Methods

Study population

The study subject was residents in seventeen municipalities located in the east of Iwate prefecture from February 2009 to May 2011 and the adult population (age ≥ 20 years) based on population statistics at October of each year was 285,111 in 2009, 285,556 in 2010, and 272,440 in 2011.

The study region included twelve general public hospitals, four of which had a cardiology department. A huge tsunami following the initial earthquake caused loss of all medical records in three hospitals (Rikuzen-takata, Otsuchi, Yamada, Figure 1). In the remaining nine general public hospitals, study teams including cardiologists and trained research nurses retrospectively checked medical charts and obtained information regarding the occurrence of AMI and SCD including age at onset, sex, and date of onset. Furthermore, to capture community cases of SCD, we checked death certificates in government offices within the target district and obtained information such as time from symptom onset to death, situation just before death, and diagnosis. Cases registered in the study were aged ≥ 20 years and occurring between February 11, 2011 (four weeks before the disaster) and May 5, 2011 (eight weeks after the disaster), and in the corresponding periods in 2009 and 2010 as a reference. Furthermore, to capture cases transferred from the study area to other municipalities, we extended the survey to include five teaching hospitals within three municipalities (Morioka, Kitakami, and Ichinoseki: Figure 1) located inland in Iwate prefecture.

Disease definitions

AMI was defined according to the criteria of the WHO MONICA Project [9]. This criteria is based on information about symptoms, changes on electrocardiograph (ECG), changes in cardiac enzyme levels, necropsy findings and, for deaths only, previous history of ischemic heart disease. [9] According to the WHO criteria for sudden death, SCD was defined as sudden unexpected death either within 1 hour of symptom onset (event witnessed), or within 24 hour of having been observed alive and symptom free (unwitnessed). [10] The validity of an identification for sudden unexpected death was determined by a committee consisting of cardiologists, neurologists, and epidemiologists on the basis of death certificates. Cases were registered if they met type 1 definition of the MONICA diagnostic AMI criteria corresponding to either definite AMI, possible coronary death or unclassifiable SCD.[9] We excluded cases not satisfying the MONICA diagnostic criteria, not having sufficient information for diagnosis, or being in the terminal stage of another disease such as cancer. Approval was obtained from the ethics review board of each participating hospital and Iwate Medical University before commencement of the study.

Statistical analysis

Numbers and characteristics of cases with AMI occurring during the twelve-week period from four weeks before to eight weeks after the day of the earthquake were compared to those during the corresponding periods in the previous two years. The chi-square test was used for comparison of categorical variables in the disaster year (2011) and the pre-disaster years (2009 and 2010). Age at baseline was expressed as mean ± standard deviation and compared between each year by one way analysis of variance with the Scheffe's post hoc test.

The fact that the northeast Japan earthquake struck during the afternoon may have resulted in a spuriously smaller number of admissions on March 11, 2011, if an augmented admission rate after the earthquake extended beyond midnight, resulting in those admissions being assigned to March 12, 2011. To account for this possibility, AMI case numbers in the two-day time periods during two weeks before and after March 11, 2011 were compared to those during the corresponding periods in 2009 and 2010.

For comparison of event incidence before and after the disaster, the relative risk (RR) of AMI incidence and its 95% confidential interval (CI) were calculated from a 2-by-2 table using the Pearson chi-square test as follows:

Years	Number of people with events	Number of people with no events
2011	a	b
2009 and 2010	c	d

The proportion of events before and after the disaster in 2011 [a/(*a*+*b*)] were compared with those in the corresponding periods in 2009 and 2010 [*c*/(*c*+*d*)]. Results are summarized by the RR: RR = [*a*/(*a*+*b*)]/[*c*/(*c*+*d*)] with 95% CIs.

Furthermore, numbers of AMI cases over these four week periods were analyzed according to sex, age group (< 70 years at onset and ≥ 70 years), and presence of tsunami-induced flooding in more than 10 % of the built-up area. [11]

In the study area, there were five seismometry facilities located in Ninohe, Kuji, Miyako, Kamaishi, and Ofunato municipalities. After the main shock, the frequency of strong earthquakes was observed at these facilities during the study period. [12] The SI scale of the Japan Meteorological Agency [13] was used. Spearman correlation coefficients were used to examine the association between the scales of weekly maximum SI and weekly incidence of AMI during the twelve-week period. In this analysis, SI scales were substituted with maximum SI measurements taken in each municipality. P values of < 0.05 were considered to be statistically significant.

Results

During the four weeks after the disaster (March 11 to April 7, 2011), 96 patients developed AMI corresponding to the MONICA diagnostic criteria. Table 1 shows clinical characteristics of patients with AMI during the twelve weeks before and after the disaster and in the corresponding periods (February 11 to May 5) in the previous two years. The crude number of AMI cases per 100,000 people has increased after the disaster, and it approximately doubled during the first to fourth weeks after the disaster compared to the corresponding periods in the previous two years (Table). Age, sex, the proportion of diagnostic type of AMI criteria (corresponding to either definite AMI, possible coronary death or unclassifiable SCD) and residential areas of AMI cases did not differ in any period between each year before and after the disaster (Table). The RR for the incidence of AMI during the first four weeks after the disaster was significantly higher compared to the corresponding periods in the previous two years ($p < 0.001$; Figure 2). This trend was not observed in the period from the fifth to the eighth weeks after the disaster.

