

Associations between the consumption of different kinds of seafood and out-of-hospital cardiac arrests of cardiac origin in Japan

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Abstract

Background: Prospective cohort studies have shown that seafood consumption is inversely related to fatal coronary heart disease, sudden cardiac death and stroke. We studied whether the kind of seafood consumed in addition to seafood consumption per se is associated with out-of-hospital cardiac arrests (OHCA) of cardiac origin.

Methods and Results: We compared the average consumption of different kinds of seafood and other risk factors to the average incidence of age-adjusted OHCA (660,672 cases of OHCA: 55.2% of cardiac origin and 44.8% of non-cardiac origin) between 2005 and 2010 in the 47 prefectures of Japan. There were many significant correlations between the incidence of age-adjusted OHCA of cardiac origin (ad-OHCA-CO) and the consumption of many kinds of seafood, but not the total consumption of seafood. The consumption of horse mackerel ($r=-0.568$, $P<0.0001$) and saury ($r=0.607$, $P<0.0001$) showed the highest negative and positive correlations, respectively, with the age-adjusted incidence of ad-OHCA-CO. Although salt consumption was not significantly associated with ad-OHCA-CO, salt consumption was significantly and positively associated with the consumption of flounder ($r=0.388$, $P<0.01$), salmon ($r=0.359$, $P<0.05$), saury ($r=0.386$, $P<0.01$), and cuttlefish ($r=0.503$, $P<0.001$).

Conclusions: In Japan, the consumption of different kinds of seafood may be an important factor in OHCA of cardiac origin. Thus, dietary habits with regard to seafood may play a role in OHCA of cardiac origin, however, the question of whether to eat fish in general or instead to eat certain kinds of fish is still unclear.

Key words: cardiac arrest, ecological study, fatty acids, seafood consumption

Introduction

Dietary prevention originated in animal studies in which the high intake of dietary cholesterol was shown to lead to hypercholesterolemia and promote atherosclerosis. However, dietary intervention trials in humans that have targeted the primary and secondary prevention of cardiovascular diseases (CVD) have not always been successful¹⁻³, since the trials were too small or too short, or the intervention itself was too weak to produce changes in lifestyle or diet⁴. However, epidemiological surveys have shown a lower prevalence of CVD in populations around the Mediterranean, where the diet is rich in olive oil, fiber and n-3 polyunsaturated fatty acids (n-3PUFAs), and in Asia (e.g., Japan), where the diet has traditionally been low in fat and high in carbohydrates with high levels of fish consumption⁵⁻⁷. Prospective cohort studies have shown that the consumption of seafood and fish oil is inversely related to fatal coronary heart disease^{8,9}, sudden cardiac death (SCD)^{10,11} and stroke^{10,12,13}, and most of the reduction in SCD could be explained by the antiarrhythmic effects of n-3PUFAs in fish^{14,15}. As a result, current guidelines for both the primary and secondary prevention of cardiovascular events¹⁵⁻¹⁷, including Japanese guidelines^{18,19}, encourage the consumption of fresh seafood or oily fish at least twice a week.

In January 2005, the Fire and Disaster Management Agency (FDMA) of Japan

launched a prospective, nationwide, population-based, cohort study in subjects who had had an out-of-hospital cardiac arrest (OHCA) to evaluate the effect of the nationwide dissemination of public-access AEDs on the rate of survival among patients who had an OHCA²⁰⁻²⁵, and the Japanese Circulation Society (JCS) Resuscitation Science Study (JCS-ReSS) Group had a suitable database. Therefore, as a working hypothesis, we assumed that the kind of seafood consumed in each prefecture, in addition to the total consumption of seafood per se in each prefecture, would be associated with OHCA of cardiac origin. We compared the total consumption of seafood and the average consumption of different kinds of seafood to the average incidence of OHCA between 2005 and 2010 in the 47 prefectures of Japan. To the best of our knowledge, this is the first study to demonstrate the relationship between seafood consumption and OHCA.

Methods

Subjects

Patients who suffered from OHCA of cardiac and non-cardiac origin (n=364,547 and 296,125, respectively, Table 1) and who were enrolled in the All-Japan Utstein

Registry of the Fire and Disaster Management Agency between 2005 and 2010 were included in this analysis²⁰⁻²². The populations in the 47 prefectures in Japan were obtained from the Population Census (2005)²⁶ and the Annual Report on Current Population Estimates (2006-2010)²⁷ published by the Ministry of Internal Affairs and Communications of Japan. The study protocol for analyses was approved by the Ethics Committee of Fukuoka University (FU-#00000403), Japan.

Age-adjusted incidence of OHCA

Using the Utstein Registry, we calculated the crude incidence of OHCA by determining the raw number of cases of OHCA by prefecture and then dividing these numbers by the population of the prefecture. The Japanese Model Population in 1985 was used as a standard population, and age-standardization was performed by a direct method. We determined the average yearly age-adjusted incidence of OHCA by prefecture from 2005 to 2010.

Seafood consumption

Data regarding the consumption of seafood in the 47 municipalities were obtained from the Family Income and Expenditure Survey published by the Ministry of Internal

Affairs and Communications of Japan²⁸. We considered 14 kinds of seafood: tuna, horse mackerel, sardine, bonito, flounder, salmon, mackerel, saury, sea bream, yellowtail, cuttlefish, octopus, shrimp, and crab. Yearly expenditures, quantities and average prices per two-or-more-person household by prefectural capital city were obtained from this Survey, which also included the quantities of different kinds of seafood and salt consumption. We calculated the daily consumption of these foods per person by dividing the yearly amounts of the different kinds of seafood by the number of household members, and determined the averages from 2005 to 2010.

Fatty acids

The yearly quantities of different kinds of seafood were determined as described in a previous section. The types of lipids that were contained in seafood were obtained from the Standard Tables of Food Composition in Japan (fifth revised and enlarged edition) published by the Ministry of Education, Culture, Sports, Science of Japan^{29, 30}.

Although various cooking methods and species of seafood were included, we used data for raw seafood and averages for species of seafood. For example, tuna encompasses 6 species and both red and fatty flesh, which have completely different lipid contents. In Japan, red flesh and fatty flesh account for 87.5% and 12.5%,

respectively, of tuna consumption, and this was considered in the calculation. The fatty acid contents in the 47 prefectures were calculated for the 14 kinds of seafood and this was considered to be the consumption of fatty acid for fish that are mainly consumed in Japan.

Other risk factors

The sex ratio was obtained from the All-Japan Utstein Registry. Data on the consumption of salt, alcohol, and tobacco were obtained from the Family Income and Expenditure Survey²⁸. We calculated the daily consumption of these foods by the approach mentioned above. The consumption of alcohol and tobacco were measured by the same method that was used to measure the consumption of seafood; i.e., in terms of money spent.

The estimated numbers of patients with hypertension and dyslipidemia were obtained from the Patient Survey published by the Ministry of Health, Labour and Welfare of Japan³¹. This survey was performed annually among patients of medical care institutions nationwide who were selected by random stratified sampling. The estimated numbers of patients who received medical treatment in hospitals and general clinics on the dates surveyed were used. We divided the estimated numbers of

patients by the population of the prefecture for each year and expressed the results as the average of the survey between 2005 and 2010. The rates of participation in sports were obtained from the Survey on Time Use and Leisure Activities published by the Ministry of Internal Affairs and Communications of Japan³². The sample was selected through a two-stage stratified sampling method, where the primary sampling unit was the enumeration district (ED) of the Population Census, and the secondary sampling unit was the household. First, the whole country was divided into its 47 prefectures, and a total of 6,700 sample EDs were selected. In the selected EDs, about 80,000 households were selected from lists of households prepared by enumerators before the survey. All persons aged 10 and over in the sample households were asked to respond to the survey. Enumerators deliver the questionnaires to each household to be surveyed, collect the completed questionnaires, and interview the households as necessary. The rate of participation in sports is derived from the total participation rate in sports. Sports include all kinds of athletic activity performed for leisure, but exclude sports performed by students as part of their educational exercises and by professional athletes as their work. This survey was performed once in five years, and we used the 2006 survey. Obesity was defined as a Body Mass Index of 25 or greater. The percentage of obesity was calculated using

age-adjusted data in males from 20 to 69 years old and the data were averaged between 2006 and 2010. The rate of advancement to high school was obtained from the School Basic Survey published by the Ministry of Education, Culture, Sports, Science of Japan³³. Other data are expressed as the average of the survey between 2005 and 2010. The raw data were divided by the population of the prefecture.

