

# Adult influenza epidemic is associated with out-of-hospital cardiac arrest

## From the All-Japan Utstein Registry, a prospective, nationwide, population-based, observational registry

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### Abstract

It has been reported that influenza infection is associated with out-of-hospital cardiac arrest of cardiac origin (OHCA-CA). However, the association between OHCA-CA and influenza epidemics in adults has not been well investigated.

We analyzed data from the All-Japan Utstein Registry, a prospective, nationwide, population-based, observational study, regarding OHCA-CA cases and the Infectious Diseases Weekly Report for influenza cases: 17,710 OHCA-CA cases and 764,808 influenza cases were recorded between 2005 and 2015 in Fukuoka, Japan. The weekly average number of OHCA-CA cases was positively associated with the number of patients with influenza infection ( $r=0.70, P<.0001$ ). To eliminate the effects of season and age, we investigated only adults in winter. The weekly number of OHCA-CA cases was positively associated with the number of patients with influenza infection in weeks when there was a high frequency of influenza infection in adults ( $r=0.36, P=.006$ ), but not in weeks with a medium ( $r=0.26, P=.05$ ) or low frequency of influenza infection ( $r=0.003, P=1.0$ ). In weeks during which there was a high frequency of influenza infection, the weekly number of OHCA-CA cases was positively associated with the number of influenza infections in males ( $r=0.37, P=.006$ ), but not females ( $r=0.18, P=.2$ ).

The number of OHCA-CA cases was positively associated with the number of influenza infections in adult males during weeks in which there was a high frequency of influenza infections. To help prevent OHCA-CA in males, it might be beneficial to announce influenza epidemics specifically in adults, in addition to all ages.

**Abbreviations:** EMS = emergency medical services, OHCA = out-of-hospital cardiac arrest, OHCA-CA = out-of-hospital cardiac arrest of cardiac origin.

**Keywords:** All-Japan Utstein Registry, influenza epidemic, out-of-hospital cardiac arrest

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The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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## 1. Introduction

Out-of-hospital cardiac arrest (OHCA) of cardiac origin (OHCA-CA) is a critical situation and has been an important public health problem.<sup>[1,2]</sup> In Japan, the Fire and Disaster Management Agency launched the All-Japan Utstein Registry, a prospective, nationwide, population-based, observational database which has registered OHCA patients since January 2005.<sup>[3]</sup> The All-Japan Utstein Registry has been used to evaluate the effects of cardiopulmonary resuscitation, factors associated with a favorable neurological outcome,<sup>[3]</sup> the effect of AED,<sup>[4]</sup> the clinical effectiveness of conventional cardiopulmonary resuscitation in children,<sup>[5,6]</sup> and the impact of prehospital resuscitation time.<sup>[7]</sup> The cause of OHCA-CA is also an important public health problem. We have reported the associations between OHCA-CA and dental caries,<sup>[8]</sup> seafood consumption,<sup>[9]</sup> and consumption of carbonated beverages<sup>[10]</sup> using the All-Japan Utstein Registry. Cold month in the toilet,<sup>[11]</sup> severe emotional stress,<sup>[12,13]</sup> climate,<sup>[14–16]</sup> and temperature<sup>[17–19]</sup> have also been reported to be causes of OHCA-CA in Japan.

Influenza infection has been reported to be associated with OHCA-CA.<sup>[20,21]</sup> Influenza infection is associated with sudden unexpected cardiopulmonary arrest.<sup>[22]</sup> In Japan, the weekly number of influenza cases is officially announced by the National Institute of Infectious Disease. Based on this data, influenza epidemics have been reported to be associated with OHCA-CA in Japan.<sup>[23]</sup> However, it would be desirable to consider the patient's age, because most influenza cases are under 20 years of age<sup>[24]</sup> and most OHCA-CA cases are over 20 years of age.<sup>[3]</sup> Seasonal effects should also be considered, because both influenza infection and OHCA-CA are more common in winter. In light of the above observations, we focused on influenza infection and OHCA-CA in adults in winter. We investigated the association between OHCA-CA and influenza infection in adults in winter in Fukuoka, Japan.

