

Seasonal Distribution of Acute Myocardial Infarction in the Second National Registry of Myocardial Infarction

FREDERICK A. SPENCER, MD, ROBERT J. GOLDBERG, PhD, RICHARD C. BECKER, MD,
JOEL M. GORE, MD, FACC, FOR THE PARTICIPANTS IN THE NATIONAL REGISTRY OF
MYOCARDIAL INFARCTION*

Worcester, Massachusetts

Objectives. This observational study sought to determine whether cases of acute myocardial infarction (AMI) reported to the second National Registry of Myocardial Infarction (NRMI-2) varied by season.

Background. The existence of circadian variation in the onset of AMI is well established. Examination of this periodicity has led to new insights into pathophysiologic triggers of atherosclerotic plaque rupture. Although a seasonal pattern for mortality from AMI has been previously noted, it remains unclear whether the occurrence of AMI also displays a seasonal rhythmicity. Documentation of such a pattern may foster investigation of new pathophysiologic determinants of plaque rupture and intracoronary thrombosis.

Methods. We analyzed the number of cases of AMI reported to NRMI-2 by season during the period July 1, 1994 to July 31, 1996. Data were normalized so that seasonal occurrence of AMI was reported according to a standard 90-day length.

Results. A total of 259,891 cases of AMI were analyzed during the study period. Approximately 53% more cases were reported in winter than during the summer. The same seasonal pattern (decreasing occurrence of reported cases from winter to fall to spring to summer) was seen in men and women, in different age groups and in 9 of 10 geographic areas. In-hospital case fatality rates for AMI also followed a seasonal pattern, with a peak of 9% in winter.

Conclusions. The present results suggest that there is a seasonal pattern in the occurrence of AMIs reported to NRMI-2 that is characterized by a marked peak of cases in the winter months and a nadir in the summer months. This pattern was seen in all subgroups analyzed as well as in different geographic areas. These findings suggest that the chronobiology of seasonal variation in AMI may be affected by variables independent of climate.

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It is now well recognized that the onset of acute myocardial infarction (AMI) follows a marked circadian periodicity, with a peak incidence in the early to late morning hours (1-8). Several of these studies also report a secondary peak in the onset of AMI in the late evening hours (7,8). Documentation of this circadian variation has directed further investigation of pathophysiologic triggers of the nonrandom occurrence of AMI. Arterial blood pressure (9), coronary artery tone (10), plasma cortisol (11) and catecholamines (12), platelet aggregability (13,14) and numerous hematologic variables (13-18) have all been shown to display a diurnal rhythm. Potential lifestyle factors associated with precipitation of AMI include physical exertion and acute psychologic stress (19-21).

From the Cardiovascular Thrombosis Research Center, Department of Medicine, Division of Cardiovascular Medicine, University of Massachusetts Medical Center, Worcester, Massachusetts. *A complete list of participants appears in reference 25. The National Registry of Myocardial Infarction is supported by Genentech, Inc., South San Francisco, California. Genentech, Inc. reimburses ClinTrials Research, Inc. for the cost of data analysis and biostatistical services.

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Address for correspondence: Dr. Frederick A. Spencer, Division of Cardiovascular Medicine, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, Massachusetts 01655. E-mail: fred.spencer@banyan.ummed.edu.

These findings have sparked renewed interest in the chronobiology of acute cardiovascular syndromes, with reexamination of a potential seasonal periodicity. An increase in mortality from AMI in the winter months was first reported in the 1930s (22,23). Since these initial observations, numerous studies have reported an increased mortality from coronary heart disease during the winter (24-28). Whether this increase in mortality is secondary to an increased incidence of AMI is much less clear. Using data from relatively small community- or hospital-based studies, several investigations have not been able to show a statistically significant difference between seasons in occurrence of AMI (29,30). These studies have been limited by their relatively small sample size and restricted geographic scope. The role of temperature and weather patterns in seasonal variation of AMI has also been explored with varying results. An increase in AMI occurrence or death due to AMI, or both, due to AMI in colder weather has been reported in such diverse locations as Wisconsin, Great Britain, India and Australia (30-33). In contrast, several investigators (36) have noted an increased occurrence of AMI with increased temperatures (34,35), whereas a study in Tasmania showed no correlation between maximal or minimal temperatures and AMI occurrence.