Statistical analysis

The statistical analysis was performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA) at Fukuoka University. We used a t-test for continuous variables and chi-squared tests for categorical variables. The Spearman Rank Correlation Coefficient was used to evaluate associations between groups. The values are expressed as the mean \pm standard deviation (SD). Statistical significance was defined as a p-value of less than 0.05.

Results

Patient characteristics in the All-Japan Utstein Registry

There were 670,313 cases of OHCA in the All- Japan Utstein registry between 2005 and 2010, including 9,641 cases who did not receive resuscitation. Table 1 shows the

patient characteristics in the All-Japan Utstein Registry between 2005 and 2010, excluding 9,641 in the no-resuscitation group: 660,672 cases of OHCA: 364,547 (55.2%) of cardiac origin and 296,125 (44.8%) of non-cardiac origin. Non-cardiac origin included cerebrovascular disease, respiratory disease, malignant tumor, and exogenous disease (10.7%, 13.0%, 7.4%, and 40.8%, respectively). Patients with OHCA of cardiac origin were significantly older, and had a lower incidence of male and a higher incidence of 1-month survival, cerebral performance category (CPC) 1 or 2, and overall performance category (OPC) 1 or 2. The initial rhythms in OHCA of cardiac origin were significantly more likely to be ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), and less likely to be pulseless electrical activity (PEA) and asystole.

Incidence of OHCA of cardiac and non-cardiac origin in the 47 prefectures of Japan

Figure 1 shows the mean age-adjusted incidence of OHCA of cardiac and non-cardiac origin in the 47 prefectures of Japan between 2005 and 2010. Northern Japan tended to show a high incidence of cardiac arrest of both cardiac and non-cardiac origin.

Time trends for the incidence of OHCA and total seafood consumption

Figure 2 shows the yearly changes in total seafood consumption and the incidence of OHCA (total, cardiac and non-cardiac origin) in the 47 prefectures of Japan and total seafood consumption in Japan from 2000 to 2010. Although the incidence of OHCA of both total and cardiac origin has been increasing, total seafood consumption has decreased yearly from 2000.

Correlations between the consumption of overall seafood, different kinds of seafood, and the incidence of OHCA of cardiac and non-cardiac origin in the 47 prefectures

Northern and Western Japan tend to show a high consumption of seafood (data not tabulated). The overall consumption of raw fish (47 prefectures) (g/day/person) was not significantly correlated with the age-adjusted incidence of total OHCA ($r=-0.036$, $p=0.81$), the age-adjusted incidence of OHCA of cardiac origin ($r=0.132$, $p=0.38$), or the age-adjusted incidence of OHCA of non-cardiac origin ($r=0.075$, $p=0.62$) (data not tabulated). Fourteen kinds of seafood were included in the analysis. According to the Spearman Rank Correlation Coefficient between the consumption of each type of seafood and the age-adjusted incidence of OHCA, there were significantly different

correlations (Table 2-A). The consumption of horse mackerel ($r=-0.568$, $p<0.0001$), sardine ($r=-0.454$, $p=0.001$), mackerel ($r=-0.513$, $p=0.0002$), sea bream ($r=-0.527$, $p=0.0001$), and yellowtail ($r=-0.517$, $p=0.0002$) showed significant negative correlations with the incidence of OHCA of cardiac origin (Table 2-A, Fig. 3-A). The consumption of tuna ($r=0.602$, $p<0.0001$), bonito ($r=0.319$, $p=0.029$), salmon ($r=0.539$, $p<0.0001$), saury ($r=0.607$, $p<0.0001$), and cuttlefish ($r=0.396$, $p=0.006$) showed significant positive correlations with the incidence of OHCA of cardiac origin (Table 2-A, Fig. 3-B). The consumption of flounder ($r=0.026$, $p=0.862$), octopus ($r=0.390$, $p=0.390$), shrimp ($r=-0.258$, $p=0.080$), and crab ($r=-0.007$, $p=0.966$) showed no significant correlations with the incidence of OHCA of cardiac origin (Table 2-A). The associations between the consumption of different kinds of seafood and salt consumption in the 47 prefectures of Japan are shown in the Table 2-B. Salt consumption was significantly and positively associated with the consumption of flounder ($r=0.388$, $p=0.007$), salmon ($r=0.359$, $p=0.013$), saury ($r=0.386$, $p=0.007$), and cuttlefish ($r=0.503$, $p=0.0003$), and negatively associated with the consumption of sea bream ($r=-0.386$, $p=0.008$).

Associations between the consumption of fatty acids from 14 kinds of seafood and the

incidence of OHCA of cardiac origin

Table 3 shows the associations between the consumption of fatty acids calculated from 14 kinds of seafood and the age-adjusted incidence of OHCA of cardiac origin. There were significant negative associations between the consumption of fatty acids including saturated fatty acid, palmitic acid, stearic acid, oleic acid, arachidonic acid, and eicosapentaenoic acid (EPA, trend of $p=0.052$) and the age-adjusted incidence of OHCA of cardiac origin, while no associations observed in alpha linolenic acid, docosahexaenoic acid (DHA) et al.

Correlations between the incidence of OHCA of cardiac origin and other risk factors in the 47 prefectures

The sex ratio, consumption of salt, alcohol and tobacco, age-adjusted incidence of hypertension, or dyslipidemia, participation in sports, % obesity, and rate of advancement to high school were included in the analysis (Table 4). There were no significant correlations between the incidence of OHCA of cardiac origin by prefecture and the sex ratio, consumption of salt, alcohol and tobacco, hypertension, dyslipidemia, participation in sports, or rate of advancement to high school, while the percentage of obesity tended ($p=0.064$) to be associated with OHCA of cardiac origin.

Trends in the consumption of different kinds of seafood and seafood interactions

Yearly changes in the consumption of each seafood in the 47 prefectures of Japan from 2000 to 2010 are shown in Fig. 4. The consumption of many of the seafoods has decreased, while the consumption of saury has seemed to be increased. There were associations among the consumption of each type of seafood, i.e., the consumption of horse mackerel was negatively associated with those the consumption of tuna, salmon, saury, and cuttlefish (Table 5-A), while the consumption of saury was positively associated with the consumption of tuna, yellowtail, and cuttlefish (Table 5-B).

Discussion

The main finding in the present study was that the consumption of certain kinds of seafood, but not total seafood consumption per se, was significantly associated with the age-adjusted incidence of OHCA of cardiac origin, although the incidence of OHCA of cardiac origin increased from 2005 to 2010 and total seafood consumption decreased yearly from 2000, as shown in Fig. 2. Epidemiological data have shown unequivocally that an increased intake of fish/fish oil is associated with lower CVD morbidity and mortality^{8,9}. In the JPHC study by Iso et al.³⁴, compared to modest

fish intake, higher fish intake was associated with a substantially reduced risk of CAD and non-fatal cardiac events among middle-aged subjects. Thus, we and others have thought that total seafood consumption might be correlated with the incidence of OHCA of cardiac origin.

The incidence of OHCA of cardiac origin was positively associated with the consumption of tuna, salmon, saury, and cuttlefish, while negative correlations were found for the consumption of horse mackerel, sardines, mackerel, sea bream, and yellowtail, and these seafoods were not significantly associated with OHCA of non-cardiac origin. Thus, the kind of seafood consumed, rather than the total consumption of seafood, may be important for predicting the age-adjusted incidence of OHCA of cardiac origin. The yearly changes in the consumption of each seafood gradually decreased except saury, and the trends were similar to the yearly change in total fish consumption (Figs. 2 and 4).