## 2. Methods

### 2.1. Study design

This cohort study used the All-Japan Utstein Registry, a prospective, nationwide, population-based, observational registry, from the Japanese Circulation Society with Resuscitation Science Study Group, and the Infectious Diseases Weekly Report in Fukuoka, from the Fukuoka Prefecture Medical Association. The procedures followed the Declaration of Helsinki and the ethical standards of the Independent Review Board of Fukuoka University. The study protocol was approved by the Ethics Committee of Fukuoka University (FU-#00000403).

### 2.2. Study setting

The All-Japan Utstein Registry has collected data from patients with OHCA who were treated by emergency medical services (EMS) responders, transported to a hospital, and followed for 1 month in Japan since 2005.<sup>[25–27]</sup> Japan has an area of approximately 378,000 km<sup>2</sup>. In 2014, the population of Japan was 127 million<sup>[28]</sup> and there were 752 fire stations with dispatch centers.<sup>[29]</sup> The Japan Fire and Disaster Management Agency manages the database of the All-Japan Utstein Registry, checks the data, and compiles the data for public use.<sup>[30]</sup> Detailed information on data collection and quality control have been published elsewhere.<sup>[4,30–33]</sup>

The Infectious Diseases Weekly Report has collected data from patients with a reportable disease under Japan's Infectious Disease Control Law. Influenza outbreaks have been reported since 1999. These data were collected by each city or prefecture medical association and registered with the National Institute of Infectious Diseases, which is organized by the Ministry of Health, Labor and Welfare in Japan. Infectious Diseases Weekly Report data are available for all of Japan from the National Institute of Infectious Diseases, but the data do not include information on sex or age group. However, in Fukuoka Prefecture, 198 medical institutions report weekly influenza cases according to sex and age group to the Fukuoka Prefecture Medical Association. Thus, we could use data from the Infectious Diseases Weekly Report including sex and age group in Fukuoka, thanks to the cooperation of the Fukuoka Prefecture Medical Association. In this study, we used data from the All-Japan Utstein Registry and Infectious Diseases Weekly Report in Fukuoka, Japan from 1 January 2005 to 31 December 2015.

### 2.3. Patient and public involvement

The patients were not involved in recruitment or the conduct of the study.

### 2.4. Study subjects

A preliminary study cohort included 17,710 OHCA-CA patients from the All-Japan Utstein Registry who received resuscitation by EMS and had arrest of cardiac origin in Fukuoka, Japan. Patients who were not in Fukuoka, who did not receive resuscitation by EMS, or who had an arrest of non-cardiac origin were excluded. The preliminary study cohort included 764,808 influenza cases from the Infectious Diseases Weekly Report in Fukuoka. The study cohort consisted of 6,304 OHCA-CA cases and 131,322 influenza cases who were more than 20 years old in winter, which was defined as weeks 1 to 15. The patient selection criteria are shown in Figure 1.

