Temporal changes in myocardial infarction incidence rates are associated with periods of perceived psychosocial stress: A SWEDEHEART national registry study

John Wallert, MSc,[a] Claes Held, MD, PhD,[b,c] Guy Madison, PhD,[d] and Erik MG Olsson, PhD[a] *Uppsala, and Umeå, Sweden*

Background Psychosocial stress might trigger myocardial infarction (MI). Increased MI incidence coincides with recurrent time periods during the year perceived as particularly stressful in the population.

Methods A stress-triggering hypothesis on the risk of MI onset was investigated with Swedish population data on MI hospital admission date and symptom onset date (N = 156,690; 148,176) as registered from 2006 through 2013 in the national quality registry database Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). Poisson regression was applied to analyze daily MI rates during days belonging to the Christmas and New Year holidays, turns of the month, Mondays, weekends, and summer vacation in July compared with remaining control days.

Results Adjusted incidence rate ratios (IRRs) for MI rates were higher during Christmas and New Year holidays (IRR = 1.07 [1.04-1.09], $P < .001$) and on Mondays (IRR = 1.11 [1.09-1.13], $P < .001$) and lower in July (IRR = 0.92 [0.90-0.94], $P < .001$) and over weekends (IRR = 0.88 [0.87-0.89], $P < .001$), yet not during the turns of the month (IRR = 1.01 [1.00–1.02], $P = .891$). These findings were also predominantly robust with symptom onset as alternative outcome, when adjusting for both established and some suggested-but-untested confounders, and in 8 subgroups.

Conclusions Fluctuations in daily MI incidence rates are systematically related to time periods of presumed psychosocial stress. Further research might clarify mechanisms that are amenable to clinical alteration. (Am Heart J 2017;191:12-20.)

Extraordinary stimuli that induce stress in individuals, such as earthquakes or national sporting events, may increase the risk of acute cardiovascular disease (CVD) events such as acute myocardial infarction (MI).[1,2] More common psychosocial stressors of daily living are also associated with increased MI risk in both men and women of different age, ethnicity, and nationality.[3] Furthermore, the widespread job-strain model predicts that low control coupled with high demand at work induces "mental strain",[4] a condition associated with increased risk of MI.[5,6]

The incidence of MI varies over time. Previous studies have reported regularities in the temporal fluctuations of CVD incidence rates. The higher CVD-related death and MI rate during the Christmas and New Year holidays is well documented.[7,8] Previous data also indicate a beginning of month,[9] week,[10] and day[11] increase in MI incidence, which tends to coincide with particularly stressful periods of modern life (eg, Christmas preparations, having bills to pay, returning to work after the weekend, and traveling to work in the mornings). Conversely, a nadir in incident MI has been identified during weekends[12] and during summer vacation in July[13] when psychosocial stress is relatively low.

Our internal biological clock, the circadian system, is partially out of synchrony with these periods, having genetically evolved over millions of years to become adapted to smooth changes in the diurnal light-dark cycle.[14] Modern life is therefore likely to challenge this primordial biological rhythm with its artificial light and often arbitrary timing of behavioral requirements, be it shift-work, early Monday mornings, or late night Christmas preparations. Accordingly, previous research suggests that even slight shifts of societal time-keeping precedes increased MI rates,

From the [a]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden, [b]Department of Medical Sciences: Cardiology, Uppsala University, Uppsala, Sweden, [c]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, and [d]Department of Psychology, Umeå University, Umeå, Sweden.

Submitted January 29, 2017; accepted May 30, 2017.

Reprint requests: John Wallert, Department of Women's and Children's Health, Uppsala University, Biomedical Center, Box 572, Husargatan 3, SE-75123, Uppsala.
E-mail: john.wallert@kbh.uu.se

0002-8703

http://dx.doi.org/10.1016/j.ahj.2017.05.015

through daylight saving time when we “lose” 1 hour in the spring but not when we “gain” 1 hour in the fall.[15] Interestingly, a psycho-neuro-endocrinological study found the morning cortisol peak to be larger for weekdays compared with weekends and that the study cohort accordingly rated themselves as being more stressed during weekdays compared with weekends.[16]

We thus hypothesized that stress triggering of MI insofar as time periods of particularly high and low stress would align with periods of particularly high and low MI rates in the unselected Swedish MI population, respectively. Using previous research and sociocultural knowledge, we defined periods of both high and low stress whose MI rates can then be compared with MI rates on remaining control days representing the time- period of intermediate or “more average” stress. This contrasts with previous studies that tend to only compare high versus control periods.[2,8] Accordingly, we presumed particularly high stress and MI rates during (1) Mondays when the workweek begins, (2) the turn of the month due to possible financial or administrative deadline stress, and (3) the often stressful turn of the year coinciding with family gatherings during the winter holidays. Conversely, we presumed particularly low stress and MI rates during (4) weekends and (5) the Swedish 4- to 6-week paid summer vacation. Because Swedes spend most of their summer vacation in July, [17] a yearly trough in population MI rates is predicted in July versus other months. Similarly, the weekend is the least time-constrained period of the week, and therefore, we presumed that weekends would have the lowest MI rates during the week. We also hypothesized that the Monday increase in MI rates would be more pronounced in the working compared with the retired patients.

