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Cumulative impact of axial, structural, and repolarization ECG findings on long-term cardiovascular mortality among healthy individuals in Japan: National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged, 1980 and 1990

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Abstract

Aims: Various cohort studies have shown a close association between long-term cardiovascular disease (CVD) outcomes and individual electrocardiographic (ECG) abnormalities such as axial, structural, and repolarization changes. The combined effect of these ECG abnormalities, each assumed to be benign, has not been thoroughly investigated.

Methods and Results: Community-dwelling Japanese residents from the National Integrated Project for Perspective Observation of Non-Communicable Disease and its Trends in the Aged, 1980–2004 and 1990–2005 (NIPPON DATA80 and 90), were included in this study. Baseline ECG findings were classified using the Minnesota Code and categorized into axial (left axis deviation, clockwise rotation), structural (left ventricular hypertrophy, atrial enlargement), and repolarization (minor and major ST–T changes) abnormalities. The hazard ratios of the cumulative impacts of ECG findings on long-term CVD death were estimated by stratified Cox proportional hazard models, including adjustments for cohort strata. In all, 16,816 participants were evaluated. The average age was 51.2 ± 13.5 years; 42.7% participants were male. The duration of follow up was 300,924 person-years (mean 17.9 ± 5.8 years); there were 1218 CVD deaths during that time. Overall, 4203 participants (25.0%) had one or more categorical ECG abnormalities: 3648 (21.7%) had a single abnormality, and 555 (3.3%) had two or more. The risk of CVD mortality increased as the number of abnormalities accumulated (single abnormality HR 1.29, 95% CI 1.13–1.48; ≥2 abnormalities HR 2.10, 95% CI 1.73–2.53).

Conclusions: Individual ECG abnormalities had an additive effect in predicting CVD outcome risk in our large-scale cohort study.

Keywords

Cardiovascular outcomes, cohort study, electrocardiography, NIPPON DATA80, NIPPON DATA90

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Introduction

The use of screening electrocardiography (ECG) in healthy individuals is controversial. The US Preventive Services Task Force (USPSTF) does not recommend the use of screening ECGs because of insufficient evidence of any benefit.[1] Similarly, the American Heart Association guidelines consider screening ECGs for cardiovascular disease (CVD) risk assessments in asymptomatic individuals reasonable only in those with risk factors, such as hypertension and diabetes.[2] In Japan, various recommendations coexist. Screening ECGs are recommended as part of the worksite annual health check up, but in community-based medical examinations, they are only recommended for individuals with a high-risk profile.[3] The reason for this inconsistency is partly due to a lack of studies that have assessed the impact of frequently seen, but nonspecific, ECG findings.

The performance of screening ECGs have been studied previously in various situations, but their obvious prognostic implications remains limited to rarely encountered, significant ECG findings in healthy individuals. These finding include ST elevations/depressions, abnormal Q-waves, high-degree atrioventricular blocks, or arrhythmias such as atrial fibrillation, atrial flutter, and Wolff-Parkinson-White (WPW) syndrome. Large-scale cohort studies, including ours, have demonstrated statistically significant but clinically negligible associations between long-term CVD outcomes and nonspecific ECG findings, including major and minor ST–T segment abnormalities, left ventricular hypertrophy, left axis deviations, and clockwise rotations.[4–15] Despite this statistical association, the additional benefit that screening ECGs provide to asymptomatic individuals and whether they reclassify a patient's CVD risk remain controversial.

We hypothesized that the presence of these nonspecific, but highly frequent, ECG findings has an additive and clinically meaningful impact on long-term CVD outcomes. To assess the cumulative impact of nonspecific ECG abnormalities, we analysed data from the National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged, 1980–2004 and 1990–2005 (NIPPON DATA80 and 90). These were cohort studies, with large sample sizes, of healthy Japanese individuals. Assessing the cumulative risk of screening ECG abnormalities was thought to possibly help identify the individuals who are at higher risk of CVD events; this would help establish the potential benefit of screening ECGs in asymptomatic individuals.

Methods

Participants

NIPPON DATA80 and 90 were studies conducted by the National Survey on Circulatory Disorders, Japan. The two cohort studies performed baseline surveys in 1980 and 1990, respectively. The details of these cohort studies have been previously reported.[13,16–27] Approval for the present study was obtained from the institutional review board of Shiga University of Medical Science (no. 12-18, 2000).

In this study, we analysed integrated data from NIPPON DATA80 and 90; a total of 18,929 healthy participants (10,546 from NIPPON DATA80 and 8383 from NIPPON DATA90) were included. There were 8143 men and 10,786 women, all aged 30 years or more, from 300 randomly selected districts throughout Japan. Participants were followed from 1980 through 2004 in NIPPON DATA80, and from 1990 through 2005 in NIPPON DATA90. The data consisted of patient histories, physical examination results, blood test results, standard 12-lead ECG recordings, and self-administered lifestyle questionnaires.