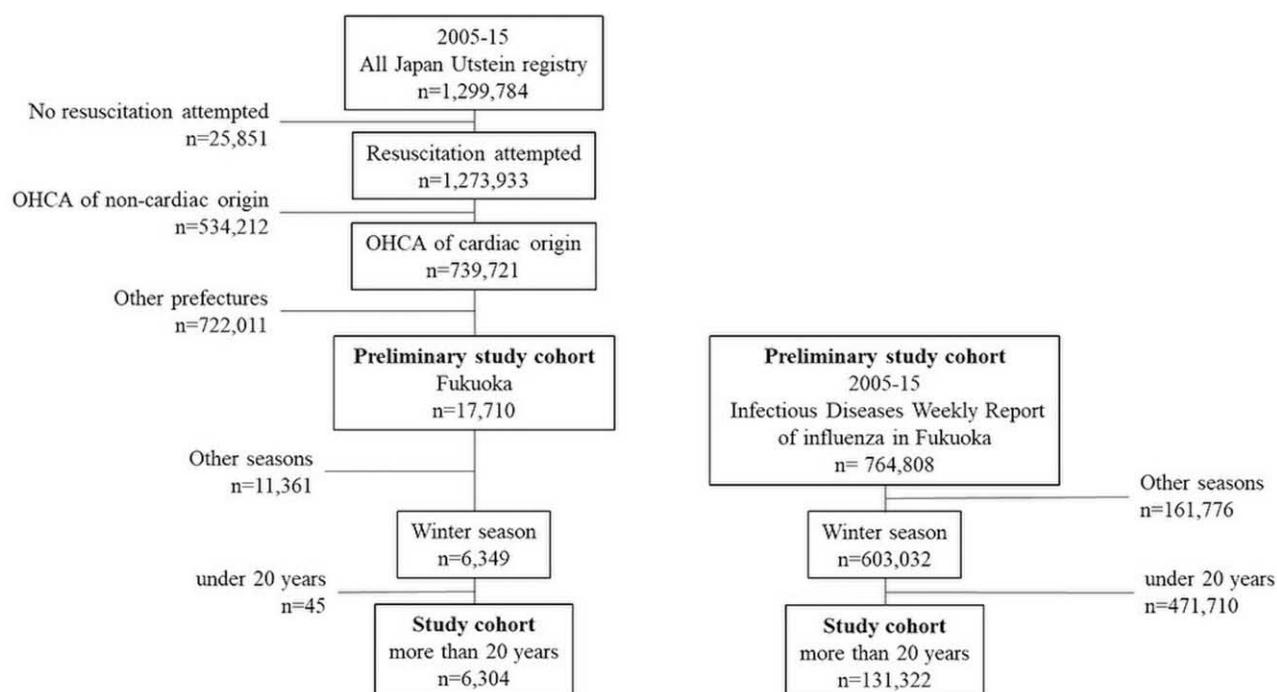
### 2.5. Variables

The All-Japan Utstein registry includes the following information: date, prefecture, resuscitation attempted by EMS personnel (yes/no), patient's age, sex, etiology (cardiac/noncardiac). The All-Japan Utstein registry does not include information on the patient background other than age and sex. Detailed variables are provided in the Supplemental file, Supplemental Digital Content, <http://links.lww.com/MD/G770>.

The Infectious Diseases Weekly Report includes weekly influenza infection cases by sex and age group (0–5 month/6–11 month/1/2/3/4/5/6/7/8/9/10–14/15–19/20–29/30–39/40–49/50–59/60–69/70–79/80-years) in Fukuoka.

### 2.6. Statistical analysis

Data analyses were performed using the SAS (Statistical Analysis System) Software Package (Ver. 9.4; SAS Institute Inc., Cary, NC) at Fukuoka University (Fukuoka, Japan). Continuous variables are expressed as mean  $\pm$  SD and categorical variables are expressed as n (%). The Student *t* test was used for continuous variables and the chi-squared test was used for categorical variables. The Pearson product-moment correlation



**Figure 1.** Patient selection criteria. From 2005 to 2015, 1,299,784 patients who had an OHCA in the All-Japan Utstein Registry database and 764,808 patients who had an influenza infection in the Infectious Diseases Weekly Report in Fukuoka, Japan were registered. OHCA=out-of-hospital cardiac arrest.

coefficient was used to evaluate associations between influenza cases and OHCA-CA cases. Statistical significance was defined as a *P* value of <.05.

### 3. Results

#### 3.1. Characteristics of OHCA-CA and influenza patients in Fukuoka, Japan

In the preliminary study cohort, 17,710 OHCA-CA patients were identified from the All-Japan Utstein registry in Fukuoka, Japan between 2005 and 2015 (Table 1). The average age was  $74.9 \pm 15.5$  years and 56.9% were male ( $n=10,073$ ). The percentages of 1 month survival, 1 month survival with minimal neurologic impairment, and 1 month survival with minimal overall performance impairment were 9.9% ( $n=1746$ ), 6.5% ( $n=1154$ ), and 6.5% ( $n=1142$ ), respectively. The percentage of patients aged under 20 years was only 0.9% ( $n=159$ ) and the overwhelming majority (99.1%) were more than 20 years of age ( $n=17,551$ ).

