BMJ Open

Regional Health Expenditure and Health Outcomes after Out-of-Hospital Cardiac Arrest in Japan: An Observational Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008374
Article Type:	Research
Date Submitted by the Author:	31-Mar-2015
Complete List of Authors:	Tsugawa, Yusuke; Harvard University, Interfaculty Initiative in Health Policy Hasegawa, Kohei; Massachusetts General Hospital, Emergency Medicine Hiraide, Atsushi; Kinki University Faculty of Medicine, Acute Medicine Jha, Ashish; Harvard School of Public Health, Health Policy and Management
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Health services research
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™ Manuscripts

Regional Health Expenditure and Health Outcomes after Out-of-Hospital Cardiac Arrest in Japan: An Observational Study

Yusuke Tsugawa, MD, MPH[1]; Kohei Hasegawa, MD, MPH[2]; Atsushi Hiraide, MD, PhD[3]; Ashish K. Jha, MD, MPH[4,5]

Author Affiliations:

1. Harvard Interfaculty Initiative in Health Policy, Cambridge, MA (14 Story Street 4th floor, Cambridge, MA 02138 USA)

2. Department of Emergency Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA (326 Cambridge Street, Suite 410, Boston, MA 02114 USA)

3. Department of Acute Medicine, Kinki University Faculty of Medicine, Osaka, Japan (3-4-1 Kowakae, Higashiosaka City, Osaka, Japan)

4. Department of Health Policy and Management, Harvard School of Public Health, Boston, MA (677 Huntington Avenue, Boston, MA 02115 USA)

5. Department of General Internal Medicine, Brigham and Women's Hospital and the Veterans Affairs Boston Healthcare System (75 Francis Street, Boston, MA 02115 USA)

Corresponding Author:

Ashish K. Jha

Department of Health Policy and Management

Harvard School of Public Health

E-mail: ajha@hsph.harvard.edu

Phone: +1-617-432-5551

Word Count: 3,700 words

Number of References: 26

Number of Figures/Tables: 3 tables and 2 figures (3 online appendices)

ABSTRACT (296 words)

Objectives: Japan is considering policies to set target health expenditure level for each region, a policy approach that has been considered in many other countries. The objective of this study was to examine the relationship between regional health expenditure and health outcomes after out-of-hospital cardiac arrest (OHCA), which incorporates the qualities of pre-hospital, in-hospital, and post-hospital care systems.

Design: We examined the association between prefecture-level per capita health expenditure and patients' health outcomes after OHCA.

Setting: We used a nationwide, population-based registry system of OHCAs that captured all OHCA cases resuscitated by emergency responders in Japan from 2005 through 2011.

Participants: All OHCA patients aged 1-100 years were analyzed.

Outcome Measures: The patients' 1-month survival rate, and favorable neurological outcome (defined as cerebral performance category 1-2) at 1-month.

Results: Among 618,154 OHCA cases, the risk-adjusted 1-month survival rate varied from 8.4% (95% CI: 7.7%-9.1%) to 3.3% (95% CI: 2.9%-3.7%) across prefectures. The risk-adjusted probabilities of favorable neurological outcome ranged from 3.7% (95%CI: 3.4%-3.9%) to 1.6% (95%CI: 1.4%-1.9%). Compared to prefectures with lowest-tertile health expenditure, 1-month survival rate was significantly higher in medium-spending (adjusted OR 1.31, 95%CI 1.03-1.66, p=0.03) and high-spending prefectures (adjusted OR 1.30, 95%CI 1.03-1.64, p=0.02), after adjusting for patient characteristics. There was no difference in the survival between medium- and high-spending regions. We observed similar patterns for favorable neurological outcome. Additional adjustment for regional per capita income did not affect our overall findings.

Conclusions: We observed a wide variation in the health outcomes after OHCA across regions. Low-spending regions had significantly worse health outcomes compared to medium or high spending regions, but no difference was observed between medium- and high-spending regions. Our findings suggest that focusing on the median spending may be the sweet spot that allows for saving money without compromising patient outcomes.

Key words: health economics, health policy, quality in health care

STRENGTHS AND LIMITATIONS OF THIS STUDY:

1. This is the first study that examined the association between regional health spending and the patient outcomes after out-of-hospital cardiac arrest (OHCA).

2. We used a nation-wide, population-based registry system of OHCAs that captured all OHCA cases resuscitated by emergency responders in Japan

3. The outcomes after OHCA reflect a collective impact of pre-hospital, in-hospital, and post-hospital care systems, and thus they may be superior to the health outcomes used in previous studies that lean heavily on the quality of in-hospital care.

4. Our study samples included only cases for which emergency medical system was activated, resuscitation was attempted, and the patients were transferred to the hospitals.

INTRODUCTION

Concerned about the rapid growth in health spending and the regional variation in health expenditure, the Japanese government is currently considering to set a target health expenditure level for each prefecture.[1] While the specifics of this approach are not yet finalized, policymakers are considering using low-spending prefectures as potential benchmarks, or to set target health expenditure levels for each prefecture. These policies, which are analogous to ones proposed in other countries including the United States and other European countries, are controversial because many of these policies do not take into account quality of care or health outcomes in setting target health expenditure level.[2] If greater health expenditures are being used in helpful ways – in ways that improve quality and reduce poor outcomes, then policies that focus only on spending can potentially be harmful for the health of the population.

Regional variations in healthcare spending have been best studied in the United States [3 4] and the studies link expenditures with outcomes have been mixed.[5-8] Regional health spending can potentially impact a variety of health outcomes, including those at the community-level and those within institutions like hospitals. Outcomes after an out-of-hospital cardiac arrest (OHCA) is particularly salient because of three reasons: it is common (in the United States. alone, an estimated 360,000 people suffer from it annually), highly morbid (only 9.5% will survive to hospital discharge),[9] and can serve as an indicator of health system performance more broadly. Outcomes after OHCA reflect a collective impact of pre-hospital, in-hospital, and post-hospital care systems, and inadequate performance of any part of this clinical chain could negatively impact the outcomes. Therefore, it can be a useful metric to assess the association between regional health expenditure and the population's health outcomes.

Given that many countries are struggling with rapidly rising health expenditure, understanding the relationship between health expenditure and health outcomes in Japan would provide important insights for other countries to examine their own strategies vis-à-vis spending and healthcare quality and outcomes. Therefore, in this study, we sought to answer three questions. First, how much variation is there in the outcomes after OHCA across 47 prefectures in Japan? Second, what is the relationship, if any, between per capita health expenditure at prefecture-level and health outcomes after OHCA? Finally, given strong policy concern that the most frugal regions may be achieving low spending by forgoing care for the oldest patients, is there any evidence that the relationship between health expenditure and health outcomes after OHCA varies by age group?

METHODS

Study design and participants

The All-Japan Utstein registry of the Fire and Disaster Management Agency (FDMA) is a nation-wide, population-based registry system of OHCAs in infants, children, and adults, with Utstein-style data collection.[10-12] All patients who had experienced non-traumatic OHCA and for whom resuscitation was attempted by emergency medical service (EMS) personnel with subsequent transport to hospitals from January 1, 2005, to December 31, 2011, with age of 1 to 100 years, were eligible for our analysis. We excluded those with age over 100 years from our analysis because the numbers were small and differential proportion of people who do not request active life-saving procedures (i.e., those people with " Do-not-resuscitate" [DNR] orders) across prefectures can potentially confound our inferences, and age is the strongest predictor of such decisions.[13]

Data were collected prospectively with an Utstein-style data form that included age, sex, etiology of arrest, first documented cardiac rhythm, bystander's witness status, presence and type of cardiopulmonary resuscitation (CPR) by bystander, and the use of a public-access automated external defibrillator (AED). Cardiac arrest was defined as the end of cardiac mechanical activity determined by the absence of signs of circulation. The etiology of arrest was deemed cardiac unless evidence suggested trauma, respiratory diseases, cerebrovascular diseases, malignant tumors, or any other non-cardiac cause. Attribution of cardiac or non-cardiac etiology was made by the attending physicians in the emergency department in collaboration with the EMS personnel. Furthermore, the EMS personnel queried the medical control director at the hospital 1 month after the OHCA event to confirm the etiology of the arrest. If there was a disagreement on the etiology, the determination at 1-month was used. The study was approved by the Office of Human Research Administration at Harvard School of Public Health. Informed consent was deemed unnecessary by the FDMA of Japan.

Japanese healthcare system

The population of Japan was roughly 128 million in 2010, with approximately 107 million people aged 18 years or older.[14] Japan consists of 47 prefectures, which are the country's first jurisdiction and administrative division levels. The population size at each prefectures ranges from approximately 13 million in Tokyo to 600,000 in Tottori.[14] The entire population is covered by the social health insurance system, and the prices and fees of the healthcare services are set uniformly regardless of the types and location of healthcare providers. The majority of healthcare providers are private, and the patients are free to choose which providers to visit. The coinsurance rate is fixed at 30% uniformly, except for the elderly and children.[15] The municipal governments provide emergency medical service (EMS) through 802 fire stations with dispatch centers. The details about the EMS system in Japan have been described elsewhere.[11]

Health outcomes

The primary health outcome measure was 1-month survival after OHCA. The secondary outcome was favorable neurological outcome 1 month after cardiac arrest, which was defined as Glasgow- Pittsburgh cerebral performance category 1 (good performance) or 2 (moderate disability).[10] The other categories — 3 (severe cerebral disability), 4 (vegetative state), and 5 (death) — were regarded as unfavorable neurological outcome. This is the standard approach for the studies examining the neurological outcomes after OHCA.[11]

To collect follow-up data about survival and neurological status 1 month after the OHCA event, the EMS personnel who treated each patient with OHCA queried the medical control director at the hospital. Patient neurological status was evaluated by the treating physician; the EMS received a written response. If the patient was not at the hospital, the EMS personnel conducted a follow-up search. Data forms were completed by EMS personnel in conjunction with the physicians who treated the patients, and the data were integrated into the Utstein registry system on the FDMA database server. Several regions developed additional local registry systems. In these areas, the information on each OHCA case was initially assembled using their data collection system. Then, the information were exported and integrated into the FDMA database in which the data underwent further review. Forms were logic-checked by the computer system and were confirmed by the FDMA. If the data form was incomplete, the FDMA returned it to the respective fire station and the missing data were obtained.

Per capita total health expenditure

The information about annual total health expenditure per capita for each prefecture was extracted from the database created by Ministry of Health, Labour and Welfare of Japan.[16] The population data were available from Statistic Bureau, Ministry of Internal Affairs and Communications.[17] The total health expenditure was defined as the sum of inpatient and outpatient care, not including the expenditures due to dental care. Per capita total health expenditure was calculated by dividing total health expenditure by the number of population for each prefecture during the study period (from January 2005 through December 2011). An exchange rate of 115 yen per US dollar was used for the analyses of health expenditure (as of November 11, 2014).

Adjustment variables

To account for differences in population characteristics across prefectures, we adjusted for demographic, clinical, and response characteristics of the OHCA patients. Demographic characteristics included age in 5-year increments (from ≥1 year of age to 4, 5 to 9, and so on through 95 to 100), sex, and the interaction between age and sex. Clinical characteristics consisted of etiology of arrest (cardiac vs. non-cardiac) and first documented rhythm (ventricular fibrillation/pulseless ventricular tachycardia vs. other). The response characteristics included witnessed status (no witness, witnesses by layperson, witness by healthcare provider), type of bystander CPR (no bystander CPR, compression-only CPR, conventional CPR), and the use of a public-access AED by bystander (yes/no). We did not include the regional characteristics, such as EMS response time (which can be a proxy for a number of hospitals in a given region), because they are in the causal pathway linking the regional health spending and the health outcomes of patients.

Statistical analysis

We used these data to generate adjusted average values of each outcome in each prefecture. We pooled seven years of data (2005 to 2011) and performed a person-level logistic regression for health outcomes. Each regression model included prefecture indicator variables, year indicators, and the patient-level risk-adjustment variables listed above. The performance of the risk-adjustment model was evaluated using C-statistics (the prefecture indicators were excluded from the analysis when the C-statistics were calculated).[18] The risk-adjustment was performed by calculating the predicted probabilities of outcomes for each patient using the regression equation with the distribution of covariates in our sample and the prefecture indicator imposed to that of a specific prefecture, and repeating the calculation across all 47 prefectures (also known as model-adjusted means, predictive margins, or g-formula).[19 20] Standard errors of the estimates were obtained by the delta method, and were used to calculate the 95% confidence intervals (CIs).[19] Conceptually, this is equivalent to simulating the potential outcomes (counterfactuals) if all individuals with OHCA in our sample took place in a given prefecture and were treated there.

We evaluated the association between prefecture's per capita health expenditure and patients' health outcomes after OHCA. The prefectures were classified into three equal sized groups (tertile) based on per capita health expenditure in order to address a potential non-linear relationship between per capita health expenditure and health outcomes after OHCA (defined as low-, medium-, and high-spending prefectures). In addition, we used per capita health expenditure as a continuous variable assuming a linear relationship between health expenditure and (log-odds of) health outcomes after OHCA. We used the person-level data for our analysis in order to avoid ecological fallacy.[21] In order to account for the potential clustering of OHCA cases within each prefecture, we used generalized estimating equations (GEE) with binomial distribution, logit-link, and an independent correlation structure.[22-24] We used GEE instead of the mixed effects models (also known as hierarchical models or multilevel models), because we were interested in the population average effects (estimated by GEE) rather than the subset-specific (individual-specific) effects (estimated by mixed effects models).[25] The regression models were adjusted for the year indicators, age, sex, the interaction between age and sex, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (ventricular fibrillation [VF] or pulseless ventricular tachycardia [VT]), witness status, CPR by bystander, and use of public-access AED by bystander.

To evaluate the possibility that low-spending regions forgo spending on specific subpopulation, such as the oldest-old population, we also examined the association between health spending and OHCA outcomes across 3 age groups: age 1 to 59, 60 to 79, and 80 to 100. We fitted the same regression model as described above. We also fitted regression models with the interaction term between health expenditure and age group, and formally examined if the impact of health expenditure on outcomes after OHCA differs by age using likelihood ratio test. As a sensitivity analysis, we added the per capita income at prefecture-level in 2011 (data extracted from Japan Statistical Yearbook [26]) to the list of risk-adjustment variables in our regression models, as a measure of the socio-economic status (SES) of the population. We did not include this variable in our primary analyses because the SES is a major determinant of access to healthcare and poor access to care is likely a mediator for the relationship between spending and patient outcomes. A two-sided p value < 0.05 was considered statistically significant. The GEE analysis was conducted using SAS, version 9.3 (SAS Institute, Cary, NC), and all other analyses were performed using Stata, version 12 (Stata-Corp, College Station, Texas).

RESULTS

Patient characteristics

In the total catchment population of 128 million, 797,422 OHCAs were reported from January 1, 2005 through December 31, 2011. From these 145,829 cases were excluded due to traumatic causes; 9,657 cases were excluded as no resuscitation was attempted; and 6,218 cases were excluded as patients' age was less than 1 or higher than 100 years. Out of remaining OHCA cases, 17,547 cases with missing data on one of the covariates were excluded. Finally, 664 arrests were excluded from the analysis of the rate of favorable neurological outcome due to missing outcome data, leaving us the final sample size of 618,154 OHCA cases for the analysis of 1-month survival rate and 617,490 cases for the analysis of favorable neurological outcome (**Appendix 1**). Median age was 78 (IQR: 67-85), and 57.9% were men. Approximately two-thirds were due to cardiac causes, and VF or pulseless VT was observed as initial cardiac rhythm in 8.7% of the cases.

Demographic, clinical, and response characteristics of our sample, stratified by prefecture-level health expenditure, are presented in **Table 1**.

Table 1. Baseline characteristics of patients with out-of-hospital cardiac arrest, by prefecture-level per capita health expenditure.

