Published in final edited form as:
Circulation. 2012 January 24; 125(3): 491–496. doi:10.1161/CIRCULATIONAHA.111.061770.

Risk of Acute Myocardial Infarction after Death of a Significant Person in One's Life: The Determinants of MI Onset Study

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Abstract

Background—Acute psychological stress is associated with an abrupt increase in the risk of cardiovascular events. Intense grief in the days following the death of a significant person may trigger the onset of acute myocardial infarction (MI), but this relationship has not been systematically studied.

Methods and Results—We conducted a case-crossover analysis of 1985 participants from the multicenter Determinants of MI Onset Study interviewed during index hospitalization for an acute MI between 1989 and 1994. We compared the observed number of deaths in the days preceding MI symptom onset to its expected frequency based on each patient's control information, defined as the occurrence of deaths in the period from 1 to 6 months prior to infarction. Among the 1985 subjects, 270 (13.6%) experienced the loss of a significant person in the prior six months, including 19 within 1 day of their MI. The incidence rate of acute MI onset was elevated 21.1 fold (95%CI 13.1 to 34.1) within 24 hours of the death of a significant person, and declined steadily on each subsequent day. The absolute risk of MI within 1 week of the death of a significant person is 1 excess MI per 1394 exposed individuals at low (5%) 10-year MI risk and 1 per 320 among individuals at high (20%) 10-year risk.

Conclusions—Grief over the death of a significant person was associated with an acutely increased risk of MI in the subsequent days. The impact may be greatest among individuals at high cardiovascular risk.

Keywords

Acute Myocardial Infarction; Bereavement; Case-Crossover; Epidemiology

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Conflict of Interest Disclosures: None

Introduction

Grief over the death of a significant person is associated with symptoms of depression, anxiety and anger. Though the death of a significant person in one's life is rare at any given moment, bereavement is a part of almost everyone's life. Among people 65 years of age and older, approximately 45% of women and 15% of men become widowed.[1] Most people adjust to the loss of a significant person, but there is a heightened risk of mortality in the early weeks and months after loss,[2, 3] with cardiovascular disease accounting for 20 to 53% of the excess deaths during spousal bereavement.[4–6] For instance, in a prospective study of 4395 married couples in Scotland, Hart and colleagues[7] found that bereaved individuals had higher rates of mortality than non-bereaved individuals. Even after adjusting for cardiovascular risk factors, death of a spouse is associated with an increased rate of mortality from cardiovascular disease (incidence rate ratio [IRR] = 1.18, 95%CI 1.08 to 1.29) and coronary heart disease (IRR=1.22, 95%CI 1.08 to 1.37).

Despite a vast literature on the association between spousal bereavement and increased risk of mortality in the subsequent weeks and months, whether bereavement for a significant person in one's life is associated with an acutely increased risk of cardiovascular events has not been systematically studied. Therefore, we evaluated whether there is an increased risk of myocardial infarction (MI) in the days following the death of a significant person in one's life among participants enrolled in the Determinants of Myocardial Infarction Onset (MIOS) Study.

Methods

Study Design

The MIOS Study used a case-crossover design, a variation of a case-control design that is appropriate when a transient exposure (death of a significant person in the patient's life) is associated with an acute change in the risk of an acute outcome (nonfatal MI).[8, 9] We compared a subject's report of the loss of a significant person in the days prior to onset of the MI (the case period) with the same subject's report of bereavement for a significant person in his or her life in the prior six months (the control period). Because control information for each subject is based on his or her own past exposure experience, self-matching eliminates confounding by risk factors that are constant within individuals over the sampling period but often differ between study subjects.

Study Population

Between 1989 and 1994, 1985 people (1,318 men and 590 women, mean age 61.6) were interviewed at 22 community hospitals and 23 tertiary care centers a median of 4 days following admission for MI. The cohort was followed prospectively for all-cause mortality through December 31, 2007. This report is based on the data collected at the time of enrollment. Interviewers identified eligible cases by reviewing coronary care unit admission logs and patients' charts. For inclusion in the study, patients were required to meet all of the following criteria: at least one creatine kinase level above the upper limit of normal for the clinical laboratory performing the test, positive MB isoenzymes, an identifiable onset of pain or other symptoms typical of infarction, and the ability to complete a structured interview. The protocol was approved by the institutional review board at each participating center and informed consent was obtained from each patient.