Horse mackerel and saury showed the highest negative and positive correlations with the age-adjusted incidence of OHCA of cardiac origin (Table 2-A, Figs. 3-A and 3-B). Interestingly, although whole salt consumption was not significantly associated with the age-adjusted incidence of OHCA of cardiac origin, salt consumption was significantly and positively associated with the consumption of

flounder ($r=0.388$, $p=0.007$), salmon ($r=0.359$, $p=0.013$), saury ($r=0.386$, $p=0.007$), and cuttlefish ($r=0.503$, $p=0.0003$), and significantly and negatively associated with the consumption of sea bream ($r=-0.383$, $p=0.008$) (Table 2-B). These data suggest that the method used to cook seafood might affect the association with the incidence of OHCA of cardiac origin. In fact, Belin et al.³⁵ showed that, in a diverse population of postmenopausal women who were at increased risk for heart failure (HF), a higher intake of baked/broiled fish was associated with a lower risk for incident HF, whereas a higher intake of fried fish was linked to a higher risk for incident HF, which suggests that dietary modification with an increase in the consumption of baked/broiled fish, and/or a decrease in the consumption of fried fish, could play a role in these associations. Although saury showed a positive association and is rich in fatty acids, it is not mostly eaten raw but with salt in Japan. The effects of saury, salmon, and cuttlefish may be reduced by the cooking methods used.

The influence of mercury in seafood should also be considered. It has been reported that exposure to high levels of mercury might reduce the beneficial effects of n-3 PUFA on sudden cardiac death³⁶. The Japanese Ministry of Health, Labour and Welfare has advised pregnant women to avoid consuming seafood that contains a large amount of mercury. Tuna and bonito are predators that occupy positions high in the

food chain, and may contain large amounts of mercury through bioaccumulation.

Mercury concentrations in tuna are positively correlated with body size^{37, 38}.

Differences between regions, which could be associated with different lifestyles and different harvests of seafood, may have also affected the results. Northern Japan tends to show a high incidence of OHCA of cardiac origin, and this could explain the positive association between the consumption of seafood, which was higher in northern Japan than in southern Japan, and OHCA of cardiac origin. Thus, we cannot exclude confounding factors.

In this study, we calculated the consumption of fatty acids in the 47 prefectures of Japan in terms of the fish that are mainly consumed. There were several significant negative associations between the consumption of fatty acids including saturated fatty acids, palmitic acid, stearic acid or arachidonic acid, and the age-adjusted incidence of OHCA of cardiac origin. Over the past decade, an inverse relationship has been observed between fish intake and fatal CVD or sudden cardiac death, which suggests that n-3 polyunsaturated fatty acids (e.g., [EPA]+ [DHA]) may have an antiarrhythmic effect^{10, 11, 14}, in addition to any platelet aggregatory^{39, 40}, anti-atherosclerotic⁴¹, anti-inflammatory⁴², or vasodilatory effects⁴². In the JELIS study⁴³ in Japan, daily treatment with EPA together with statin was associated with a

relative reduction in major coronary events. The DART⁴⁴, GISSI-Prevenzione (P)¹⁰,¹¹ and GISSI-HF⁴⁵ studies have also shown that supplementation with n-3 polyunsaturated fatty acids has beneficial effects on cardiovascular outcomes in different patient populations. Our results cannot be compared to those of studies involving supplementation with fatty acids. In particular, the amount of fatty acids in our analysis was significantly lower than the dose used in supplementation, since fatty acid contents were simply calculated from the consumption of each kind of seafood, not from total intake of diet. In addition, the amount of fatty acids contained in seafood can change dramatically with preparation, and in our study we did not know how the different seafoods were cooked. Many nutrients such as proteins, calcium, vitamins A, B and D, iron and taurine should be considered together.

Recent meta-analyses have shown that supplementation with n-3 polyunsaturated fatty acids not only does not reduce the incidence of cardiovascular⁴⁶ and cerebrovascular diseases⁴⁷, but also has no beneficial effect. These data also indicate that supplementation with fish oils may have different effects than the intake of fish itself, although meta-analyses have both publication and selection biases.

Finally, we performed an analysis with the crude incidence of OHCA, and the results were almost the same as those for the age-adjusted incidence of OHCA (data not shown). We also performed an analysis with the mean age-adjusted incidence of OHCA between 2000 and 2005 (carry-over effects of seafood consumption) (data not shown), and the results were almost the same as those in the present study.

Limitations

Since this is an ecological study and the baseline characteristics in these surveys are different, we may need to consider an ecological fallacy, and thus the results may not be completely accurate, although the data from 660,672 individuals should be sufficient to discuss our hypothesis. The data on the average consumption of seafood, salt, alcohol, and tobacco in the 47 prefectures of Japan do not include single-person households and only included information for the prefectural capital. However, this information should reflect the characteristics of the prefectures. Furthermore, the results were estimated from data on consumer spending rather than from a dietary questionnaire. Therefore, salt consumption should be considered in the intake of other foods, such as when eating out. Other confounding factors, such as the climate or lifestyle in the 47 prefectures, should also be considered. Unfortunately, we could

not stratify other risks. Although the amount of fatty acids varies according to the cooking style, in our data it is not clear how the seafood was cooked, and our study did not consider relations with other foods.

Conclusion

In Japan, the consumption of different kinds of seafood may be an important factor in OHCA of cardiac origin. Thus, dietary habits with regard to seafood may play a role in the incidence of OHCA of cardiac origin, however, the question of whether to eat fish in general or instead to eat certain kinds of fish is still unclear.

Disclosures

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Figure Legends

Fig.1: Mean age-adjusted incidence of OHCA of cardiac origin (left panel) or non-cardiac origin (right panel) in the 47 prefectures of Japan between 2005 and 2010.

Fig. 2: Yearly changes in overall seafood consumption and the incidence of OHCA in the 47 prefectures of Japan from 2000 to 2010.

Green line indicates the consumption of overall fish. Orange, red, and blue lines indicate the incidence of OHCA in all patients, cardiac and non-cardiac origin, respectively.

Fig. 3-A and 3-B: Correlations between the age-adjusted incidence of OHCA and the consumption of different kinds of seafood in the 47 prefectures of Japan. Red lines and circles indicate the correlation to OHCA of cardiac origin. Blue lines and circles indicate the correlation to OHCA of non-cardiac origin.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Fig. 4: Yearly changes in the consumption of each seafood in the 47 prefectures of

Japan from 2000 to 2010. The trends in the consumption of most of the seafoods were negative. Green shows total seafood consumption, while the consumption of each type of fish is shown in blue (tuna), grey (saury), orange (horse mackerel), black (bonito), and red (sardine).

References

1. Frantz ID, Jr., Dawson EA, Ashman PL, Gatewood LC, Bartsch GE, Kuba K, Brewer ER. Test of effect of lipid lowering by diet on cardiovascular risk. The minnesota coronary survey. *Arteriosclerosis*. 1989;9:129-135
2. Miettinen M, Turpeinen O, Karvonen MJ, Elosuo R, Paavilainen E. Effect of cholesterol-lowering diet on mortality from coronary heart-disease and other causes. A twelve-year clinical trial in men and women. *Lancet*. 1972;2:835-838
3. Low-fat diet in myocardial infarction: A controlled trial. *Lancet*. 1965;2:501-504
4. Noda K, Zhang B, Iwata A, Nishikawa H, Ogawa M, Nomiya T, Miura S, Sako H, Matsuo K, Yahiro E, Yanase T, Saku K. Lifestyle changes through the use of delivered meals and dietary counseling in a single-blind study. The stylist study. *Circ J*. 2012;76:1335-1344
5. Kromhout D, Keys A, Aravanis C, Buzina R, Fidanza F, Giampaoli S, Jansen A, Menotti A, Nedeljkovic S, Pekkarinen M, et al. Food consumption patterns in the 1960s in seven countries. *Am J Clin Nutr*. 1989;49:889-894
6. Japanese Circulation Society. Guidelines for the primary prevention of ischemic heart disease revised version (JCS 2006)
http://www.j-circ.or.jp/guideline/pdf/JCS2006_kitabatake_h.pdf
2006: (accessed January 6th, 2013)
7. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T. Cardiovascular disease and risk factors in asia: A selected review. *Circulation*. 2008;118:2702-2709
8. Daviglius ML, Stamler J, Orenca AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D, Shekelle RB. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med*. 1997;336:1046-1053
9. Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, Hunter D, Manson JE. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA*. 2002;287:1815-1821
10. GISSI-Prevenzione I. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin e after myocardial infarction: Results of the gissi-prevenzione trial. Gruppo italiano per lo studio della sopravvivenza nell'infarto miocardico. *Lancet*. 1999;354:447-455
11. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E, Levantesi G, Maggioni AP, Mantini L, Marfisi RM, Mastrogiuseppe

