual duration during the past year." The best argument against any serious misclassification is that the usual-frequency, pair-matched, and common case-referent analyses resulted in effect estimates of approximately the same magnitude. To this we can add that a case-crossover analysis conducted among referents resulted in a relative risk close to unity, as it should have.

A problem with the questionnaire is that it does not ask for affirmation of very low usual frequencies, making it impossible to distinguish between this category and persons with missing answers. This is probably the major reason behind the extremely high relative risk in the low usual-frequency category (table 5). Cross-tabulation of usual trigger frequency and exercise habits further supports this suspicion. Approximately 40 percent of persons having a usual trigger frequency of zero in the past year are found among those who exercised occasionally or regularly. We also had some problems with missing answers regarding usual duration, and in those relatively few instances where there was information on usual frequency but not on usual duration we gave the subject a duration approximately the same as the median duration among persons who supplied this information. To test the influence of the missing information, we also repeated the analysis keeping only the subjects with full information, then deliberately also excluding the low-usual-frequency, high-risk subjects. As a result, the relative risk changed from 6.1 to 4.7 (95 percent CI: 2.8, 8.0). We also tested various assumptions about usual duration among persons with missing information, but this had only minor effects. We think that the usual frequency of trigger exposure is underestimated by many subjects, which implies dependent misclassification, but this does not invalidate the findings. To lower the relative risk of 6.1 to unity, the subjects should have reported an average usual trigger frequency of 11 times per week instead of twice weekly, and this amount of underreporting is unlikely.

Because incidence rates per hour were available from the SHEEP Study, we were able to estimate risk differences. The absolute risk of myocardial infarction per hour was low. In the age group 45–70 years, there were 0.46 new cases per million person-hours among males and 0.15 per million among females (table 6). Although the relative risk implies a sixfold increase in risk, the absolute risk per hour increased only from 0.3

TABLE 6. Relative risk, rate difference, and attributable proportion for heavy physical exertion as a trigger of myocardial infarction, Stockholm County, Sweden, 1993–1994

	Incidence rate* (per million person-hours)	Relative risk†	Rate difference‡	Attributable proportion§ (%)
All patients	0.30	6.1	1.5	5.7
Sex				
Male	0.46	6.3	2.4	6.5
Female	0.15	5.1	0.6	2.8
Age group (years)				
45–60	0.18	7.2	1.1	9.3
61–70	0.57	4.1	1.8	2.2

* Estimated from the cases (1992–1994) in the Stockholm Heart Epidemiology Program (SHEEP) and population denominators.

† Estimated using the exposure odds ratio from the Onset portion of the SHEEP Study.

‡ Estimated as (RR − 1) × IR.

§ Estimated using the proportion of exposed cases and the relative risks in the Onset portion of the SHEEP Study. Available data did not permit a separation of earlier cases from excess cases (11).

per million to 1.8 per million; that is, the risk difference was 1.5 per million person-hours (table 6). We conclude that triggering from heavy physical exertion accounts for 5.7 percent of the myocardial infarctions in this age group.

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