As previously described,[10] detailed chart reviews and patient interviews were conducted by trained research personnel. Data were collected on standard demographic variables and risk

factors for coronary artery disease. The interview identified the time, place and quality of MI pain and other symptoms, as well as the timing and estimated usual frequency of exposure to potential triggers of MI onset during the prior year. In addition, patients were asked "During the past year did you hear news of the death of a friend, relative, or someone who was very significant in your life?" If a patient answered affirmatively, they were asked to identify the time of occurrence of the death, to describe their relationship to the person who had died and to rate the significance of this death in terms of meaningfulness (slightly, moderately or extremely meaningful).

Statistical Analysis

Each subject in a case-crossover study forms his or her own stratum and thus is his or her own control.[8, 9] We evaluated the incidence rate of MI within 1 day, 2–3 days, 3–7 days, and 7–30 days (case periods) following the death of a significant person. *A priori*, we selected a control period of 1 to 6 months (150 days, i.e., 31–180 days prior to infarction) since it is recent enough that patients are likely to correctly report the loss of a significant person in one's life and health characteristics remain fairly stable over a span of only 6 months. The number of exposed control days was equal to the number of reported deaths of a significant person in one's life during that time period, and the remaining days were considered non-exposed. We compared the observed number of deaths that occurred during each of these periods to the number expected based on each patient's control information using the Mantel-Haenszel estimator of the incidence rate ratio (IRR). In this analysis, the proportion of exposed days in the control period represents the expected frequency of exposure in the case period.

For ease of interpretation, we estimated the absolute risk of MI associated with the death of a significant person within 1 day and 1 week for populations with baseline 10-year MI risk of 5%, 10% and 20% based on the Framingham Risk Score.[11] To estimate the absolute risk of MI in the days following the death of a significant person, we calculated the baseline risk of MI per day for individuals with 10-year risk of 5%, 10% and 20% using the following formula:

$$\text{Risk}_x = 1 - exp^{-\left(\left[\frac{-ln(1-\text{Risk}_{10y})}{3652.5}\right]*x\right)}$$

Where Risk_x is the baseline risk of MI for x days (in this case, 1 day or 7days) for an individual with a 10-year (3652.5 days) risk of Risk_{10y} (5%, 10% or 20%).

We calculated the risk among the exposed as the baseline risk multiplied by the IRR. As an estimate of absolute risk, we computed the risk difference by subtracting the baseline risk from the risk among the exposed; the reciprocal of this value represents the number needed to harm, i.e., the number of individuals who recently experienced the loss of a significant person that would result in one excess case of MI.

We stratified by sex, age (<65 vs. ≥65 years), smoking status (former vs. current), frequency of habitual physical activity (3 or more times per week vs. fewer than 3 times per week) and history of coronary artery disease (CAD; prior MI or angina vs. neither) and compared the IRRs by means of a test for homogeneity.[12] We conducted several sensitivity analyses; in the first sensitivity analysis, we estimated the association between MI onset and death of a significant person in the past week. We also conducted an analysis using days 3 to 7 as the control period, an analysis excluding subjects reporting a history of MI and an analysis restricted to subjects reporting that the recent death was moderately or extremely meaningful. All reported *p* values are 2-sided.

Results

The characteristics of the population interviewed are summarized in Table 1. Among the 1985 MIOS participants, 270 (13.6%) reported the death of at least one significant person in the 6 months preceding MI onset. Of the 270 subjects reporting a death in the prior 6 months, 193 provided details about the decedent; 12 had lost a parent, 2 lost a child, 20 lost a sibling, 6 lost a spouse and 153 lost a more distant relative or friend. There were 19 patients who reported the death of a significant person within 24 hours of the onset of their infarction symptoms. For the days leading up to the infarction, there were 7 patients that reported a death 24–48 hours before their symptoms, 5 patients that reported a death 48–72 hours before their symptoms, and 21 patients that reported deaths from 4–7 days before the onset of MI. Among the 19 patients reporting the death a significant person within 24 hours of the onset of their infarction symptoms, 12 (63%) found it moderately or extremely meaningful.