The Infectious Diseases Weekly Report provided data on 764,808 influenza cases in Fukuoka, Japan between 2005 and 2015. The percentages of males, patients aged under 20 years, and patients aged more than 20 years were 50.6% ( $n=387,063$ ), 79.3% ( $n=606,859$ ), and 20.7% ( $n=157,949$ ), respectively (data not shown).

#### 3.2. Average weekly changes and correlation between the incidence of OHCA-CA and influenza

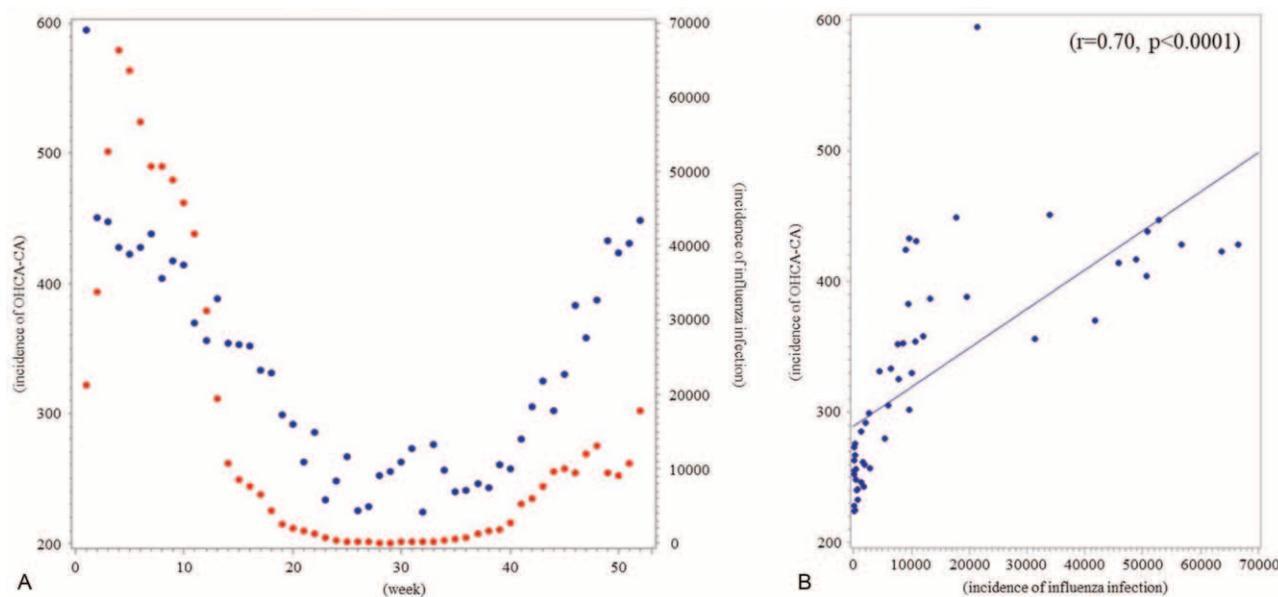
The average weekly numbers of cases of OHCA-CA and influenza infection between 2005 and 2015 were investigated. Cases in week 53 were excluded because this is the last week of the year and contains less than 7 days. In addition, the number of days varies each year. Weekly changes in the number of cases of influenza infection and OHCA-CA in Fukuoka, Japan from 2005 to 2015 are shown in Figure 2A. The weekly average number of OHCA-CA cases was positively associated with the weekly average number of influenza cases during weeks 1 to 52 ( $r=0.70$ ,  $P<.0001$ ) (Fig. 2B).

**Table 1**

Patient characteristics of All-Japan Utstein registry in Fukuoka, Japan.

	Total (n = 739,721)	Fukuoka (n = 17,710)	P
Age, y	$75.5 \pm 15.5$	$74.9 \pm 15.5$	<.0001
Male, n (%)	424,550 (57.4)	10,073 (56.9)	.2
One month survival, n (%)	45,152 (6.1)	1746 (9.9)	<.0001
CPC 1 or 2, n (%)	27,350 (3.7)	1154 (6.5)	<.0001
OPC 1 or 2, n (%)	27,038 (3.7)	1142 (6.5)	<.0001

One month survival with minimal neurologic impairment and overall performance impairment were defined as CPC 1 or 2 and OPC 1 or 2, respectively.  
CPC=cerebral performance category, OPC=overall performance category.