- G, Mininni N, Nicolosi GL, Santini M, Schweiger C, Tavazzi L, Tognoni G, Tucci C, Valagussa F. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: Time-course analysis of the results of the gruppo italiano per lo studio della sopravvivenza nell'infarto miocardico (gissi)-prevenzione. *Circulation*. 2002;105:1897-1903
12. Iso H, Sato S, Umemura U, Kudo M, Koike K, Kitamura A, Imano H, Okamura T, Naito Y, Shimamoto T. Linoleic acid, other fatty acids, and the risk of stroke. *Stroke*. 2002;33:2086-2093
 13. Simon JA, Fong J, Bernert JT, Jr., Browner WS. Serum fatty acids and the risk of stroke. *Stroke*. 1995;26:778-782
 14. Reiffel JA, McDonald A. Antiarrhythmic effects of omega-3 fatty acids. *Am J Cardiol*. 2006;98:50i-60i
 15. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Perrone Filardi P, Riccardi G, Storey RF, Wood D. Esc/eas guidelines for the management of dyslipidaemias: The task force for the management of dyslipidaemias of the european society of cardiology (esc) and the european atherosclerosis society (EAS). *Atherosclerosis*. 2011;217 Suppl 1:S1-44
 16. Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA. Aha/accf secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the american heart association and american college of cardiology foundation endorsed by the world heart federation and the preventive cardiovascular nurses association. *J Am Coll Cardiol*. 2011;58:2432-2446
 17. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Pina IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Jr., Sopko G, Chandra-Strobo N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: A guideline from the american heart association. *Circulation*. 2011;123:1243-1262
 18. Japan Atherosclerosis Society. Japan atherosclerosis society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2012.

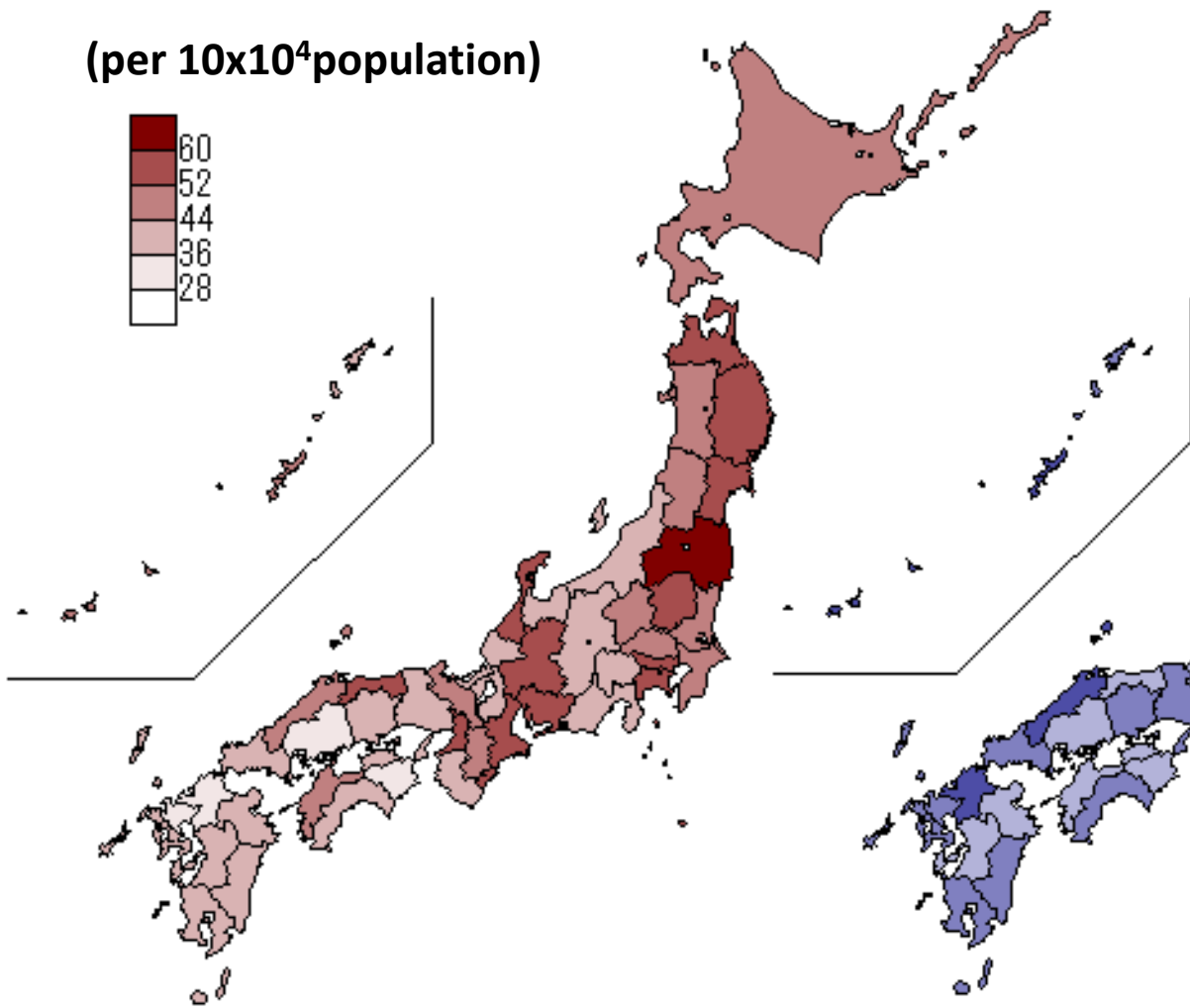
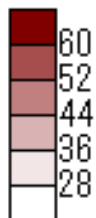
19. Japanese Circulation Society. Guidelines for secondary prevention of myocardial infarction (JCS 2011) http://www.j-circ.or.jp/guideline/pdf/JCS2011_ogawah_h.pdf. 2011 (accessed January 5th, 2013)
20. Kitamura T, Iwami T, Kawamura T, Nagao K, Tanaka H, Hiraide A. Nationwide public-access defibrillation in Japan. *N Engl J Med*. 2010;362:994-1004
21. Kitamura T, Iwami T, Kawamura T, Nitta M, Nagao K, Nonogi H, Yonemoto N, Kimura T. Nationwide improvements in survival from out-of-hospital cardiac arrest in Japan. *Circulation*. 2012;126:2834-2843
22. Iwami T, Kitamura T, Kawamura T, Mitamura H, Nagao K, Takayama M, Seino Y, Tanaka H, Nonogi H, Yonemoto N, Kimura T. Chest compression-only cardiopulmonary resuscitation for out-of-hospital cardiac arrest with public-access defibrillation: A nationwide cohort study. *Circulation*. 2012;126:2844-2851
23. Sasaki M, Iwami T, Kitamura T, Nomoto S, Nishiyama C, Sakai T, Tanigawa K, Kajino K, Irisawa T, Nishiuchi T, Hayashida S, Hiraide A, Kawamura T. Incidence and outcome of out-of-hospital cardiac arrest with public-access defibrillation. A descriptive epidemiological study in a large urban community. *Circ J*. 2011;75:2821-2826
24. Hayashi Y, Iwami T, Kitamura T, Nishiuchi T, Kajino K, Sakai T, Nishiyama C, Nitta M, Hiraide A, Kai T. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. *Circ J*. 2012;76:1639-1645
25. Kobayashi N, Hata N, Shimura T, Yokoyama S, Shirakabe A, Shinada T, Tomita K, Murakami D, Takano M, Seino Y, Matsumoto H, Mashiko K, Mizuno K. Characteristics of patients with cardiac arrest caused by coronary vasospasm. *Circ J*. 2013;77:673-678
26. Ministry of Internal Affairs and Communications. [Http://www.Stat.Go.Jp/data/kokusei/2005/index.Htm](http://www.Stat.Go.Jp/data/kokusei/2005/index.Htm). 2005 (accessed January 5th, 2013)
27. Ministry of Internal Affairs and Communications. [Http://www.Stat.Go.Jp/data/jinsui/](http://www.Stat.Go.Jp/data/jinsui/). 2006-2010 (accessed January 5th, 2013)
28. Ministry of Internal Affairs and Communications. [Http://www.Stat.Go.Jp/data/kakei/index.Htm](http://www.Stat.Go.Jp/data/kakei/index.Htm). 2005-2010 (accessed January 5th, 2013)
29. Food Substitution Table for diabetes mellitus diet therapy 6th version of the Japan Diabetes Society. *Japan Diabetes Society*. 2002:(in Japanese)
30. Ministry of Education C, Sports, Science of Japan,. [Http://www.Mext.Go.Jp/b_menu/shingi/gijyutu/gijyutu3/toushin/05031802.Htm](http://www.Mext.Go.Jp/b_menu/shingi/gijyutu/gijyutu3/toushin/05031802.Htm).