Methods

Data

From 1 January 2006 to 31 December 2013, 156,690 MIs were registered prospectively in the unselected national quality database Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA), covering 90% of all MIs in Sweden for individuals <80 years old and 70% for individuals ≥80 years old. RIKS-HIA was the first of the SWEDEHEART registries to be established as a national quality registry in 1995 and enrolls consecutive patients from all coronary care units (CCUs) in the country admitted for symptoms suggestive of acute coronary syndrome. Information is collected prospectively on >100 variables including date and time of symptom onset and admission. SWEDEHEART/RIKS-HIA data are randomly audited and monitored regularly by specialized monitors who visit hospitals for source data verification of the health records versus registry data for quality checks. Overall, the data agreement rate is >95%. The registry is approved by an ethics committee, the Swedish National Board of Health and Welfare, and the Swedish Data Protection Authority. Patients are informed of their inclusion and that they are free to be excluded and have their data erased. No patient requested exclusion between 2011 and 2013, and only a handful did so before 2011.[18] This opt-out procedure is a rare strength of this registry because it effectively reduces sampling bias. The present study was approved by the regional ethics committee in Uppsala and complies with the Declaration of Helsinki. The present manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[19]

Main outcome was the acute hospital admission date, calculated from whichever time stamp for percutaneous coronary intervention laboratory arrival or CCU arrival (dependent on MI type) came first. Alternative outcome was the registered symptom onset date. Inclusion criterion was confirmed discharge diagnosis of MI (*International Classification of Diseases, 10th Revision*, codes I21-I23),[20] as decided by the local hospital cardiologist based on symptoms, biomarkers, electrocardiogram, and additional information.

Temperature data (°C) were retrieved from the Swedish Meteorological and Hydrological Institute measurement station closest to the local CCU that registered a particular MI (median distance to CCU = 6.57 km). Air pollution data (NO_2, μg/m^3) were gathered the Swedish Environmental Protection Agency from the closest urban background measurement station to the local CCU (median distance to CCU = 1.91). Data on the monthly number of individual passengers traveling in and out of the country by air as registered by all airports in Sweden were retrieved from the Swedish Transport Agency.

Classification of exposure and statistical analyses

Unless further specified, we present continuous variables as mean ± SD and categorical variables as count (%). Poisson regression was used to model daily MI rates, defining a day from 00:00 to 23:59 hours. Presumed stress increases (–I) were defined a priori and categorically as days belonging to the Christmas and New Year holidays (Holidays-I) = 15 December-6 January, the turns of the month (Month-I) = 4 days before and 4 days after the turn, and Mondays (Monday-I) = Mondays. Presumed decreases in stress (–D) were defined, also a priori, as days belonging to the summer vacation (Summer-D) = 1 July-31 July and the weekends (Weekend-D) = Saturdays and Sundays. The remaining days were used as control days. The 3-week time span for the Holidays-I is motivated by our aim to investigate possible stress triggering of MI, partially different from previous studies more specifically focused on studying the twin peaks during this period. Naturally, there is some arbitrariness in choosing these time spans, although choosing periods of both particularly low and high stress would automatically select control periods that should be intermediate to high/low periods. Importantly, the chosen periods are unambiguously defined for future replication. Daily MI counts were high enough to avoid problems with excess zeros and low counts per unit (median = 53, interquartile range = 47-60). Overdispersion was present (main analysis grand variance/mean = 1.19), and quasi-Poisson regression was therefore applied. The exponents of the estimated coefficients and their 95% CIs provided the mean and uncertainty of the adjusted incidence rate ratios (IRRs) relative to control days. These IRRs are interpretable as factor changes in the outcome variable relative to control days (eg, IRR = 1.20 [1.10-1.30] = between 10% and 30% increase relative to control with 20% being the most probable point estimate). We report IRRs and associated statistics for the whole population main analysis and for predefined subgroup analyses in Figure 2 and for additional analyses in text. Statistical significance was set to 5% (2-tailed). The Holm-Bonferroni method was applied to correct the main analysis *P* values for multiple comparisons. Covariates were checked for log-linearity against the outcome. Model appropriateness was confirmed in several ways, for instance, with F tests and through inspecting the standardized deviance residuals versus the log-predicted values. Statistical power allowed for comprehensive subgroup analyses. Subgroup *z* test comparisons assumed approximate normality of parameter estimates and independence of observations. Unadjusted daily MI rates are also presented descriptively.