Given the conflicting published data, it remains important

Abbreviations and Acronyms

AMI = acute myocardial infarction
NRMI = National Registry of Myocardial Infarction

to ascertain whether there is seasonal variation in the occurrence of AMI and whether this variation is present irrespective of geographic area. The purpose of the present study was to determine whether hospital admission of patients with AMI varies seasonally in a large U.S. registry of cases of AMI. We also examined whether geographic area, gender or age influenced seasonality of AMI occurrence.

Methods

Study inclusion characteristics. The National Registry of Myocardial Infarction (NRMI) is a cross-sectional observational database of patients admitted to the hospital with AMI at 1,474 U.S. hospitals enrolling patients since 1990. The data collection process at each site and quality control features of the initial study registry (NRMI-1) have been previously described (25). Data from the second study registry (NRMI-2), which began in June 1994, were utilized for purposes of the present study. The primary purpose of the registry is to monitor temporal trends in institutional and national treatment practices in patients admitted to the hospital with AMI.

At the time of the study, 1,474 U.S. hospitals were participating and contributing data to NRMI-2. These hospitals represent ~15% of all acute medical/surgical hospitals in the United States. Participating hospitals tended to be larger and were more likely to be affiliated with a medical school, more likely to be certified by the Joint Commission on Accreditation of Health Care Organizations and more likely to have facilities for cardiac catheterization, coronary angioplasty and cardiac surgery than nonregistry U.S. hospitals.

To be included in NRMI-2, patients must have had an AMI before hospital discharge according to criteria such as patient history, serial enzymes levels or electrocardiographic findings. Patients could have initially presented to a registry hospital or have been transferred there after first being seen at another acute care facility.

Study data collection. For purposes of the study, the seasons were defined as follows: *winter* = December 21 to March 19; *spring* = March 20 to June 19; *summer* = June 20 to September 21; *fall* = September 22 to December 20. All patients enrolled in the NRMI 2 database from July 1, 1994 to July 31, 1996 comprised the present study sample. The date of AMI symptom onset was used to characterize seasonal patterns in the occurrence of AMI. *Symptom onset* was defined as the time when acute ischemic symptoms appeared or became constant in quality and intensity such that the patient decided to seek medical treatment.

Participation in the registry is entirely voluntary, and hospitals are encouraged to enter consecutive patients with AMI

irrespective of treatment strategy and outcome. Individual institutions participating in NRMI-2 designate a local coordinator who is responsible for abstracting and forwarding data to the central registry. Before initiation of the registry, the clinical coordinator at each site received a training manual that explained how to complete the case report form, defined each variable to be included and provided examples of correct responses. Audits are performed electronically to detect out of range variables, inconsistencies, errors and omissions. Queries are telephoned to local registry coordinators for resolution of discrepant entries. Periodic regional meetings of registry coordinators and investigators are held to discuss data entry procedures and registry findings (25). Data are obtained by periodic retrospective chart review of all patients with AMI. These patients were identified by periodic review of emergency department and hospital admission logs. Completed case report forms were then sent to an independent data coordinating center (ClinTrials Research, Inc.).

Study end point calculation. The adjusted seasonal average of AMI cases was used as the primary study end point and was calculated by normalizing the total number of cases for each season to a standard 90-day length. For example, the number of AMI cases occurring in the winter equaled the number of AMI cases from December 21, 1994 to March 19, 1995 plus AMI cases occurring from December 21, 1995 to March 19, 1996 divided by the total number of days in these periods multiplied by 90. Adjusted seasonal mean values were reported for different geographic areas, age specific subgroups and separately for men and women.

Statistical analysis. Differences in the distribution of selected categoric and continuous factors according to season were examined through the use of chi-square tests and analysis of variance for statistical significance. Formal tests of statistical significance (e.g., p values) were not applied in the examination of seasonal occurrence of AMI given the large size of the database (and to avoid confusion as to their interpretation), descriptive purposes of the present study, the multiplicity of comparisons carried out and the lack of available at risk denominator data to calculate incidence rates.