Figure 3 shows weekly maximum SI and relative risks for weekly incidence of AMI during the twelve weeks before and after the disaster compared to the corresponding periods in the pre-disaster years. The incidence peaked during the first week after the disaster (RR 2.77, 95% CI 1.73 to 4.43) and then decreased to the levels seen in the preceding years during the second week. The incidence then increased over the following two weeks (RR 1.84, 95% CI 1.05 to 3.24 in the third week; RR 2.00, 95% CI 1.13 to 3.55 in the fourth week, Figure 3). From the fifth week after the disaster, AMI incidence did not differ significantly from the corresponding periods in the previous two years. These trends in weekly incidence of AMI were closely related to the weekly maximum seismic intensity of each earthquake (Figure 3, open columns) as strong intensity aftershocks occurred repeatedly during the four weeks after the main shock and then decreased markedly. As shown in Figure 4, a positive correlation was found between the degree of SI and weekly incidence of AMI ($r = 0.75$) as well as in the changes in weekly incidence of AMI (number of AMI cases in 2011 – average number of AMI cases in the corresponding periods of 2009 and 2010, $r = 0.71$).

Figure 5 shows the number of AMI cases over two-day period during the two weeks before and after March 11, 2011 plus the corresponding periods in 2009 and 2010. The number of AMI cases peaked over the first two-day period after the disaster. Compared to the corresponding periods in 2009 and 2010, the increase in events was significant for the first (RR 3.89, 95% CI 1.45 to 10.7) and following two-day periods (RR 5.76, 95% CI 1.70 to 21.4) after the disaster. There was no significant difference in the incidence for any of the two-day period before March 11 between the disaster and pre-disaster years.

As shown in figure 6, the number of AMI cases trended to increase for the first to fourth weeks (RR 2.34, 95% CI 1.54 to 3.56) and the fifth to eighth weeks (RR 1.56, 95% CI 0.98 to 2.48) after the disaster, especially in women, and for the first to fourth weeks after the disaster in the cases aged 70 years and older (RR 2.03, 95% CI 1.47 to 2.81). There was no difference in incidence after the disaster in municipal areas with and without high levels of tsunami flooding.

Discussion

The northeast Japan earthquake was the most severe of any studies conducted to this day in relation to earthquake related acute cardiac events. This is the first population based report to clarify the relationship between this unprecedented major earthquake and the incidence of AMI based on the MONICA diagnostic criteria. The present study showed that; 1) the main shock caused by a massive earthquake was associated with an immediate increase in AMI events; 2) after decreasing back to the levels seen in preceding years, the number of AMI events increased again following high magnitude aftershocks; 3) the incidence of AMI was positively correlated with the seismic scale of each earthquake.

Several reports have investigated the effect of earthquakes on cardiac events [1-7], yet the results of those reports have not necessarily been consistent. Three community based studies found increase in cardiac mortality on the basis of death certificate reviews; those related to the 1981 earthquake in Athens, Greece [1], the 1994 Northridge earthquake in the Los Angeles area [3,7], and the 1995 Hanshin-Awaji earthquake in Japan.[4] Hospital based studies have shown less consistent results, with an increase in AMI admissions after the Northridge earthquake [14,15], but no increase was observed after the 1989 Loma Prieta earthquake in the San Francisco area [15] nor after the 2011 northeast Japan earthquake in Miyagi prefecture, Japan. [16] After the 2004 Niigata-Chuetsu earthquake in Japan [6], the number of hospital consultations for SCD increased clearly but admissions for acute coronary syndrome did so only slightly. These disparate results may be due to the variety of end points analyzed in association with earthquakes of different magnitudes along with differences in case identification methodology. Generally, hospital based registration of AMI incidences cannot capture out-of-hospital coronary deaths, while the registration of cardiac mortality based on death certificate review cannot necessarily capture every incidence of

AMI events. This suggests that previous studies may have had a limited ability to identify earthquake related AMI events.

In contrast to the present study, a population based study after the Newcastle earthquake in Australia [5] found no significant increase in AMI according to the MONICA diagnostic criteria. This discrepancy may have arisen due to the difference in degrees of magnitude of the two disasters, with the Japanese event measuring magnitude 9.0 and the Newcastle earthquake measuring magnitude 5.6. [5] Furthermore, the Newcastle study was conducted among the population aged < 70 years old, while the present study found a higher incidence of earthquake related AMI events in individuals aged 70 years and older. In the Northridge earthquake of magnitude 6.7, coronary deaths increased only on the day of the main shock, and then decreased the next day and during the two weeks after. [3,7] In contrast, after the Hanshin-Awaji earthquake of magnitude 7.2 [4], coronary deaths remained elevated over the subsequent two week period compared to the preceding years. In the present study, AMI incidence increased and peaked over the first week after the initial earthquake and increased again during the third and fourth weeks. These disparate results may be related to the fact that high intensity aftershocks occurred repeatedly after the Hanshin-Awaji and the northeast Japan earthquake, as suggested by the present finding of a positive correlation between weekly incidence of AMI and the degree of SI. For the first time, the present study has identified a direct relationship between the incidence of AMI and earthquake SI.