**Figure 2.** Average weekly changes and correlation between the incidences of OHCA-CA and influenza infection in Fukuoka, Japan from 2005 to 2015. (A) Average weekly changes in influenza infection and OHCA-CA in Fukuoka, Japan from 2005 to 2015. Red dot indicates incidence of influenza infection and blue dot indicates incidence of OHCA-CA (B) Correlation between the average weekly number of OHCA-CA cases and the average weekly number of influenza infections during weeks 1 to 52. OHCA-CA=out-of-hospital cardiac arrest of cardiac origin.

### 3.3. Correlation between the incidences of OHCA-CA and influenza infection in adults in winter according to the epidemic phases

In Japan, weekly influenza outbreaks are announced officially by the National Institute of Infectious Diseases. An “alert phase” is issued when more than 10.0 cases of influenza are reported per registered institute. A “pandemic phase” is issued when more than 30.0 cases of influenza are reported per registered institute. Figure S1, Supplemental Digital Content, <http://links.lww.com/MD/G771> shows weekly reports of influenza virus detected per sentinel institute in Fukuoka, Japan from 2005 to 2015.

In the study cohort, 6,304 OHCA-CA cases and 131,322 influenza cases in adults during winter in Fukuoka, Japan from 2005 to 2015 were investigated (Fig. 1). The correlation between the weekly OHCA-CA and influenza infection cases in adults in winter according to the epidemic phase are shown in Figure 3A–D. In all phases, weekly OHCA-CA cases were positively associated with weekly influenza infection cases [total phases (165 weeks):  $r=0.37, P<.0001$ , non-epidemic phase (59 weeks):  $r=0.28, P=.02$ , alert phase (54 weeks):  $r=0.34, P=.01$ , pandemic phase (52 weeks):  $r=0.41, P=.007$ ].

### 3.4. Correlation between the incidences of OHCA-CA and influenza infection in adults in winter according to the frequency of influenza infection in adults

We investigated the correlation between weekly OHCA-CA cases and weekly influenza infection cases in adults in winter according to the frequency of influenza infection in adults, since the official influenza epidemic phase was calculated using all patients. Interestingly, weekly OHCA-CA cases were positively associated with weekly influenza infection cases in the high-frequency group (55 weeks,  $r=0.36, P=.006$ ), but not the medium- (55 weeks,  $r=0.26, P=.05$ ) or low-frequency groups