We excluded 2113 of the 18,929 participants for the following reasons: absence of a permanent address that was needed to link to vital statistical records ($n=1388$; 1104 from NIPPON DATA80 and 284 from NIPPON DATA90); missing information in the baseline survey ($n=118$; 2 from NIPPON DATA80 and 116 from NIPPON DATA90); history of known myocardial infarction or stroke ($n=392$; 153 from NIPPON DATA80 and 239 from NIPPON DATA90); and specific ECG findings, including a moderate or severe Q-wave abnormality (Minnesota Code, MC, 1-1, 1-2), complete atrioventricular block (MC 6-1), WPW syndrome (MC 6-4), or atrial fibrillation or flutter (MC 8-3-1 or 8-3-2) ($n=215$; 122 from NIPPON DATA80 and 93 from NIPPON DATA90). The final sample comprised 16,816 participants (Figure 1).

Baseline examination

At the time of the baseline survey (1980 for NIPPON DATA80 and 1990 for NIPPON DATA90), a standard 12-lead ECG was recorded, with each patient in the supine position. A Working Group of ECG Coding for the National Survey on Circulatory Disorders evaluated the electrocardiograms; two independently trained coders in accordance with the MC guidelines.[13,16,17,20,25] In cases of discordant results, the final judgment was made by a panel of study epidemiologists and cardiologists.

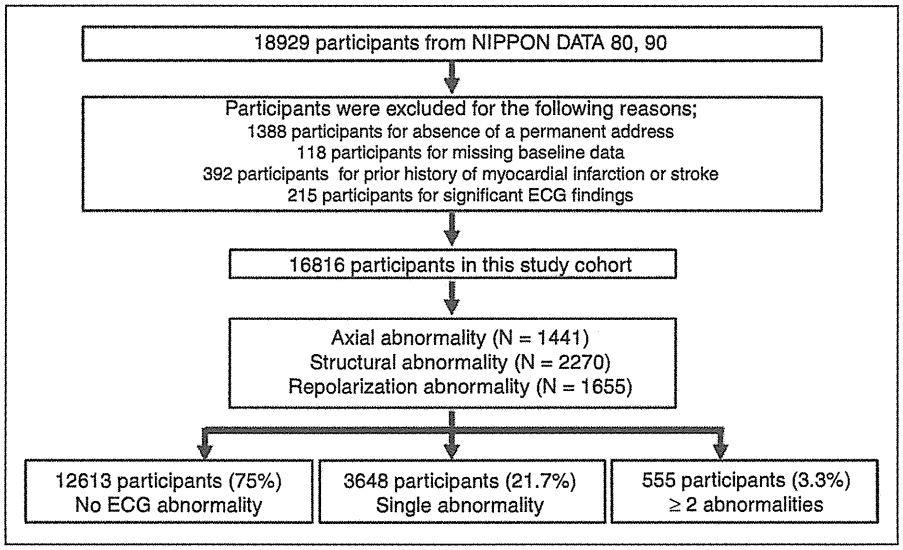

Figure 1. Study cohort creation.
ECG, electrocardiogram.

After exclusion of the above-mentioned, significant ECG findings that required medical attention, the remaining ECG findings were classified into three categorical abnormalities based on their electrophysiological perspectives: axial (left axis deviation or clockwise rotation; MC 2-1 or 9-4-2), structural (left ventricular hypertrophy or atrial enlargement; MC 3-1, 3-3, 9-3-1, or 9-3-2), and repolarization (minor and major ST–T changes; MC 4-1, 4-2, 4-3, 4-4, 5-1, 5-2, 5-3, or 5-4). Patients were classified into three groups: no ECG abnormality, a single categorical abnormality, and ≥2 categorical abnormalities.

Baseline blood pressures were measured in the right arm of seated participants in both cohorts by a trained public health nurse, using a standard mercury sphygmomanometer. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, use of antihypertensive agents, or any combination of these. Nonfasting blood samples were drawn, centrifuged within 60 minutes of collection, and stored at −70°C until analysis. Serum total cholesterol was measured by the Liebermann-Burchard direct method in NIPPON DATA80[23] and enzymically in NIPPON DATA90.[27] Serum glucose was measured by the neocuproine method in NIPPON DATA80.[24] Because the current standard method of blood glucose levels is the hexokinase method, the neocuproine serum glucose levels were adjusted by the following formula: 0.047 × (glucose concentration in mg/dl) − 0.541.24 Plasma glucose was measured enzymically in NIPPON DATA90.[18] Diabetes mellitus was defined as a plasma or serum glucose level of ≥11.1 mmol/l, the use of medications for diabetes mellitus, or both. Serum creatinine was measured using the alkaline picric acid method (Jaffe's method) in both cohorts. Body mass indexes were calculated as the patient's weight in kg divided by the square of his/her height in metres. Public health nurses obtained medical histories, including each patient's smoking and alcohol consumption status.