Results

Participating hospitals reported 259,891 cases of AMI to NRMI 2 during the 25-month study period. There were no marked seasonal differences in the study sample according to age (mean age 65.7 years), gender (64% male) or AMI location (40% inferior, 29% anterior/septal).

Seasonal variation. Adjusting for the varied lengths of each season, there were 53% more cases of AMI reported during the winter months than in summer (Fig. 1). Analysis by month (normalized to a 30-day length) revealed January as the month with the most reported cases (13,025 cases/30-day month). The number of reported cases decreased in a consistent manner to a marked nadir in July (5,978 cases/30-day month), with increases thereafter (Fig. 2).

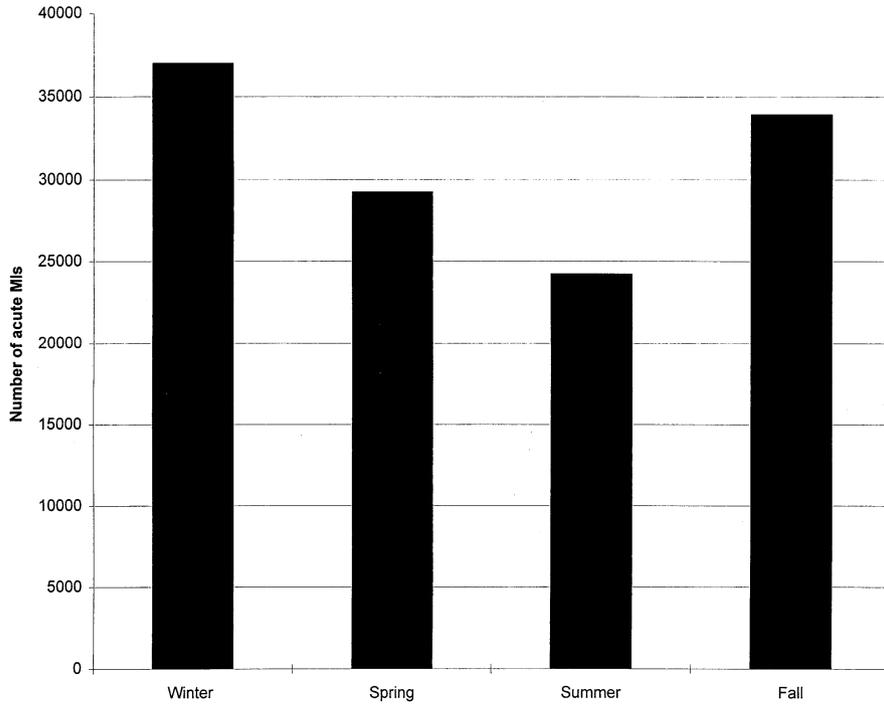


Figure 1. Cases of AMI reported each season to the NRMI-2. Counts were normalized to a 90-day season length.

Seasonal variation by geographic region. The seasonally adjusted number of cases of AMI were examined for each of 10 distinct geographic areas (Table 1, Fig. 3). All areas, with the exception of the West North Central states, displayed the same seasonal pattern previously observed, namely a peak in winter followed by progressively fewer cases of AMI in the fall, spring and summer. The South Atlantic region displayed the largest seasonal differences in AMI occurrence, with ~43% more cases reported in winter than in summer; the Pacific region had

the smallest difference, with ~28% more cases occurring in winter than in summer.

Seasonal variation by gender and age group. Seasonal patterns in AMI occurrence were similarly seen for men and women. Men had ~52% more AMIs, and women had 54% more AMIs reported in the winter than in the summer. The same pattern was seen for each of four different age groups and for men and women within each age group (Table 2, Fig. 4 and 5). In-hospital case fatality rates for AMI also followed