The rate of acute MI onset was elevated 21.1 fold (95%CI 13.1 to 34.1) within 24 hours of learning of the death of a significant person. Figure 1 shows that the IRR declined each day following the death, but remained significantly elevated for at least one month following the death of a significant person.

To put this finding into context, we estimated the absolute risk on the day after the death of a significant person among individuals at different levels of 10-year MI risk. Among individuals at relatively low risk (5%) there would be 1 excess MI per 3,543 exposed individuals; for intermediate risk (10%) 1 excess MI per 1725 exposed individuals; and for high risk (20%) 1 excess MI per 815 exposed individuals. Furthermore, our data suggest that within 1 week of the death of a significant person there would be 1 excess MI per 1394, 678, 320 exposed individuals at 5%, 10%, and 20% 10-year MI risk respectively.

There were no statistically significant differences defined by age, sex, frequency of physical activity or history of CAD. The estimated IRR was greater for men than women, for those less than for those 65 years of age than people 65 years of age and older, for those reporting physical activity 3 or more times per week compared to those reporting less frequent physical activity and for those with no history of CAD (Table 2).

In a sensitivity analysis, the IRR remained elevated when the hazard period was defined as the entire week prior to MI onset (IRR=8.3, 95%CI 6.0 to 11.4), when we defined the control period as days 3 to 7 (IRR=3.6, 95%CI 2.0 to 6.7) and when the analysis was restricted to patients with no history of MI (IRR=25.9, 95%CI 15.0 to 44.7). Compared to the overall estimate of 21.1, the IRR was higher among patients reporting that the recent death was moderately or extremely meaningful (IRR=27.7, 95%CI 15.0 to 51.3).

Discussion

In the MIOS Study, the risk of MI onset was greatly elevated in the days following the death of a significant person. The IRR was greatest in the first 24 hours (IRR=21.1, 95%CI 13.1 to 34.1) and progressively declined over time to 5.8 (95%CI 3.7 to 9.2) by the end of the first week. Although death of a significant person is a rare event for an individual, the risk of MI within the first week may be substantial, ranging from 1 excess MI per 320 exposed individuals to 1 per 1394 for individuals at high and low baseline MI risk respectively. These results require confirmation in prospective studies.

Almost all of the prior studies on cardiovascular risk associated with bereavement have been focused on the death of a spouse, comparing bereaved to non-bereaved individuals.[2, 3] Initial studies ignored the fact that the elevated risk may be due to the emotional stress of grief, but

it may also be due to the fact that couples may share similar lifestyle and risk factors. Therefore, people who lose a spouse may also be the same people who are already at increased risk of cardiovascular disease or all-cause mortality. Subsequent studies (e.g.[7, 13]) addressed this potential confounding by adjusting for cardiovascular risk factors in their statistical model. In our study, we used the case-crossover design, which compares each person to himself or herself. Thus, there is no variability in traditional cardiovascular risk factors within each stratum so there is no confounding by these chronic risk factors.

Although there have been no prospective studies showing the acute impact of bereavement on MI risk, Fang and colleagues[14] have used population-based registry data to examine whether cancer diagnosis is associated with an acutely increased risk of suicide and cardiovascular death. Future research using registry data to examine the association between bereavement and cardiovascular risk would provide an opportunity to examine this question using data on the timing of death and MI that is collected prospectively and not vulnerable to misclassification inherent in self-report.

In our study, 6 participants reported the loss of a spouse within 6 months of MI onset, but none were within the prior day. Though our study examines the MI risk associated with the loss of any significant person, our findings are consistent with prior studies, showing that men are more vulnerable to the health consequences from bereavement than women,[15] and that younger bereaved people are more vulnerable than older bereaved people.[2]

Our study is the first to examine whether the death of a significant person triggers MI. Previous research has shown that related emotional stressors, such as anger,[16, 17] anxiety[16] and depression[18] may trigger cardiovascular events in the following hour(s).[19, 20] For instance, in our study population,[16] 39 of the 1623 (2.4%) patients recruited by 1995 reported an episode of anger in the 2 hours prior to MI onset, resulting in a 2.3-fold (95%CI 1.7 to 3.2) increased risk of MI; there was a 1.6-fold (95% CI 1.1 to 2.2) elevated risk of MI in the 2 hours following episodes of marked anxiety. In a study of 295 patients interviewed immediately following an acute coronary event,[18] 46 (18.2%) reported a time-limited episode of depression in the 2 hours before symptom onset. The odds of ACS were 4.33-fold (95% CI 3.39 to 6.11) greater in the two hours following an acute episode of depression compared to other times.