Follow-up survey

The National Vital Statistics Database of Japan was used to obtain the underlying causes of death for patients who died during the study period, with permission from the Management and Coordination Agency, Government of Japan. The causes of death were coded in accordance with the International Classification of Diseases ninth revision (ICD-9) through to the end of 1994 and the ICD tenth revision (ICD-10) from the beginning of 1995. The details of the cause-of-death classification in the present study are described elsewhere.[13,16–27]

Statistical analysis

We compared the hazard ratios among the three groups (no ECG abnormality, a single categorical abnormality, and ≥2 categorical abnormalities). To compare baseline characteristics, the chi-squared test or Fisher's exact test was used for categorical variables and one-way analysis of variance (ANOVA) was used for continuous variables. Event-free survival was estimated by the Kaplan–Meier method and statistical differences were evaluated using a Log-rank test. Cox proportional

hazards models were used to examine the cumulative effects of ECG categorical abnormalities on CVD outcomes. We analysed the integrated data of the NIPPON DATA80 and 90 cohorts to ensure sufficient numbers of events. Baseline hazards between the study cohorts were allowed to be different by including an adjustment for cohort strata in the Cox models.[28]

The covariates included in the model were age, gender, body mass index, smoking status (never or past versus current smoker), diabetes mellitus, systolic blood pressure, total cholesterol, and serum creatinine. These covariates were clinically related to CVD events and significantly associated with CVD deaths in our univariate analysis ($p < 0.05$). All p-values were 2-sided, and the significance level was set at $p = 0.05$ for all analyses. All statistical analyses were performed using Statistical Package for the Social Sciences version 20 (SPSS, Chicago, IL, USA).

Results

A total of 16,816 participants were analysed. The age of the participants was (mean ± SD) 51.2 ± 13.5 years, and 42.7% were male. The total duration of follow up was 300,924 person-years (mean 17.9 ± 5.8 years). There were 1218 CVD deaths during the follow-up period: 248 due to coronary artery disease, 239 due to heart failure, and 548 due to stroke events. Overall, 4203 participants (25.0%) had one or more categorical ECG abnormalities: 3648 (21.7%) had a single categorical abnormality (1127 axis abnormalities, 1808 structural abnormalities, 713 repolarization abnormalities) and 555 (3.3%) had two or more categorical abnormalities (Figure 1).

Table 1 shows the baseline characteristics of the participants, according to the number of categorical ECG abnormalities. The comparison of the baseline characteristics of NIPPON DATA80 and 90 are described in Supplementary Table 1 (available online). The number of abnormalities increased with increasing age, systolic and diastolic blood pressure values, fasting blood glucose levels, and creatinine levels. Furthermore, the number of abnormalities was also correlated with the prevalence of hypertension, diabetes mellitus, and current smoking.

Figure 2 shows Kaplan–Meier survival curves for CVD deaths, according to the numbers of categorical ECG abnormalities. As indicated in the curve, participants with single or more categorical ECG abnormalities at baseline had a significantly lower survival rate during the follow-up period, and individual ECG categorical abnormalities had an additive effect on CVD mortality (Log-rank test; $p < 0.001$).

Table 2 shows the adjusted hazard ratios for each outcome. After adjusting for confounding factors, the risk of CVD mortality increased as the number of categorical ECG abnormalities accumulated (HR 1.29, 95% CI 1.13–1.48 in patients with a single abnormality; HR 2.10, 95% CI 1.73–2.53 in patients with ≥2 abnormalities). The prognostic impact of the accumulated categorical ECG abnormalities was significant in all types of CVD deaths. Each study cohort (NIPPON DATA80 versus 90) demonstrated the same tendencies seen in the overall analysis (Supplementary Table 2), although there were insufficient event numbers to draw conclusive results from the individual cohorts.

Figure 3 shows the adjusted hazard ratios for CVD mortality in each group. The presence of axial,

Table 1. Baseline demographics according to the numbers of electrocardiogram categorical abnormality

	No abnormality ($n = 12613$)	Single abnormality ($n = 3648$)	≥2 abnormalities ($n = 555$)	p-value
Male	4895 (38.8)	1995 (54.7)	283 (51.0)	<0.001
Age (years)	50.1 ± 13.2	53.5 ± 13.5	61.0 ± 13.1	<0.001
Body mass index (kg/m^2)	22.8 ± 3.1	22.8 ± 3.3	22.9 ± 3.5	0.696
Hypertension	2097 (16.6)	1054 (28.9)	285 (51.4)	<0.001
Diabetes mellitus	442 (3.5)	166 (4.6)	34 (6.1)	<0.001
Current smoking	3575 (28.4)	1399 (38.4)	206 (37.1)	<0.001
Systolic blood pressure (mmHg)	133 ± 19	141 ± 22	158 ± 26	<0.001
Diastolic blood pressure (mmHg)	80 ± 11	84 ± 12	89 ± 15	<0.001
Laboratory tests				
Total cholesterol (mg/dl)	195 ± 36	195 ± 37	196 ± 38	0.732
Nonfasting blood glucose (mg/dl)	100 ± 29	103 ± 33	113 ± 43	<0.001
Creatinine (mg/dl)	0.87 ± 0.28	0.91 ± 0.28	0.95 ± 0.25	<0.001