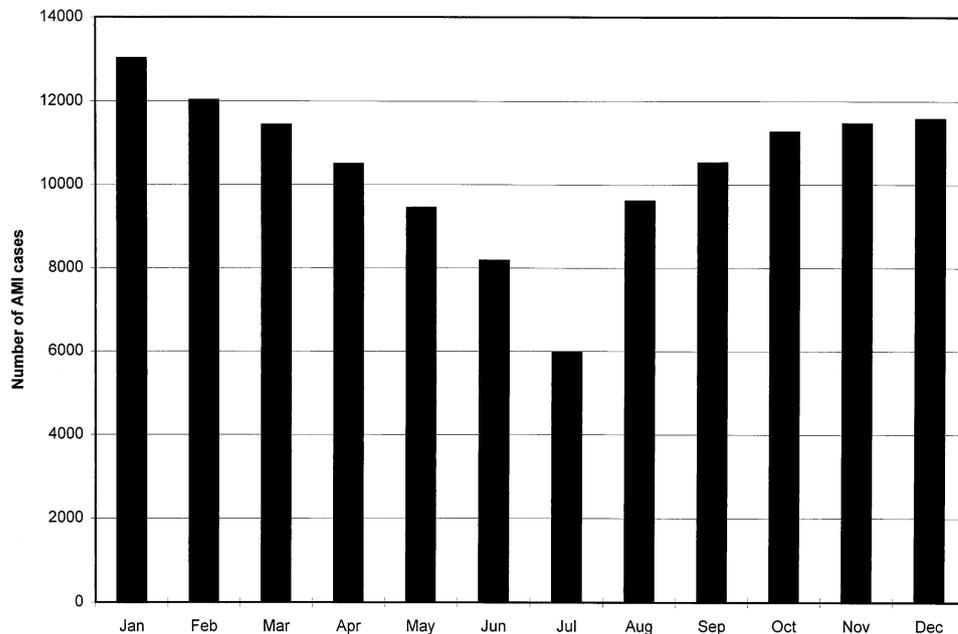


Figure 2. Cases of AMI reported each month to the NRMI-2. Monthly counts were normalized to a 30-day length.

Table 1. Cases of Acute Myocardial Infarction Reported to the Second National Registry of Myocardial Infarction by Region

Region	Winter [no. (%)]	Spring [no. (%)]	Summer [no. (%)]	Fall [no. (%)]	Summer to Winter Change (%)
All cases	36,964 (29.8)	29,217 (23.5)	24,178 (19.5)	33,880 (27.3)	+52.8
NE	1,897 (29.7)	1,663 (26.1)	1,124 (17.6)	1,695 (26.6)	+68.8
Mid Atl	4,798 (27.9)	4,255 (24.8)	3,373 (19.6)	4,745 (27.6)	+42.2
S Atl	7,438 (31.2)	5,573 (23.4)	4,256 (17.9)	6,568 (27.6)	+74.8
ENC	7,327 (29.5)	5,816 (23.4)	5,029 (20.2)	6,674 (26.9)	+45.7
ESC	2,549 (30.5)	1,822 (21.8)	1,539 (18.4)	2,437 (29.2)	+65.6
WNC	2,873 (28.1)	2,442 (23.9)	1,933 (18.9)	2,978 (29.1)	+48.6
WSC	2,333 (29.8)	1,841 (23.5)	1,618 (20.7)	2,039 (26.0)	+44.2
Mountain	2,489 (30.3)	1,847 (22.5)	1,656 (20.2)	2,209 (26.9)	+50.3
Pacific	5,080 (29.5)	3,958 (23.0)	3,649 (21.2)	4,537 (26.3)	+39.2

ENC = East North Central (Ohio, Indiana, Illinois, Michigan, Wisconsin); ESC = East South Central (Kentucky, Tennessee, Alabama, Mississippi); Mid Atl = Middle Atlantic (New York, New Jersey, Pennsylvania); Mountain = Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada; NE = New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut); Pacific = Washington, Oregon, California, Alaska, Hawaii, Guam; S Atl = South Atlantic (Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida); WNC = West North Central (Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, Kansas); WSC = West South Central (Arkansas, Louisiana, Oklahoma, Texas).

a seasonal pattern. These rates were greatest in winter and lowest in spring: winter 9.0%, fall 8.7%, spring 8.4%, and summer 8.7%.

Discussion

AMI is a dynamic event resulting from the rupture of a once quiescent atherosclerotic plaque and the development of an occlusive intracoronary thrombus. Considerable advances in identifying the pathophysiologic disturbances that may predispose to rupture have occurred in the past decade, delineating the key roles of a high lipid content, a thin fibrous cap, high

macrophage and low smooth muscle content and exposure to high shear stress (37-41). Considerably less information is known about the inciting event or events leading to actual plaque rupture. By documenting circadian variation in the onset of AMI approximately one decade ago, Muller et al. (1) and others (2-6) have prompted investigators to search for pathophysiologic triggers of AMI that display diurnal variation. This work has led to an increased understanding of the sequence of events leading to AMI and to the eventual development of novel preventive and therapeutic approaches.