- 2005 (accessed January 5th, 2013)
31. Ministry of Health Labour and Welfare of Japan.
[Http://www.Mhlw.Go.Jp/toukei/list/10-20.Html](http://www.Mhlw.Go.Jp/toukei/list/10-20.Html) 2010 (accessed January 5th, 2013)
 32. Ministry of Internal Affairs and Communications.
[Http://www.Stat.Go.Jp/data/shakai/2006/index.Htm](http://www.Stat.Go.Jp/data/shakai/2006/index.Htm). 2010 (accessed January 5th, 2013)
 33. Ministry of Education C, Sports, Science of Japan.,.
[Http://www.Mext.Go.Jp/b_menu/toukei/chousa01/kihon/1267995.Htm](http://www.Mext.Go.Jp/b_menu/toukei/chousa01/kihon/1267995.Htm). 2010 (accessed January 5th, 2013)
 34. Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S. Intake of fish and n3 fatty acids and risk of coronary heart disease among japanese: The japan public health center-based (JPHC) study cohort i. *Circulation*. 2006;113:195-202
 35. Belin RJ, Greenland P, Martin L, Oberman A, Tinker L, Robinson J, Larson J, Van Horn L, Lloyd-Jones D. Fish intake and the risk of incident heart failure: The women's health initiative. *Circ Heart Fail*. 2011;4:404-413
 36. Virtanen JK, Laukkanen JA, Mursu J, Voutilainen S, Tuomainen TP. Serum long-chain n-3 polyunsaturated fatty acids, mercury, and risk of sudden cardiac death in men: A prospective population-based study. *PLoS One*. 2012;7:e41046
 37. Storelli MM, Marcotrigiano GO. Mercury speciation and relationship between mercury and selenium in liver of galeus melastomus from the mediterranean sea. *Bull Environ Contam Toxicol*. 2002;69:516-522
 38. Nakata H, Shimada H, Yoshimoto M, Narumi R, Akimoto K, Yamashita T, Matsunaga T, Nishimura K, Tanaka M, Hiraki K, Shimasaki H, Takikawa K. Concentrations and distribution of mercury and other heavy metals in surface sediments of the yatsushiro sea including minamata bay, japan. *Bull Environ Contam Toxicol*. 2008;80:78-84
 39. Hirai A, Terano T, Hamazaki T, Sajiki J, Kondo S, Ozawa A, Fujita T, Miyamoto T, Tamura Y, Kumagai A. The effects of the oral administration of fish oil concentrate on the release and the metabolism of [14c]arachidonic acid and [14c]eicosapentaenoic acid by human platelets. *Thromb Res*. 1982;28:285-298
 40. Tamura Y, Hirai A, Terano T, Takenaga M, Saitoh H, Tahara K, Yoshida S. Clinical and epidemiological studies of eicosapentaenoic acid (EPA) in japan. *Prog Lipid Res*. 1986;25:461-466
 41. Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PC, Grimble RF. Association of n-3 polyunsaturated fatty acids with

- stability of atherosclerotic plaques: A randomised controlled trial. *Lancet*. 2003;361:477-485
42. Cawood AL, Ding R, Napper FL, Young RH, Williams JA, Ward MJ, Gudmundsen O, Vige R, Payne SP, Ye S, Shearman CP, Gallagher PJ, Grimble RF, Calder PC. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque epa is associated with decreased plaque inflammation and increased stability. *Atherosclerosis*. 2010;212:252-259
 43. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369:1090-1098
 44. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and reinfarction trial (DART). *Lancet*. 1989;2:757-761
 45. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): A randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1223-1230
 46. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: A systematic review and meta-analysis. *JAMA*. 2012;308:1024-1033
 47. Chowdhury R, Stevens S, Gorman D, Pan A, Warnakula S, Chowdhury S, Ward H, Johnson L, Crowe F, Hu FB, Franco OH. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: Systematic review and meta-analysis. *BMJ*. 2012;345:e6698

Cardiac origin

(per 10×10^4 population)



Non-cardiac origin

(per 10×10^4 population)

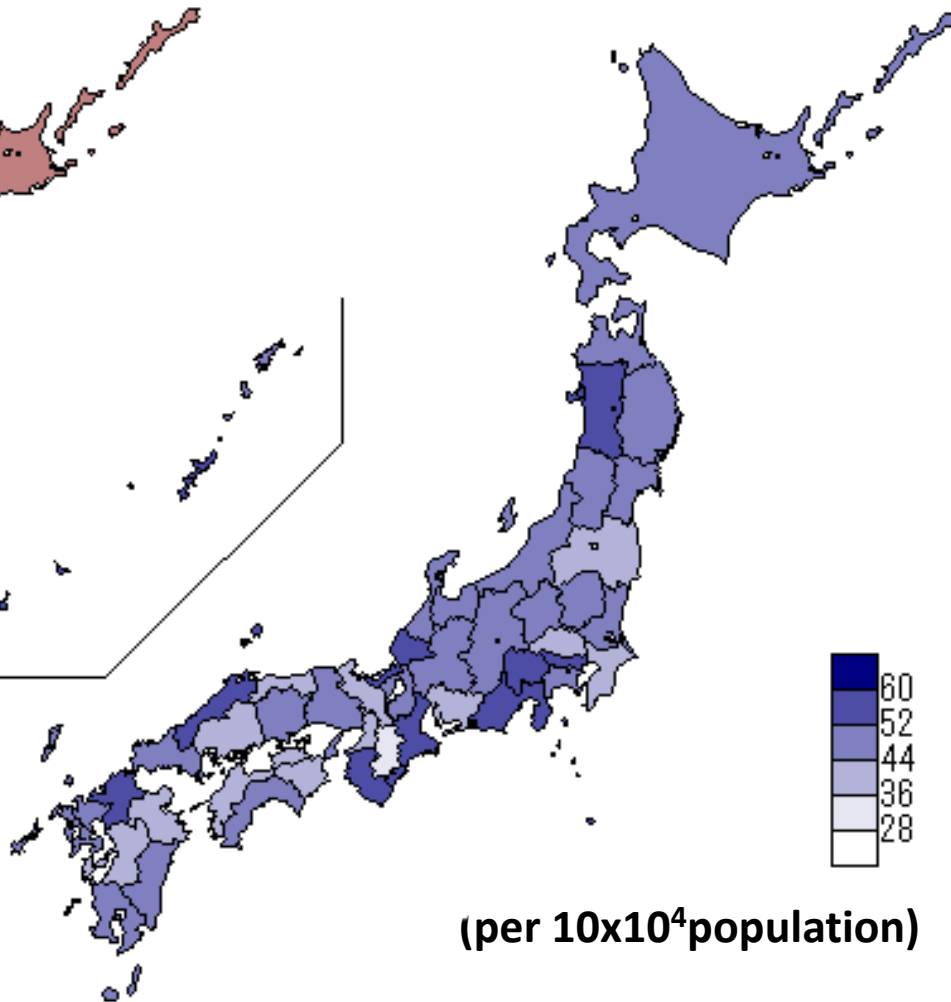
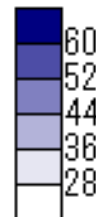