Values are mean ± SD or n (%).

structural, and repolarization abnormalities was independently associated with adverse CVD events (HR 1.30, 95% CI 1.05–1.61 for axial abnormalities; HR 1.25, 95% CI 1.04–1.50 for structural abnormalities; HR 1.37, 95% CI 1.11–1.70 for repolarization abnormalities). A cumulative effect of ECG abnormalities on increasing CVD mortality was also identified (HR 2.10, 95% CI 1.73–2.53 for ≥2 categorical abnormalities).

Discussion

Individual, nonspecific ECG abnormalities were shown to have a cumulative impact on predicting the risk of CVD outcomes in a Japanese population without a history of myocardial infarction or stroke. This impact was applicable to all types of CVD mortalities, including coronary heart disease, heart failure, and stroke. The cumulative effect of individual ECG abnormalities may be useful for risk stratification in healthy individuals.

Whether screening ECGs provide benefits to asymptomatic individuals, or whether they aid in reclassifying their CVD risk, remains controversial.[1–3] CVD is the leading cause of death throughout the world[29] and is often asymptomatic before the first cardiac event, which may consist of sudden cardiac death, myocardial infarction, or heart failure.[30] In Japan, regular health checkups are widely conducted, particularly among the working population. Screening ECGs are mandated for all employees, under legal regulations on industrial safety and health.[3] In contrast, no regulations or guidelines mandate routine ECG screenings for individuals who are self-employed, homemakers, or retired. In 2004, the USPSTF recommended against screening

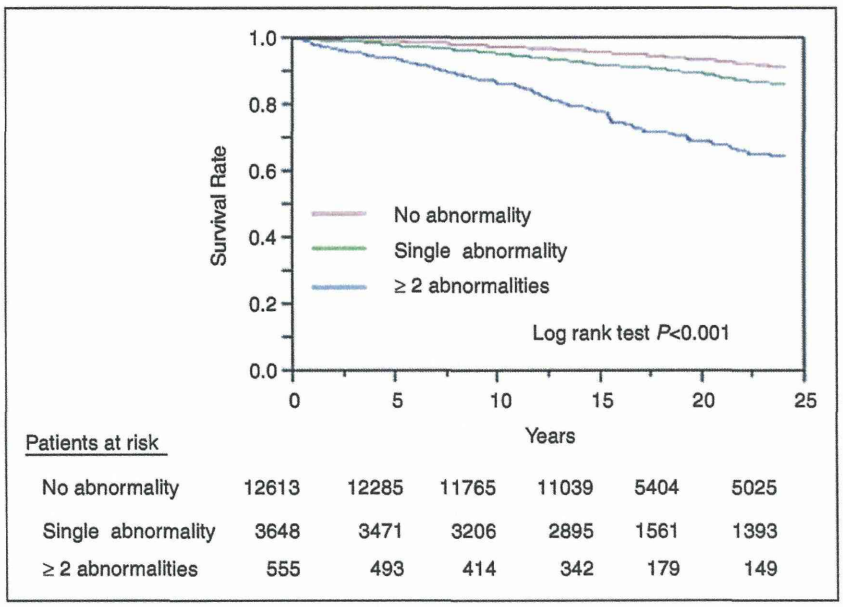

Figure 2. Kaplan–Meier estimates of cardiovascular disease cumulative hazard in accordance with the numbers of categorical electrocardiogram abnormalities.

Table 2. Adjusted hazard ratios in accordance with the numbers of categorical abnormalities

	Single abnormality	*p*-value	≥2 abnormalities	*p*-value
All-cause death	1.23 (1.14–1.32)	<0.001	1.44 (1.26–1.64)	<0.001
Cardiovascular death	1.29 (1.13–1.48)	0.001	2.10 (1.73–2.53)	<0.001
Coronary artery disease	1.33 (1.00–1.78)	0.053	2.24 (1.47–3.43)	<0.001
Heart failure	1.36 (1.02–1.83)	0.038	1.82 (1.17–2.83)	0.008
Stroke	1.25 (1.02–1.51)	0.028	1.93 (1.45–2.57)	<0.001

Values are hazard ratio (95% CI).; Multivariate analysis adjusted for age, sex, body mass index, smoking habit, diabetes mellitus, systolic blood pressure, total cholesterol, and serum creatinine. All analyses were stratified by cohort.