Previous studies. Whether the incidence of AMI is governed by other chronologic rhythms remains to be determined.

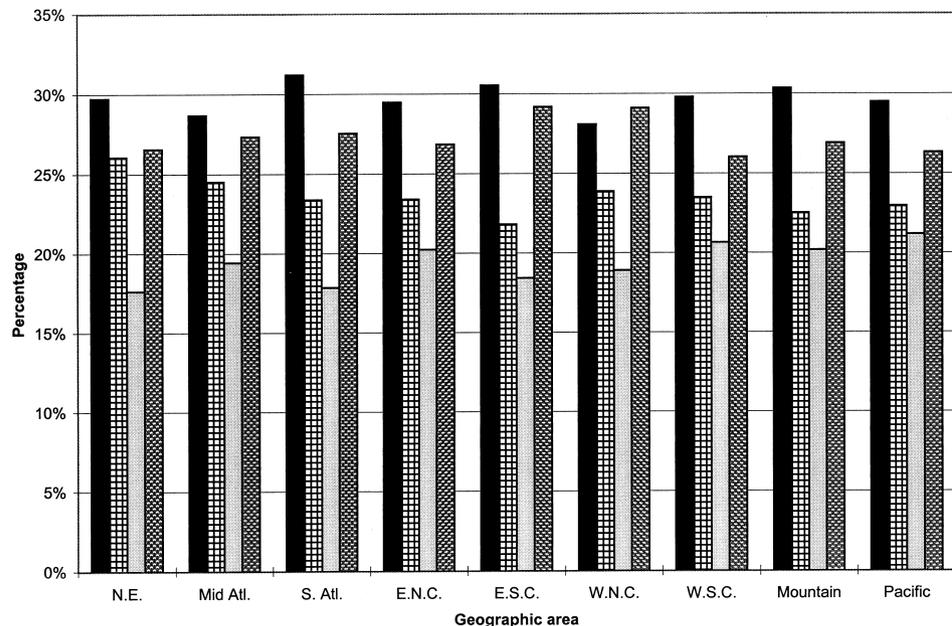


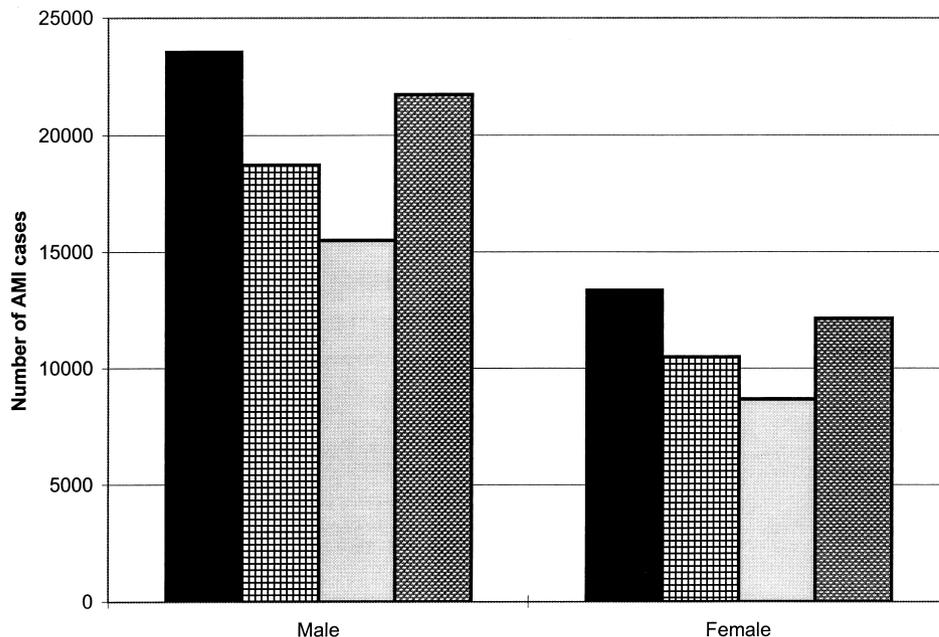
Figure 3. Percent of cases of AMI reported each season to the NRMI-2 by region. E.N.C. = East North Central; E.S.C. = East South Central; Mid Atl. = Middle Atlantic; N.E. = New England; S. Atl. = South Atlantic; W.N.C. = West North Central; W.S.C. = West South Central. **Solid bars** = winter; **checkered bars** = spring; **shaded bars** = summer; **dotted bars** = fall. See Table 1 for list of states within each region.