Covariates for the adjusted analyses were prepared and used as follows: For temperature, a locally weighted daily average was calculated. For a particular date, each MI was registered at a specific hospital. Each MI in the data set was then matched with the corresponding local daily mean temperature. Temperature values were then averaged for each date according to where in the country the MIs of that date occurred. To control for possible short-term delayed effects of temperature on MI rates, delayed temperature averages for the 3 days preceding the outcome were also included in all adjusted analyses. In addition, NO_2 data were available for a subgroup of 39,634 MIs for which data from some stations for some hours were missing (~5% missing of total). Average daily mean values from complete days were imputed if missing. NO_2 was then prepared as temperature for this subgroup. To control for changes in the population base due to traveling abroad, the total amount of abroad traveling by air was available as monthly net numbers of abroad travelers from all Swedish airports and modeled as such with both no delay and 1-month delay. To complement the whole population analysis, we repeated the regression analyses in the 8 predefined subgroups: male, female, working, pensioners (retired), first MI, recurrent MI, ST-elevation MI (STEMI), and non-STEMI (NSTEMI). We chose to stratify these analyses because weighted averages of categorical variables would have been artificial and less interpretable. Stratification on work status also meant comparing relatively young and old patients. When included, the locally weighted covariates (eg, temperature) had to be recalculated for each of the 8 subgroup analyses and for the alternative outcome symptom onset because daily MI locations and counts were different.

Software

Data preprocessing and analyses were done in R (version 3.2.0; R Development Core Team, Austria, Vienna) with packages *base, MASS*, *sandwich*, *stats*, *vcd,* and *zoo.*[22-25]

Sources of funding

This work was supported by the Swedish Research Council for Health, Working Life, and Welfare (2014-4947); the Vårdal Foundation (2014-0114); and part of the strategic research program U-CARE (2009-1093).

Results

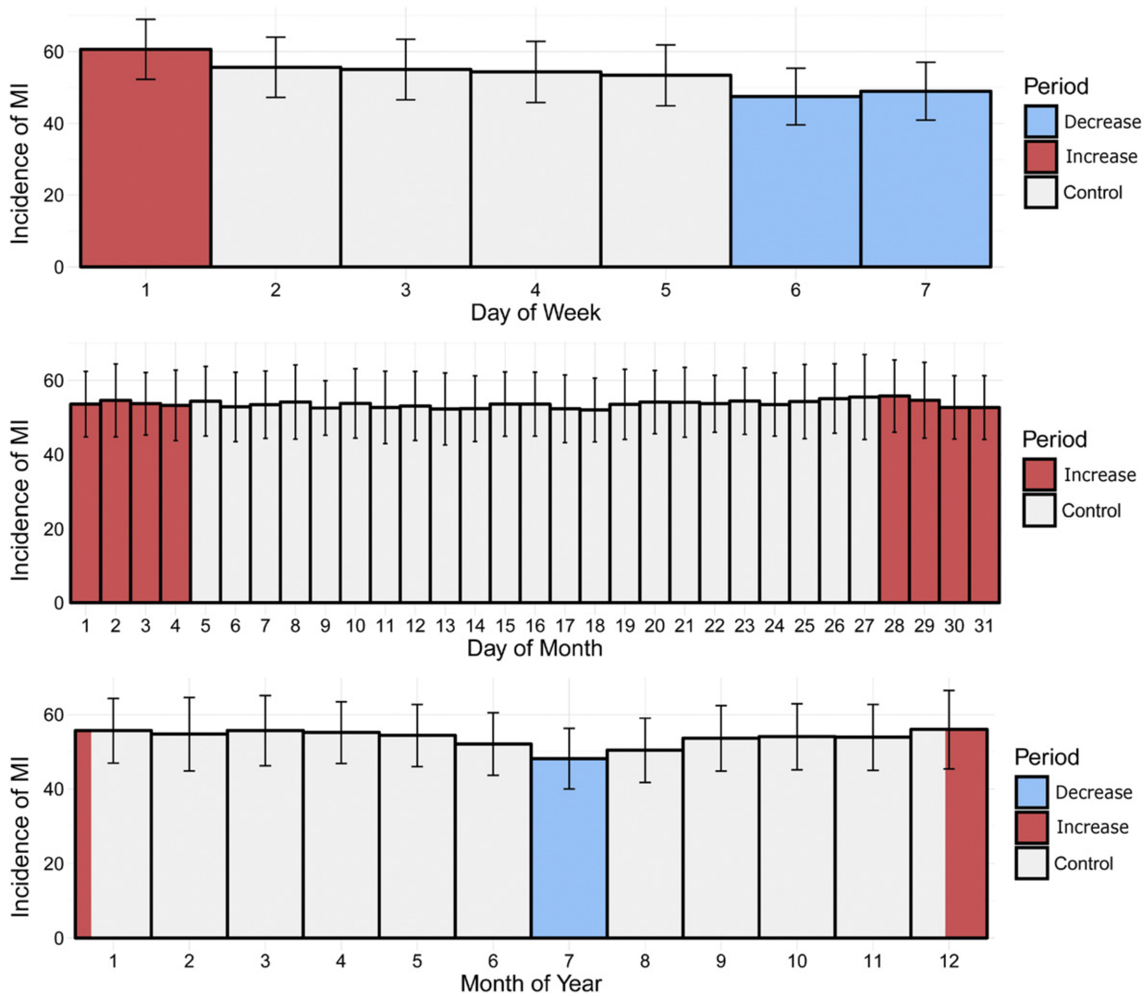
After excluding 163 duplicates and 1 case with missing hospital admission date, a total of 156,690 MIs were analyzed. For reference, patient event characteristics are presented in Table which shows high similarities across compared periods.