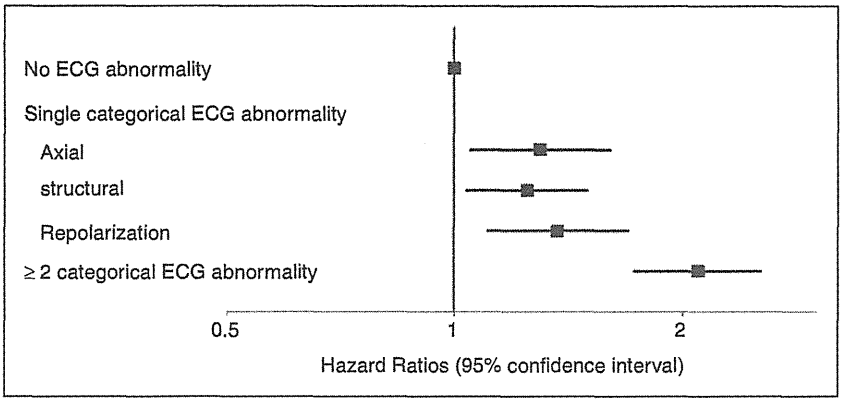

Figure 3. Cardiovascular disease deaths.
Multivariate analysis adjusted for age, gender, body mass index, smoking status, diabetes mellitus, systolic blood pressure, total cholesterol, and serum creatinine.
ECG, electrocardiogram.

with resting ECGs in asymptomatic individuals.[1] This recommendation was based on the lack of clinical trials evaluating outcomes after ECG screenings and on the concept that abnormalities in resting ECGs are unlikely to change management decisions for persons who are already classified on the basis of traditional risk factor assessments.[31] The results of our study, that a single ECG abnormality has a minimal impact on CVD outcomes, would seem to agree with the USPSTF recommendation. However, we also observed that cumulative ECG abnormalities have a strong impact on CVD outcomes; this may indicate a potential benefit for screening ECGs.

Unlike findings in other studies, our findings suggest that adding up the relatively benign ECG findings of axial, structural, and repolarization abnormalities to obtain a cumulative number may be more beneficial than focusing on the individual ECG findings. Many previous studies addressed the concept of 'major' and 'minor' abnormalities in screening ECGs, and the impact of these abnormalities on CVD outcomes;[4,11,14,32–34] however, these studies had several limitations. First, the definitions of 'major' and 'minor' abnormalities varied.[31] Second, these studies did not address some ECG abnormalities, such as clockwise rotations, which have recently been reported as important. Third, the same categorical abnormalities, such as ST–T changes or T-wave inversions, were included in both 'major' and 'minor' abnormality classifications. Therefore, the additive effect of ECG abnormalities was not assessed. As some changes were assigned to both the 'major' and 'minor' categories, adding these categories would have led to duplication and misrepresentation of the additive effect. Our new concept of using cumulative ECG abnormalities may help physicians to understand the clinical significance of these abnormalities and to stratify their potential hazards.

Limitations

Our study has several limitations. Although the current study involved only Japanese participants, previous studies have shown that the prognostic value of several ECG findings, proven in the USA and Europe, was also applicable to Japanese populations.[16,20,25] Second, we used a single, baseline ECG result for analysis. Single biological measurements are known to be subject to variability and the observed ECG abnormalities may have changed over time. Third, although we had independently trained ECG readers to code each tracing, automated measurement systems for ECGs were not available at the time of the baseline evaluations (1980 and 1990). Therefore, a panel of experts, including epidemiologists and cardiologists, confirmed the findings. Fourth, we did not analyse a single cohort but the integrated data from two cohorts. However, as discussed above, the two study populations showed the same trends in individual analyses as in the combined analysis, and the ECG findings are objective and, therefore, insensitive to differences between cohorts. Fifth, only a single underlying cause of death is described in the National Vital Statistics Database of Japan, which was used to obtain the causes of death in this study. For this reason, the mortality statistics for coronary heart disease may have been underestimated because deaths coded as 'heart failure' may have hidden some coronary events.[35] However, we believe this does not affect our results since we also assessed 'heart failure' as an endpoint, and the present study focused mainly on all cardiovascular mortality. Finally, the present study did not show the actual reclassification based on the results of screening ECGs,

according to the previously established risk stratifications (e.g. Framingham risk scores). However, using Framingham risk scores is probably not helpful, because they have been proven to not work well in Japanese populations, in which the age-adjusted mortality due to coronary artery disease is the lowest amongst all developed countries.[36] The new guidelines of the Japan Atherosclerosis Society (JAS) do not use Framingham risk scores for absolute risk assessment;[37] instead, they use the NIPPON DATA risk chart.[38] An assessment of how accurately the model containing nonspecific ECG findings classifies subjects into risk categories per the JAS guidelines may be feasible; however, such an analysis was not within the scope of the present study.