The relationship found in this analysis between weekly seismic activity and cardiac events that occurred in the same week will be relatively novel. This suggests a rapid causal effect in seismic activity, the associated stress and cardiac events. The aftershocks, most of which caused little environmental damage, could apparently also cause significant psychological distress. In addition, residents have experienced physical distress due to environmental situations such as housing damages and a lack of heating because of power outages after the main shock. [8] Mittleman et al. have offered a hypothesis that psychological or physical stressors lead to activation of the sympathetic nervous system and have cardiovascular effects through hemodynamic alterations acting on vulnerable atherosclerotic plaque or hemostatic alterations such as activation of procoagulant factors.[17] However, there was no significant increase in risk of AMI associated with the tsunami flood even though it undoubtedly put on additional impact subsequent to environmental damages and disruption to residents. Therefore, it can be hypothesized that the increased incidence of AMI seen after the earthquake was caused by earthquake induced direct stress rather than by indirect stress induced by environmental damages. However, since the present study did not evaluate different degrees of stress among residents with and without tsunami damages, we cannot provide an explanation for the influence of the tsunami on AMI risk.

The hazard of AMI incidence triggered by the present disaster was relatively higher in women and elderly people. In the report on the Hanshin-Awaji earthquake, women made up a higher proportion of hospital admissions for AMI and experienced more post traumatic stress than men did. [18] In addition, this earthquake induced transient increase in BP, blood viscosity determinants and fibrin turnover in elderly subjects with hypertension. [19] These factors may have a bearing on the modest difference in risk for sex or age specific AMI events after the disaster in the present study.

The present findings of a correlation between the risk of AMI and the scale of aftershocks suggest that, in large scale earthquakes, it is necessary to recognize the event risk in conjunction with aftershocks as well as the main shock. In this regard, several approaches can be considered for risk prevention. First, medical supports should be maintained after a major earthquake or ensure that such supports are restored as quickly as possible. Lifeline damages and traffic cutoff after disasters would hinder intervention for AMI cases that require an urgent transportation by an ambulance. Second, a preventive approach can be instituted at a public health level with provision of defibrillators and rapid cardiac resuscitation capability to reduce incidences of cardiac death.[20] Third, modification or avoidance of the disaster-induced physical and emotional distress, which can transiently increase the risk of plaque rupture and thrombosis, may play a role in prevention of AMI. With high intensity aftershocks, the number of incidence of AMI increased again during the third and fourth weeks after the main shock. Recognition of this period of vulnerability should spur physicians and other health care professionals to review such individuals more closely for symptoms or changes in cardiovascular risk factors. When high magnitude aftershocks are predicted, administration of agents which are commonly recognized to have a preventive effect on coronary events may be worthy of consideration. For example, it has been suggested that β-blockers reduce the somatic symptoms associated with anxiety.[21] However, it remains unclear whether earthquake related coronary events are attributable to psychological distress and whether administration of such agents is valid for prevention of earthquake related coronary events. Answers to those questions would require further studies.

Study limitations

The present study had several limitations. First, there might have been problems and insecurities in diagnosing AMI events, especially after a major disaster with a strained health care system. In fact, it was impossible to review the medical records of three hospitals located in the survey areas that were flooded by the tsunami. However, the influence on the incidence of AMI would be small because these hospitals did not have a cardiology department and barely any AMI patients were admitted there. Approximately 6,000 persons, corresponding to 5 % of the study area population, were found dead due to drowning or missing after the tsunami following the initial earthquake, and those persons may have included the cases of AMI. In addition, although we extended the survey to the teaching hospitals of several remote municipalities located in the Iwate prefecture, it is possible that the identification of some cases that were transferred out of the study area has been insufficient. However, these could lead to an underestimation of tsunami related AMI risk. Secondly, we have previously reported that the incidence of sudden unexpected death was doubled immediately after the disaster. [22] This observation may be similar to the present study. However, in the previous study, only 16% of sudden unexpected death fulfilled the definition of MONICA-AMI. [22] In contrast, more than half of the present study cases were definite non-fatal AMI or coronary death (Table). These suggest that the subjects of the present study are different from those of the previous study. Moreover, the observed increase in the incidence of AMI for the first four weeks after the disaster remained to be significant even after exclusion of the cases with unclassifiable sudden death (RR 2.03, 95% CI 1.39 to 2.95). Third, for analysis of a correlation between SI and overall weekly incidence of AMI, the scale selected for analysis was from the municipality where the maximum SI was recorded. Therefore, these scales may not have reflected the actual SI in each municipality. However, this limitation would not affect the relationship between SI and the incidence of AMI, since the difference in SI scales measured among the municipalities was small (average difference between two municipalities: 0.3). Finally, although the ascertainment of the case was done according to the standard criteria (MONICA), event classification was not done blinded as the nature of the retrospective study. This could be a limitation for classification of suspected AMI events.

Conclusions

This population based study suggests that the increase in AMI events after a major earthquake varies depending on the seismic scale of the initial shock and each aftershock.

Acknowledgements

This research was supported in part by grants-in-aid from the scientific research fund of the Ministry of Education, Science, and Culture of Japan (26461082), Tokyo, Japan; the Japan Arteriosclerosis Prevention Fund (JAPF), Tokyo, Japan; the Takeda Science Foundation, Osaka, Japan; and JSPS KAKENHI Grant Number 26461083.