	Low-spending prefectures	Medium-spending prefectures	High-spending prefectures	P-value
Number of patients	332,213 (53.7%)	155,077 (25.1%)	130,864 (21.2%)	
Demographic characteristics				
Age, median (IQR), y	78 (67-85)	78 (67-85)	78 (67-85)	<0.01
Male sex	58.1%	57.4%	58.0%	<0.01
Clinical characteristics				
Etiology of arrest				<0.01
Non-cardiac	32.8%	27.9%	36.4%	
Cardiac	67.2%	72.1%	63.6%	
VF or pulseless VT as initial cardiac rhythm	8.3%	8.9%	9.3%	<0.01
Response characteristics				
Type of bystander-witness status				<0.01
No witness	58.2%	56.7%	58.5%	
Layperson	33.3%	34.2%	32.9%	
Healthcare provider	8.5%	9.1%	8.6%	
CPR by bystander				<0.01
No bystander CPR	62.1%	57.8%	58.6%	
Compression-only CPR	26.7%	28.2%	28.4%	
Conventional CPR	11.2%	13.9%	13.0%	
Use of public-access AED by bystander	0.7%	0.6%	0.6%	<0.01
Prefecture-level characteristics				
Per capita income (US$)	25,343 (3,901)	21,827 (2,674)	22,764 (1,923)	<0.01

Samples are those cases with no missing data on all variables used in the regression analysis. Data are expressed as n (%) for categorical variables and mean (SD) for continuous variable, unless otherwise indicated. P-values are calculated using chi-square test for categorical variables and ANOVA for continuous variables. CPR denotes cardiopulmonary resuscitation; and VT and VF denote ventricular tachycardia and ventricular fibrillation respectively. Conventional CPR consists of chest compression and rescue breathing.

Regional variation in patients' health outcomes after OHCA

Figures 1 and **Appendix 2** show the variation in risk-adjusted outcomes of OHCA across prefectures. The C-statistics (area under the ROC curve) were 0.81 for the risk-adjustment model for 1-month survival rate and 0.88 for that for the favorable neurological outcome, indicating good discriminating power of the models.[18] The risk-adjusted 1-month survival rate ranged from 8.4% (95%CI: 7.7%-9.1%) in Toyama prefecture to 3.3% (95%CI: 2.9%-3.7%) in Iwate prefecture. Tokyo (the most populated prefecture in Japan) was the prefecture with one of the poorest risk-adjusted survival rate of 3.4% (95%CI: 3.3%-3.5%), whereas Osaka (the most populated prefecture in western Japan) exhibited one of the higher survival rate of 6.6% (95%CI: 6.4%-6.9%).

The risk-adjusted probability of favorable neurological outcome varied from 3.7% (95%CI: 3.4%-3.9%) in Fukuoka prefecture to 1.6% (95%CI: 1.4%-1.9%) in Iwate prefecture. Tokyo was again one of the poor-outcome prefectures with 2.0% (95%CI: 1.9%-2.1%) chance of experiencing good neurological outcome. In contrast, Osaka was one of the best with 3.5% (95%CI: 3.3%-3.7%) chance of favorable neurological outcome. Per capita health expenditure in 2005-2011 varied from US$ 2,504 (¥287,925 JPY) per year in Kochi prefecture to US$ 1,315 (¥151,272) per year in Saitama prefecture.

Association between prefecture-level health expenditure and patient health outcomes after OHCA

The relationships between prefecture's per capita health expenditure and the risk-adjusted health outcomes after OHCA aggregated at prefecture-level are shown in **Figure 2**.The association between per capita health expenditure at prefecture and patient-level outcomes after OHCA is presented in **Table 2**. We found that higher per capita health expenditure at the prefecture was associated with significantly better health outcomes after OHCA. For every US$ 100 increase in per capita health expenditure at prefecture, the OHCA patients exhibited 1.04 times higher odds of survival at 1 month (95%CI 1.01-1.07, $p<0.01$), and 1.04 times higher odds of favorable neurological outcome (95%CI 1.02-1.07, $p<0.01$), after adjusting for patients' risks (data not shown).

Table 2. Association between per capita health expenditure at prefecture-level and patients' health outcomes after out-of-hospital cardiac arrest.

1-month survival rate		**Unadjusted (N=635,710)**		**Adjusted* (N=618,154)**	
		OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Tertile of prefecture-level health expenditure per capita	**Low**	Ref		Ref	
	Medium	1.31 (1.02-1.67)	0.03	1.31 (1.03-1.66)	0.03
	High	1.30 (1.04-1.62)	0.02	1.30 (1.03-1.64)	0.02
Favorable neurological outcome at 1 month		**Unadjusted (N=635,046)**		**Adjusted* (N=617,490)**	
		OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Tertile of prefecture-level health expenditure per capita	**Low**	Ref		Ref	
	Medium	1.30 (1.02-1.67)	0.04	1.29 (1.03-1.62)	0.03
	High	1.26 (1.04-1.53)	0.02	1.28 (1.06-1.55)	0.01

*Adjusted for age, sex, the interaction between age and sex, year indicators, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (VF or pulseless VT), witness status, CPR by bystander, and use of public-access AED by bystander.

The crude mean survival rate at 1 month after OHCA was 4.4% (95%CI: 4.3%-4.4%) in low-spending prefectures, 5.7% (95%CI: 5.5%-5.8%) in medium-spending prefectures, and 5.6% (95%CI: 5.5%-5.7%) in high-spending prefectures. The unadjusted probabilities of favorable neurological outcome after OHCA was 2.1% (95%CI: 2.1%-2.2%) in low-spending prefectures, 2.8% (95%CI: 2.7%-2.9%) in medium-spending prefectures, and 2.7% (95%CI: 2.6%-2.8%) in high-spending prefectures. Similar to the results of the linear regression analysis, compared to OHCA cases in the prefectures with lowest-tertile health expenditure, those in the medium-spending and high-spending prefectures exhibited significantly higher survival rates (**Table 2**). The 1-month survival rate was 1.31 times higher odds (95%CI: 1.03-1.66, p=0.03) in medium-spending prefectures, and 1.30 times higher odds (95%CI: 1.03-1.64, p=0.02) in highest-spending prefectures, compared to lowest-spending prefectures. Likewise, the odds of favorable neurological outcome was 1.29 times higher (95%CI: 1.03-1.62, p=0.03) in medium-spending prefectures, and 1.28 times higher (95%CI: 1.06-1.55, p=0.01) in high-spending prefectures. We did not observe significant difference in health outcomes between OHCA cases in medium-spending and those in high-spending prefectures (data not shown). Additional adjustment for the prefecture-level per capita income-level did not qualitatively affect our overall findings (**Appendix 3**). Both medium- and high-spending regions had higher probabilities of favorable neurological outcomes and better survival compared to low-spending regions, although some of these differences were no longer statistically significant (even though the effect sizes were similar).

Relationships between health expenditure and OHCA outcomes across different age groups

We found that the relationships between health expenditure and OHCA outcomes were consistent across all 3 age groups (**Table 3**). Compared to low-spending prefectures, both medium- and high-spending prefectures showed higher 1-month survival rates and higher probabilities of favorable neurological outcomes after OHCA. Although the statistical power is limited in a small number of metrics, we still observed higher odds of better OHCA outcomes in these prefectures. We observed a trend toward stronger relationship among OHCA patients aged 80 to 100, compared to younger age groups; however, the results of the likelihood ratio test did not show statistically significant interaction between age group and health expenditure (p=0.30 for survival and p=0.36 for favorable neurological outcome).

Table 3. Adjusted association between per capita health expenditure at prefecture-level and patients' health outcomes after out-of-hospital cardiac arrest, stratified by age group*

1-month survival rate		**Age 1 to 59 (N=91,108)**		**Age 60 to 79 (N=250,705)**		**Age 80 to 100 (N=276,341)**	
		Adjusted OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Tertile of prefecture-level health expenditure per capita	**Low**	Ref		Ref		Ref	
	Medium	1.25 (1.01-1.55)	0.04	1.32 (1.01-1.71)	0.04	1.37 (1.07-1.74)	0.01
	High	1.29 (1.05-1.60)	0.02	1.26 (0.99-1.61)	0.06	1.39 (1.09-1.78)	<0.01
Favorable neurological outcome at 1 month		**Age 1 to 59 (N=90,996)**		**Age 60 to 79 (N=250,403)**		**Age 80 to 100 (N=276,091)**	
		Adjusted OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Tertile of prefecture-level health expenditure per capita	**Low**	Ref		Ref		Ref	
	Medium	1.24 (0.98-1.57)	0.07	1.30 (1.02-1.66)	0.04	1.37 (1.10-1.70)	<0.01
	High	1.27 (1.05-1.54)	0.01	1.23 (1.01-1.50)	0.04	1.46 (1.14-1.86)	<0.01

*Adjusted for age, sex, the interaction between age and sex, year indicators, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (VF or pulseless VT), witness status, CPR by bystander, and use of public-access AED by bystander.

DISCUSSION

In the national study of patients with OHCA in Japan, we found more than a two-fold variation in health outcomes after OHCA across prefectures. Our results showed that low-spending regions had significantly worse health outcomes after OHCA, compared to medium- or high-spending regions; however, the health outcomes of the high-spending regions were not better than that of the medium-spending regions. These relationships appeared to be stronger among the oldest age group (age 80 to 100) compared to younger age groups, although the formal interaction test was not statistically significant. These findings suggest that any policy interventions targeted towards health care costs alone and not taking into account health outcomes potentially have detrimental effect on the population health, especially among the oldest.

While we found the positive association between regional health expenditure and health outcome after OHCA, the relationship was not linear. Low-spending prefectures exhibited worse health outcomes, but the health outcomes in high-spending prefectures were not better than that in medium-spending prefectures. This has two important policy implications. Setting target to lowest group is not likely to be beneficial for the health of the population. But spending at high end might not generate value either. Our findings indicate that spending medium level of health expenditure can potentially rein in health care costs without compromising health outcomes of the population.

We are unaware of any prior study that has studied the relationship between health spending and outcomes after OHCA. Fisher and colleagues studied the relationship between regional health spending and mortality rate among Medicare enrollees hospitalized for 3 common conditions in the US.[6] They found that higher regional spending was associated with slightly higher risk of death for colorectal cancer and acute myocardial infarction (AMI), but had no impact on the mortality among hip fracture patients. Baicker and Chandra conducted a state-level analysis and reported that states with higher Medicare spending had lower quality of care, using process measures for treatment of six common conditions (AMI, breast cancer, diabetes, heart failure, pneumonia, and stroke).[7] These studies lean heavily on the quality of in-hospital care, in contrast to the outcomes after OHCA which are affected by a quality of pre-hospital, in-hospital, and post-hospital care, collectively.

Even though there is no single health outcome metric that can comprehensively measure the performance of the regional health system, the OHCA outcomes have several advantages over other health outcomes. The health outcomes after OHCA reflect a broader performance of regional health system including pre-hospital (immediate recognition of cardiac arrest and activation of the emergency response system, early CPR, and rapid defibrillation), in-hospital (integrated post-cardiac arrest care), and post-hospital care systems (rehabilitation). As a consequence, the study of OHCA outcomes enabled us to evaluate a composite performance of different aspects of health care delivery system. In addition, by focusing on both mortality and neurological outcome, we could evaluate not only the quality of services to keep patients alive, but also the quality of care that help the clinically recover, which indeed is the ultimate goal of the health system for treating patients with OHCA.

Our study has several limitations. First, we could not assess why low spending regions had worse outcomes – whether it reflected lower investment in pre-hospital care – or lower quality care once patients arrived at the hospital. This is an important area for examination in future work. A second limitation is that our study samples included only cases for which emergency medical system was activated, resuscitation was attempted, and the patients were transferred to the hospitals. Different prefectures may have different criteria whether the OHCA patients with low probabilities of survival to be pronounced dead at the scene and not being transferred to hospitals. However, for that to be the explanation for our findings, low spending regions would have to be *more* likely to send OHCA patients with low probabilities of survival to the hospitals, which seems unlikely. Similarly, the study population may include individuals who do not wish life-saving treatment (e.g., individuals with DNR orders) such as those with advance age, disabilities, or late-stage cancer patients. It is also possible that the likelihood of making DNR orders is influenced by local norms and thus differs across prefectures. Lastly, the integrity and validity of the data, and ascertainment bias, are potential source of bias. The use of uniform data collection based on Utstein-style guidelines for reporting and recording the cardiac arrest cases, the large sample size, and the population-based design are expected to minimize these potential threats to validity.

In conclusion, we found more than two-fold variations in OHCA outcomes across prefectures in Japan. We observed a non-linear relationship between regional health spending and patients' outcomes after OHCA. Low-spending regions had significantly worse health outcomes, but the health outcomes in high-spending regions were not better than that in medium-spending regions. Our findings indicate that setting target to lowest-spending group may be harmful in terms of health outcomes, especially for emergency cases such as out-of-hospital cardiac arrest. The fact that spending at high end does not appear to generate additional value suggest that for national policymakers in countries who wish to set budget targets, focusing on the median spending may be the sweet spot that allows for saving money without compromising patient outcomes.

FIGURE LEGENDS

Figure 1. Risk-adjusted 1-month survival (A) and favorable neurological outcome (B) after out-of-hospital cardiac arrest across prefectures.

95% confidence intervals are shown in bars.

Figure 2. Association between total health expenditure per capita and risk-adjusted health survival (A) and favorable neurological outcome (B) after out-of-hospital cardiac arrest at prefecture-level**.**

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

Dr. Tsugawa had full access to all of data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tsugawa, Jha, Hasegawa

Acquisition of data: Hasegawa, Hiraide

Analysis and interpretation of data: Tsugawa, Jha

Drafting of the manuscript: Tsugawa, Jha

Critical revision of the manuscript for important intellectual content: Tsugawa, Jha, Hasegawa, Hiraide

Statistical analysis: Tsugawa

Administrative, technical, or material support: Tsugawa, Jha, Hiraide

DATA SHARING

The dataset is not publicly available. Please contact the authors for the statistical code and the dataset.