The predefined time periods and unadjusted daily MI rates aggregated over days of the week, days of the month, and months of the year are available in Figure 1. Regarding weekdays, most MIs were registered on Mondays (60.6 ± 8.6) and least on Saturdays (47.5 ± 7.9). For monthly days, the 28th (55.8 ± 9.8) and the 18th (52.0 ± 8.6) held the most and least MIs, respectively. For months, December had the highest MIs per day (56.0 ± 10.6) and July the lowest (48.1 ± 8.1).

Next, the main analysis was performed. The adjusted whole population result showed highly significant increases in adjusted daily MI rates during the Holidays-I and the Monday-I, and highly significant decreases during the Summer-D and Weekend-D, compared with control days. The only hypothesis that was not supported was that adjusted daily MI rates during the Month-I did not differ compared with control days. See Figure 2 for explicit parameter values. Daily temperature was negatively associated with MI rates (IRR = 0.98 [0.97-0.99] per 10°C increase, $P < .001$).

Secondary analyses considered possible confounding variables. Repeating the regression procedure in the subgroup for which both temperature and NO_2 air pollution were available (n = 39,634) showed that the previously identified significant MI rate changes during the defined periods remained in the predicted direction and were also highly significant with the exception of the Holidays-I which was rendered borderline significant (IRR = 1.04

Figure 1



Unadjusted daily MI rates in the whole population aggregated over days of the week, days of the month, and months of the year. Bars represent mean ± SD. Period labels signifies the lower (decrease), higher (increase), and more average (control) days of hypothesized psychosocial stress. * For months shorter than 31 days, the last 4 days of the turn of the month period were adjusted accordingly.

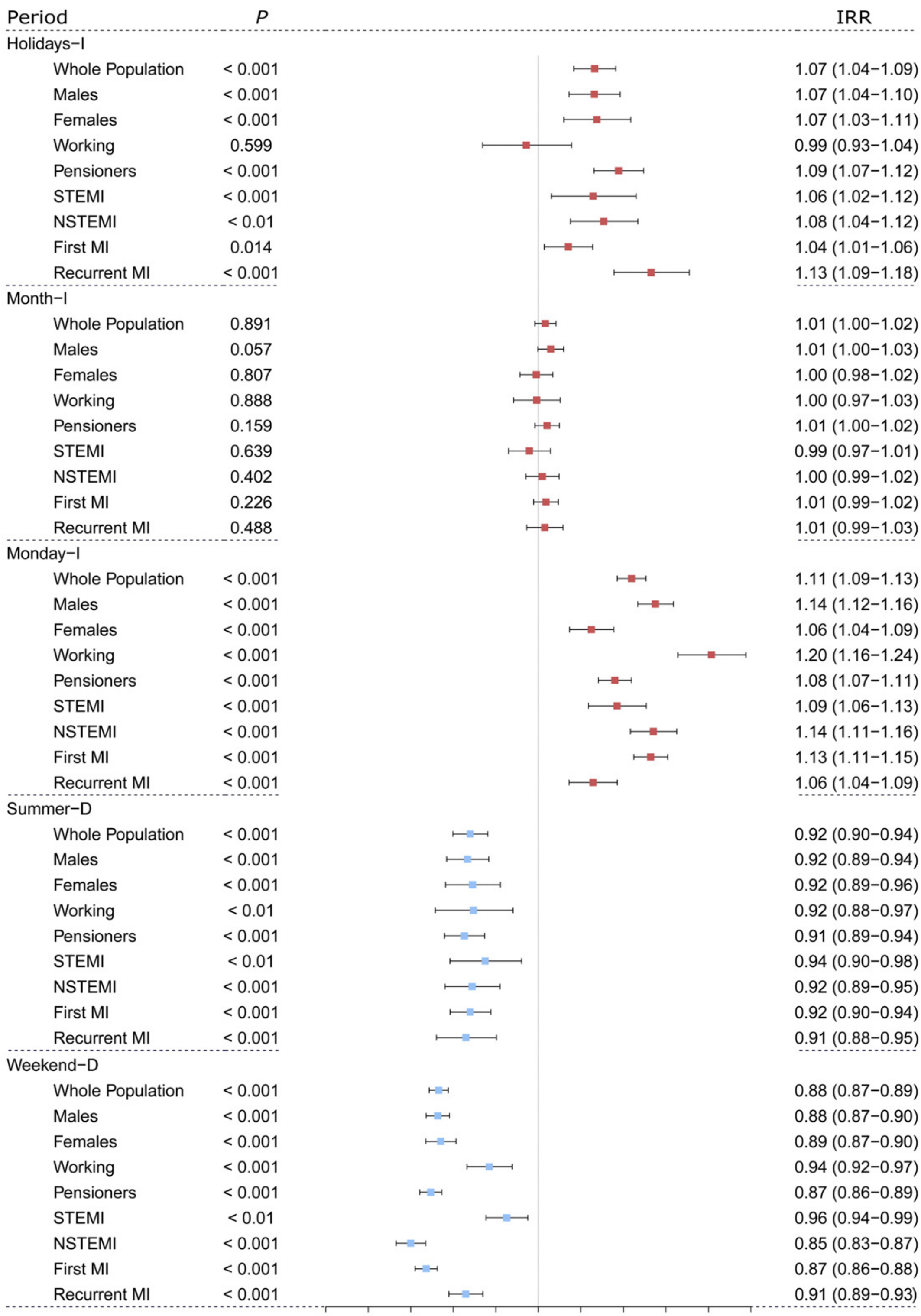
[1.00-1.09], P = .049). NO_2 was not associated with MI rates (IRR = 1.00 [0.99-1.00] per 10 $\mu g/m^3$ increase, P = .38) in this model and is not reported further.