Table 2. Cases of Acute Myocardial Infarction Reported to the Second National Registry of Myocardial Infarction by Gender and Age Group

Region	Winter [no. (%)]	Spring [no. (%)]	Summer [no. (%)]	Fall [no. (%)]	Summer to Winter Change (%)
All cases	36,964 (29.8)	29,217 (23.5)	24,178 (19.5)	33,880 (27.3)	+52.8
Gender					
Men	23,577 (29.6)	18,730 (23.5)	15,499 (19.5)	21,739 (27.3)	+52.1
Women	13,387 (30.0)	10,487 (23.5)	8,679 (19.4)	12,141 (27.2)	+54.2
Age (yr)					
<55	8,741 (29.4)	7,017 (23.6)	5,910 (19.9)	8,017 (27.0)	+47.9
55-64	7,842 (29.6)	6,294 (23.7)	5,095 (19.2)	7,297 (27.5)	+53.9
65-74	10,088 (29.8)	7,818 (23.1)	6,665 (19.7)	9,295 (27.4)	+51.4
>75	10,294 (30.1)	8,088 (23.7)	6,508 (19.1)	9,271 (27.1)	+57.9
Men only					
<55	6,917 (29.3)	5,593 (23.7)	4,716 (20.0)	6,386 (27.0)	+46.7
55-64	5,630 (29.6)	4,518 (23.7)	3,666 (19.2)	5,238 (27.5)	+53.6
65-74	6,284 (29.9)	4,857 (23.1)	4,103 (19.5)	5,749 (27.4)	+53.2
>75	4,745 (29.9)	3,761 (23.7)	3,014 (19.0)	4,367 (27.5)	+57.4
Women only					
<55	1,824 (30.0)	1,423 (23.4)	1,194 (19.7)	1,631 (26.9)	+53.0
55-64	2,211 (29.6)	1,776 (23.8)	1,428 (19.1)	2,059 (27.5)	+54.8
65-74	3,803 (29.5)	2,961 (23.0)	2,563 (19.9)	3,547 (27.6)	+48.4
>75	5,548 (30.4)	4,327 (23.7)	3,494 (19.1)	4,905 (26.8)	+58.8

Documentation of seasonal variation in the occurrence of AMI will provide further insights to the pathophysiologic triggers of plaque rupture and thrombogenesis. Many studies have reported an increased mortality due to AMI in the winter season (22-28), but it is unclear if such an increase is due to an increased incidence of AMI or is simply secondary to a higher case fatality rate. The majority of previous studies examining seasonal differences in AMI mortality have failed to adjust for seasonal differences in the population at risk for dying of AMI

because only the absolute number of deaths were considered and not death rates. In the present study we adjusted for the population at risk through the calculation of in-hospital case fatality rates. We observed limited seasonal variation in the in-hospital death rates due to AMI. Because of our methods of data collection, we were only able to examine in-hospital, and not out of hospital, deaths due to AMI. Differences in the manner in which deaths attributed to coronary disease were classified as well as the inclusion of out of hospital and

**Figure 4.** Cases of AMI reported each season to the NRMI-2 for men and women. Counts were normalized to a 90-day season length. Symbols as in Figure 3.