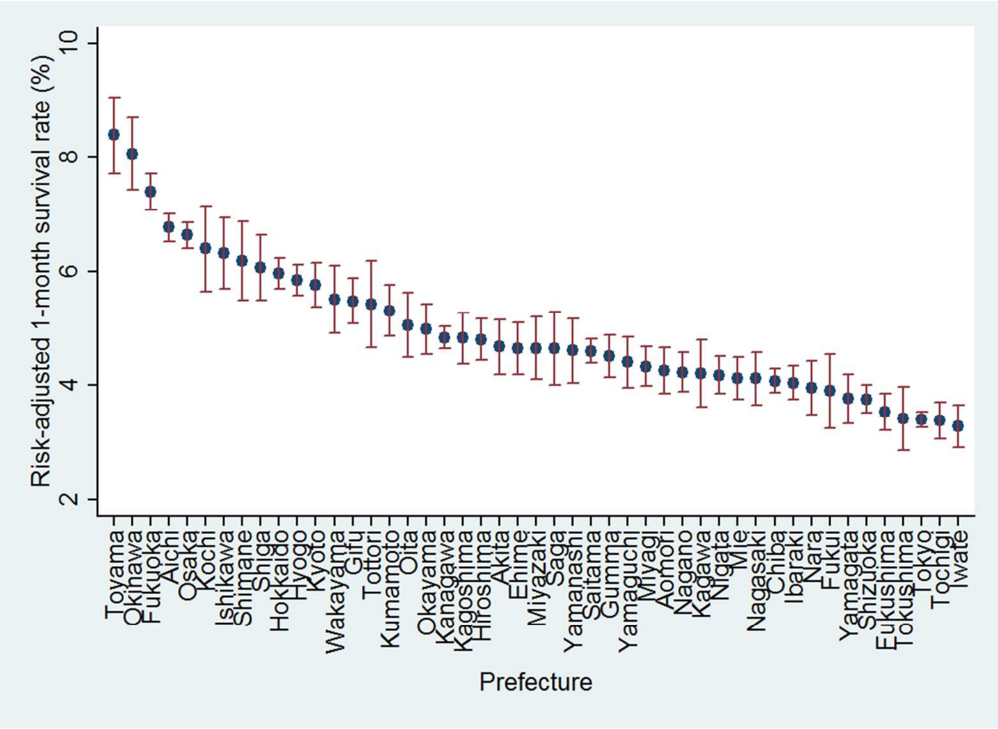
COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

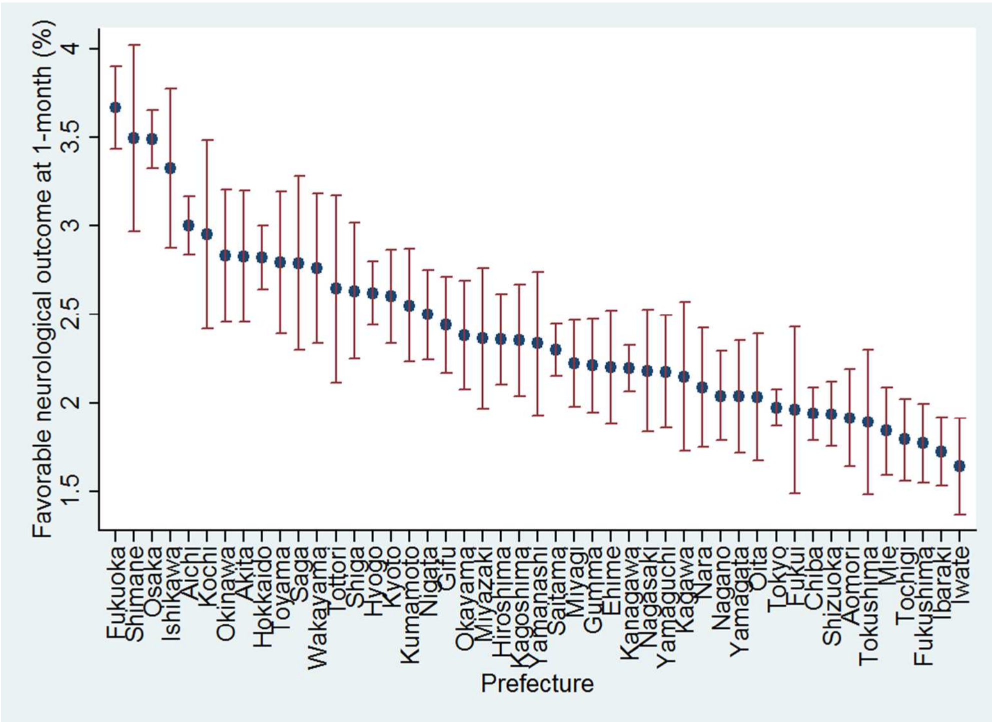
REFERENCES

1. Curbing health expenditure, tackling high hospitalization costs, as large as 2.1 times difference in health expenditure between prefectures (in Japanese). *Nihon Keizai Shinbun* 2014 August 12.
2. Ministry of Health Labour and Welfare. Regional variation of health expenditure in Japan (in Japanese). Secondary Regional variation of health expenditure in Japan (in Japanese) 2012. http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/database/iryomap/index.html.
3. Chassin MR, Brook RH, Park RE, et al. Variations in the use of medical and surgical services by the Medicare population. N Engl J Med 1986;**314**(5):285-90.
4. Wennberg J, Gittelsohn. Small area variations in health care delivery. Science 1973;**182**(4117):1102-8.
5. Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 1: the content, quality, and accessibility of care. Ann Intern Med 2003;**138**(4):273-87 doi: 10.7326/0003-4819-138-4-200302180-00006 [published Online First: 15 February 2003].
6. Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. Ann Intern Med 2003;**138**(4):288-98 doi: 10.7326/0003-4819-138-4-200302180-00006 [published Online First: 15 February 2003].
7. Baicker K, Chandra A. Medicare spending, the physician workforce, and beneficiaries' quality of care. Health Aff (Millwood) 2004;**Suppl Web Exclusives**:W4-184-97. doi: 10.1377/hlthaff.w4.184 [published Online First: 29 September 2004].
8. Landrum MB, Meara ER, Chandra A, et al. Is spending more always wasteful? The appropriateness of care and outcomes among colorectal cancer patients. Health Aff (Millwood) 2008;**27**(1):159-68. doi: 10.1377/hlthaff.27.1.159 [published Online First: 9 January 2008].
9. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 2013;**127**(1):e6-e245. doi: 10.1161/CIR.0b013e31828124ad [published Online First: 15 December 2012].
10. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). Circulation 2004;**110**(21):3385-97. doi: 10.1161/01.CIR.0000147236.85306.15 [published Online First: 24 November 2004].
11. Hasegawa K, Hiraide A, Chang Y, et al. Association of prehospital advanced airway management with neurologic outcome and survival in patients with out-of-hospital cardiac arrest. JAMA 2013;**309**(3):257-66 doi: 10.1001/jama.2012.187612 [published Online First: 16 January 2013].
12. Hasegawa K, Tsugawa Y, Camargo CA, Jr., et al. Regional variability in survival outcomes of out-of-hospital cardiac arrest: the All-Japan Utstein Registry. Resuscitation 2013;**84**(8):1099-107 doi: 10.1016/j.resuscitation.2013.03.007

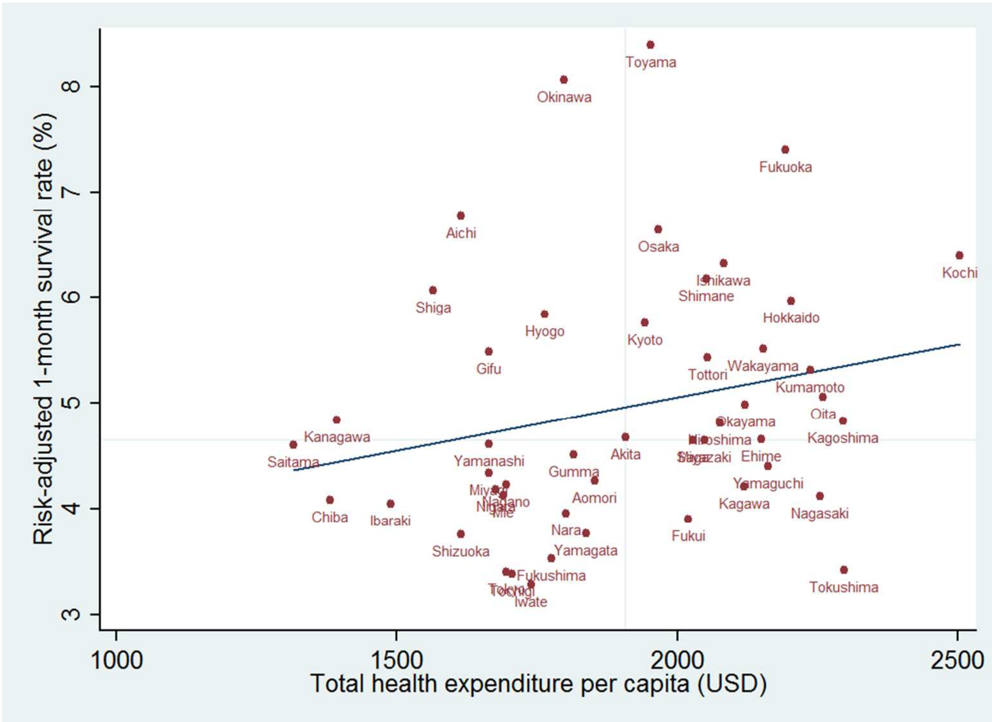
[published Online First: 19 March 2013].
13. Messinger-Rapport BJ, Kamel HK. Predictors of do not resuscitate orders in the nursing home. Journal of the American Medical Directors Association 2005;**6**(1):18-21. doi: http://dx.doi.org/10.1016/j.jamda.2004.12.006.
14. Ministry of Internal Affairs and Communications. Population data by prefecture. Secondary Population data by prefecture. http://www.e-stat.go.jp/SG1/estat/List.do?bid=000001039703.
15. Ikegami N, Yoo B-K, Hashimoto H, et al. Japanese universal health coverage: evolution, achievements, and challenges. The Lancet 2011;**378**(9796):1106-15. doi: 10.1016/S0140-6736(11)60828-3 [published Online First: 30 August 2011].
16. Ministry of Health Labour and Welfare. Health expenditure database. Secondary Health expenditure database. http://www.mhlw.go.jp/bunya/iryouhoken/iryouhoken03/01.html.
17. Ministry of Internal Affairs and Communications. e-Stat: Portal Site of Official Statistics of Japan. Secondary e-Stat: Portal Site of Official Statistics of Japan. http://www.e-stat.go.jp/SG1/estat/eStatTopPortalE.do.
18. Aylin P, Bottle A, Majeed A. Use of administrative data or clinical databases as predictors of risk of death in hospital: comparison of models. BMJ 2007;**334**(7602):1044. doi: 10.1136/bmj.39168.496366.55 [published Online First: 17 May 2007].
19. Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. Stata Journal 2012;**12**(2):308.
20. Zhang Y, Baik SH, Fendrick AM, et al. Comparing local and regional variation in health care spending. N Engl J Med 2012;**367**(18):1724-31. doi: 10.1056/NEJMsa1203980 [published Online First: 2 November 2012].
21. Robinson WS. Ecological correlations and the behavior of individuals. American Sociological Review 1950;**15**(3):351–57.
22. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;**73**(1):13-22.
23. Hanley JA, Negassa A, Edwardes MD, et al. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol 2003;**157**(4):364-75. doi: 10.1093/aje/kwf215 [published Online First: 13 February 2003].
24. Panageas KS, Schrag D, Riedel E, et al. The effect of clustering of outcomes on the association of procedure volume and surgical outcomes. Ann Intern Med 2003;**139**(8):658-65. doi: 10.7326/0003-4819-139-8-200310210-00009 [published Online First: 21 October 2003].
25. Hu FB, Goldberg J, Hedeker D, et al. Comparison of population-averaged and subject-specific approaches for analyzing repeated binary outcomes. Am J Epidemiol 1998;**147**(7):694-703 [published Online First: 29 April 1998].
26. Statistics Bureau MoIAaC. Prefectural accounts: Economic growth rate and prefectural income per capita. Japan Statistical Yearbook 2015. Tokyo, Japan, 2015.



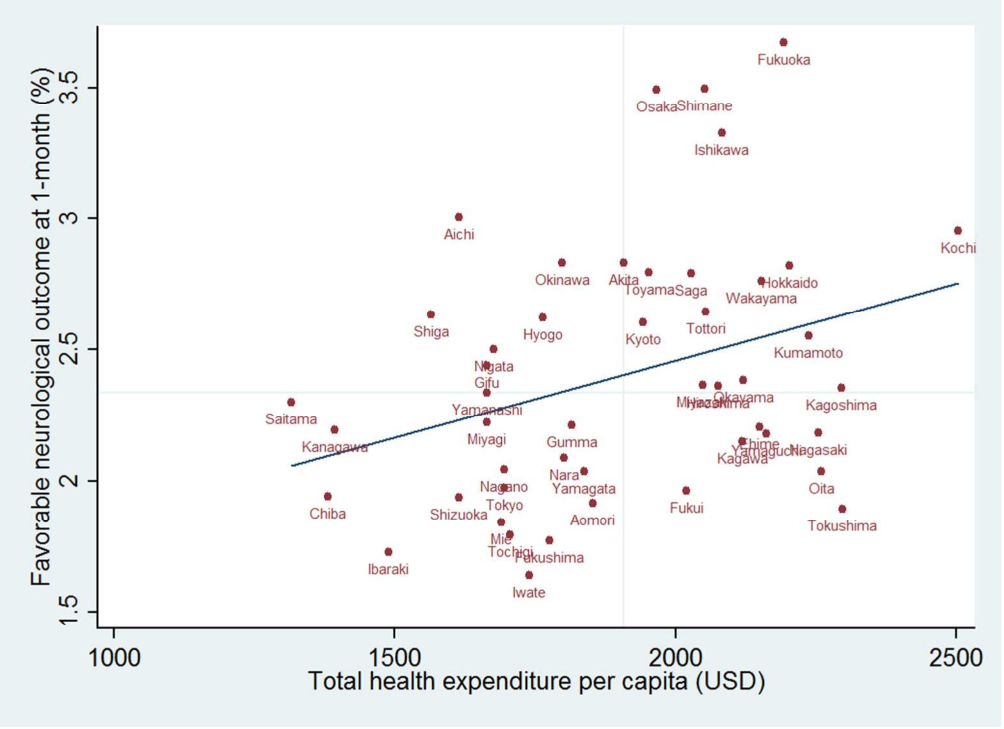
Risk-adjusted 1-month survival after out-of-hospital cardiac arrest across prefectures.
366x266mm (72 x 72 DPI)



Favorable neurological outcome after out-of-hospital cardiac arrest across prefectures.
366x266mm (72 x 72 DPI)

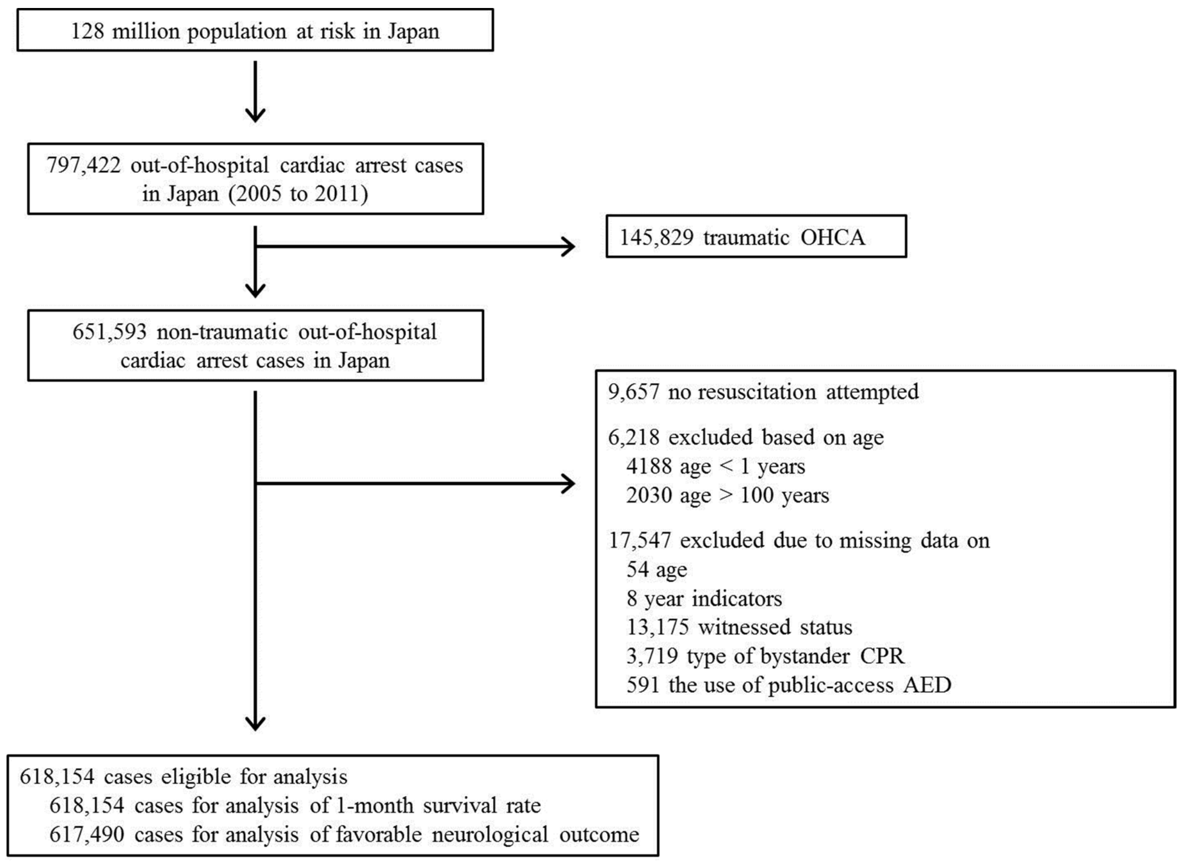


Association between total health expenditure per capita and risk-adjusted health survival after out-of-hospital cardiac arrest at prefecture-level.
366x266mm (72 x 72 DPI)



Association between total health expenditure per capita and favorable neurological outcome after out-of-hospital cardiac arrest at prefecture-level.
366x266mm (72 x 72 DPI)

Appendix 1. Study participants selection.