We also ran the regression analysis in 8 subgroups. Figure 2 shows results by sex (male [n = 99,827], female [n = 56,825]) and working status (working [n = 30,131], pensioner [n = 111,931]). Adjusting for temperature and age, men had a larger Monday-I compared with women. Those working had a larger Monday-I but a smaller Weekend-D compared with pensioners. Also, the pensioners exclusively drove the Holidays-I relative to those working. Workers and pensioners were therefore also analyzed as 1 group controlling for age, which resulted in a highly significant Holidays-I (IRR = 1.07 [1.05-1.10], P < .001) but no significant influence of age on daily MI rates (IRR = 1.00 [1.00-1.00] per year increase, P = .79).

Subgroup results for STEMI (n = 34,138), NSTEMI (n = 73,858), first MI (n = 106,724), and recurrent MI (n = 48,960) are also displayed in Figure 2. The Weekend-D was smaller for STEMIs compared with NSTEMIs. Comparisons of first MIs versus recurrent MIs showed a smaller Holidays-I, a larger Monday-I, and a smaller Weekend-D for first MIs. Regardless of infarct type, all but the Month-I were in their respective hypothesized directions and highly significant.

To investigate if our main results were related to a systematic delay of seeking appropriate care, we ran the regression procedure with symptom onset date as

Figure 2



Adjusted daily MI IRRs during days belonging to different periods compared with control days in the whole population and subgroups. Squares (point estimate IRR) with error bars (95% CI) represent the partial factor change compared with control days (vertical line). The main analysis whole population *P* values are Bonferroni-Holm corrected. Data on STEMI/NSTEMI were only available from 1 January 2008 to 31 December 2013.

Table. Patient event characteristics during different periods and all days

Characteristic	Holiday-I (9835)	Month-I (41,246)	Monday-I (25,338)	Summer-D (11,935)	Weekend-D (40,255)	All days (156,690)
Age (y)	72.5 ± 12.3	71.8 ± 12.3	71.2 ± 12.4	71.7 ± 12.4	71.7 ± 12.6	71.8 ± 12.4
Male sex	63.9	64.0	65.1	63.2	63.4	63.7
Heart rate (beats/min)	83.4 ± 23.3	81.9 ± 23.3	81.8 ± 23.2	81.5 ± 23.6	82.7 ± 23.8	82.0 ± 23.4
SBP (mm Hg)	146.6 ± 29.9	145.9 ± 29.8	147.1 ± 29.6	144.8 ± 29.4	145.8 ± 30.1	146.0 ± 29.9
Smoking	18.6	19.5	19.6	20.0	20.1	19.5
Diabetes	23.7	23.0	22.2	22.3	22.6	22.7
Hypertension	50.2	48.8	47.8	48.9	49.1	49.0
History of						
MI	33.1	31.5	29.8	30.7	32.2	31.2
Stroke	10.3	10.0	9.4	9.9	10.3	10.1
PCI	16.6	16.2	16.0	15.7	16.1	16.0
Job status						
Pensioners	73.2	71.6	70.5	71.0	71.1	71.5
Working	18.0	19.1	20.2	19.2	19.9	19.2
Other*	8.8	9.3	9.3	9.8	9.0	9.3
Infarct type						
STEMI	23.7	21.7	21.2	21.8	23.6	22.1
NSTEMI	50.7	47.7	48.9	47.7	46.3	47.8
Unspecified†	25.6	30.6	29.9	30.5	30.1	30.1

Values are mean ± SD or % of total. Counts are in parenthesis. *SBP*, Systolic blood pressure; *PCI*, percutaneous coronary intervention.
* Includes unemployment, sick leave, and unknown job status.
† Infarct type was not registered during the first 2 years of data.

alternative outcome (n = 148,176; 95.6% of total). This analysis rendered a diminished but still highly significant Weekend-D (IRR = 0.96 [0.95-0.97], $P < .001$) and Monday-I (IRR = 1.09 [1.07-1.11], $P < .001$) and a significant Month-I relative to control days (IRR = 1.01 [1.00-1.03], $P = .041$), whereas the rest of the main model did not change.

Additional control for traveling by air from all Swedish airports only attenuated the Summer-D minimally (IRR without traveling = 0.920 [0.900-0.941]; IRR with traveling = 0.925 [0.903-0.946]), which remained highly significant ($P < .001$); the other model coefficients did not change, and traveling itself was nonsignificant in the model ($P = .82$).