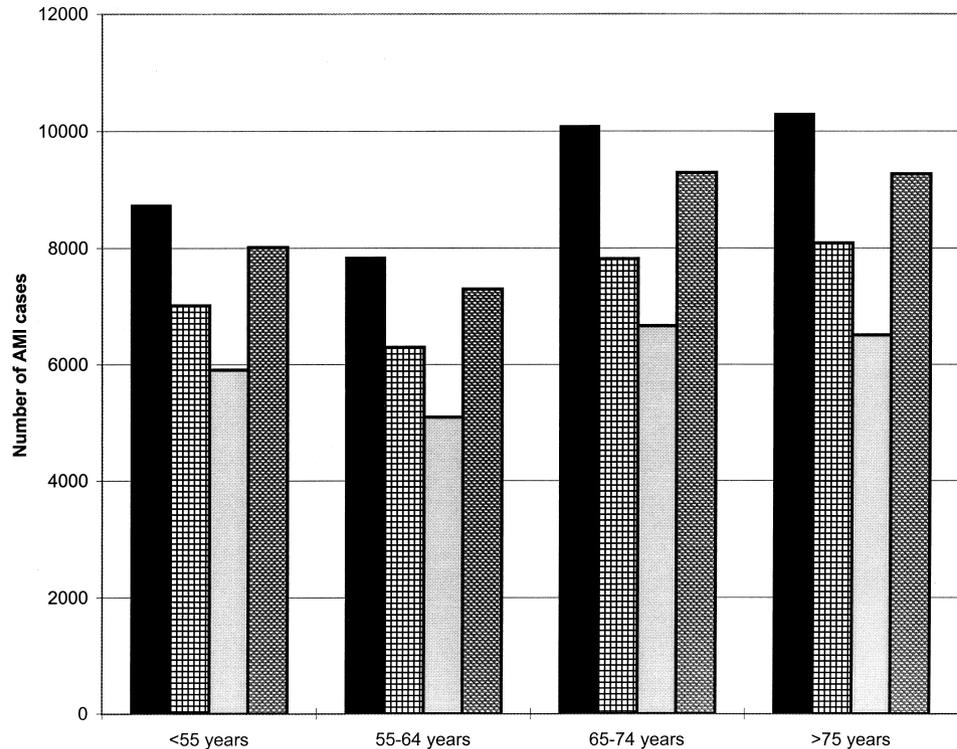


Figure 5. Cases of AMI reported each season to the NRMI-2 by age group. Counts were normalized to a 90-day season length. Symbols as in Figure 3.

in-hospital deaths may also explain some of the discrepant findings between the results of the present study and previously published work.

The development of community registries for acute coronary syndromes in the past three decades provides a means by which the seasonal variation in AMI can be explored. Investigators using data from a Scottish registry in 1970 (42) were among the first to note a seasonal pattern for nonfatal coronary events. Data from the population-based Australian Monitoring Trends and Determinants in Cardiovascular Disease Project (MONICA) site (30) revealed both fatal and nonfatal coronary events to be between 20% and 40% more common in winter (June to August) and spring (September to November) than during other times of the year. Data from the Myocardial Infarction Community Register for Dessau, Germany (29) also revealed a trend toward an increased incidence of AMI in the winter months, with a statistically significant peak in March.

In the largest study to date, Ornato et al. (43) analyzed data from the initial NRMI 1 registry for seasonal variation in the onset of AMI. They found that there were ~10% more cases enrolled in the spring and winter seasons than in the summer. The same seasonal trends were seen in all subgroups studied, including men and women, middle-aged and elderly patients, patients from northern and southern states and those with Q wave and non-Q wave AMI.

Present study. In the present study, ~53% more AMI cases were reported to participating NRMI-2 hospitals in the winter than in the summer. These results differ substantially from those derived from the NRMI-1 registry, and the reasons for these discrepant results are not immediately apparent. In

the NRMI-1 study, only cases submitted to 138 “high volume” core hospitals (of 1,073 total NRMI hospitals) were analyzed, resulting in an available sample of 83,541 cases of AMI. In the present study, no such restriction criteria were imposed, resulting in a more than threefold greater number of cases studied and most likely a more representative sample of patients with AMI. The increased number of AMI cases observed in the present study may have allowed for a better differentiation of true seasonal variation in the onset of AMI. The magnitude of the seasonal variation observed in the present study was greater than that seen in the Australian MONICA population (20% to 40%) and in the Dessau Registry (17%).

Given the data available for analysis, we cannot comment on the cause of the increased hospital case fatality rate in winter. It is most likely affected by a multitude of factors that may also display a seasonal periodicity, including physiologic effects of climate or weather, concomitant illnesses (i.e., influenza or pneumonia and comorbidity), time to treatment, hospital staffing and other potentially confounding prognostic factors.