Fig.1

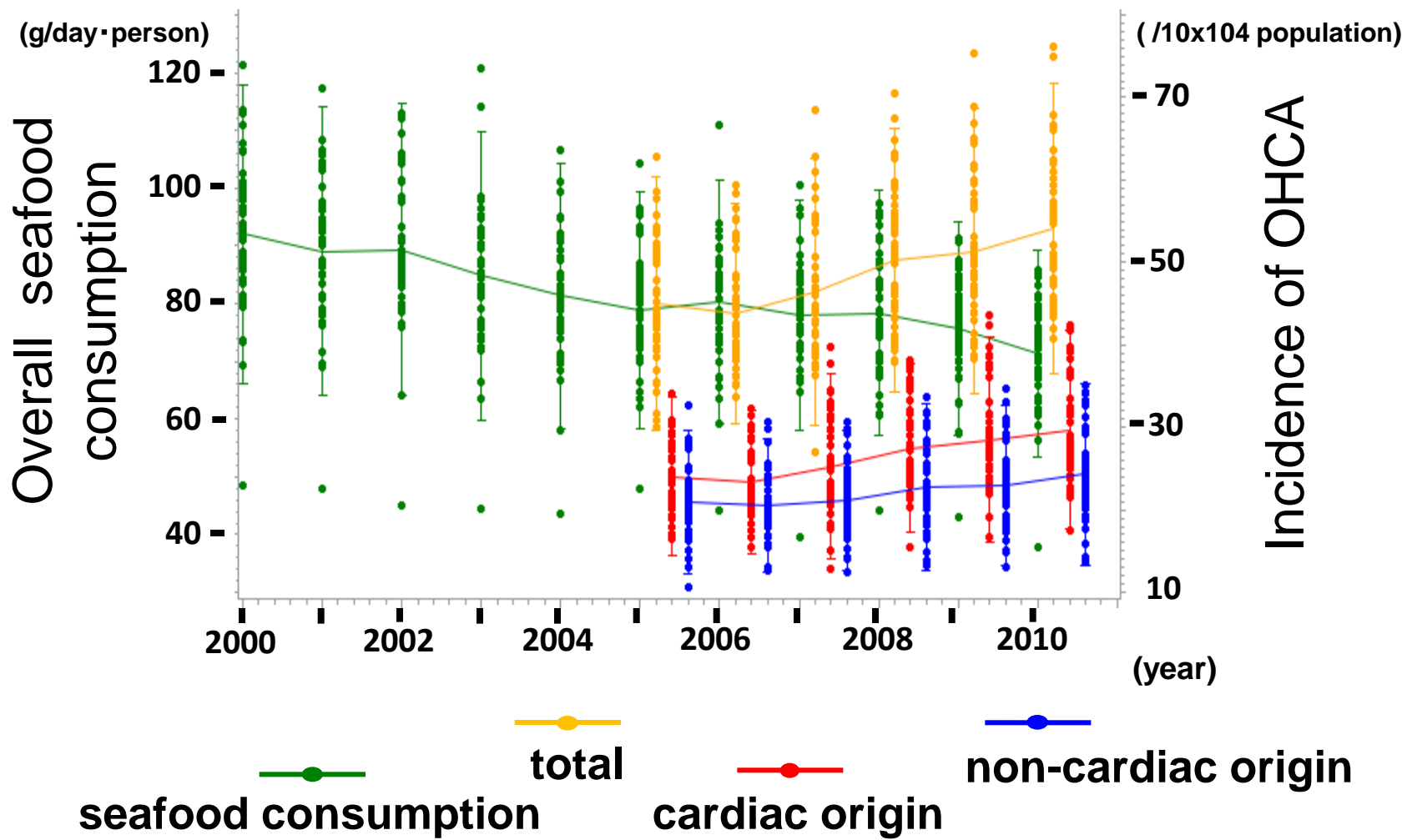
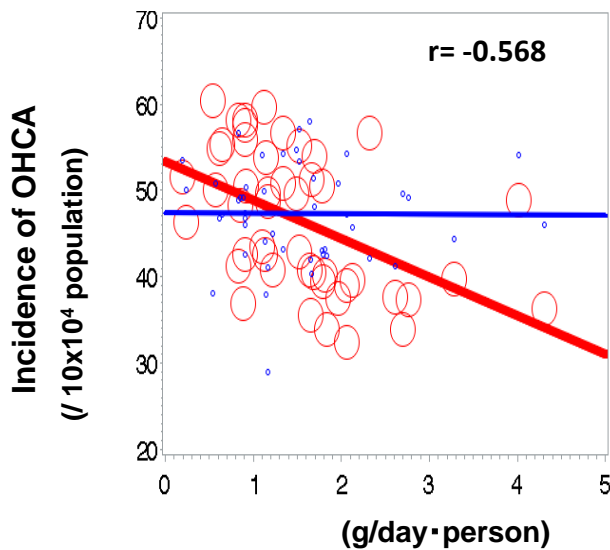