The authors thank the members of the event committee, Drs. Toshiaki Sakai, Mikio Kawakami, Hiroshi Endo, Tatsuya Matsumoto, the staff of hospitals and government offices for support and cooperation, Tomohiro Takahashi, Satoshi Nakajima, Yoshihiro Morino for their contribution.

The contributions of authors were conception and design: MN, TO, KS; analysis and interpretation: FT, MN; drafting of the manuscript: FT; revising the manuscript critically: MN, SM, TI; and final approval of the manuscript: SM, TI, TO, KS, MN.

References

1. Trichopoulos D, Katsouyanni K, Zavitsanos X, et al. Psychological stress and fatal heart attack: the Athens (1981) earthquake natural experiment. Lancet 1983;1(8426):441-4.
2. Katsouyanni K, Kogevinas M, Trichopoulos D. Earthquake-related stress and cardiac mortality. Int J Epidemiol 1986;15(3):326-30.
3. Kloner RA, Leor J, Poole WK, et al. Population-based analysis of the effect of the Northridge Earthquake on cardiac death in Los Angeles County, California. J Am Coll Cardiol 1997;30(5):1174-80.
4. Ogawa K, Tsuji I, Shiono K, et al. Increased acute myocardial infarction mortality following the 1995 Great Hanshin-Awaji earthquake in Japan. Int J Epidemiol 2000;29(3):449-55.
5. Dobson AJ, Alexander HM, Malcolm JA, et al. Heart attacks and the Newcastle earthquake. Med J Aust 1991;155(11-12):757-61.
6. Watanabe H, Kodama M, Okura Y, et al. Impact of earthquakes on Takotsubo cardiomyopathy. JAMA 2005;294(3):305-7.
7. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med 1996;334(7):413-9.
8. National Police Agency of Japan. Damage Situation and Police Countermeasures associated with 2011Tohoku district - off the Pacific Ocean Earthquake, November 8, 2013. Available at: http://www.npa.go.jp/archive/keibi/biki/higaijokyo_e.pdf. Accessed November 17, 2013.
9. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four

continents. Circulation 1994;90(1):583-612.

10. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol. 2004;44(6):1268-75.

11. Nakajima H, Koarai M. Assessment of Tsunami Flood Situation from the Great East Japan Earthquake. Available at: http://www.gsi.go.jp/common/000065837.pdf. Accessed April 26, 2014.

12. Japan Meteorological Agency. The 2011 off the Pacific coast of Tohoku Earthquake. Available at: http://www.jma.go.jp/jma/en/Activities/jishintsunami/jishintsunami_low2.pdf. Accessed November 17, 2013.

13. Japan Meteorological Agency. Monitoring of Earthquakes, Tsunamis and Volcanic Activity. Available at: http://www.jma.go.jp/jma/en/Activities/earthquake.html. Accessed November 17, 2013.

14. Leor J, Kloner RA. The Northridge earthquake as a trigger for acute myocardial infarction. Am J Cardiol 1996;77(14):1230-2.

15. Brown DL. Disparate effects of the 1989 Loma Prieta and 1994 Northridge earthquakes on hospital admissions for acute myocardial infarction: importance of superimposition of triggers. Am Heart J 1999;137(5):830-6.

16. Aoki T, Takahashi J, Fukumoto Y, et al. Effect of the Great East Japan Earthquake on cardiovascular diseases--report from the 10 hospitals in the disaster area. Circ J 2013;77(2):490-3.

17. Mittleman MA, Mostofsky E. Physical, psychological and chemical triggers of acute cardiovascular events: preventive strategies. Circulation 2011;124(3):346-54.

18. Suzuki S, Sakamoto S, Koide M, et al. Hanshin-Awaji earthquake as a trigger for acute

myocardial infarction. Am Heart J 1997;134 (5 Pt 1):974-7.

19. Kario K, Matsuo T, Kobayashi H, et al. Earthquake-induced potentiation of acute risk factors in hypertensive elderly patients: possible triggering of cardiovascular events after a major earthquake. J Am Coll Cardiol 1997;29(5):926-33.

20. Hallstrom AP, Ornato JP, Weisfeldt M, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. N Engl J Med 2004;351(7):637-46.

21. Sherman DG, Easton JD. Beta-adrenergic blockade and anxiety. Lancet 1976;23(2):911-2.

22. Niiyama M, Tanaka F, Nakajima S, et al. Population-based incidence of sudden cardiac and unexpected death before and after the 2011 earthquake and tsunami in Iwate, northeast Japan. J Am Heart Assoc. 2014;3(3):e000798.

Figure legends

Figure 1:

Map of the study area. Black zone shows the study area. Municipalities (numbers), locations of general hospitals in where the survey was conducted (white dots), and the earthquake epicenter (triple circle) are displayed.

Figure 2:

The incidence per four weeks of acute myocardial infarction according to the MONICA diagnostic criteria before and after the disaster in 2011 compared to the corresponding periods in 2009 and 2010. *$P<0.001$ vs. mean for 2009 to 2010. RR indicates relative risk; CI, confidence interval.

Figure 3:

Relative risks for weekly incidence of acute myocardial infarction in the disaster year vs. the pre-disaster years and weekly maximum seismic intensity (open columns). CI indicates confidence interval; AMI, acute myocardial infarction.