Conclusions

We found that individual nonspecific ECG abnormalities had an additive effect on predicting the risk of CVD outcomes in this large-scale Japanese cohort. This cumulative impact was notable for all types of CVD mortality, indicating the potential benefit of screening ECGs in healthy individuals.

Declaration

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

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Conflict of interest

The authors declare that there is no conflict of interest.

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６．メタボリック症候群が日米の循環器疾患死亡リスクに及ぼす影響

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背景・目的：メタボリック症候群(MS)の有病率および循環器疾患（CVD）死亡は、日本に比べて米国の方が高い。しかし両国における MS 有病率の差がどれほど CVD 死亡の差を説明するかに関しては不明である。
本研究の目的は、MS が CVD 過剰死亡に及ぼす影響を米国と日本とで比較することである。

方法：第三次《米》国民健康栄養調査(NHANESIII 対象者数 12,561 人)および NIPPON DATA（対象者数 7453 人）とのデータを解析した。
MS は以下の 5 項目のうち 3 つ以上を満たすものと定義した：肥満、血圧高値、HDL-コレステロール低値、 HbA1c（糖化ヘモグロビン）高値、中性脂肪高値。

結果：米国では、追跡期間 13.8 年（中央値）のうちに 1683 例の CVD 死亡（11.75 例/1000 人年）が、日本では、追跡期間 15 年（中央値）のうちに 369 例の CVD 死亡（3.56 例/1000 人年）が観察された。MS の年齢調整有病率は米国で 26.7%、日本で 19.3%であった。MS の 5 項目のうち CVD 死亡の有意な危険因子であったのは、米国では肥満、血圧高値、中性脂肪高値、HbA1c 高値、日本では血圧高値、HbA1c 高値であった。日本に比べた場合の米国における循環器疾患過剰死亡のうち 13.4%が MS により、また 44%が MS およびベースラインにおける CVD 既往にて説明できた。

結論：米国の CVD 死亡リスクが日本より高い点に関して、MS とベースラインの CVD 既往により（ある程度）説明できることが本研究により初めて定量的に示された。

Impact of Metabolic Syndrome on the Risk of Cardiovascular Disease Mortality in the United States and in Japan

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The United States has a higher prevalence of metabolic syndrome (MS) and cardiovascular disease (CVD) mortality than Japan, but it is unknown how much of the difference in MS accounts for the mortality difference. The aim of this study was to examine the impact of MS on the excess CVD mortality in the United States compared with that in Japan. Data from the United States Third National Health and Nutrition Examination Survey (NHANES III; n = 12,561) and the Japanese National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in Aged (NIPPON DATA; n = 7,453) were analyzed. MS was defined as ≥3 of 5 risk factors (obesity, high blood pressure, decreased high-density lipoprotein cholesterol, elevated glycosylated hemoglobin, and elevated triglycerides). The results show that after a median of 13.8 years of follow-up in the United States, 1,683 patients died from CVD (11.75 per 1,000 person-years), and after a median of 15 years of follow-up in Japan, 369 patients died from CVD (3.56 per 1,000 person-years). The age-adjusted prevalence of MS was 26.7% in the United States and 19.3% in Japan. Of 5 MS factors, obesity, high blood pressure, elevated triglycerides, and glycosylated hemoglobin in the United States, and high blood pressure and elevated glycosylated hemoglobin in Japan were significant risk factors for CVD mortality. Estimates of 13.3% and 44% of the excess CVD mortality for the United States could be explained by the higher prevalence of MS and MS plus baseline CVD history than in Japan. In conclusion, the present study is the first to quantitatively demonstrate that MS and MS plus baseline CVD history may significantly contribute to the explanation of excess CVD mortality in the United States compared with Japan. (Am J Cardiol 2014;113:84–89)

Cardiovascular disease (CVD) has been established as a clear threat to human health. A number of studies have reported that metabolic risk factors, a group of cofactors, increase the risk for CVD.[1–6] The United States has higher CVD mortality than most developed countries, including Japan. However, few internationally comparative studies have been conducted to examine the impact of metabolic factors on the risk for CVD mortality across countries.[7] Given the differences in the burden of CVD and potential differences in the risk factors, a comparative study of the outcome and risk factors, using nationally representative samples, may add new insights into the studies of CVD. In the present study, we hypothesized that the prevalence of metabolic risk factors was significantly higher in the United States and that the difference is a significant contributor to the excess CVD mortality for the United States compared with Japan. To test these hypotheses, we used data from the United States Third National Health and Nutrition Examination Survey (NHANES III)[8] and the Japanese National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in Aged (NIPPON DATA).[4,9–12]

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See page 89 for disclosure information.