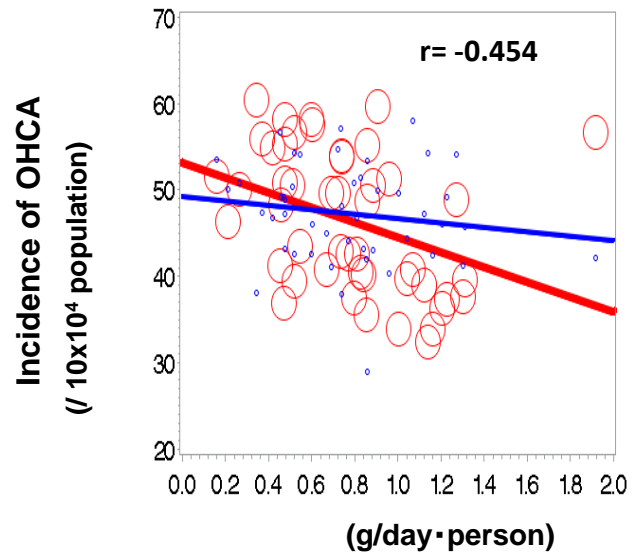
Fig.2

Fig. 3-A

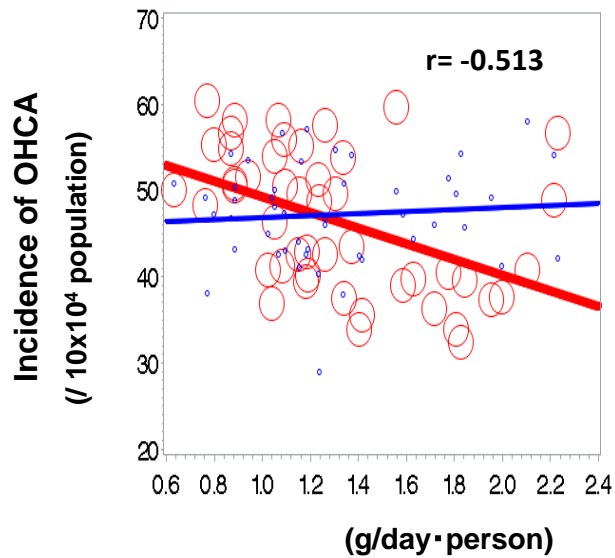
a *** Horse mackerel



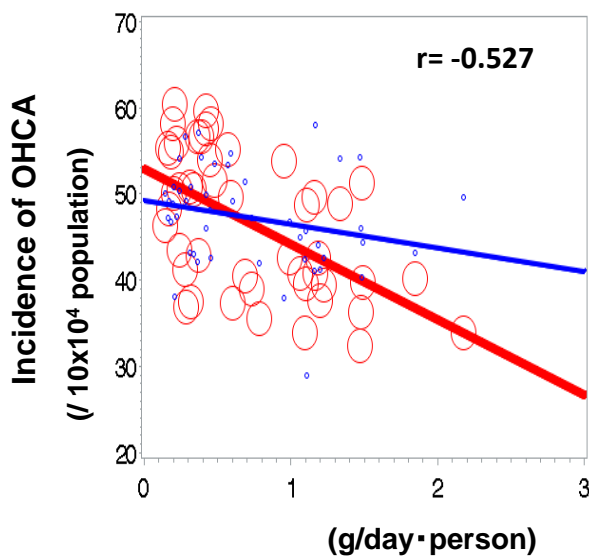
b ** Sardine



c *** Mackerel



d *** Sea bream



e *** Yellowtail

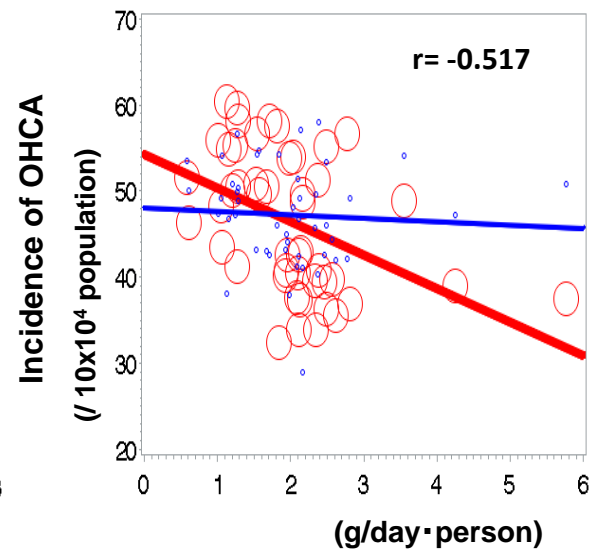
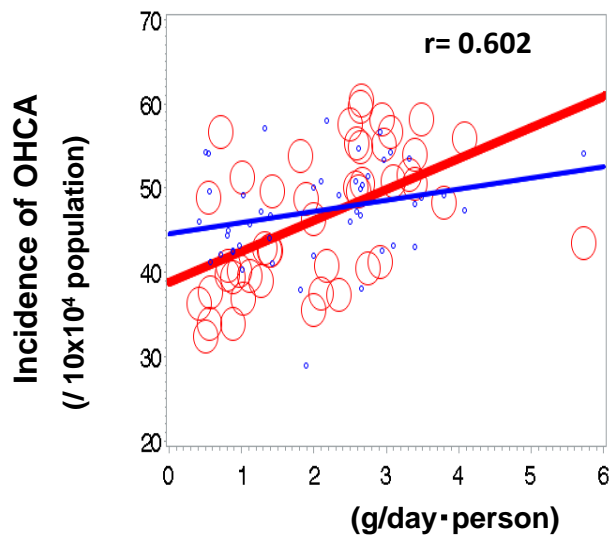
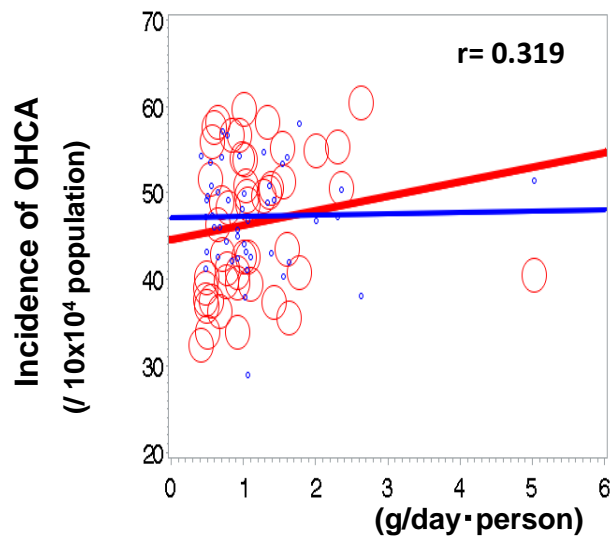