Discussion

The present study investigated the coincident temporal variation in daily MI rates that can possibly be triggered by psychosocial stress. Eight years of accumulated national SWEDEHEART/RIKS-HIA registry data on MI incidence in Sweden was used to test the predictions. In correspondence with the idea of stress triggering of MI and the bulk of previous research,[7-12,26] our results showed significantly higher daily MI rates during Mondays and the Christmas and New Year holidays versus rates during control days. Furthermore, there were significantly lower daily MI rates during the weekends and summer vacations in July compared with control days. These findings remained largely robust after adjusting for temperature and air pollution; abroad traveling; when using symptom onset as alternative outcome; and in male, female, working, pensioner, STEMI, NSTEMI, first MI, and recurrent MI subgroups.

Sex differences in the incidence of acute cardiovascular event rates have been reported, such as higher MI rates among men than women during World Cup soccer, suggesting that watching sports may engage more men or that men might be more susceptible to MI triggering during World Cup Soccer.[2] The present study found that men had a greater increase in MIs during Mondays than women. Congruently, men in this age group spend more time than women doing paid work in Sweden,[27] implying that men are more exposed to work stress.

Previous studies suggest that time-bound effects on MI rates might be caused by delays in seeking appropriate health care.[7] The present study partially supports this. The SWEDEHEART/RIKS-HIA registry contains almost complete data on symptom onset date, collected by nurses guided by explicit instructions to clarify and confirm the time when MI symptoms started. This allowed for repeating the regression analysis with symptom onset date as alternative MI outcome, resulting in attenuated Monday and weekend IRRs, yet still significant and substantial relative to control days. This might suggest that MI rate changes during these periods are partly related to both particularly high and low stress and delays in seeking appropriate care.

Routine traveling abroad in the Swedish population peaks in the summer and could thus in theory explain part of the present lower MI rates during the month of July. However, controlling for the monthly net amount of traveling abroad by air from all Swedish airports did not change our modeling results. The highest monthly net deficit of Swedish citizens due to traveling constitutes ~1%-2% of the total Swedish population, which in itself makes abroad traveling highly unlikely as explanatory for the 8% whole population MI rate decrease in July observed in the present study.

Three interesting deviations from the predictions were evident. First, the MI increase during Christmas and New Year holidays was driven by the pensioners. This is in part at odds with previous research indicating a general winter increase in MI for both workers and pensioners, and over age strata, although smaller in younger strata.[11,12] From a stress perspective, one interpretation of the present finding might be that those working are considerably younger and healthier, and perhaps stress during the holidays has an exclusive triggering effect on the more fragile pensioners. The higher MI rates during the holidays among the older NSTEMI/recurrent MI versus the younger STEMI/first MI patients lend some support to this suggestion. However, age was nonsignificant in the combined subgroup analysis of workers and pensioners, which is inconsistent with this interpretation. Those still working might also experience both increased winter holiday stress and decreased stress from temporary work leave, which cancel each other out. In contrast, pensioners might—relative to their normally quite calm lifestyle in Sweden—be exposed to particular winter holiday stress which could hypothetically generate their MI rate increase. Data are not available to test this possibility. Holiday changes in alcohol, food, and tobacco consumption—known MI triggers—might also be related to the exclusive increase in MI rates among pensioners.[28] This is however contradicted by the present finding of particularly low MI rates in both workers and pensioners during both weekend and summer days—the time periods when weekly and yearly alcohol consumption peaks in Sweden.[29,30] Second, with additional adjustment for NO_2, the winter holidays increase diminished to borderline significance. Air pollution is more extensive and variable from day-to-day in the large cities and predominantly lower in other parts of Sweden, and it is seems reasonable that air pollution would exert a particularly strong influence on MI triggering in these densely populated areas and additionally more so for the more fragile pensioners. The winter holiday period typically includes 2 peak days (spikes) within a 2-week period starting with the celebration of Christmas and including New Year's Eve, and the 3-week time span in the present study may have diluted the holidays increase. The twin spikes were also present in these data. However, separating them from the longer 3-week period under study would imply that these spikes would be independent of stress, which is highly unlikely. The winter holiday increase in both mortality and MI has been extensively studied,[7,8,11,12,31,32] for which psychosocial stress is probably a partial explanatory factor. Third, the predicted turn of the month increase was consistently nonsignificant. This finding deviates from a previous study suggesting increased MI rates during the first week of the month[9] but corroborates a later study.[7] The selected period in the present study was also somewhat different. We do not attach particular weight to the very small and marginally significant increase in MI rate during the turn of the month when symptom onset was used as regression outcome. Overall, our study suggests that the turn of the month is unlikely to be particularly related to stress-triggered MI. As we should reason about our findings, peak monthly stress might instead be related to salary and pension payment, suggesting a different time span of dates surrounding the 17th and the 25th of each month when payments are most common in Sweden. Considerable variation in payment timing precludes testing this possibility.

Regarding confounding by environmental factors, previous research has shown a generally positive association between increased MI risk and exposure to common air pollutants (eg, NO_2, CO, O_3, PM2.5, PM10, SO_2),[33] of which NO_2 seems especially important for MI triggering,[34] but results have been conflicting.[35] The present study used high-quality data on temperature that allowed control for 0- to 3-day lagged temperature in all adjusted analyses.