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Table 1
Baseline characteristics of participants aged >30 years in the Third National Health and Nutrition Examination Survey (1988 to 1994) and in the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in Aged (1990)

Variable	Men			Women		
	United States (n = 5,896)	Japan (n = 3,129)	p Value*	United States (n = 6,665)	Japan (n = 4,324)	p Value*
Continuous variables						
Age (yrs)	49.48 ± 0.36	53.36 ± 0.24	<0.001	51.32 ± 0.52	52.48 ± 0.21	0.03
BMI (kg/m^2)	27.00 ± 0.11	22.96 ± 0.05	<0.001	26.98 ± 0.17	22.86 ± 0.05	<0.001
Systolic BP (mm Hg)	126.83 ± 0.43	138.01 ± 0.36	<0.001	123.86 ± 0.54	133.72 ± 0.32	<0.001
Diastolic BP (mm Hg)	78.01 ± 0.22	83.78 ± 0.21	<0.001	73.27 ± 0.22	79.62 ± 0.18	<0.001
Total cholesterol (mg/dl)	208.83 ± 1.03	198.58 ± 0.66	<0.001	212.64 ± 0.94	206.82 ± 0.59	<0.001
HDL cholesterol (mg/dl)	45.32 ± 0.38	50.37 ± 0.27	<0.001	55.34 ± 0.42	56.73 ± 0.23	0.002
TG (mg/dl)†	165.73 ± 3.10	147.62 ± 1.88	<0.001	139.33 ± 3.09	121.12 ± 1.20	<0.001
HbA_{1c} (%)	5.49 ± 0.02	5.37 ± 0.01	<0.001	5.45 ± 0.03	5.25 ± 0.01	<0.001
Categorical variables						
Smoking status			<0.001			<0.001
Never	53.77%	20.29%		71.63%	88.32%	
Former	8.76%	24.32%		4.77%	2.52%	
Current	37.47%	55.39%		23.60%	9.16%	
Current alcohol use‡	62.00%	65.10%	<0.001	39.16%	7.54%	<0.001
Hypertension§	37.47%	53.563%	<0.001	37.15%	46.21%	<0.001
Hypercholesterolemia‖	35.31%	17.034%	<0.001	36.92%	22.94%	<0.001
Diabetes mellitus¶	9.14%	8.69%	0.35	9.57%	5.20%	<0.001
Coronary heart disease#	6.13%	3.10%	<0.001	3.27%	2.61%	0.10
Stroke#	2.49%	2.52%	0.13	2.49%	1.36%	<0.001

Data are expressed as mean ± SEM or percentages. To convert total and HDL cholesterol from milligrams per deciliter to millimoles per liter, divide by 38.61. To convert TG from milligrams per deciliter to millimoles per liter, divide by 89.

* For age-adjusted tests using analysis of covariance for continuous variables and chi-square tests for categorical variables, expect for testing difference in age between countries.

† Nonfasting in Japanese data.

‡ Defined by self-report, if a subject had consumed >1 drink of any type (beer, wine, or liquor) per month.

§ Defined as self-report of physician diagnosis of hypertension, systolic BP >140 mm Hg or diastolic BP >90 mm Hg, or use of antihypertensive medication.

‖ Defined as self-report of physician diagnosis of hyperlipidemia or total cholesterol >240 mg/dl (6.2 mmol/L).

¶ Defined as self-report of physician diagnosis of diabetes mellitus or serum HbA_{1c} >6.5% or use of medication to treat diabetes.

Defined as self-report of physician diagnosis of each disease.

Methods

NHANES III (1988 to 1994) is a nationwide survey conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention in the United States, which gathers information representing the health and nutritional status of the noninstitutionalized civilian United States population aged ≥2 months.[8] The study consists of interviews, physical examinations, and data from blood sample analyses. A detailed description of the survey and its sampling procedures is available at the NHANES III Web site.[8] The NHANES III mortality follow-up study was conducted and linked with the National Death Index.[13] This linked study provides mortality follow-up from the date of baseline NHANES III participants (1988 to 1994) through December 31, 2006.[13] In the study, we included participants aged ≥30 years because CVD mortality is substantially lower in those aged <30 years. Of 15,042 participants aged ≥30 years, we excluded 22 who had ineligible measurements on their vital statistics and 2,459 who did not complete all measurements of 5 metabolic factors (body mass index [BMI], blood pressure [BP], serum high-density lipoprotein cholesterol, triglyceride [TG], and/or glycemia). The remaining 12,561 subjects (83.5% of 15,042) were included in the study sample (5,896 male, 6,665 female). Data from NIPPON DATA90 used in the present study were approved by the NIPPON DATA steering committee and the institutional review board of Shiga University of Medical Science.