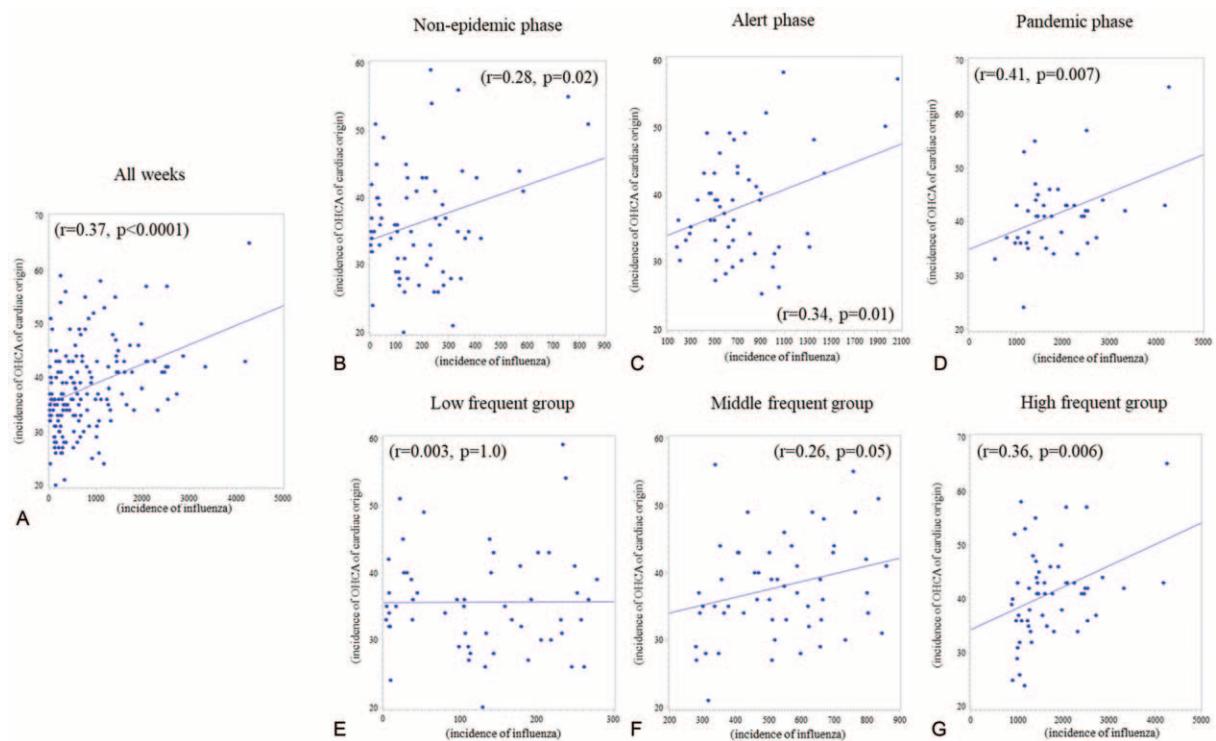
(55 weeks,  $r=0.003, P=1.0$ ) (Fig. 3E–G). In the high-frequency group in adults, weekly OHCA-CA cases were positively associated with weekly influenza infection cases in males (55 weeks,  $r=0.37, P=.006$ ), but not females (55 weeks,  $r=0.18, P=.2$ ) (Fig. 4).

## 4. Discussion

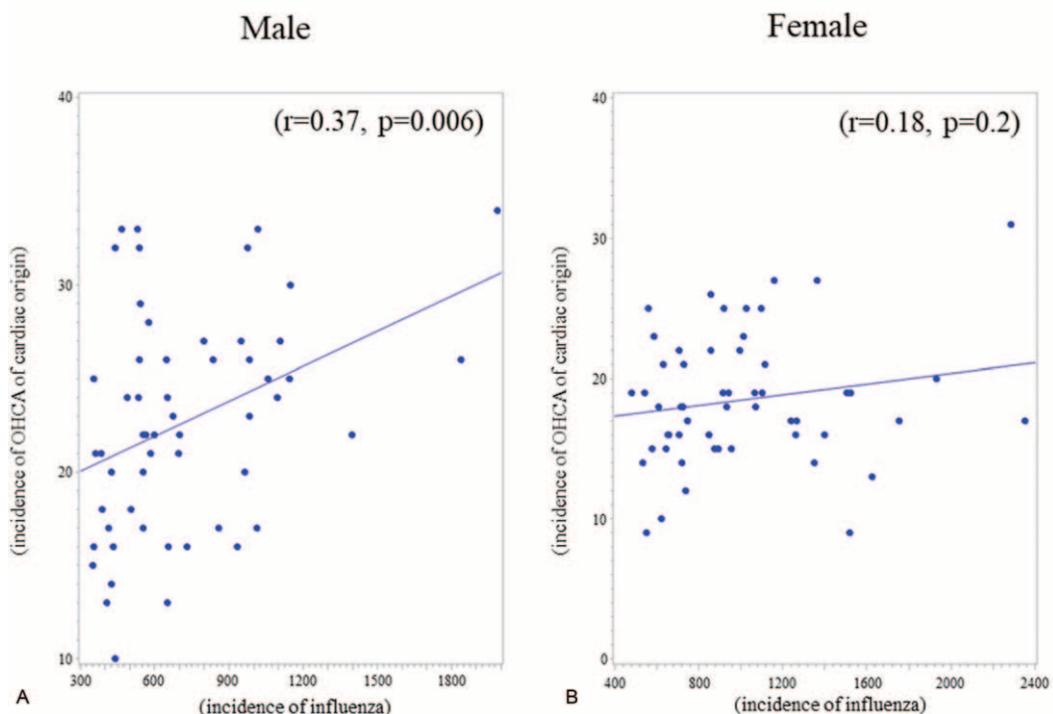
The weekly number of OHCA-CA cases in adults was positively associated with the weekly number of influenza infection cases when there was a high frequency of influenza infection in adults in winter, especially in males.