The present findings align well with a previous study that identified a small but robust increase in MI incidence rates during the first week following the artificial daylight saving shift during spring when we "lose" 1 hour but not during fall when we "gain" 1 hour.[15] The spring loss entails only 1 hour of artificial manipulation of time, suggesting considerable somatic sensitivity in MI patients to artificial time manipulations. In our study, the adjusted 20% increase in MI rates during Mondays for the relatively young, working subgroup is substantial and warrants further research, as do several of the other estimates. In general, the present study lends additional support to stress triggering of MI and suggests that it is probably beneficial to minimize manipulations of our innate biological rhythms, also keeping in mind that a substantial portion of time constraints imposed on us by culture is necessary and harmonizes well with our biological predisposition. The suggested cascade of sociocultural norms instigating the human stress response that in turn triggers MI appears reasonable.

Main limitations/strengths

The observational study precludes definite causal conclusions, mainly because of possible unmeasured confounding. The observed temporal variation in MI rates might not be causally related to psychosocial stress. However, the present control for both previously established and suggested-but-untested confounders with novel high-quality data suggests that psychosocial stress is a quite plausible contributing cause of these MI rate changes. Another limitation is that patients from a single country were included and general conclusions for other countries cannot be drawn. Also, perceived stress was not directly measured in the population, as this was practically unfeasible. A smaller population-representative study with direct measurement of stress variables may therefore prove valuable. On the other hand, self-reported stress may not be more valid because subjective measures are notoriously unreliable, and effective stress levels may be subliminal or obscured by emotional and cognitive states, such as anticipations of holiday pleasures. Stress is arguably an extremely difficult concept, being partly a multifaceted biopsychosocial phenomenon and partly a psychological construct. It is nevertheless of profound real-life relevance. Studying stress therefore means making do with proxies of stress. If necessary data are made available, ethnic and/or religious minorities in Sweden could fruitfully be studied to confirm the stress-MI relationship, as they celebrate holidays at different times than do the secular Christian majority population. Because stress is also socially "contagious", stress levels in the cultural majority would probably also influence stress levels in cultural minorities. Another limitation was the lower inclusion of patients that are ≥80 years old, many of whom suffer an MI in dementia care. Regarding psychosocial stress, these patients' group context is quite different, their cognitive functioning is severely deteriorated, and clinical interventions are limited. The lower coverage of the very old might also have attenuated the Holiday-I because it is evidently driven by pensioners in Sweden. Furthermore, the analysis including NO_2 used a subgroup of urban and suburban dwellers for which NO_2 data were available. This selection may have biased the result beyond controlling for the influence of NO_2 on MI rates. The present findings should also be tested with non-Western population data for which high or low stress periods might differ. Climate-different Western countries in the Southern Hemisphere (eg, Australia, New Zealand) are particularly interesting, and research might then be focused on the alternative outcome of MI symptom onset date because both hospital admission and death likely have comparatively more systematic error from registration delay. The main strengths of the present study include the use of both the more trigger-relevant, alternative outcome symptom start date and the hospital admission date; the control for both established and some previously suggested-but-untested confounders; and that it reflects incidence rates of MI during different time periods in both the whole population and 8 subgroups based on a large, almost complete, nationwide registry with high measurement accuracy and statistical power.

Conclusion

Incidence rates of MI were higher on Mondays and over the Christmas and New Year holidays and lower in weekends and during the vacation month of July. The observed variability of incident MI at different time periods during the year may be systematically related to psychosocial stress levels. Further research should seek to delineate possible pathways and might clarify mechanisms that are amenable to clinical intervention.

Authors' contributions

J. W., E. O., C. H., and G. M. designed the study, acquired and analyzed data, interpreted the result, wrote the article, and approved its final form and submission. The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper.

Data sharing

No additional data available.

Patient involvement

There was no patient involvement in the preparation, execution, or translation of the present study.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

We are deeply grateful to the SWEDEHEART/RIKS-HIA patients. We thank Ronnie Pingel and Lars Lindhagen for statistical support and Urban Ekman for manuscript comments.

References

1. Takegami M, Miyamoto Y, Yasuda S, et al. Comparison of cardiovascular mortality in the Great East Japan and the Great Hanshin-Awaji Earthquakes—a large-scale data analysis of death certificates. Circ J 2015;79(5):1000-8, http://dx.doi.org/10.1253/circj.CJ-15-0223.
2. Wilbert-Lampen U, Leistner D, Greven S, et al. Cardiovascular events during World Cup Soccer. N Engl J Med 2008;358:475-83, http://dx.doi.org/10.1056/NEJMoa0707427.
3. Rosengren A, Hawken S, Ôunpuu S, et al. 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. Lancet 2004;364:953-62, http://dx.doi.org/10.1016/s0140-6736(04)17019-0.
4. Karasek RA. Job demands, job decision latitude, and mental strain: implications for job redesign. Adm Sci Q 1979;24(2):285-308, http://dx.doi.org/10.2307/2392498.
5. Netterstrøm B, Nielsen FE, Kristensen TS, et al. Relation between job strain and myocardial infarction: a case-control study. Occup Environ Med 1999;56:339-42.