Figure 4:

The scatter diagram and regression lines show weekly maximum seismic intensity and numbers (A) or change numbers (difference of numbers between the disaster and pre-disaster years, B) of weekly incidence of acute myocardial infarction according to the MONICA diagnostic criteria. The plots represent data for twelve weeks (four weeks before and eight weeks after the disaster). AMI indicates acute myocardial infarction.

Figure 5:

The incidence per two days of acute myocardial infarction according to the MONICA diagnostic criteria before and after the disaster in 2011 compared to the corresponding periods in 2009 and 2010. *$p < 0.001$ vs. mean for 2009 to 2010. AMI indicates acute myocardial infarction.

Figure 6:

Relative risks for the incidence of acute myocardial infarction according to the MONICA diagnostic criteria per four week period before and after the disaster in 2011 compared to the corresponding periods in 2009 and 2010 in the respective groups of age, sex, and residential area. CI indicates confidence interval; AMI, acute myocardial infarction. *Patients who lived in the areas that were flooded more than 10 % of built-up area by the tsunami.

Figure 1

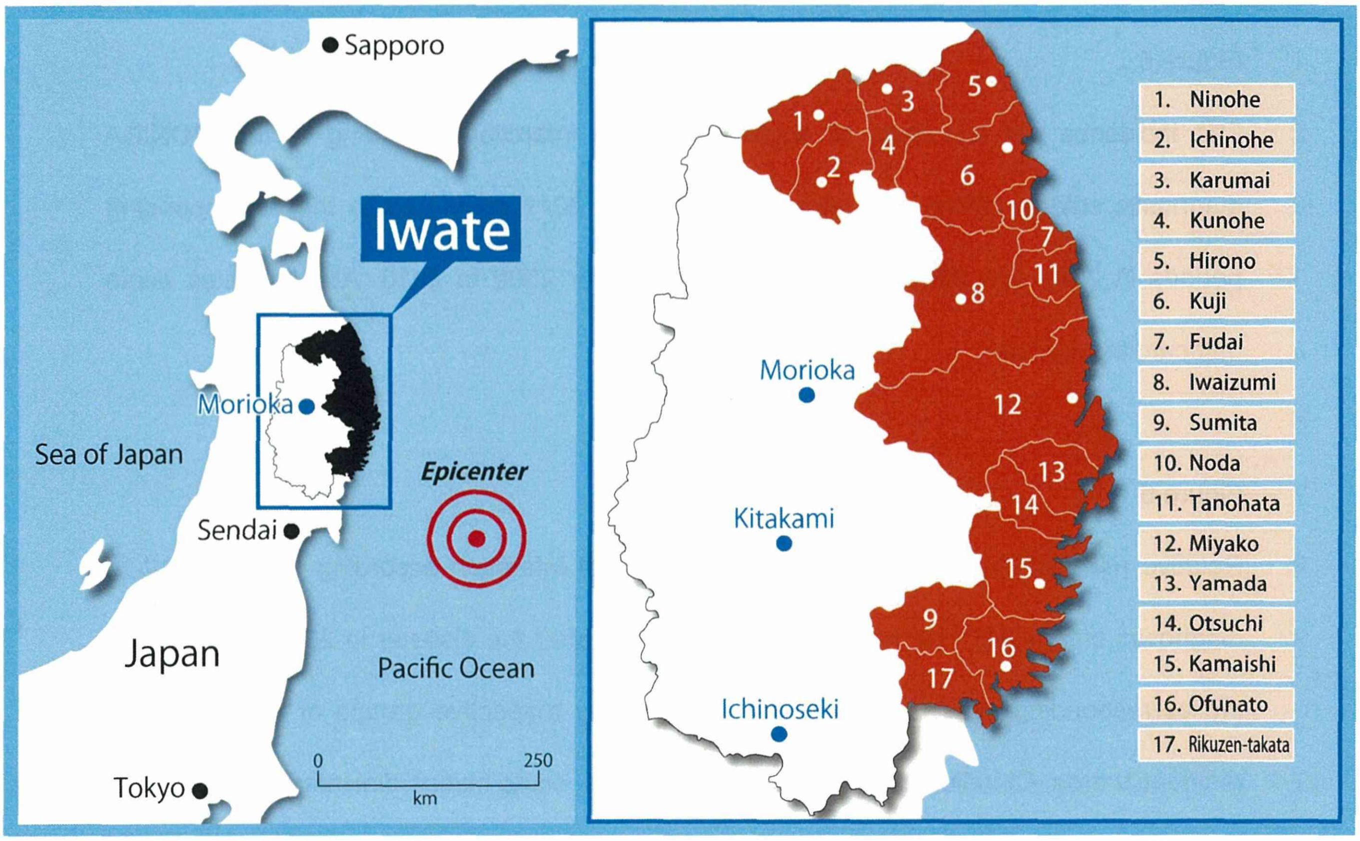

Figure 2

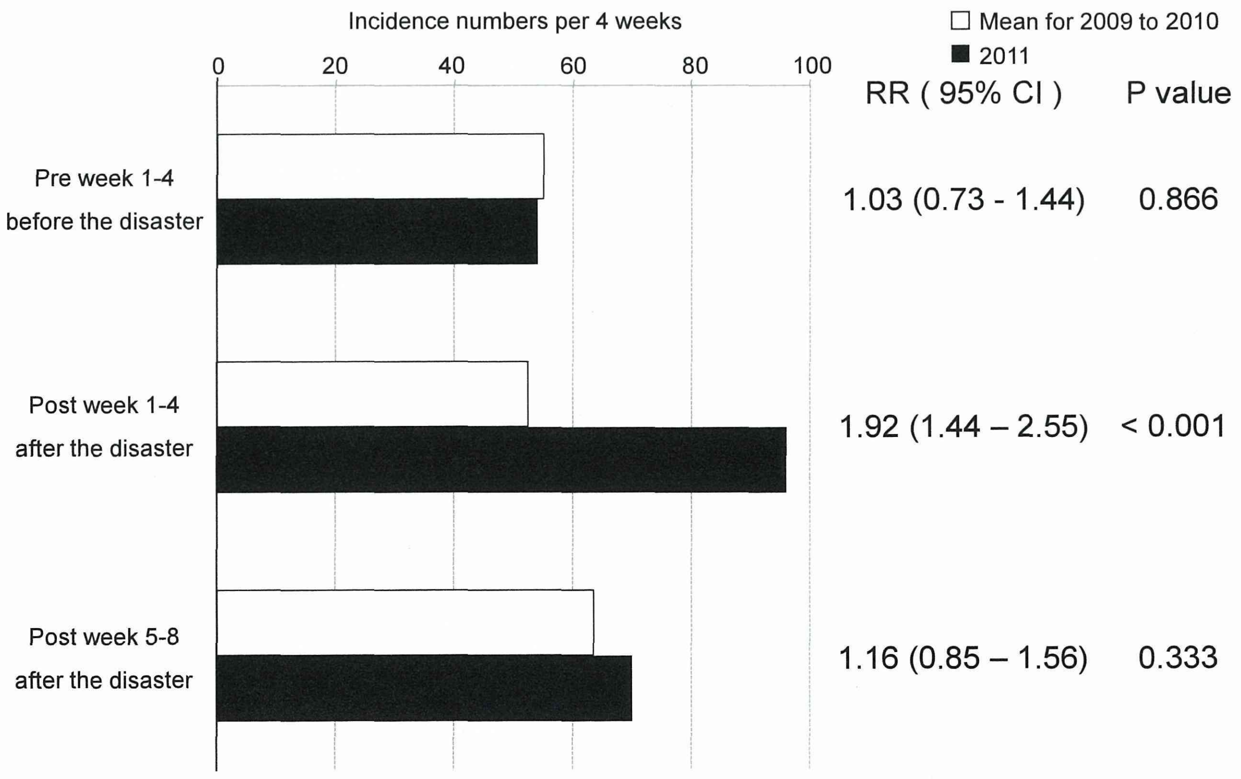

Figure 3

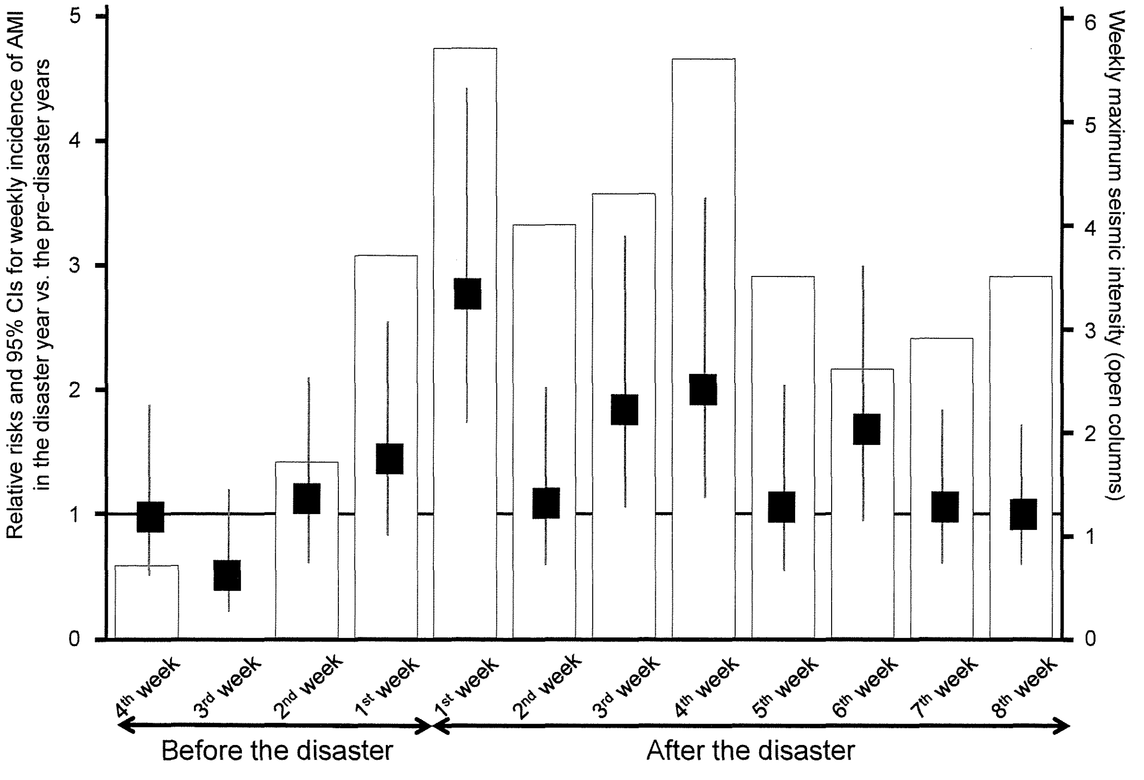

Figure 4

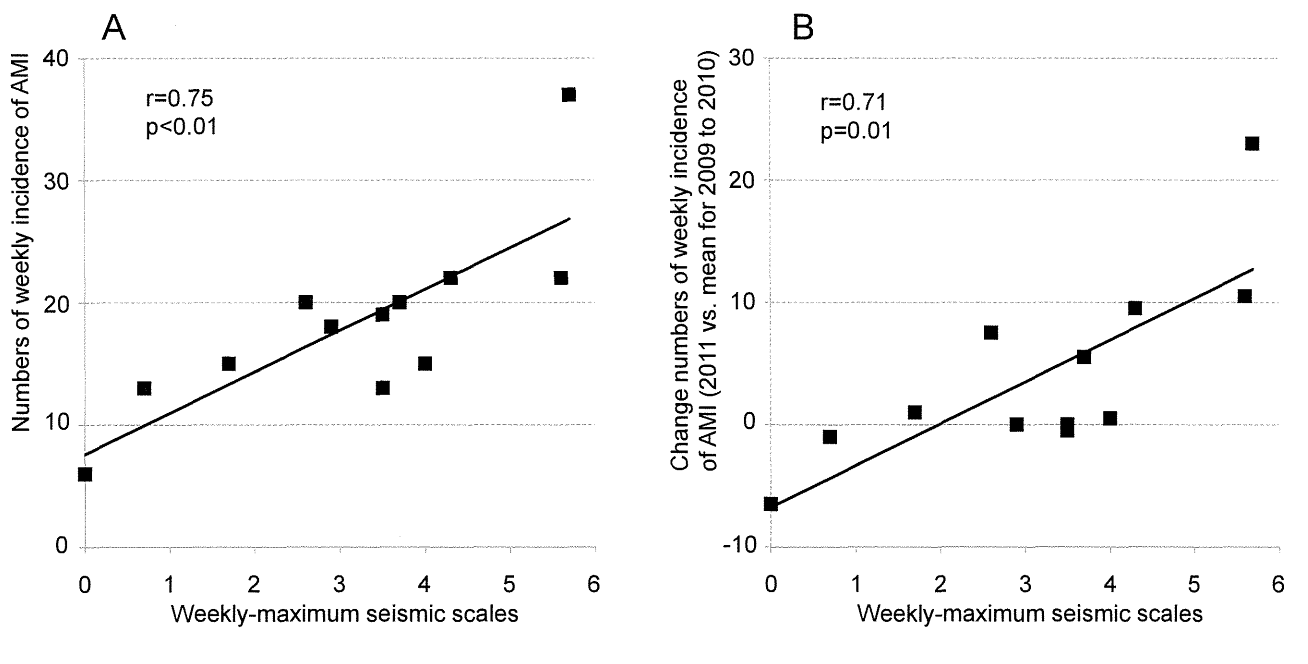

Figure 5