Appendix 2. Health outcomes after out-of-hospital cardiac arrest and per capita total health expenditure by prefecture

Prefecture	Survival rate at 1 month (95%CI)		Neurologically favorable outcome (95%CI)		Annual health expenditure per capita		
	Unadjusted	Adjusted	Unadjusted	Adjusted	JPY	USD	Tertile
Kochi	5.9% (5.1% - 6.7%)	6.4% (5.6% - 7.2%)	2.5% (2.0% - 3.0%)	3.0% (2.4% - 3.5%)	287,925	2,504	High
Tokushima	3.8% (3.2% - 4.5%)	3.4% (2.9% - 4.0%)	2.2% (1.7% - 2.6%)	1.9% (1.5% - 2.3%)	264,169	2,297	
Kagoshima	4.7% (4.2% - 5.2%)	4.8% (4.4% - 5.3%)	2.3% (1.9% - 2.6%)	2.4% (2.0% - 2.7%)	264,055	2,296	
Oita	5.3% (4.7% - 5.9%)	5.1% (4.5% - 5.6%)	2.2% (1.7% - 2.6%)	2.0% (1.7% - 2.4%)	259,836	2,259	
Nagasaki	4.2% (3.7% - 4.7%)	4.1% (3.6% - 4.6%)	2.2% (1.8% - 2.5%)	2.2% (1.8% - 2.5%)	259,250	2,254	
Kumamoto	5.3% (4.8% - 5.7%)	5.3% (4.9% - 5.8%)	2.5% (2.2% - 2.9%)	2.6% (2.2% - 2.9%)	257,367	2,238	
Hokkaido	6.2% (5.9% - 6.5%)	6.0% (5.7% - 6.2%)	3.0% (2.8% - 3.2%)	2.8% (2.6% - 3.0%)	253,361	2,203	
Fukuoka	7.7% (7.3% - 8.0%)	7.4% (7.1% - 7.7%)	3.8% (3.5% - 4.0%)	3.7% (3.4% - 3.9%)	252,144	2,193	
Yamaguchi	4.5% (4.0% - 5.0%)	4.4% (4.0% - 4.9%)	2.2% (1.9% - 2.6%)	2.2% (1.9% - 2.5%)	248,632	2,162	
Wakayama	5.2% (4.6% - 5.8%)	5.5% (4.9% - 6.1%)	2.5% (2.1% - 2.9%)	2.8% (2.3% - 3.2%)	247,759	2,154	
Ehime	4.4% (3.9% - 4.9%)	4.7% (4.2% - 5.1%)	2.0% (1.7% - 2.4%)	2.2% (1.9% - 2.5%)	247,342	2,151	
Okayama	4.8% (4.4% - 5.2%)	5.0% (4.6% - 5.4%)	2.2% (1.9% - 2.5%)	2.4% (2.1% - 2.7%)	243,946	2,121	
Kagawa	3.9% (3.3% - 4.5%)	4.2% (3.6% - 4.8%)	2.0% (1.6% - 2.4%)	2.1% (1.7% - 2.6%)	243,645	2,119	
Ishikawa	6.7% (6.0% - 7.4%)	6.3% (5.7% - 7.0%)	3.6% (3.1% - 4.1%)	3.3% (2.9% - 3.8%)	239,565	2,083	
Hiroshima	5.1% (4.7% - 5.5%)	4.8% (4.4% - 5.2%)	2.5% (2.2% - 2.8%)	2.4% (2.1% - 2.6%)	238,875	2,077	
Tottori	5.3% (4.5% - 6.1%)	5.4% (4.7% - 6.2%)	2.6% (2.0% - 3.1%)	2.6% (2.1% - 3.2%)	236,214	2,054	Medium
Shimane	5.8% (5.1% - 6.5%)	6.2% (5.5% - 6.9%)	3.1% (2.6% - 3.7%)	3.5% (3.0% - 4.0%)	235,968	2,052	
Miyazaki	4.6% (4.0% - 5.2%)	4.7% (4.1% - 5.2%)	2.3% (1.9% - 2.7%)	2.4% (2.0% - 2.8%)	235,709	2,050	
Saga	4.7% (4.0% - 5.4%)	4.6% (4.0% - 5.3%)	2.8% (2.3% - 3.3%)	2.8% (2.3% - 3.3%)	233,157	2,027	
Fukui	3.5% (2.9% - 4.1%)	3.9% (3.3% - 4.6%)	1.7% (1.2% - 2.1%)	2.0% (1.5% - 2.4%)	232,293	2,020	
Osaka	7.1% (6.9% - 7.4%)	6.6% (6.4% - 6.9%)	3.9% (3.7% - 4.1%)	3.5% (3.3% - 3.7%)	226,081	1,966	
Toyama	8.3% (7.6% - 9.0%)	8.4% (7.7% - 9.1%)	2.8% (2.3% - 3.2%)	2.8% (2.4% - 3.2%)	224,596	1,953	
Kyoto	6.0% (5.6% - 6.4%)	5.8% (5.4% - 6.1%)	2.8% (2.5% - 3.1%)	2.6% (2.3% - 2.9%)	223,388	1,943	
Akita	4.2% (3.8% - 4.7%)	4.7% (4.2% - 5.2%)	2.5% (2.1% - 2.8%)	2.8% (2.5% - 3.2%)	219,345	1,907	
Aomori	4.2% (3.8% - 4.7%)	4.3% (3.9%- 4.7%)	1.9% (1.6% - 2.2%)	1.9% (1.6% - 2.2%)	213,084	1,853	
Yamagata	3.3% (2.9% - 3.7%)	3.8% (3.3% - 4.2%)	1.7% (1.4% - 2.0%)	2.0% (1.7% - 2.4%)	211,407	1,838	
Gumma	4.4% (4.0% - 4.8%)	4.5% (4.1% - 4.9%)	2.1% (1.9% - 2.4%)	2.2% (1.9% - 2.5%)	208,711	1,815	
Nara	4.0% (3.5% - 4.5%)	4.0% (3.5% - 4.4%)	2.2% (1.8% - 2.5%)	2.1% (1.8% - 2.4%)	207,181	1,802	
Okinawa	9.1% (8.3% - 9.8%)	8.1% (7.4% - 8.7%)	3.4% (2.9% - 3.9%)	2.8% (2.5% - 3.2%)	206,845	1,799	
Fukushima	3.5% (3.2% - 3.8%)	3.5% (3.2% - 3.8%)	1.8% (1.6% - 2.0%)	1.8% (1.5% - 2.0%)	204,142	1,775	
Hyogo	6.2% (5.9% - 6.5%)	5.8% (5.6% - 6.1%)	2.8% (2.6% - 3.1%)	2.6% (2.4% - 2.8%)	202,829	1,764	
Iwate	2.9% (2.6% - 3.3%)	3.3% (2.9% - 3.7%)	1.4% (1.2% - 1.7%)	1.6% (1.4% - 1.9%)	200,099	1,740	Low
Tochigi	3.4% (3.1% - 3.8%)	3.4% (3.1% - 3.7%)	1.8% (1.6% - 2.1%)	1.8% (1.6% - 2.0%)	196,225	1,706	
Nagano	3.8% (3.4% - 4.1%)	4.2% (3.9% - 4.6%)	1.7% (1.5% - 1.9%)	2.0% (1.8% - 2.3%)	194,999	1,696	
Tokyo	3.2% (3.1% - 3.3%)	3.4% (3.3% - 3.5%)	1.8% (1.7% - 1.9%)	2.0% (1.9% - 2.1%)	194,947	1,695	
Mie	4.0% (3.7% - 4.4%)	4.1% (3.8% - 4.5%)	1.8% (1.5% - 2.0%)	1.8% (1.6% - 2.1%)	194,425	1,691	
Nigata	4.0% (3.7% - 4.3%)	4.2% (3.9% - 4.5%)	2.3% (2.1% - 2.6%)	2.5% (2.2% - 2.8%)	192,820	1,677	

Yamanashi	4.3% (3.7% - 4.9%)	4.6% (4.0% - 5.2%)	2.1% (1.7% - 2.5%)	2.3% (1.9% - 2.7%)	191,488	1,665
Miyagi	4.3% (3.9% - 4.6%)	4.3% (4.0% - 4.7%)	2.2% (1.9% - 2.4%)	2.2% (2.0% - 2.5%)	191,412	1,664
Gifu	5.1% (4.7% - 5.5%)	5.5% (5.1% - 5.9%)	2.3% (2.0% - 2.6%)	2.4% (2.2% - 2.7%)	191,359	1,664
Aichi	6.9% (6.6% - 7.2%)	6.8% (6.5% - 7.0%)	3.1% (2.9% - 3.3%)	3.0% (2.8% - 3.2%)	185,712	1,615
Shizuoka	3.7% (3.5% - 4.0%)	3.8% (3.5% - 4.0%)	1.9% (1.7% - 2.0%)	1.9% (1.8% - 2.1%)	185,693	1,615
Shiga	5.8% (5.3% - 6.5%)	6.1% (5.5% - 6.6%)	2.5% (2.1% - 2.9%)	2.6% (2.2% - 3.0%)	179,995	1,565
Ibaraki	4.1% (3.8% - 4.4%)	4.0% (3.8% - 4.3%)	1.8% (1.6% - 2.0%)	1.7% (1.5% - 1.9%)	171,339	1,490
Kanagawa	4.8% (4.6% - 5.0%)	4.8% (4.6% - 5.0%)	2.2% (2.0% - 2.3%)	2.2% (2.1% - 2.3%)	160,195	1,393
Chiba	4.2% (4.0% - 4.5%)	4.1% (3.9% - 4.3%)	2.0% (1.9% - 2.2%)	1.9% (1.8% - 2.1%)	158,745	1,380
Saitama	5.1% (4.8% - 5.3%)	4.6% (4.4% - 4.8%)	2.6% (2.4% - 2.8%)	2.3% (2.2% - 2.4%)	151,272	1,315

* An exchange rate of 115 yen per US dollar was used for calculating per capita health expenditure

Appendix 3. Adjusted association between per capita health expenditure at prefecture-level and patients' health outcomes after out-of-hospital cardiac arrest, additional adjustment for per capita income at prefecture-level

1-month survival	**Overall**		**Age 1 to 59**		**Age 60 to 79**		**Age 80 to 100**	
	Adj OR (95% CI)	**P-value**	**Adj OR (95% CI)**	**P-value**	**Adj OR (95% CI)**	**P-value**	**Adj OR (95% CI)**	**P-value**
Sample size	618,154		91,108		250,705		276,341	
Tertile of prefecture-level health expenditure per capita								
Q1 (Lowest)	Ref		Ref		Ref		Ref	
Q2	1.24 (0.97 to 1.59)	0.08	1.19 (0.95 to 1.51)	0.14	1.26 (0.96 to 1.65)	0.10	1.27 (1.001 to 1.62)	0.049
Q3 (Highest)	1.24 (0.99 to 1.55)	0.06	1.24 (1.00 to 1.54)	0.055	1.21 (0.95 to 1.53)	0.13	1.30 (1.03 to 1.65)	0.03
Favorable neurological outcome at 1 month	**Adj OR (95% CI)**	**P-value**	**Adj OR (95% CI)**	**P-value**	**Adj OR (95% CI)**	**P-value**	**Adj OR (95% CI)**	**P-value**
Sample size	617,490		90,996		250,403		276,091	
Tertile of prefecture-level health expenditure per capita								
Q1 (Lowest)	Ref		Ref		Ref		Ref	
Q2	1.29 (1.002 to 1.67)	0.049	1.20 (0.91 to 1.57)	0.19	1.32 (1.004 to 1.73)	0.047	1.44 (1.13 to 1.83)	<0.01
Q3 (Highest)	1.29 (1.05 to 1.58)	0.02	1.23 (1.01 to 1.50)	0.04	1.25 (1.004 to 1.55)	0.046	1.52 (1.17 to 1.99)	<0.01

*Adjusted for age, sex, the interaction between age and sex, year indicators, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (VF or pulseless VT), witness status, CPR by bystander, use of public-access AED by bystander, and per capita income at prefecture-level.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	We used a nation-wide population-based registry of all OHCA cases resuscitated by emergency responders in Japan from January 2005 through December 2011 … We examined the association between per capita health expenditure at prefecture-level and patients' health outcomes after OHCA.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	We analyzed 618,154 OHCA cases…Each US$ 100 increase in per capita health expenditure was associated with 1.04 times higher odds of 1-month survival.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	Concerned about the rapid growth in health spending and the regional variation in health expenditure, the Japanese government is currently planning to set a target health expenditure

				level for each prefecture…These policies, which are analogous to ones proposed in other countries, are controversial because they do not take into account quality of care or health outcomes in setting their goals
Objectives	3	State specific objectives, including any prespecified hypotheses	4	First, how much variation is there in the outcomes after OHCA across 47 prefectures in Japan? Second, what is the relationship, if any, between per capita health expenditure at prefecture-level and health outcomes after OHCA? Finally, given strong policy concern that the most frugal regions may be achieving low spending by forgoing care for the oldest patients, is there any evidence that the relationship between health expenditure and health outcomes after OHCA varies by age group?
Methods				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Regional Health Expenditure and Health Outcomes after Out-of-Hospital Cardiac Arrest in Japan: An Observational Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008374.R1
Article Type:	Research
Date Submitted by the Author:	13-Jul-2015
Complete List of Authors:	Tsugawa, Yusuke; Harvard University, Interfaculty Initiative in Health Policy Hasegawa, Kohei; Massachusetts General Hospital, Emergency Medicine Hiraide, Atsushi; Kinki University Faculty of Medicine, Acute Medicine Jha, Ashish; Harvard School of Public Health, Health Policy and Management
Primary Subject Heading:	Health services research
Secondary Subject Heading:	Health services research, Health policy, Health economics, Global health
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Regional Health Expenditure and Health Outcomes after Out-of-Hospital Cardiac Arrest in Japan: An Observational Study

Yusuke Tsugawa, MD, MPH[1]; Kohei Hasegawa, MD, MPH[2]; Atsushi Hiraide, MD, PhD[3]; Ashish K. Jha, MD, MPH[4,5]

Author Affiliations:

1. Harvard Interfaculty Initiative in Health Policy, Cambridge, MA (14 Story Street 4th floor, Cambridge, MA 02138 USA)

2. Department of Emergency Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA (326 Cambridge Street, Suite 410, Boston, MA 02114 USA)

3. Department of Acute Medicine, Kinki University Faculty of Medicine, Osaka, Japan (3-4-1 Kowakae, Higashiosaka City, Osaka, Japan)

4. Department of Health Policy and Management, Harvard School of Public Health, Boston, MA (677 Huntington Avenue, Boston, MA 02115 USA)

5. Department of General Internal Medicine, Brigham and Women's Hospital and the Veterans Affairs Boston Healthcare System (75 Francis Street, Boston, MA 02115 USA)

Corresponding Author:

Yusuke Tsugawa

Harvard Interfaculty Initiative in Health Policy

E-mail: tsugawa@fas.harvard.edu

Word Count: 3,931 words

Number of References: 26

Number of Figures/Tables: 3 tables and 2 figures (6 online appendices)

ABSTRACT (296 words)

Objectives: Japan is considering policies to set target health expenditure level for each region, a policy approach that has been considered in many other countries. The objective of this study was to examine the relationship between regional health expenditure and health outcomes after out-of-hospital cardiac arrest (OHCA), which incorporates the qualities of pre-hospital, in-hospital, and post-hospital care systems.

Design: We examined the association between prefecture-level per capita health expenditure and patients' health outcomes after OHCA.

Setting: We used a nationwide, population-based registry system of OHCAs that captured all OHCA cases resuscitated by emergency responders in Japan from 2005 through 2011.

Participants: All OHCA patients aged 1-100 years were analyzed.

Outcome Measures: The patients' 1-month survival rate, and favorable neurological outcome (defined as cerebral performance category 1-2) at 1-month.