There are a number of pathways that may explain the link between emotional triggers and the onset of acute cardiac events.[21, 22] Acute bereavement is associated with psychological, behavioral and physiologic sequelae.[20–22] In particular, bereavement is associated with higher levels of negative affect, including symptoms of depression, anxiety and anger.[20] Acute bereavement is also associated with reduced sleep time, reduced appetite, lower total cholesterol and low density lipoprotein and higher cortisol levels. These changes may contribute to the increased cardiovascular risk.[20] The emotional stress of bereavement stimulates heightened sympathetic activation. The hemodynamic changes that result, such as increased vascular resistance, may cause transient myocardial ischemia and/or disruption of a vulnerable coronary plaque, especially among susceptible patients. Furthermore, it may stimulate an inflammatory and pro-thrombotic response.[23] These physiologic changes may lead to occlusive coronary arterial thrombosis by increasing thrombogenicity and vasoconstriction.

Emotional and physical stress can lead to symptoms similar to those seen in acute myocardial infarction, including chest pain, ST segment elevation and increased creatine kinase and troponin levels.[24, 25] This stress myocardiopathy (also known as Takotsubo cardiomyopathy or broken heart syndrome) is associated with severe but transient left ventricular dysfunction that is usually resolved within days or weeks. Because angiographic

data is not available, we cannot rule out the possibility that some of the cases included in our sample had Takotsubo cardiomyopathy rather than an acute coronary syndrome.

It is possible that bereavement results in poor medication compliance, which thereby increases cardiovascular risk.[20] However, in our study the magnitude of the association between bereavement and MI was strongest in the day following the loss of a significant person, suggesting that our findings are not due to acute washout of a missed dose of a drug. Among the 19 patients reporting the death a significant person within 24 hours of the onset of their infarction symptoms, one patient missed a dose of an oral hypoglycemic agent on the day before symptom onset. Among the 52 patients reporting the death a significant person within 7 days of symptom onset, one patient missed a dose of a short-acting ace inhibitor 14 hours before symptoms of infarction. Importantly, no patients reported skipped doses of beta blockers that could have caused a rebound in hypertension and subsequent onset of infarction symptoms. Since behavioral changes represent factors occurring after the loss of a significant person, we do not account for these factors in our analysis, since they mediate rather than confound the relationship of interest.

There are some limitations that warrant discussion. Only 19 people were exposed to the death of a significant person in the 24 hours prior to MI onset, so we did not have sufficient data to evaluate whether the association varies by the relationship between the deceased and the bereaved or by the reason for the significant person's death. Future research is needed to examine whether these factors are associated with a higher risk. However, we found that the risk of MI following the death of a significant person was particularly high among those reporting that the loss was moderately or extremely meaningful. In a case-crossover study, each individual provides information about exposure during both the hazard and control periods. Patients may attempt to explain their cardiac event by emphasizing emotional stressors immediately prior to symptom onset and inadvertently underestimate exposure during the control period, which may lack the salience of the hours preceding symptom onset. This can result in an overestimation of IRR. In order to reduce recall bias, we restricted our analysis to include only deaths reported during the 6 months prior to MI onset. Furthermore, in a sensitivity analysis using days 3 to 7 as the control period, the association remained statistically significant. A second concern is that some people may have incorrectly reported the timing of the death of the significant person, resulting in misclassification of the time between the death and symptom onset. However, the death of a significant person is a major life event, so it is probable that the timing is correctly reported. Also, even if some patients reported the timing of the death incorrectly by a day or two, the association remained elevated when the hazard period was defined as the entire week prior to MI onset. Since the case-crossover design uses subjects as their own controls, there can be no confounding by risk factors that are stable over time, but confounding by factors that change over time within individuals can occur if other transient risk factors occur during the case period.[8] However, it is unlikely that patients experienced other rare potential triggers at the same time as the death of a significant person. It is possible that compared to other MI cases, patients who experienced the death of a significant person are more likely to survive and participate in our study, resulting in an overestimate of the IRR and the frequency of MI associated with bereavement. Alternatively, patients experiencing bereavement may be less likely to survive, resulting in an underestimate of the IRR and the frequency with which this occurs. However, it seems unlikely that MI survival is different for cases triggered by different mechanisms. Though it cannot be easily tested in a randomized clinical trial, it seems plausible that providing social support at the time of bereavement may help mitigate the heightened risk.[26] Another approach is to consider the use of preventive agents to address hemodynamic and thrombosis related changes. The data were collected prior to common use of statins. Future research could examine if the risk is mitigated with regular statin use. One of us (G.H.T.) is currently conducting a randomized clinical trial to evaluate