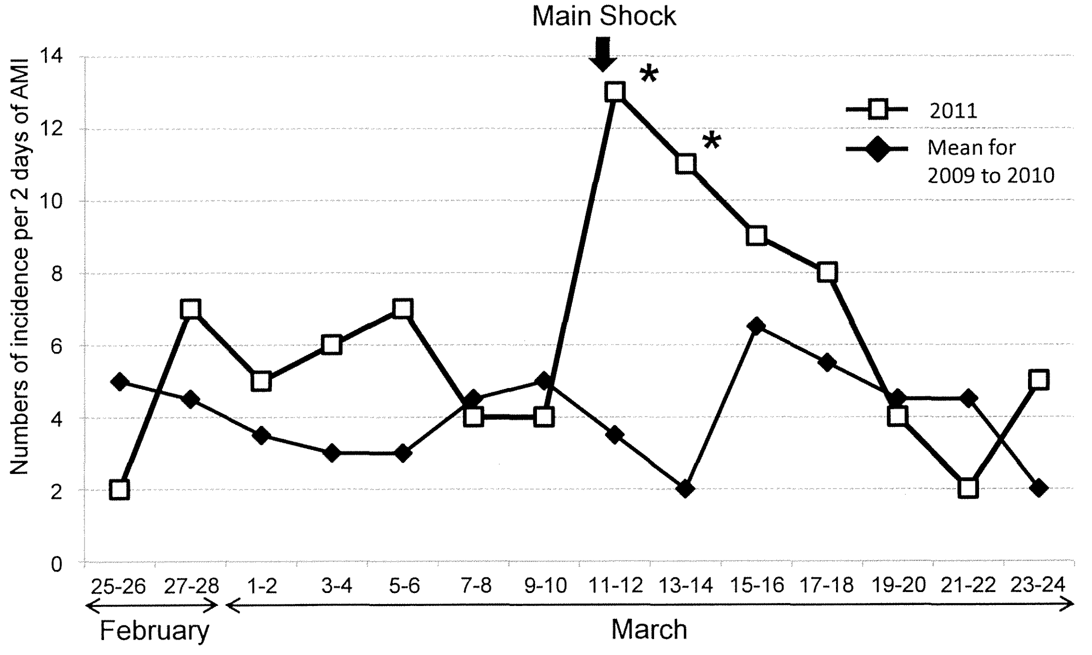

Figure 6

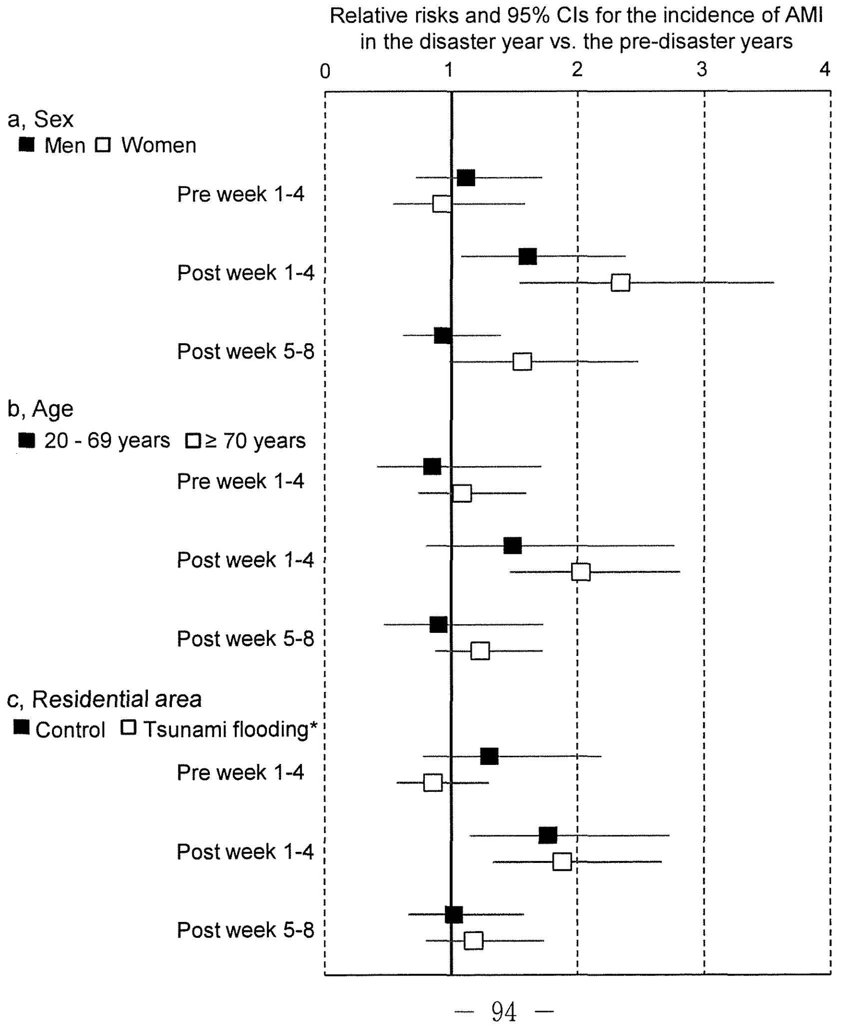

Table: Clinical Characteristics of Patients with AMI on the MONICA Diagnostic Criteria before and after the Disaster in 2011 and in the Corresponding Periods in 2009 to 2010

	The 1st to 4th Week Before				The 1st to 4th Week After				The 5th to 8th Week After			
	2009	2010	2011	P value	2009	2010	2011	P value	2009	2010	2011	P value
Patient Number	43	67	54		59	46	96		68	59	70	
Incidence Rates for 4 weeks per 100,000 people	15.1	23.5	19.8		20.7	16.1	35.2		23.9	20.7	25.7	
Mean Age (±SD)	75.1 ± 12.7	76.9 ± 10.5	74.9 ± 13.7	0.619	76.4 ± 13.0	75.2 ± 14.6	77.2 ± 11.3	0.683	74.3 ± 13.8	75.5 ± 14.9	78.0± 12.4	0.276
Age ≥ 70 years	69.8%	74.6%	77.8%	0.667	76.3%	71.7%	80.2%	0.523	72.1%	76.3%	80.0%	0.549
Female Gender	51.2%	38.8%	38.9%	0.372	45.8%	39.1%	52.1%	0.338	35.3%	37.3%	48.6%	0.234
AMI categories				0.795				0.550				0.725
Definite AMI	27.9%	34.3%	33.3%		33.9%	37.0%	36.5%		19.1%	28.8%	25.7%	
Possible coronary death	20.9%	26.9%	24.1%		16.9%	28.3%	24.0%		30.9%	28.8%	25.7%	
Unclassifiable SCD	51.2%	38.8%	42.6%		49.2%	34.8%	39.6%		50.0%	42.4%	48.6%	
Flooded Area*	53.5%	76.1%	57.4%	0.025	62.7%	58.7%	60.4%	0.914	57.4%	50.8%	55.7%	0.750

AMI: acute myocardial infarction, SCD: sudden cardiac death, CI: confidential interval, SD: standard deviation

*Patients who lived in areas flooded more than 10 % of built-up area by the tunami