Results: Among 618,154 OHCA cases, the risk-adjusted 1-month survival rate varied from 3.3% (95% CI: 2.9%-3.7%) to 8.4% (95% CI: 7.7%-9.1%) across prefectures. The risk-adjusted probabilities of favorable neurological outcome ranged from 1.6% (95%CI: 1.4%-1.9%) to 3.7% (95%CI: 3.4%-3.9%). Compared to prefectures with lowest-tertile health expenditure, 1-month survival rate was significantly higher in medium-spending (adjusted OR 1.31, 95%CI 1.03-1.66, p=0.03) and high-spending prefectures (adjusted OR 1.30, 95%CI 1.03-1.64, p=0.02), after adjusting for patient characteristics. There was no difference in the survival between medium- and high-spending regions. We observed similar patterns for favorable neurological outcome. Additional adjustment for regional per capita income did not affect our overall findings.

Conclusions: We observed a wide variation in the health outcomes after OHCA across regions. Low-spending regions had significantly worse health outcomes compared to medium or high spending regions, but no difference was observed between medium- and high-spending regions. Our findings suggest that focusing on the median spending may be the sweet spot that allows for saving money without compromising patient outcomes.

Key words: health economics, health policy, quality in health care

STRENGTHS AND LIMITATIONS OF THIS STUDY:

1. This is the first study that examined the association between regional health spending and the patient outcomes after out-of-hospital cardiac arrest (OHCA).

2. We used a nation-wide, population-based registry system of OHCAs that captured all OHCA cases resuscitated by emergency responders in Japan

3. The outcomes after OHCA reflect a collective impact of pre-hospital, in-hospital, and post-hospital care systems, and thus they may be superior to the health outcomes used in previous studies that lean heavily on the quality of in-hospital care.

4. Our study samples included only cases for which emergency medical system was activated, resuscitation was attempted, and the patients were transferred to the hospitals.

INTRODUCTION

Concerned about the rapid growth in health spending and the regional variation in health expenditure, the Japanese government is currently considering to set a target health expenditure level for each prefecture.[1] While the specifics of this approach are not yet finalized, policymakers are considering using low-spending prefectures as potential benchmarks, or to set target health expenditure levels for each prefecture. These policies, which are analogous to ones proposed in other countries including the United States and other European countries, are controversial because many of these policies do not take into account quality of care or health outcomes in setting target health expenditure level.[2] If greater health expenditures are being used in helpful ways – in ways that improve quality and reduce poor outcomes, then policies that focus only on spending can potentially be harmful for the health of the population.

Regional variations in healthcare spending have been best studied in the United States [3 4] and the studies link expenditures with outcomes have been mixed.[5-8] Regional health spending can potentially impact a variety of health outcomes, including those at the community-level and those within institutions like hospitals. Outcomes after an out-of-hospital cardiac arrest (OHCA) is particularly salient because of three reasons: it is common (in the United States. alone, an estimated 360,000 people suffer from it annually), highly morbid (only 9.5% will survive to hospital discharge),[9] and can serve as an indicator of health system performance more broadly. Outcomes after OHCA reflect a collective impact of pre-hospital, in-hospital, and post-hospital care systems, and inadequate performance of any part of this clinical chain could negatively impact the outcomes. Therefore, it can be a useful metric to assess the association between regional health expenditure and the population's health outcomes.

Given that many countries are struggling with rapidly rising health expenditure, understanding the relationship between health expenditure and health outcomes in Japan would provide important insights for other countries to examine their own strategies vis-à-vis spending and healthcare quality and outcomes. Therefore, in this study, we sought to answer three questions. First, how much variation is there in the outcomes after OHCA across 47 prefectures in Japan? Second, what is the relationship, if any, between per capita health expenditure at prefecture-level and health outcomes after OHCA? Finally, given strong policy concern that the most frugal regions may be achieving low spending by forgoing care for the oldest patients, is there any evidence that the relationship between health expenditure and health outcomes after OHCA varies by age group?

METHODS

Study design and participants

The All-Japan Utstein registry of the Fire and Disaster Management Agency (FDMA) is a nation-wide, population-based registry system of OHCAs in infants, children, and adults, with Utstein-style data collection.[10-12] All patients who had experienced non-traumatic OHCA and for whom resuscitation was attempted by emergency medical service (EMS) personnel with subsequent transport to hospitals from January 1, 2005, to December 31, 2011, with age of 1 to 100 years, were eligible for our analysis. We excluded those with age over 100 years from our analysis because the numbers were small and differential proportion of people who do not request active life-saving procedures (i.e., those people with " Do-not-resuscitate" [DNR] orders) across prefectures can potentially confound our inferences, and age is the strongest predictor of such decisions.[13]

Data were collected prospectively with an Utstein-style data form that included age, sex, etiology of arrest, first documented cardiac rhythm, bystander's witness status, presence and type of cardiopulmonary resuscitation (CPR) by bystander, and the use of a public-access automated external defibrillator (AED). Cardiac arrest was defined as the end of cardiac mechanical activity determined by the absence of signs of circulation. The etiology of arrest was deemed cardiac unless evidence suggested trauma, respiratory diseases, cerebrovascular diseases, malignant tumors, or any other non-cardiac cause. Attribution of cardiac or non-cardiac etiology was made by the attending physicians in the emergency department in collaboration with the EMS personnel. Furthermore, the EMS personnel queried the medical control director at the hospital 1 month after the OHCA event to confirm the etiology of the arrest. If there was a disagreement on the etiology, the determination at 1-month was used. The study was approved by the Office of Human Research Administration at Harvard School of Public Health. Informed consent was deemed unnecessary by the FDMA of Japan.

Japanese healthcare system

The population of Japan was roughly 128 million in 2010, with approximately 107 million people aged 18 years or older.[14] Japan consists of 47 prefectures, which are the country's first jurisdiction and administrative division levels. The population size at each prefectures ranges from approximately 13 million in Tokyo to 600,000 in Tottori.[14] The land area and population size for each prefecture are listed in **Appendix 1**. The entire population is covered by the social health insurance system, and the prices and fees of the healthcare services are set uniformly regardless of the types and location of healthcare providers. The majority of healthcare providers are private, and the patients are free to choose which providers to visit. The coinsurance rate is fixed at 30% uniformly, except for the elderly and children.[15] The municipal governments provide emergency medical service (EMS) through 802 fire stations with dispatch centers. The details about the EMS system in Japan have been described elsewhere.[11]

Health outcomes

The primary health outcome measure was 1-month survival after OHCA. The secondary outcome was favorable neurological outcome 1 month after cardiac arrest, which was defined as Glasgow- Pittsburgh cerebral performance category 1 (good performance) or 2 (moderate disability).[10] The other categories — 3 (severe cerebral disability), 4 (vegetative state), and 5 (death) — were regarded as unfavorable neurological outcome. This is the standard approach for the studies examining the neurological outcomes after OHCA.[11]

To collect follow-up data about survival and neurological status 1 month after the OHCA event, the EMS personnel who treated each patient with OHCA queried the medical control director at the hospital. Patient neurological status was evaluated by the treating physician; the EMS received a written response. If the patient was not at the hospital, the EMS personnel conducted a follow-up search. Data forms were completed by EMS personnel in conjunction with the physicians who treated the patients, and the data were integrated into the Utstein registry system on the FDMA database server. Several regions developed additional local registry systems. In these areas, the information on each OHCA case was initially assembled using their data collection system. Then, the information were exported and integrated into the FDMA database in which the data underwent further review. Forms were logic-checked by the computer system and were confirmed by the FDMA. If the data form was incomplete, the FDMA returned it to the respective fire station and the missing data were obtained.

Per capita total health expenditure

The information about annual total health expenditure per capita for each prefecture was extracted from the database created by Ministry of Health, Labour and Welfare of Japan.[16] The population data were available from Statistic Bureau, Ministry of Internal Affairs and Communications.[17] The total health expenditure was defined as the sum of inpatient and outpatient care, not including the expenditures due to dental care. Per capita total health expenditure was calculated by dividing total health expenditure by the number of population for each prefecture during the study period (from January 2005 through December 2011). An exchange rate of 115 yen per US dollar was used for the analyses of health expenditure (as of November 11, 2014).

Adjustment variables

To account for differences in population characteristics across prefectures, we adjusted for demographic, clinical, and response characteristics of the OHCA patients. Demographic characteristics included age in 5-year increments (from ≥1 year of age to 4, 5 to 9, and so on through 95 to 100), sex, and the interaction between age and sex. Clinical characteristics consisted of etiology of arrest (cardiac vs. non-cardiac) and first documented rhythm (ventricular fibrillation/pulseless ventricular tachycardia vs. other). The response characteristics included witnessed status (no witness, witnesses by layperson, witness by healthcare provider), type of bystander CPR (no bystander CPR, compression-only CPR, conventional CPR), and the use of a public-access AED by bystander (yes/no). We did not include the regional characteristics, such as EMS response time (which can be a proxy for a number of hospitals in a given region), because they are in the causal pathway linking the regional health spending and the health outcomes of patients.

Statistical analysis

We used these data to generate adjusted average values of each outcome in each prefecture. We pooled seven years of data (2005 to 2011) and performed a person-level logistic regression for health outcomes. Each regression model included prefecture indicator variables, year indicators, and the patient-level risk-adjustment variables listed above. The performance of the risk-adjustment model was evaluated using C-statistics (the prefecture indicators were excluded from the analysis when the C-statistics were calculated).[18] The risk-adjustment was performed by calculating the predicted probabilities of outcomes for each patient using the regression equation with the distribution of covariates in our sample and the prefecture indicator imposed to that of a specific prefecture, and repeating the calculation across all 47 prefectures (also known as model-adjusted means, predictive margins, or g-formula).[19 20] Standard errors of the estimates were obtained by the delta method, and were used to calculate the 95% confidence intervals (CIs).[19] Conceptually, this is equivalent to simulating the potential outcomes (counterfactuals) if all individuals with OHCA in our sample took place in a given prefecture and were treated there.

We evaluated the association between prefecture's per capita health expenditure and patients' health outcomes after OHCA. The prefectures were classified into three equal sized groups (tertile) based on per capita health expenditure in order to address a potential non-linear relationship between per capita health expenditure and health outcomes after OHCA (defined as low-, medium-, and high-spending prefectures). In addition, we used per capita health expenditure as a continuous variable assuming a linear relationship between health expenditure and (log-odds of) health outcomes after OHCA. We used the person-level data for our analysis in order to avoid ecological fallacy.[21] In order to account for the potential clustering of OHCA cases within each prefecture, we used generalized estimating equations (GEE) with binomial distribution, logit-link, and an independent correlation structure.[22-24] We used GEE instead of the mixed effects models (also known as hierarchical models or multilevel models), because we were interested in the population average effects (estimated by GEE) rather than the subset-specific (individual-specific) effects (estimated by mixed effects models).[25] The regression models were adjusted for the year indicators, age, sex, the interaction between age and sex, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (ventricular fibrillation [VF] or pulseless ventricular tachycardia [VT]), witness status, CPR by bystander, and use of public-access AED by bystander.

To evaluate the possibility that low-spending regions forgo spending on specific subpopulation, such as the oldest-old population, we also examined the association between health spending and OHCA outcomes across 3 age groups: age 1 to 59, 60 to 79, and 80 to 100. We fitted the same regression model as described above. We also fitted regression models with the interaction term between health expenditure and age group, and formally examined if the impact of health expenditure on outcomes after OHCA differs by age using likelihood ratio test. We conducted a set of sensitivity analyses. First, we added the per capita income at prefecture-level in 2011 (data extracted from Japan Statistical Yearbook [26]) to the list of risk-adjustment variables in our regression models, as a measure of the socio-economic status (SES) of the population. We did not include this variable in our primary analyses because the SES is a major determinant of access to healthcare and poor access to care is likely a mediator for the relationship between spending and patient outcomes. Second, in order to evaluate if there is a plateau in the effect of regional health expenditure on health outcomes, we reanalyzed the data using quintile of health expenditure instead of tertile. We also examined the association between regional health expenditure and the rate of return of spontaneous circulation (ROSC). Given that the rate of ROSC is a marker of the quality pre-hospital care, we aimed to investigate whether the difference in health outcomes across regions stem from quality of pre-hospital care versus in- and post-hospital care systems. A two-sided p value < 0.05 was considered statistically significant. The GEE analysis was conducted using SAS, version 9.3 (SAS Institute, Cary, NC), and all other analyses were performed using Stata, version 12 (Stata-Corp, College Station, Texas).

RESULTS

Patient characteristics

In the total catchment population of 128 million, 797,422 OHCAs were reported from January 1, 2005 through December 31, 2011. From these 145,829 cases were excluded due to traumatic causes; 9,657 cases were excluded as no resuscitation was attempted; and 6,218 cases were excluded as patients' age was less than 1 or higher than 100 years. Out of remaining OHCA cases, 17,547 cases with missing data on one of the covariates were excluded. Finally, 664 arrests were excluded from the analysis of the rate of favorable neurological outcome due to missing outcome data, leaving us the final sample size of 618,154 OHCA cases for the analysis of 1-month survival rate and 617,490 cases for the analysis of favorable neurological outcome (**Appendix 2**). Median age was 78 (IQR: 67-85), and 57.9% were men. Approximately two-thirds were due to cardiac causes, and VF or pulseless VT was observed as initial cardiac rhythm in 8.7% of the cases. Demographic, clinical, and response characteristics of our sample, stratified by prefecture-level health expenditure, are presented in **Table 1**.

Table 1. Baseline characteristics of patients with out-of-hospital cardiac arrest, by prefecture-level per capita health expenditure.

	Low-spending prefectures	Medium-spending prefectures	High-spending prefectures	P-value
Number of patients	332,213 (53.7%)	155,077 (25.1%)	130,864 (21.2%)	
Demographic characteristics				
Age, median (IQR), y	78 (67-85)	78 (67-85)	78 (67-85)	<0.01
Male sex	58.1%	57.4%	58.0%	<0.01
Clinical characteristics				
Etiology of arrest				<0.01
Non-cardiac	32.8%	27.9%	36.4%	
Cardiac	67.2%	72.1%	63.6%	
VF or pulseless VT as initial cardiac rhythm	8.3%	8.9%	9.3%	<0.01
Response characteristics				
Type of bystander-witness status				<0.01
No witness	58.2%	56.7%	58.5%	
Layperson	33.3%	34.2%	32.9%	
Healthcare provider	8.5%	9.1%	8.6%	
CPR by bystander				<0.01

No bystander CPR	62.1%	57.8%	58.6%	
Compression-only CPR	26.7%	28.2%	28.4%	
Conventional CPR	11.2%	13.9%	13.0%	
Use of public-access AED by bystander	0.7%	0.6%	0.6%	<0.01
Prefecture-level characteristics				
Per capita income (US$)	25,343 (3,901)	21,827 (2,674)	22,764 (1,923)	<0.01

Samples are those cases with no missing data on all variables used in the regression analysis. Data are expressed as n (%) for categorical variables and mean (SD) for continuous variable, unless otherwise indicated. P-values are calculated using chi-square test for categorical variables and ANOVA for continuous variables. CPR denotes cardiopulmonary resuscitation; and VT and VF denote ventricular tachycardia and ventricular fibrillation respectively. Conventional CPR consists of chest compression and rescue breathing.

Regional variation in patients' health outcomes after OHCA

Figures 1 and **Appendix 3** show the variation in risk-adjusted outcomes of OHCA across prefectures. The C-statistics (area under the ROC curve) were 0.81 for the risk-adjustment model for 1-month survival rate and 0.88 for that for the favorable neurological outcome, indicating good discriminating power of the models.[18] The risk-adjusted 1-month survival rate ranged from 3.3% (95%CI: 2.9%-3.7%) in Iwate prefecture to 8.4% (95%CI: 7.7%-9.1%) in Toyama prefecture. Tokyo (the most populated prefecture in Japan) was the prefecture with one of the poorest risk-adjusted survival rate of 3.4% (95%CI: 3.3%-3.5%), whereas Osaka (the most populated prefecture in western Japan) exhibited one of the higher survival rate of 6.6% (95%CI: 6.4%-6.9%).