Fig. 3-B

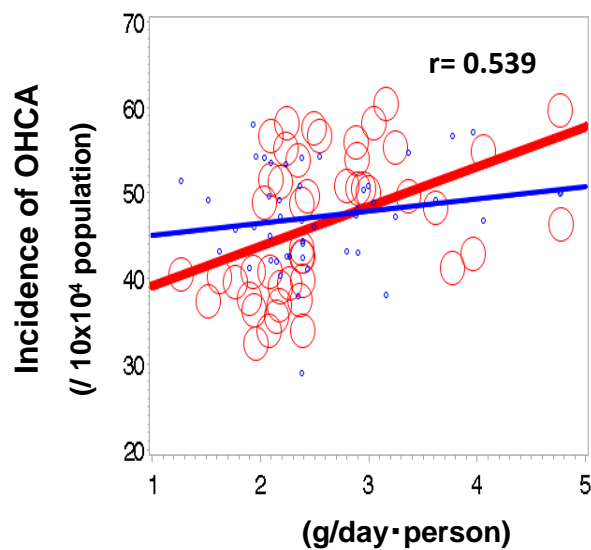
a *** Tuna



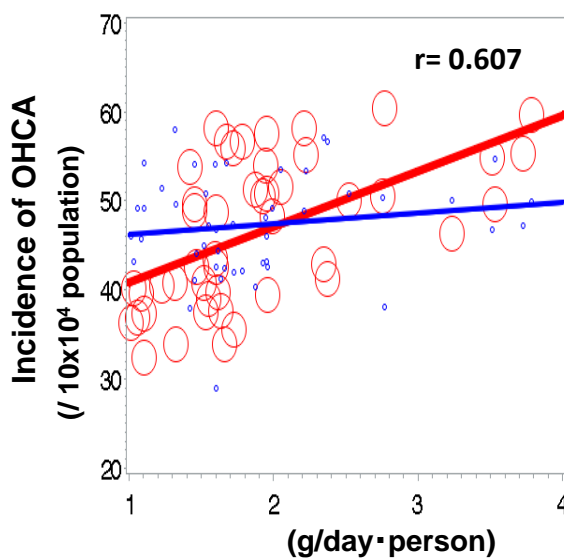
b * Bonito



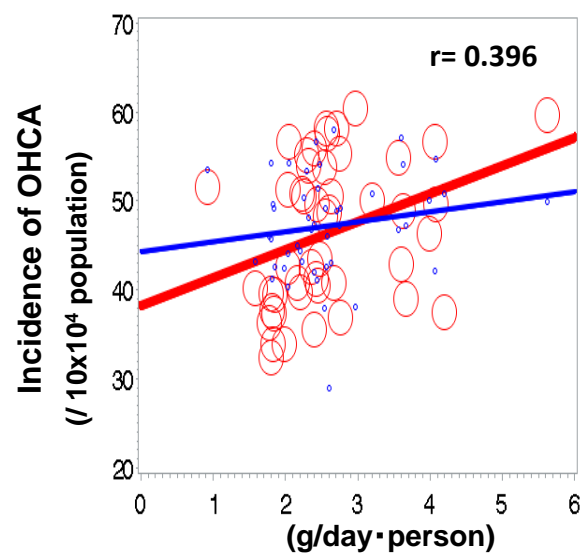
c *** Salmon



d *** Saury



e ** Cuttlefish



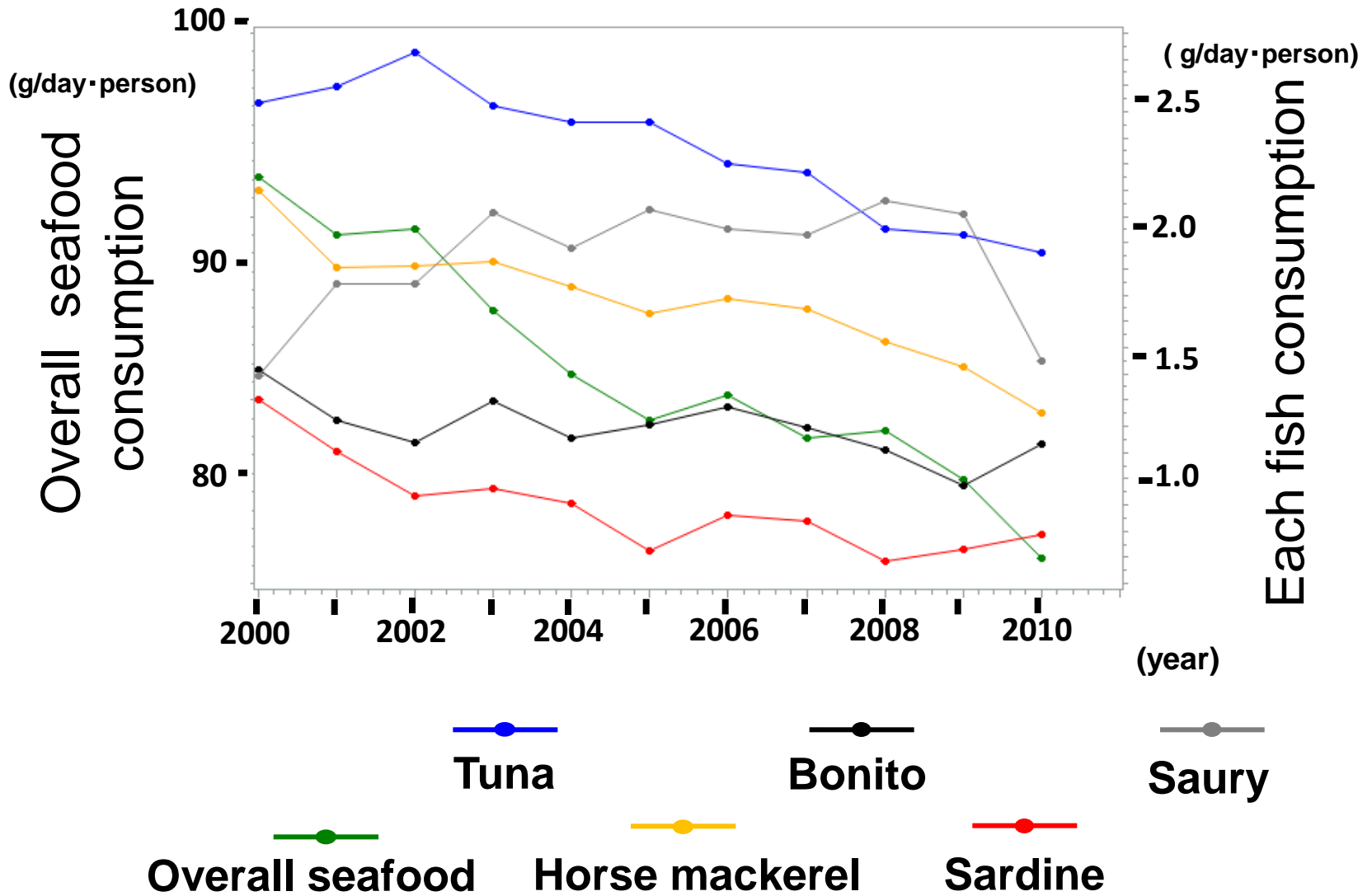


Fig.4

Table 1. Patient Characteristics

	Total (n=660,672)	Cardiac origin (n=364,547)	Non-cardiac origin (n=296,125)
Age, yrs	72 ± 18	75 ± 16*	68 ± 21
Male, n (%)	387,059(58.6)	211,623(58.1)*	175,436(59.2)
ROSC, n (%)	42,899(6.5)	23,587(6.5)	19,312(6.5)
1-month survival, n (%)	31,707(4.8)	19,530(5.4)*	12,177(4.1)
CPC1 or 2, n (%)	14,337(2.2)	10,812(3.0)*	3,525(1.2)
OPC1 or 2, n (%)	14,188(2.1)	10,714(2.9)*	3,474(1.2)
Initial rhythm			
VF	47,158(7.1)	40,549(11.1)*	6,609(2.2)
pulseless VT	1,627(0.2)	1,058(0.3)*	569(0.2)
PEA	140,691(21.3)	73,357(20.1)*	67,334(22.7)
Asystole	443,209(67.1)	235,657(64.6)*	207,552(70.1)

ROSC= return of spontaneous circulation

CPC= cerebral performance category, OPC= overall performance category

VF=ventricular fibrillation, VT=ventricular tachycardia, PEA=pulseless electrical activity

*: P<0.01 vs. Non-cardiac origin.

Table 2-A. Associations between the consumption of kinds of seafood and the age-adjust incidence of out-of-hospital cardiac arrest of cardiac origin

	consumption	r	p
Tuna, g	2.1 ± 1.2	0.602	<0.0001
Horse mackerel, g	1.5 ± 0.9	-0.568	<0.0001
Sardine, g	0.8 ± 0.4	-0.454	0.001
Bonito, g	1.2 ± 0.8	0.319	0.029
Flounder, g	1.3 ± 0.9	0.026	0.862
Salmon, g	2.6 ± 0.8	0.539	<0.0001
Mackerel, g	1.3 ± 0.4	-0.513	0.0002
Saury, g	1.9 ± 0.7	0.607	<0.0001
Sea bream, g	0.7 ± 0.5	-0.527	0.0001
Yellowtail, g	2.0 ± 0.9	-0.517	0.0002
Cuttlefish, g	2.6 ± 0.9	0.396	0.006
Octopus, g	0.7 ± 0.2	0.390	0.390
Shrimp, g	1.8 ± 0.4	-0.258	0.080
Crab, g	0.9 ± 0.7	0.007	0.966

Table 2-B. Associations between the consumption of kinds of seafood and salt consumption in the 47 prefectures of Japan

	consumption	r	p
Tuna, g	2.1 ± 1.2	-0.004	0.978
Horse mackerel, g	1.5 ± 0.9	-0.083	0.578
Sardine, g	0.8 ± 0.4	-0.14	0.345
Bonito, g	1.2 ± 0.8	0.002	0.991
Flounder, g	1.3 ± 0.9	0.388	0.007
Salmon, g	2.6 ± 0.8	0.359	0.013
Mackerel, g	1.3 ± 0.4	-0.042	0.781
Saury, g	1.9 ± 0.7	0.386	0.007
Sea bream, g	0.7 ± 0.5	-0.386	0.008
Yellowtail, g	2.0 ± 0.9	-0.116	0.436
Cuttlefish, g	2.6 ± 0.9	0.503	0.0003
Octopus, g	0.7 ± 0.2	-0.245	0.097
Shrimp, g	1.8 ± 0.4	-0.206	0.165
Crab, g	0.9 ± 0.7	-0.067	0.653

Table 3. Associations between the consumption of fatty acids and the age-adjust incidence of out-of-hospital cardiac arrest of cardiac origin

Fatty acid		r	p
Lipid	1.73 ± 0.27	-0.17	0.253
Total fatty acid, g	1.27 ± 0.20	-0.117	0.435
Saturated fatty acids, g	0.36 ± 0.06	-0.321	0.028
Monounsaturated fatty acid, g	0.55 ± 0.09	0.039	0.797
Polyunsaturated fatty acid, g	0.37 ± 0.06	-0.201	0.177
Omega-3 fatty acid, g	0.32 ± 0.05	-0.195	0.189
Omega-6 fatty acid, g	0.04 ± 0.01	-0.155	0.298
Lauric acid, mg	0.41 ± 0.08	-0.227	0.125
Myristic acid, mg	65.4 ± 11.3	0.087	0.561
Palmitic acid, mg	206.9 ± 36.2	-0.353	0.015
Stearic acid, mg	51.6 ± 9.7	-0.426	0.003
Oleic acid, mg	189.4 ± 32.1	-0.403	0.005
Linoleic acid, mg	21.2 ± 3.1	-0.086	0.566
Alpha linolenic acid, mg	12 ± 1.8	-0.059	0.693
Gamma linolenic acid, mg	1.3 ± 0.2	-0.117	0.434
Arachidonic acid, mg	12.4 ± 2.3	-0.384	0.008
Eicosapentaenoic acid , mg	88.3 ± 16.0	-0.286	0.052
Docosahexaenoic acid, mg	152.1 ± 23.0	-0.166	0.266

Table 4. Associations between risk factors and age-adjusted incidence of out-of-hospital cardiac arrest of cardiac origin

Risk factors		r	p
Sex ratio, %	58.0	-0.241	0.102
Salt consumption, g	2.1 ± 0.5	-0.123	0.411
Alcohol consumption, yen	38.2 ± 5.0	0.046	0.761
Tobacco consumption, yen	9.5 ± 2.0	0.122	0.414
Age-adjusted incidence of hypertension*	570.0 ± 77.0	-0.142	0.340
Age-adjusted incidence of dyslipidemia*	114.9 ± 23.3	-0.091	0.544
Participation rate in sports, %	63.5	0.108	0.470
Percentage of obesity, %	31.6	0.273	0.064
Rate of advancement to high school, %	98.0	-0.090	0.548

*: /10x 10⁴ person