Influenza infection is associated with cardiovascular complications and influenza pandemics are associated with increased cardiovascular mortality.<sup>[34]</sup> It has been reported that influenza infection within 7 days after laboratory-confirmed detection increases acute myocardial infarction.<sup>[35]</sup> In a pathological investigation, myocardial disruption was observed rather than inflammation in a mouse model of influenza infection and in autopsy subjects.<sup>[36]</sup> Endothelial dysfunction has also been discussed as the cause of cardiovascular collapse and death during influenza infection.<sup>[37]</sup> Vicente et al reported that acute infection triggers acute coronary syndromes via inflammation, endothelial damage, platelet thrombi, increased sympathetic activity,<sup>[38]</sup> reduced blood flow, and decreased central blood pressure.<sup>[38]</sup> The prevention of influenza infection is effective for the prevention of OHCA-CA.

We found an association between OHCA-CA and influenza outbreaks for all ages and all seasons, as in previous reports.<sup>[23,39]</sup> Our investigation considered two additional factors including the patient's age and season. The patient age distribution is quite different between influenza infection and OHCA-CA: most influenza cases are under 20 years of age<sup>[24]</sup> and most OHCA-CA cases are over 20 years of age.<sup>[3]</sup> It might be



**Figure 3.** Correlation between the weekly number of OHCA-CA and influenza infection cases in adults in winter according to the epidemic phase in all age groups and the frequency of adult influenza infection in Fukuoka, Japan from 2005 to 2015. Correlation between weekly OHCA-CA cases and weekly influenza infection cases in adults in winter in all weeks (A), non-epidemic phase (B), alert phase (C), pandemic phase (D), high-frequency group (E), medium-frequency group (F), and low-frequency group (G). OHCA-CA=out-of-hospital cardiac arrest of cardiac origin.



**Figure 4.** Correlation between the weekly numbers of OHCA-CA and influenza infection cases in adults during weeks with a high frequency of influenza in winter by sex in Fukuoka, Japan from 2005 to 2015. Correlation between the weekly numbers of OHCA-CA and influenza infection cases in males (A) and females (B) in weeks with a high-frequency of adult influenza infection. OHCA-CA=out-of-hospital cardiac arrest of cardiac origin.

more informative to investigate the association between OHCA-CA and influenza infection according to age group. Seasonal effects should also be considered. It would be easy to show an association between influenza infection and OHCA-CA over time because both influenza infection and OHCA-CA are more common in winter. When the data were studied according to the frequency of influenza infection in adults, OHCA-CA was positively associated with influenza infection only in weeks with a high frequency of influenza, but not in weeks with medium or low frequencies of infections, especially in males. Therefore, it might help to prevent OHCA-CA in males by announcing influenza epidemics in adults in addition to all ages.

This study had some limitations. First, since this was an observational study, we could not investigate the direct association between influenza infection and OHCA-CA. Detailed data on the patient backgrounds including cardiovascular risk factors, past histories of cardiovascular disease, and the cause of OHCA-CA were not available in the All-Japan Utstein registry. We did not consider the time lag from influenza infection to the onset of OHCA-CA, but our study accepted a 7-day time lag,<sup>[35]</sup> because we used weekly data. Information on influenza vaccination was not available, but many reports have suggested that influenza vaccination helps prevent OHCA-CA.<sup>[20,21,40]</sup> The data from 17,710 OHCA-CA individuals could be suitable for discussing our hypothesis, although we need further clinical studies.

In conclusion, the number of OHCA-CA cases was positively associated with the number of influenza cases in adult males in weeks with a high frequency of influenza infection. It might help to prevent OHCA-CA in males by announcing influenza outbreaks in adults in addition to all ages.

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