6. Kuper H, Marmot M. Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study. J Epidemiol Community Health 2002;57:147-53, http://dx.doi.org/10.1136/jech.57.2.147.
7. Phillips DP, Jarvinen JR, Abramson IS, et al. Cardiac mortality is higher around Christmas and New Year's than at any other time: the holidays as a risk factor for death. Circulation 2004;110(25):3781-8, http://dx.doi.org/10.1161/01.CIR.0000151424.02045.F7.
8. Kloner RA. The "Merry Christmas Coronary" and "Happy New Year" heart attack phenomenon. Circulation 2004;110(25):3744-5, http://dx.doi.org/10.1161/01.CIR.0000151786.03797.18.
9. Phillips DP, Christenfeld N, Ryan NM. An increase in the number of deaths in the United States in the first week of the month. N Engl J Med 1999;341(2):93-8, http://dx.doi.org/10.1056/NEJM199907083410206.
10. Collart P, Coppieters Y, Godin Y, et al. Day-of-the-week variations in myocardial infarction onset over a 27-year period: the importance of age and other risk factors. Am J Emerg Med 2014;32:558-62, http://dx.doi.org/10.1016/j.ajem.2014.02.012.
11. Muller JE, Stone PH, Turi ZG, et al. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315-22, http://dx.doi.org/10.1056/NEJM198511213132103.
12. Spencer FA, Goldberg RJ, Becker RC, et al. Seasonal distribution of acute myocardial infarction in the Second National Registry of Myocardial Infarction. J Am Coll Cardiol 1998;31:1226-33, http://dx.doi.org/10.1016/S0735-1097(98)00098-9.
13. Spielberg C, Falkenhahn D, Willich S, et al. Circadian, day-of-week, and seasonal variability in myocardial infarction: comparison between working and retired patients. Am Heart J 1996;132:579-85, http://dx.doi.org/10.1016/S0002-8703(96)90241-0.
14. Bass J. Circadian topology of metabolism. Nature 2012;491:348-56, http://dx.doi.org/10.1038/nature11704.
15. Janszky I, Ahnve S, Ljung R, et al. Daylight saving time shifts and incidence of acute myocardial infarction—Swedish Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). Sleep Med 2012;13(3):237-42, http://dx.doi.org/10.1016/j.sleep.2011.07.019.
16. Kunz-Ebrecht SR, Kirschbaum C, Marmot M, et al. Differences in cortisol awakening response on work days and weekends in women and men from the Whitehall II cohort. Psychoneuroendocrinology 2004;29:516-28.
17. Statistics Sweden. *Work abseenteism due to vacation per month 2006-2013. Statistics Sweden: Sweden. 2015.*
18. SWEDEHEART. *Annual report 2014. Stockholm, Sweden: Karolinska University Hospital. 2015:1-138.*
19. von Elm E, Altman D, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806-8, http://dx.doi.org/10.1136/bmj.39335.541782.AD.
20. World Health Organisation. *International statistical classification of diseases and related health problems, 10th revision (ICD-10). 1992.*
21. R Development Core Team. *R: a language and environment for statistical computing. Vienna, Austria: Foundation for Statistical Computing. 2015.*
22. Venables WN, Ripley BD. *Modern applied statistics with S. New York: Springer. 2002.*
23. Lumley T, Zeileis A. *Robust covariance matrix estimators. CRAN. 2015.*
24. Meyer D, Zeileis A, Hornik K. *Visualizing categorical data. R package version 1.4-1. 2015.*
25. Zeileis A, Grothendieck G. zoo: S3 infrastructure for regular and irregular time series. J Stat Softw 2005;14(6):1-27, http://dx.doi.org/10.18637/jss.v014.i06.
26. Kloner RA, Poole K, Perritt RL. When throughout the year is coronary death most likely to occur? A 12-year population-based analysis of more than 220 000 cases. Circulation 1999;100:1630-4, http://dx.doi.org/10.1161/01.CIR.100.15.1630.
27. Statistics Sweden. *Women and men in Sweden: facts and figures 2012. Sweden: Statistics Sweden. 2012.*
28. Nawrot TS, Perez L, Künzli N, et al. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet 2011;377(9767):732-40, http://dx.doi.org/10.1016/s0140-6736(10)62296-9.
29. Statistics Sweden. *Living conditions, report no. 114: use of alcohol and tobacco. Sweden: Statistics Sweden. 2007.*
30. Raninen J. *Ingen dricker som Svensson: CAN Rapport 153. 2015.*
31. Phillips D, Barker GE, Brewer KM. Christmas and New Year as risk factors for death. Soc Sci Med 2010;71:1463-71.
32. Knight J, Schilling C, Barnett A, et al. Revisiting the "Christmas holiday effect" in the Southern Hemisphere. JAHA 2016;5.
33. Mustafi'c H, Jabre P, Caussin C, et al. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. JAMA 2012;307(7):713-21, http://dx.doi.org/10.1001/jama.2012.126.
34. Milojevic A, Wilkinson P, Armstrong B, et al. Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality. Heart 2014;100(14):1093-8, http://dx.doi.org/10.1136/heartjnl-2013-304963.
35. Bhaskaran K, Hajat S, Haines A, et al. Effects of air pollution on the incidence of myocardial infarction. Heart 2009;95(21):1746-59, http://dx.doi.org/10.1136/hrt.2009.175018.