whether low dose aspirin and/or beta blockers may prevent the hemodynamic and thrombotic changes associated with early bereavement.

Compared to other cardiovascular triggers, such as physical activity or episodes of anger, bereavement is obviously rarer, so the absolute lifetime risk of a bereavement-induced MI may be extremely low. However, as our results indicate, the absolute risk in the week following this life event can be large and warrants attention by the clinical community.

Acknowledgments

Funding Sources: This work was supported by grant T32-AI007535-12 and T32-HL098048-02 from the National Institutes of Health. No funding organization had any role in the design and conduct of the study; collection; management, analysis and interpretation of the data; and preparation of the manuscript.

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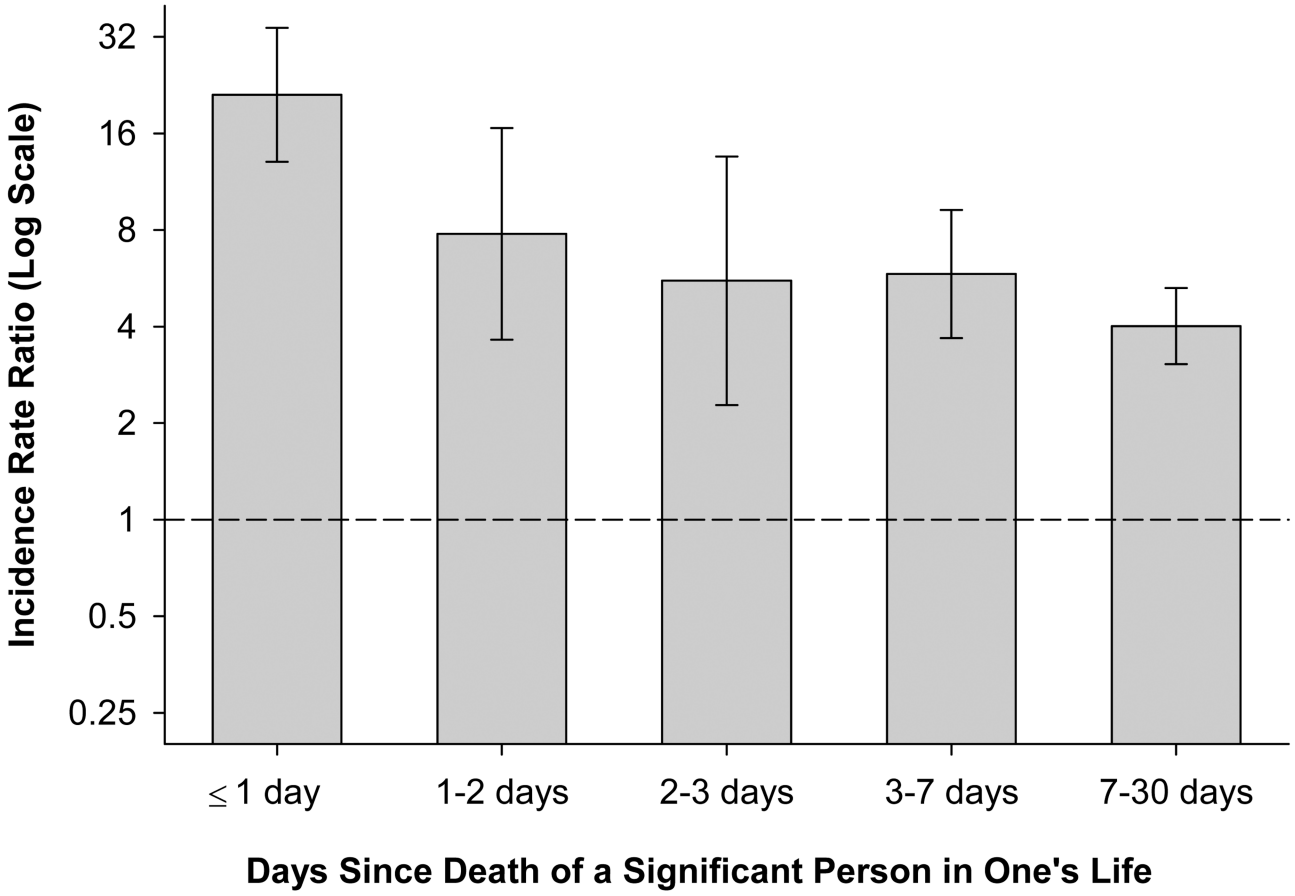