The risk-adjusted probability of favorable neurological outcome varied from 1.6% (95%CI: 1.4%-1.9%) in Iwate prefecture to 3.7% (95%CI: 3.4%-3.9%) in Fukuoka prefecture. Tokyo was again one of the poor-outcome prefectures with 2.0% (95%CI: 1.9%-2.1%) chance of experiencing good neurological outcome. In contrast, Osaka was one of the best with 3.5% (95%CI: 3.3%-3.7%) chance of favorable neurological outcome. Per capita health expenditure in 2005-2011 varied from US$ 2,504 (¥287,925 JPY) per year in Kochi prefecture to US$ 1,315 (¥151,272) per year in Saitama prefecture.

Association between prefecture-level health expenditure and patient health outcomes after OHCA

The relationships between prefecture's per capita health expenditure and the risk-adjusted health outcomes after OHCA aggregated at prefecture-level are shown in **Figure 2**.The association between per capita health expenditure at prefecture and patient-level outcomes after OHCA is presented in **Table 2**. We found that higher per capita health expenditure at the prefecture was associated with significantly better health outcomes after OHCA. For every US$ 100 increase in per capita health expenditure at prefecture, the OHCA patients exhibited 1.04 times higher odds of survival at 1 month (95%CI 1.01-1.07, $p<0.01$), and 1.04 times higher odds of favorable neurological outcome (95%CI 1.02-1.07, $p<0.01$), after adjusting for patients' risks (data not shown).

Table 2. Association between per capita health expenditure at prefecture-level and patients' health outcomes after out-of-hospital cardiac arrest.

1-month survival rate		**Unadjusted (N=635,710)**		**Adjusted* (N=618,154)**	
		OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Tertile of prefecture-level health expenditure per capita	**Low**	Ref		Ref	
	Medium	1.31 (1.02-1.67)	0.03	1.31 (1.03-1.66)	0.03
	High	1.30 (1.04-1.62)	0.02	1.30 (1.03-1.64)	0.02
Favorable neurological outcome at 1 month		**Unadjusted (N=635,046)**		**Adjusted* (N=617,490)**	
		OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Tertile of prefecture-level health expenditure per capita	**Low**	Ref		Ref	
	Medium	1.30 (1.02-1.67)	0.04	1.29 (1.03-1.62)	0.03
	High	1.26 (1.04-1.53)	0.02	1.28 (1.06-1.55)	0.01

*Adjusted for age, sex, the interaction between age and sex, year indicators, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (VF or pulseless VT), witness status, CPR by bystander, and use of public-access AED by bystander.

The crude mean survival rate at 1 month after OHCA was 4.4% (95%CI: 4.3%-4.4%) in low-spending prefectures, 5.7% (95%CI: 5.5%-5.8%) in medium-spending prefectures, and 5.6% (95%CI: 5.5%-5.7%) in high-spending prefectures. The unadjusted probabilities of favorable neurological outcome after OHCA was 2.1% (95%CI: 2.1%-2.2%) in low-spending prefectures, 2.8% (95%CI: 2.7%-2.9%) in medium-spending prefectures, and 2.7% (95%CI: 2.6%-2.8%) in high-spending prefectures. Similar to the results of the linear regression analysis, compared to OHCA cases in the prefectures with lowest-tertile health expenditure, those in the medium-spending and high-spending prefectures exhibited significantly higher survival rates (**Table 2**). The 1-month survival rate was 1.31 times higher odds (95%CI: 1.03-1.66, p=0.03) in medium-spending prefectures, and 1.30 times higher odds (95%CI: 1.03-1.64, p=0.02) in highest-spending prefectures, compared to lowest-spending prefectures. Likewise, the odds of favorable neurological outcome was 1.29 times higher (95%CI: 1.03-1.62, p=0.03) in medium-spending prefectures, and 1.28 times higher (95%CI: 1.06-1.55, p=0.01) in high-spending prefectures. We did not observe significant difference in health outcomes between OHCA cases in medium-spending and those in high-spending prefectures (data not shown). Additional adjustment for the prefecture-level per capita income-level did not qualitatively affect our overall findings (**Appendix 4**). Both medium- and high-spending regions had higher probabilities of favorable neurological outcomes and better survival compared to low-spending regions, although some of these differences were no longer statistically significant (even though the effect sizes were similar). The analysis using the quintile of regional health expenditure showed a positive association between regional spending and outcomes after OHCA; however, we did not observe a clear plateau effect in the relationship between regional health expenditure and health outcomes, probably due to the lack of statistical power to precisely make estimates (**Appendix 5**). We did not observe significant relationship between regional health expenditure and the rate of ROSC, suggesting that low-spending regions had worse health outcomes mainly due to lower quality of in- and post-hospital care systems rather than that of pre-hospital care (**Appendix 5**).

Relationships between health expenditure and OHCA outcomes across different age groups

We found that the relationships between health expenditure and OHCA outcomes were consistent across all 3 age groups (**Table 3**). Compared to low-spending prefectures, both medium- and high-spending prefectures showed higher 1-month survival rates and higher probabilities of favorable neurological outcomes after OHCA. Although the statistical power is limited in a small number of metrics, we still observed higher odds of better OHCA outcomes in these prefectures. We observed a trend toward stronger relationship among OHCA patients aged 80 to 100, compared to younger age groups; however, the results of the likelihood ratio test did not show statistically significant interaction between age group and health expenditure (p=0.30 for survival and p=0.36 for favorable neurological outcome).

Table 3. Adjusted association between per capita health expenditure at prefecture-level and patients' health outcomes after out-of-hospital cardiac arrest, stratified by age group*

1-month survival rate		**Age 1 to 59 (N=91,108)**		**Age 60 to 79 (N=250,705)**		**Age 80 to 100 (N=276,341)**	
		Adjusted OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Tertile of prefecture-level health expenditure per capita	**Low**	Ref		Ref		Ref	
	Medium	1.25 (1.01-1.55)	0.04	1.32 (1.01-1.71)	0.04	1.37 (1.07-1.74)	0.01
	High	1.29 (1.05-1.60)	0.02	1.26 (0.99-1.61)	0.06	1.39 (1.09-1.78)	<0.01
Favorable neurological outcome at 1 month		**Age 1 to 59 (N=90,996)**		**Age 60 to 79 (N=250,403)**		**Age 80 to 100 (N=276,091)**	
		Adjusted OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Tertile of prefecture-level health expenditure per capita	**Low**	Ref		Ref		Ref	
	Medium	1.24 (0.98-1.57)	0.07	1.30 (1.02-1.66)	0.04	1.37 (1.10-1.70)	<0.01
	High	1.27 (1.05-1.54)	0.01	1.23 (1.01-1.50)	0.04	1.46 (1.14-1.86)	<0.01

*Adjusted for age, sex, the interaction between age and sex, year indicators, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (VF or pulseless VT), witness status, CPR by bystander, and use of public-access AED by bystander.

DISCUSSION

In the national study of patients with OHCA in Japan, we found more than a two-fold variation in health outcomes after OHCA across prefectures. Our results showed that low-spending regions had significantly worse health outcomes after OHCA, compared to medium- or high-spending regions; however, the health outcomes of the high-spending regions were not better than that of the medium-spending regions. These relationships appeared to be stronger among the oldest age group (age 80 to 100) compared to younger age groups, although the formal interaction test was not statistically significant. These findings suggest that any policy interventions targeted towards health care costs alone and not taking into account health outcomes may have detrimental effect on the population health, especially among the oldest.

While we found the positive association between regional health expenditure and health outcome after OHCA, the relationship was not linear. Low-spending prefectures exhibited worse health outcomes, but the health outcomes in high-spending prefectures were not better than that in medium-spending prefectures. This has two important policy implications. Setting target to lowest group is not likely to be beneficial for the health of the population. But spending at high end might not generate value either. Our findings indicate that spending medium level of health expenditure can potentially rein in health care costs without compromising health outcomes of the population.

We are unaware of any prior study that has studied the relationship between health spending and outcomes after OHCA. Fisher and colleagues studied the relationship between regional health spending and mortality rate among Medicare enrollees hospitalized for 3 common conditions in the US.[6] They found that higher regional spending was associated with slightly higher risk of death for colorectal cancer and acute myocardial infarction (AMI), but had no impact on the mortality among hip fracture patients. Baicker and Chandra conducted a state-level analysis and reported that states with higher Medicare spending had lower quality of care, using process measures for treatment of six common conditions (AMI, breast cancer, diabetes, heart failure, pneumonia, and stroke).[7] These studies lean heavily on the quality of in-hospital care, in contrast to the outcomes after OHCA which are affected by a quality of pre-hospital, in-hospital, and post-hospital care, collectively.

Even though there is no single health outcome metric that can comprehensively measure the performance of the regional health system, the OHCA outcomes have several advantages over other health outcomes. The health outcomes after OHCA reflect a broader performance of regional health system including pre-hospital (immediate recognition of cardiac arrest and activation of the emergency response system, early CPR, and rapid defibrillation), in-hospital (integrated post-cardiac arrest care), and post-hospital care systems (rehabilitation). As a consequence, the study of OHCA outcomes enabled us to evaluate a composite performance of different aspects of health care delivery system. In addition, by focusing on both mortality and neurological outcome, we could evaluate not only the quality of services to keep patients alive, but also the quality of care that help the clinically recover, which indeed is the ultimate goal of the health system for treating patients with OHCA. We found that regional health expenditure did not have significant impact on the rate of ROSC, which indicates that lower regional spending had detrimental effect on the outcomes after OHCA through lower quality of in- and post-hospital care systems, rather than that of pre-hospital care.

Our study has several limitations. First, we could not assess why low spending regions had worse outcomes – whether it reflected lower investment in pre-hospital care – or lower quality care once patients arrived at the hospital. This is an important area for examination in future work. A second limitation is that our study samples included only cases for which emergency medical system was activated, resuscitation was attempted, and the patients were transferred to the hospitals. Different prefectures may have different criteria whether the OHCA patients with low probabilities of survival to be pronounced dead at the scene and not being transferred to hospitals. Similarly, the study population may include individuals who do not wish life-saving treatment (e.g., individuals with DNR orders) such as those with advance age, disabilities, or late-stage cancer patients. It is also possible that the likelihood of making DNR orders is influenced by local norms and thus differs across prefectures. Third, the outcomes after OHCA may not capture the quality of outpatient care. Further research is warranted to evaluate if higher regional health spending leads to better quality of outpatient care. Lastly, the integrity and validity of the data, and ascertainment bias, are potential source of bias. The use of uniform data collection based on Utstein-style guidelines for reporting and recording the cardiac arrest cases, the large sample size, and the population-based design are expected to minimize these potential threats to validity.

In conclusion, we found more than two-fold variations in OHCA outcomes across prefectures in Japan. We observed a non-linear relationship between regional health spending and patients' outcomes after OHCA. Low-spending regions had significantly worse health outcomes, but the health outcomes in high-spending regions were not better than that in medium-spending regions. Our findings indicate that setting target to lowest-spending group may be harmful in terms of health outcomes, especially for emergency cases such as out-of-hospital cardiac arrest. The fact that spending at high end does not appear to generate additional value suggest that for national policymakers in countries who wish to set budget targets, focusing on the median spending may be the sweet spot that allows for saving money without compromising patient outcomes.

FIGURE LEGENDS

Figure 1. Risk-adjusted 1-month survival (A) and favorable neurological outcome (B) after out-of-hospital cardiac arrest across prefectures. 95% confidence intervals are shown in bars.

Figure 2. Association between total health expenditure per capita and risk-adjusted health survival (A) and favorable neurological outcome (B) after out-of-hospital cardiac arrest at prefecture-level.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

Dr. Tsugawa had full access to all of data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tsugawa, Jha, Hasegawa

Acquisition of data: Hasegawa, Hiraide

Analysis and interpretation of data: Tsugawa, Jha

Drafting of the manuscript: Tsugawa, Jha

Critical revision of the manuscript for important intellectual content: Tsugawa, Jha, Hasegawa, Hiraide

Statistical analysis: Tsugawa

Administrative, technical, or material support: Tsugawa, Jha, Hiraide

DATA SHARING

The dataset is not publicly available. Please contact the authors for the statistical code and the dataset.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1. Curbing health expenditure, tackling high hospitalization costs, as large as 2.1 times difference in health expenditure between prefectures (in Japanese). *Nihon Keizai Shinbun* 2014 August 12.

2. Ministry of Health Labour and Welfare. Regional variation of health expenditure in Japan (in Japanese). Secondary Regional variation of health expenditure in Japan (in Japanese) 2012. http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/database/iryomap/index.html.

3. Chassin MR, Brook RH, Park RE, et al. Variations in the use of medical and surgical services by the Medicare population. N Engl J Med 1986;**314**(5):285-90.

4. Wennberg J, Gittelsohn. Small area variations in health care delivery. Science 1973;**182**(4117):1102-8.

5. Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 1: the content, quality, and accessibility of care. Ann Intern Med 2003;**138**(4):273-87 doi: 10.7326/0003-4819-138-4-200302180-00006 [published Online First: 15 February 2003].

6. Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. Ann Intern Med 2003;**138**(4):288-98 doi: 10.7326/0003-4819-138-4-200302180-00006 [published Online First: 15

February 2003].

7. Baicker K, Chandra A. Medicare spending, the physician workforce, and beneficiaries' quality of care. Health Aff (Millwood) 2004;**Suppl Web Exclusives**:W4-184-97. doi: 10.1377/hlthaff.w4.184 [published Online First: 29 September 2004].

8. Landrum MB, Meara ER, Chandra A, et al. Is spending more always wasteful? The appropriateness of care and outcomes among colorectal cancer patients. Health Aff (Millwood) 2008;**27**(1):159-68. doi: 10.1377/hlthaff.27.1.159 [published Online First: 9 January 2008].

9. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 2013;**127**(1):e6-e245. doi: 10.1161/CIR.0b013e31828124ad [published Online First: 15 December 2012].

10. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). Circulation 2004;**110**(21):3385-97. doi: 10.1161/01.CIR.0000147236.85306.15 [published Online First: 24 November 2004].

11. Hasegawa K, Hiraide A, Chang Y, et al. Association of prehospital advanced airway management with neurologic outcome and survival in patients with out-of-hospital cardiac arrest. JAMA 2013;**309**(3):257-66 doi: 10.1001/jama.2012.187612 [published Online First: 16 January 2013].

12. Hasegawa K, Tsugawa Y, Camargo CA, Jr., et al. Regional variability in survival outcomes of out-of-hospital cardiac arrest: the All-Japan Utstein Registry. Resuscitation 2013;**84**(8):1099-107 doi: 10.1016/j.resuscitation.2013.03.007 [published Online First: 19 March 2013].

13. Messinger-Rapport BJ, Kamel HK. Predictors of do not resuscitate orders in the nursing home. Journal of the American Medical Directors Association 2005;**6**(1):18-21. doi: http://dx.doi.org/10.1016/j.jamda.2004.12.006.

14. Ministry of Internal Affairs and Communications. Population data by prefecture. Secondary Population data by prefecture. http://www.e-stat.go.jp/SG1/estat/List.do?bid=000001039703.

15. Ikegami N, Yoo B-K, Hashimoto H, et al. Japanese universal health coverage: evolution, achievements, and challenges. The Lancet 2011;**378**(9796):1106-15. doi: 10.1016/S0140-6736(11)60828-3 [published Online First: 30 August 2011].

16. Ministry of Health Labour and Welfare. Health expenditure database. Secondary Health expenditure database. http://www.mhlw.go.jp/bunya/iryouhoken/iryouhoken03/01.html.

17. Ministry of Internal Affairs and Communications. e-Stat: Portal Site of

Official Statistics of Japan. Secondary e-Stat: Portal Site of Official Statistics of Japan. http://www.e-stat.go.jp/SG1/estat/eStatTopPortalE.do.