Study limitations. As in any voluntary registry dependent on existing hospital staff in hundreds of hospitals, we cannot claim to have captured every case of AMI admitted to registry hospitals during the study period. Coordinators are encouraged to enter consecutive AMI patients irrespective of treatment strategy and outcome. However, no independent validation of data forms is carried out, and the potential for nonconsecutive patient enrollment exists. Despite this potential concern, seasonal variation in patient accrual (e.g., due to vacations, work absences) should be minimized because data

abstraction is accomplished through periodic review of hospital patient logs. As previously noted, registry hospitals may not be representative of all hospitals within the United States. Moreover, because this study is not population based but is based on the reporting of hospital-specific data, we are unable to sufficiently characterize the population at risk for AMI and how this population may vary by season. We can only describe the seasonal occurrence of AMI reported to registry hospitals and not the true incidence of AMI, and are therefore unable to determine whether the actual incidence rates of AMI vary by season. Another potential limitation is that NRM-2 does not collect information on all cardiac risk factors or possible precipitating factors for AMI. These factors may vary by season and may represent potential confounding variables in the interpretation of any possible seasonal trends in AMI occurrence. It should also be noted that data from patients enrolled over a 25-month period from July 1, 1994 to July 31, 1996 were analyzed. Because July had the fewest reported AMIs of any season, inclusion of the "extra month" from July 1996 would tend to decrease the average seasonal occurrence of AMIs reported in summer (despite normalization to a 90-day season length). However, the magnitude of this effect is small, ~6 percentage points of the observed 53% difference from summer to winter.

Potential etiologies for seasonal pattern. The etiologic mechanism underlying the seasonal pattern of AMI observed in this study are unclear. Many investigators have documented an increase in mortality from AMI in colder weather (24,30,31,44). An influence of temperature on the incidence of AMI has also been hypothesized. Some have reported an increased rate of AMI with decreased temperatures in winter (32,33,42), whereas others have noted a similar increase with rises in temperature in summer (34,35). In a study carried out in London (32), an excess number of infarctions on colder days in both winter and summer was noted, suggesting an independent effect of environmental temperature. Mechanisms leading to the possible influence of environmental temperature on the onset of AMI are most likely multifactorial. Sympathetic tone, blood pressure, myocardial oxygen consumption, red blood cell and platelet count, plasma beta-thromboglobulin, platelet factor 4 and plasma fibrinogen have been shown to increase, and antithrombin III to decrease, with colder weather (45-48).

With the exception of the Pacific and Mountain regions, states within each of the other groupings have fairly similar climates. The consistency of seasonal variation of AMI occurrence seen in these geographic subdivisions, despite their markedly different climates, suggests that this pattern may also be governed by variables independent of environmental temperatures. The duration of light per day changes with season throughout the United States, and it is well known that light has an influence on a number of physiologic variables. In one study (49), patients with AMI had significantly lower mean 25-hydroxy vitamin D3 levels than paired control subjects; importantly, these levels were lowest in the winter months. This study is in accord with two others (50,51) reporting decreased vitamin D levels in patients with coronary disease.

Collectively, these studies suggest that increased exposure to sunlight may be protective against coronary disease, providing a potential alternative explanation for a seasonal pattern to AMI onset.

Other physiologic variables shown to have seasonal periodicity include fibrinolytic activity, plasma cortisol levels, serum lipids and platelet serotonin levels (52-54). There are abundant published reports exploring seasonal occurrence of affective disorders, some of which suggest seasonal changes in platelet serotonin concentration and uptake, platelet binding sites and platelet membrane proteins, which may play a role in the development of these conditions (55-58). It is possible that other seasonal variations in platelet physiology are involved in the observed periodicity of AMI.

Conclusions. There was a marked winter increase or summer decrease, or both, in the number of AMI cases reported in a large, prospective U.S. registry of AMI cases. This pattern was seen irrespective of geographic area, age or gender. Research into physiologic variables and lifestyle characteristics associated with seasonal variation of AMI may provide further insights into the mechanism or mechanisms by which abrupt rupture of atherosclerotic plaques and vascular thrombosis occur.

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