Figure 1.
Time of onset of acute myocardial infarction after the loss of a significant person in one's life. Each of the hazard periods before MI onset was assessed as independent hazard periods, and each window was compared with exposure during the control period of 1 to 6 months. The error bars indicate the 95% confidence limits. The dashed line indicates the baseline risk.

Table 1

Clinical Characteristics of the MIOS Study Population.

		Death of Significant Person in One's Life within Past Six Months	
		Yes n=(270)	**No n=(1,715)**
Age, y		60.7±11.8	61.8±12.8
Female		101 (37.4%)	489 (28.5%)
White race		219 (81.1%)	1490 (86.9%)
Married		164 (60.7%)	1088 (63.4%)
Income, $		36,965.5±17,567.7	39,435.3±17,118.6
Education			
	Less than high school	2 (0.7%)	55 (3.2%)
	Completed high school	113 (41.9%)	643 (37.5%)
	Some college	87 (32.2%)	555 (32.4%)
BMI, kg/m^2		27.9±5.7	27.2±5.1
Smoking status			
	Former	95 (35.2%)	694 (40.5%)
	Current	102 (37.8%)	524 (30.6%)
Physical Activity (times/week)			
	<3	242 (89.6%)	1555 (90.7%)
	≥3	22 (8.2%)	89 (5.2%)
History of			
	Hypertension	98 (36.3%)	744 (43.4%)
	Diabetes mellitus	59 (21.9%)	343 (20.0%)
	Angina	72 (26.7%)	412 (24.0%)
	Myocardial infarction	76 (28.2%)	463 (27.0%)
	Congestive heart failure	9 (3.3%)	74 (4.3%)
Regular use of			
	ACE inhibitors	38 (14.0%)	190 (11.1%)
	Aspirin	124 (45.9%)	605 (35.3%)
	Beta blockers	56 (20.7%)	327 (19.1%)
	Calcium channel blockers	62 (23.0%)	405 (23.6%)
	Digoxin	17 (6.3%)	127 (7.4%)

Mean ± standard deviation or n (%)

Table 2

Incidence Rate Ratio for Myocardial Infarction within 1 Day of the Death of a Significant Person in One's Life among 1,985 Patients Hospitalized for Myocardial Infarction, According to Patient Characteristics, Determinants of Myocardial Infarction Onset Study, 1989–1994.

	# Exposed in Past 1–6 Months	# Exposed in Past Day	IRR	95%CI	*P*-Value[a]	*P*-Homogeneity[b]
All Patients	135	19	21.1	13.1–34.1	<0.001	
Sex						0.10
Male	74	14	28.4	16.0–50.2	<0.001	
Female	56	4	10.7	3.9–29.6	<0.001	
Age						0.22
<65	72	13	27.1	15.0–48.9	<0.001	
≥65	63	6	14.3	6.2–33.0	<0.001	
Smoking Status						0.85
Current	49	7	21.4	9.7–47.3	<0.001	
Former	53	8	22.6	10.8–47.6	<0.001	
Physical Activity (times/week)						0.71
<3	119	16	20.2	12.0–34.0	<0.001	
≥3	11	2	27.3	6.0–123.0	<0.001	
History of Myocardial infarction						0.19
Yes	41	3	11.0	3.4–35.4	<0.001	
No	87	15	25.9	15.0–44.7	<0.001	

Abbreviations: IRR, Mantel-Haenszel incidence rate ratio; CI, confidence interval

[a] *P*-value for the stratum-specific Mantel-Haenszel rate ratio

[b] *P*-value for the χ^2 test for homogeneity