18. Aylin P, Bottle A, Majeed A. Use of administrative data or clinical databases as predictors of risk of death in hospital: comparison of models. BMJ 2007;**334**(7602):1044. doi: 10.1136/bmj.39168.496366.55 [published Online First: 17 May 2007].

19. Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. Stata Journal 2012;**12**(2):308.

20. Zhang Y, Baik SH, Fendrick AM, et al. Comparing local and regional variation in health care spending. N Engl J Med 2012;**367**(18):1724-31. doi: 10.1056/NEJMsa1203980 [published Online First: 2 November 2012].

21. Robinson WS. Ecological correlations and the behavior of individuals. American Sociological Review 1950;**15**(3):351–57.

22. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;**73**(1):13-22.

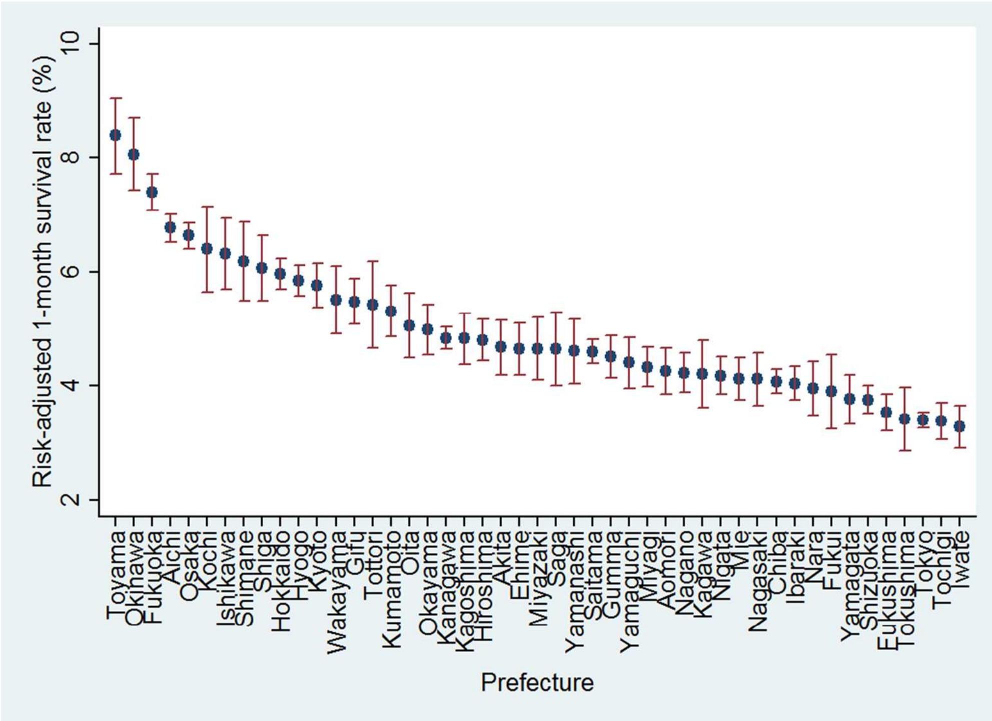
23. Hanley JA, Negassa A, Edwardes MD, et al. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol 2003;**157**(4):364-75. doi: 10.1093/aje/kwf215 [published Online First: 13 February 2003].

24. Panageas KS, Schrag D, Riedel E, et al. The effect of clustering of outcomes on the association of procedure volume and surgical outcomes. Ann Intern Med 2003;**139**(8):658-65. doi: 10.7326/0003-4819-139-8-200310210-00009 [published Online First: 21

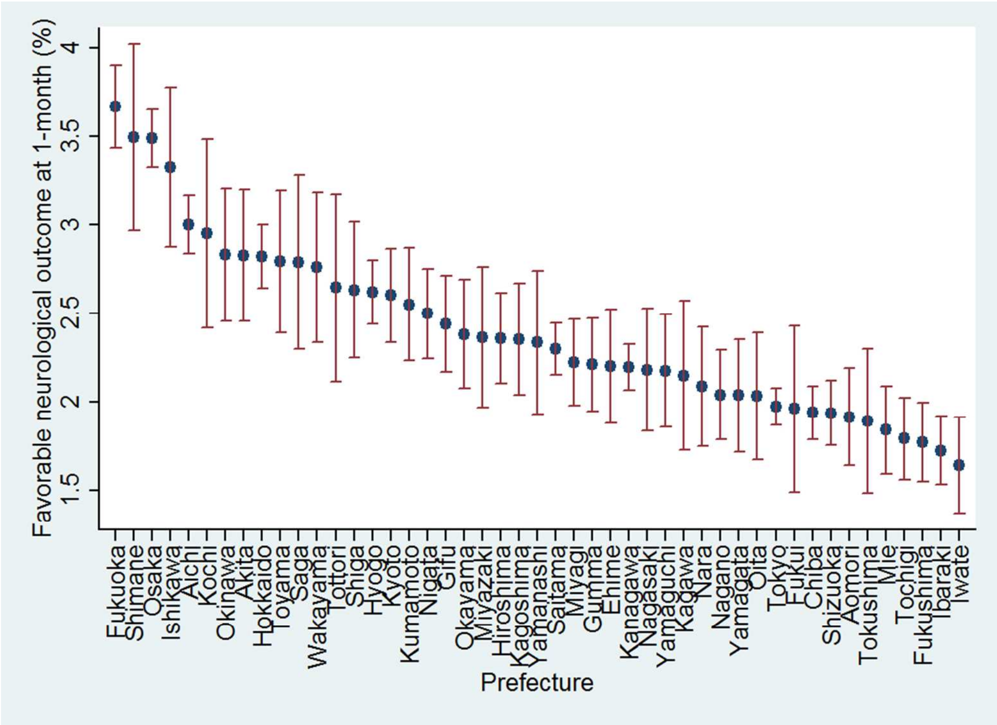
October 2003].

25. Hu FB, Goldberg J, Hedeker D, et al. Comparison of population-averaged and subject-specific approaches for analyzing repeated binary outcomes. Am J Epidemiol 1998;**147**(7):694-703 [published Online First: 29 April 1998].

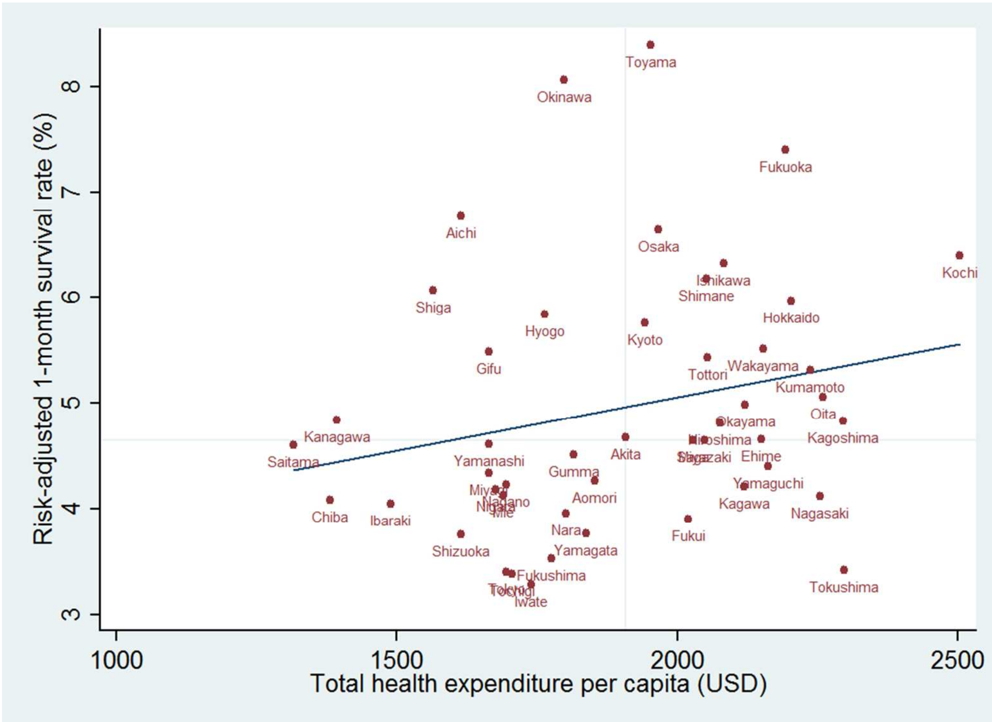
26. Statistics Bureau MoIAaC. Prefectural accounts: Economic growth rate and prefectural income per capita. Japan Statistical Yearbook 2015. Tokyo, Japan, 2015.



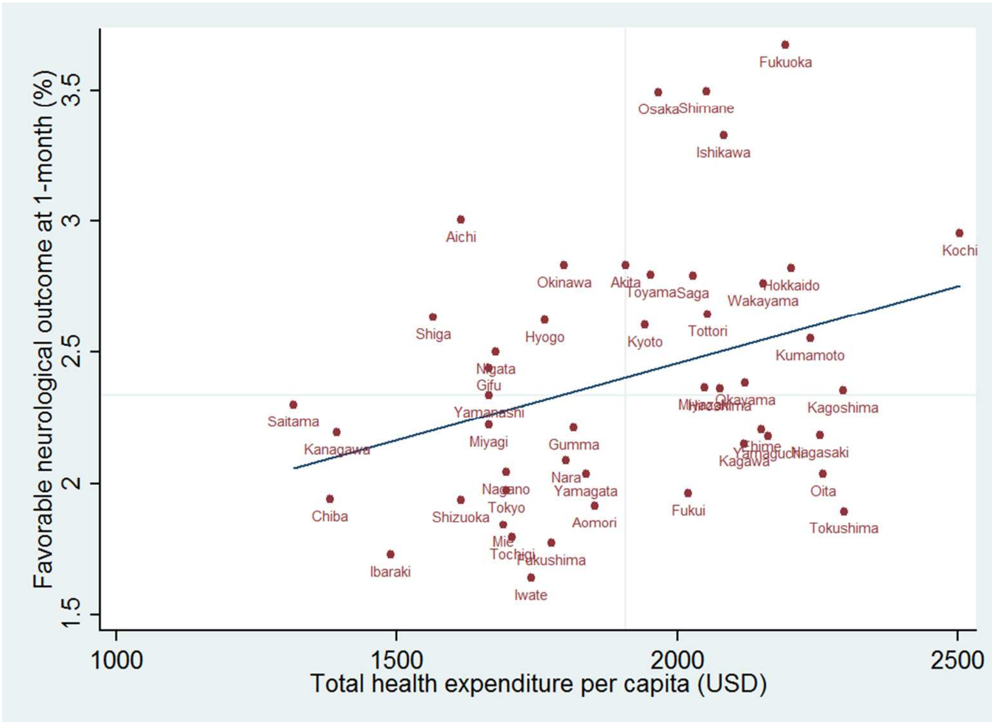
Risk-adjusted 1-month survival after out-of-hospital cardiac arrest across prefectures.
366x266mm (72 x 72 DPI)



Favorable neurological outcome after out-of-hospital cardiac arrest across prefectures.
366x266mm (72 x 72 DPI)



Association between total health expenditure per capita and risk-adjusted health survival after out-of-hospital cardiac arrest at prefecture-level.
366x266mm (72 x 72 DPI)



Association between total health expenditure per capita and favorable neurological outcome after out-of-hospital cardiac arrest at prefecture-level.
366x266mm (72 x 72 DPI)

Appendix 1. Population size, land area and population density by prefecture in Japan

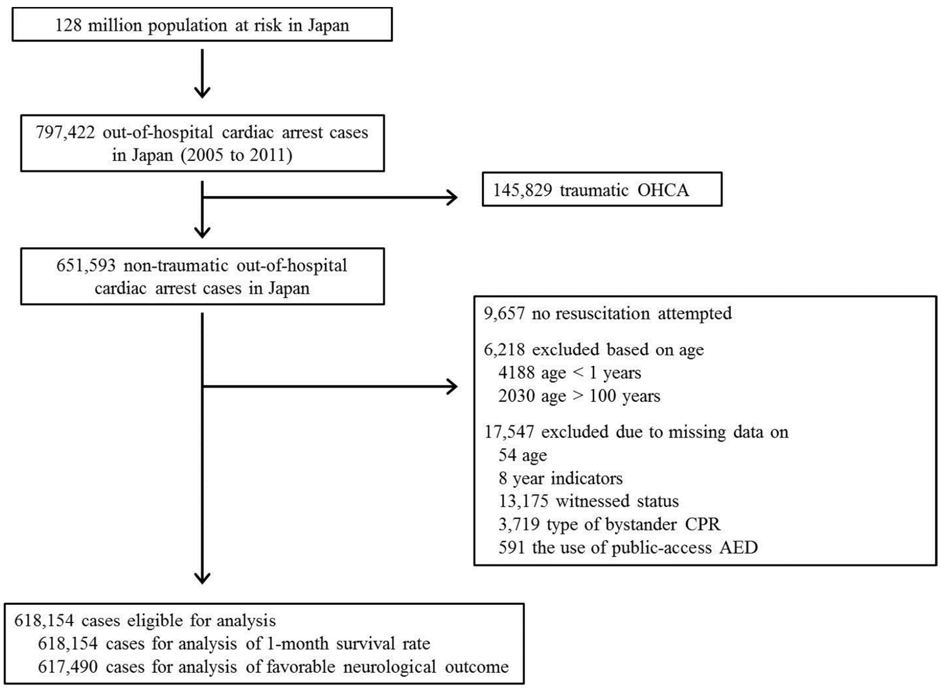
	Population in 2010 (thousand persons)	Land area (km^2)	Population density ($person/km^2$)
Japan	128,057	377,972	338.8
Hokkaido	5,506	83,424	66.0
Aomori	1,373	9,645	142.3
Iwate	1,330	15,275	87.1
Miyagi	2,348	7,282	322.4
Akita	1,086	11,638	93.3
Yamagata	1,169	9,323	125.4
Fukushima	2,029	13,784	147.2
Ibaraki	2,970	6,097	487.1
Tochigi	2,008	6,408	313.4
Gumma	2,008	6,362	315.6
Saitama	7,195	3,798	1894.5
Chiba	6,216	5,158	1205.2
Tokyo	13,159	2,191	6006.2
Kanagawa	9,048	2,416	3745.3
Niigata	2,374	12,584	188.7
Toyama	1,093	4,248	257.3
Ishikawa	1,170	4,186	279.5
Fukui	806	4,190	192.3
Yamanashi	863	4,465	193.3
Nagano	2,152	13,562	158.7
Gifu	2,081	10,621	195.9
Shizuoka	3,765	7,779	484.0
Aichi	7,411	5,172	1432.8
Mie	1,855	5,774	321.2
Shiga	1,411	4,017	351.2
Kyoto-fu	2,636	4,612	571.5
Osaka-fu	8,865	1,905	4653.6
Hyogo	5,588	8,401	665.2
Nara	1,401	3,691	379.6
Wakayama	1,002	4,725	212.1
Tottori	589	3,507	167.9
Shimane	717	6,708	106.9
Okayama	1,945	7,115	273.4
Hiroshima	2,861	8,479	337.4
Yamaguchi	1,451	6,112	237.4

Tokushima	785	4,147	189.3
Kagawa	996	1,877	530.7
Ehime	1,431	5,676	252.1
Kochi	764	7,104	107.5
Fukuoka	5,072	4,986	1017.2
Saga	850	2,441	348.3
Nagasaki	1,427	4,132	345.3
Kumamoto	1,817	7,409	245.2
Oita	1,197	6,341	188.8
Miyazaki	1,135	7,735	146.7
Kagoshima	1,706	9,188	185.7
Okinawa	1,393	2,281	610.7

Formatted: Line spacing: Double

Appendix 2~~1~~. Study participants selection.

Formatted: Font: 12 pt, Expanded by 1 pt
Formatted: Line spacing: Double
Formatted: Font: 12 pt, Expanded by 1 pt



Appendix ~~2~~3. Health outcomes after out-of-hospital cardiac arrest and per capita total health expenditure by prefecture

Formatted: Font: 12 pt, Expanded by 1 pt

Formatted: Line spacing: Double

Prefecture	Survival rate at 1 month (95%CI)		Neurologically favorable outcome (95%CI)		Annual health expenditure per capita		
	Unadjusted	Adjusted	Unadjusted	Adjusted	JPY	USD	Tertile
Kochi	5.9% (5.1% - 6.7%)	6.4% (5.6% - 7.2%)	2.5% (2.0% - 3.0%)	3.0% (2.4% - 3.5%)	287,925	2,504	High
Tokushima	3.8% (3.2% - 4.5%)	3.4% (2.9% - 4.0%)	2.2% (1.7% - 2.6%)	1.9% (1.5% - 2.3%)	264,169	2,297	
Kagoshima	4.7% (4.2% - 5.2%)	4.8% (4.4% - 5.3%)	2.3% (1.9% - 2.6%)	2.4% (2.0% - 2.7%)	264,055	2,296	
Oita	5.3% (4.7% - 5.9%)	5.1% (4.5% - 5.6%)	2.2% (1.7% - 2.6%)	2.0% (1.7% - 2.4%)	259,836	2,259	
Nagasaki	4.2% (3.7% - 4.7%)	4.1% (3.6% - 4.6%)	2.2% (1.8% - 2.5%)	2.2% (1.8% - 2.5%)	259,250	2,254	
Kumamoto	5.3% (4.8% - 5.7%)	5.3% (4.9% - 5.8%)	2.5% (2.2% - 2.9%)	2.6% (2.2% - 2.9%)	257,367	2,238	
Hokkaido	6.2% (5.9% - 6.5%)	6.0% (5.7% - 6.2%)	3.0% (2.8% - 3.2%)	2.8% (2.6% - 3.0%)	253,361	2,203	
Fukuoka	7.7% (7.3% - 8.0%)	7.4% (7.1% - 7.7%)	3.8% (3.5% - 4.0%)	3.7% (3.4% - 3.9%)	252,144	2,193	
Yamaguchi	4.5% (4.0% - 5.0%)	4.4% (4.0% - 4.9%)	2.2% (1.9% - 2.6%)	2.2% (1.9% - 2.5%)	248,632	2,162	
Wakayama	5.2% (4.6% - 5.8%)	5.5% (4.9% - 6.1%)	2.5% (2.1% - 2.9%)	2.8% (2.3% - 3.2%)	247,759	2,154	
Ehime	4.4% (3.9% - 4.9%)	4.7% (4.2% - 5.1%)	2.0% (1.7% - 2.4%)	2.2% (1.9% - 2.5%)	247,342	2,151	
Okayama	4.8% (4.4% - 5.2%)	5.0% (4.6% - 5.4%)	2.2% (1.9% - 2.5%)	2.4% (2.1% - 2.7%)	243,946	2,121	
Kagawa	3.9% (3.3% - 4.5%)	4.2% (3.6% - 4.8%)	2.0% (1.6% - 2.4%)	2.1% (1.7% - 2.6%)	243,645	2,119	
Ishikawa	6.7% (6.0% - 7.4%)	6.3% (5.7% - 7.0%)	3.6% (3.1% - 4.1%)	3.3% (2.9% - 3.8%)	239,565	2,083	
Hiroshima	5.1% (4.7% - 5.5%)	4.8% (4.4% - 5.2%)	2.5% (2.2% - 2.8%)	2.4% (2.1% - 2.6%)	238,875	2,077	
Tottori	5.3% (4.5% - 6.1%)	5.4% (4.7% - 6.2%)	2.6% (2.0% - 3.1%)	2.6% (2.1% - 3.2%)	236,214	2,054	Medium
Shimane	5.8% (5.1% - 6.5%)	6.2% (5.5% - 6.9%)	3.1% (2.6% - 3.7%)	3.5% (3.0% - 4.0%)	235,968	2,052	
Miyazaki	4.6% (4.0% - 5.2%)	4.7% (4.1% - 5.2%)	2.3% (1.9% - 2.7%)	2.4% (2.0% - 2.8%)	235,709	2,050	
Saga	4.7% (4.0% - 5.4%)	4.6% (4.0% - 5.3%)	2.8% (2.3% - 3.3%)	2.8% (2.3% - 3.3%)	233,157	2,027	
Fukui	3.5% (2.9% - 4.1%)	3.9% (3.3% - 4.6%)	1.7% (1.2% - 2.1%)	2.0% (1.5% - 2.4%)	232,293	2,020	
Osaka	7.1% (6.9% - 7.4%)	6.6% (6.4% - 6.9%)	3.9% (3.7% - 4.1%)	3.5% (3.3% - 3.7%)	226,081	1,966	
Toyama	8.3% (7.6% - 9.0%)	8.4% (7.7% - 9.1%)	2.8% (2.3% - 3.2%)	2.8% (2.4% - 3.2%)	224,596	1,953	
Kyoto	6.0% (5.6% - 6.4%)	5.8% (5.4% - 6.1%)	2.8% (2.5% - 3.1%)	2.6% (2.3% - 2.9%)	223,388	1,943	
Akita	4.2% (3.8% - 4.7%)	4.7% (4.2% - 5.2%)	2.5% (2.1% - 2.8%)	2.8% (2.5% - 3.2%)	219,345	1,907	
Aomori	4.2% (3.8% - 4.7%)	4.3% (3.9%- 4.7%)	1.9% (1.6% - 2.2%)	1.9% (1.6% - 2.2%)	213,084	1,853	
Yamagata	3.3% (2.9% - 3.7%)	3.8% (3.3% - 4.2%)	1.7% (1.4% - 2.0%)	2.0% (1.7% - 2.4%)	211,407	1,838	
Gumma	4.4% (4.0% - 4.8%)	4.5% (4.1% - 4.9%)	2.1% (1.9% - 2.4%)	2.2% (1.9% - 2.5%)	208,711	1,815	
Nara	4.0% (3.5% - 4.5%)	4.0% (3.5% - 4.4%)	2.2% (1.8% - 2.5%)	2.1% (1.8% - 2.4%)	207,181	1,802	
Okinawa	9.1% (8.3% - 9.8%)	8.1% (7.4% - 8.7%)	3.4% (2.9% - 3.9%)	2.8% (2.5% - 3.2%)	206,845	1,799	
Fukushima	3.5% (3.2% - 3.8%)	3.5% (3.2% - 3.8%)	1.8% (1.6% - 2.0%)	1.8% (1.5% - 2.0%)	204,142	1,775	
Hyogo	6.2% (5.9% - 6.5%)	5.8% (5.6% - 6.1%)	2.8% (2.6% - 3.1%)	2.6% (2.4% - 2.8%)	202,829	1,764	
Iwate	2.9% (2.6% - 3.3%)	3.3% (2.9% - 3.7%)	1.4% (1.2% - 1.7%)	1.6% (1.4% - 1.9%)	200,099	1,740	Low
Tochigi	3.4% (3.1% - 3.8%)	3.4% (3.1% - 3.7%)	1.8% (1.6% - 2.1%)	1.8% (1.6% - 2.0%)	196,225	1,706	
Nagano	3.8% (3.4% - 4.1%)	4.2% (3.9% - 4.6%)	1.7% (1.5% - 1.9%)	2.0% (1.8% - 2.3%)	194,999	1,696	

Tokyo	3.2% (3.1% - 3.3%)	3.4% (3.3% - 3.5%)	1.8% (1.7% - 1.9%)	2.0% (1.9% - 2.1%)	194,947	1,695
Mie	4.0% (3.7% - 4.4%)	4.1% (3.8% - 4.5%)	1.8% (1.5% - 2.0%)	1.8% (1.6% - 2.1%)	194,425	1,691
Nigata	4.0% (3.7% - 4.3%)	4.2% (3.9% - 4.5%)	2.3% (2.1% - 2.6%)	2.5% (2.2% - 2.8%)	192,820	1,677
Yamanashi	4.3% (3.7% - 4.9%)	4.6% (4.0% - 5.2%)	2.1% (1.7% - 2.5%)	2.3% (1.9% - 2.7%)	191,488	1,665
Miyagi	4.3% (3.9% - 4.6%)	4.3% (4.0% - 4.7%)	2.2% (1.9% - 2.4%)	2.2% (2.0% - 2.5%)	191,412	1,664
Gifu	5.1% (4.7% - 5.5%)	5.5% (5.1% - 5.9%)	2.3% (2.0% - 2.6%)	2.4% (2.2% - 2.7%)	191,359	1,664
Aichi	6.9% (6.6% - 7.2%)	6.8% (6.5% - 7.0%)	3.1% (2.9% - 3.3%)	3.0% (2.8% - 3.2%)	185,712	1,615
Shizuoka	3.7% (3.5% - 4.0%)	3.8% (3.5% - 4.0%)	1.9% (1.7% - 2.0%)	1.9% (1.8% - 2.1%)	185,693	1,615
Shiga	5.8% (5.3% - 6.5%)	6.1% (5.5% - 6.6%)	2.5% (2.1% - 2.9%)	2.6% (2.2% - 3.0%)	179,995	1,565
Ibaraki	4.1% (3.8% - 4.4%)	4.0% (3.8% - 4.3%)	1.8% (1.6% - 2.0%)	1.7% (1.5% - 1.9%)	171,339	1,490
Kanagawa	4.8% (4.6% - 5.0%)	4.8% (4.6% - 5.0%)	2.2% (2.0% - 2.3%)	2.2% (2.1% - 2.3%)	160,195	1,393
Chiba	4.2% (4.0% - 4.5%)	4.1% (3.9% - 4.3%)	2.0% (1.9% - 2.2%)	1.9% (1.8% - 2.1%)	158,745	1,380
Saitama	5.1% (4.8% - 5.3%)	4.6% (4.4% - 4.8%)	2.6% (2.4% - 2.8%)	2.3% (2.2% - 2.4%)	151,272	1,315

* An exchange rate of 115 yen per US dollar was used for calculating per capita health expenditure

Formatted: Font: 12 pt, Expanded by 1 pt

Formatted: Line spacing: Double

Appendix 34. Adjusted association between tertile of per capita health expenditure at prefecture-level and patients' health outcomes after out-of-hospital cardiac arrest, additional adjustment for per capita income at prefecture-level*

Formatted: Font: 12 pt, Expanded by 1 pt
Formatted: Line spacing: Double
Formatted: Font: 12 pt, Superscript, Expanded by 1 pt
Formatted: Font: 12 pt, Expanded by 1 pt

1-month survival	**Overall**		**Age 1 to 59**		**Age 60 to 79**		**Age 80 to 100**	
	Adjusted OR (95% CI)	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Sample size	618,154		91,108		250,705		276,341	
Tertile of prefecture-level health expenditure per capita								
Q1 (Lowest)	Ref		Ref		Ref		Ref	
Q2	1.24 (0.97 to 1.59)	0.08	1.19 (0.95 to 1.51)	0.14	1.26 (0.96 to 1.65)	0.10	1.27 (1.001 to 1.62)	0.049
Q3 (Highest)	1.24 (0.99 to 1.55)	0.06	1.24 (1.00 to 1.54)	0.055	1.21 (0.95 to 1.53)	0.13	1.30 (1.03 to 1.65)	0.03
Favorable neurological outcome at 1 month	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**	**Adjusted OR (95% CI)**	**P-value**
Sample size	617,490		90,996		250,403		276,091	
Tertile of prefecture-level health expenditure per capita								
Q1 (Lowest)	Ref		Ref		Ref		Ref	
Q2	1.29 (1.002 to 1.67)	0.049	1.20 (0.91 to 1.57)	0.19	1.32 (1.004 to 1.73)	0.047	1.44 (1.13 to 1.83)	<0.01
Q3 (Highest)	1.29 (1.05 to 1.58)	0.02	1.23 (1.01 to 1.50)	0.04	1.25 (1.004 to 1.55)	0.046	1.52 (1.17 to 1.99)	<0.01

*Adjusted for age, sex, the interaction between age and sex, year indicators, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (VF or pulseless VT), witness status, CPR by bystander, use of public-access AED by bystander, and per capita income at prefecture-level.

Formatted: Font: 12 pt, Expanded by 1 pt
Formatted: Line spacing: Double

Appendix 5. Adjusted association between quintile of per capita health expenditure at prefecture-level and patients' health outcomes after out-of-hospital cardiac arrest

1-month survival rate		Unadjusted (N=635,710)		Adjusted* (N=618,154)	
		OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Quintile of prefecture-level health expenditure per capita	Q1 (Lowest)	Reference		Reference	
	Q2	0.80 (0.60-1.08)	0.14	0.82 (0.61-1.09)	0.19
	Q3	1.15 (0.87-1.52)	0.33	1.17 (0.90-1.54)	0.25
	Q4	1.01 (0.85-1.19)	0.94	1.05 (0.87-1.28)	0.60
	Q5 (Highest)	1.20 (0.96-1.51)	0.10	1.22 (0.95-1.57)	0.13
Favorable neurological outcome at 1 month		**Unadjusted (N=618,081)**		**Adjusted* (N=617,490)**	
		OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Quintile of prefecture-level health expenditure per capita	Q1 (Lowest)	Reference		Reference	
	Q2	0.87 (0.70-1.07)	0.19	0.91 (0.75-1.10)	0.33
	Q3	1.24 (0.90-1.69)	0.18	1.28 (0.96-1.70)	0.09
	Q4	1.07 (0.89-1.28)	0.47	1.14 (0.95-1.38)	0.15
	Q5 (Highest)	1.22 (0.98-1.53)	0.07	1.26 (0.99-1.60)	0.06

*Adjusted for age, sex, the interaction between age and sex, year indicators, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (VF or pulseless VT), witness status, CPR by bystander, use of public-access AED by bystander, and per capita income at prefecture-level.

Formatted: Font: 12 pt, Expanded by 1 pt
Formatted: Left, Line spacing: Double
Formatted: Font: (Default) Times New Roman, 12 pt, Expanded by 1 pt
Formatted: Font: 12 pt, Expanded by 1 pt
Formatted: Line spacing: Double

Appendix 6. Adjusted association between tertile of per capita health expenditure at prefecture-level and patients' return of spontaneous circulation after out-of-hospital cardiac arrest

Return of spontaneous circulation		Unadjusted (N=618,748)		Adjusted* (N=618,157)	
		Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Tertile of prefecture-level health expenditure per capita	Low	Reference		Reference	
	Medium	1.06 (0.86-1.30)	0.60	1.03 (0.85-1.26)	0.74
	High	0.95 (0.80-1.14)	0.62	0.92 (0.76-1.10)	0.36

*Adjusted for age, sex, the interaction between age and sex, year indicators, etiology of arrest (cardiac vs. non-cardiac), initial cardiac rhythm (VF or pulseless VT), witness status, CPR by bystander, use of public-access AED by bystander, and per capita income at prefecture-level.

Formatted: Font: 12 pt, Expanded by 1 pt
Formatted: Left, Line spacing: Double
Formatted: Font: (Default) Times New Roman, 12 pt, Expanded by 1 pt
Formatted: Superscript
Formatted: Font: 12 pt, Expanded by 1 pt
Formatted: Line spacing: Double

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	We used a nation-wide population-based registry of all OHCA cases resuscitated by emergency responders in Japan from January 2005 through December 2011 … We examined the association between per capita health expenditure at prefecture-level and patients' health outcomes after OHCA.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	We analyzed 618,154 OHCA cases…Each US$ 100 increase in per capita health expenditure was associated with 1.04 times higher odds of 1-month survival.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	Concerned about the rapid growth in health spending and the regional variation in health expenditure, the Japanese government is currently planning to set a target health expenditure

				level for each prefecture…These policies, which are analogous to ones proposed in other countries, are controversial because they do not take into account quality of care or health outcomes in setting their goals
Objectives	3	State specific objectives, including any prespecified hypotheses	4	First, how much variation is there in the outcomes after OHCA across 47 prefectures in Japan? Second, what is the relationship, if any, between per capita health expenditure at prefecture-level and health outcomes after OHCA? Finally, given strong policy concern that the most frugal regions may be achieving low spending by forgoing care for the oldest patients, is there any evidence that the relationship between health expenditure and health outcomes after OHCA varies by age group?
Methods				
Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		

Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.