NIPPON DATA90, supported by the Ministry of Health and Welfare of Japan, is a cohort study of representative Japanese subjects aged ≥30 years at baseline surveys (1990). Participants in the study were randomly selected from 300 districts throughout Japan. Data from physical examinations, blood tests, and a self-administered questionnaire on lifestyle were collected in person at individual districts' health care centers. Mortality follow-up was conducted for all participants from baseline to November 2005.[9,14,15] For the purpose of the comparison, we used NIPPON DATA90 because it was conducted approximately in the same time period (1990 to 2005) and had the same measures and standardizations as NHANES III (1988 to 2006).[9,11,12,16,17] Of 8,383 baseline participants aged ≥30 years, we excluded 284 who had invalid follow-up data and 646 who had no measurements of 5 metabolic risk factors. The remaining 7,453 patients (88.9% of 8,383) were included in the study. NHANES III was approved by the institutional review board of the National Center for Health Statistics.[8,13]

Several criteria for the definition of metabolic syndrome (MS) have been proposed.[12,18–20] In the present study, we

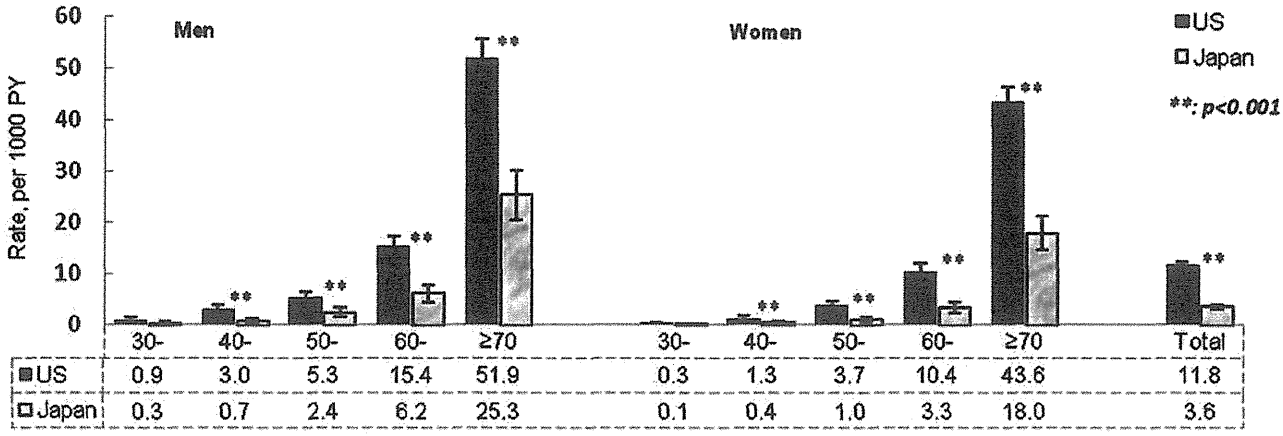

Figure 1. Age-specific mortality rate (per 1,000 person-years) from CVD for adult men and women in the United States and in Japan.

Table 2
Multivariate-adjusted hazard ratios of individual metabolic syndrome factors and metabolic syndrome for cardiovascular mortality in the United States and Japan

MS Relation to CVD Mortality		United States			Japan		
		Rate*	HR (95% CI)	p Value	Rate*	HR (95% CI)	p Value
In total participants							
1a	BMI >30 kg/m^2 (U.S.), BMI >25 kg/m^2 (Japan)†	25.3%	1.27 (1.05–1.55)	0.017	23.7%	0.80 (0.62–1.04)	0.09
1b	BMI >30 kg/m^2 (both countries)†	25.3%	1.27 (1.05–1.55)	0.017	2.4%	0.89 (0.39–2.06)	0.79
2	High BP‡	43.9%	1.51 (1.18–1.93)	<0.001	60.5%	2.62 (1.74–3.96)	<0.001
3	Low HDL cholesterol§	38.0%	1.18 (1.00–1.40)	0.06	29.1%	1.06 (0.85–1.33)	0.59
4	Elevated triglycerides‖	35.8%	1.17 (1.02–1.35)	0.028	19.1%	1.21 (0.95–1.54)	0.13
5	Elevated HbA_{1c}¶	25.7%	1.45 (1.25–1.68)	<0.001	12.4%	1.64 (1.31–2.07)	<0.001
	MS (Japan, >3 of 1a to 5 components)#	26.7%	1.43 (1.24–1.64)	<0.001	19.3%	1.35 (1.08–1.69)	0.027
	MS (U.S., >3 of 1b to 5 components)#	26.7%	1.43 (1.24–1.64)	<0.001	12.6%	1.53 (1.20–1.94)	0.001
In participants without baseline CVD histories							
1a	BMI >30 kg/m^2 (U.S.), BMI >25 kg/m^2 (Japan)†	25.0%	1.37 (1.10–1.69)	0.01	23.6%	0.83 (0.62–1.10)	0.18
1b	BMI >30 kg/m^2 (both countries)†	25.0%	1.37 (1.10–1.69)	0.01	2.4%	1.04 (0.45–2.39)	0.94
2	High BP‡	42.5%	1.66 (1.27–2.16)	<0.001	60.0%	2.58 (1.68–3.97)	<0.001
3	Low HDL cholesterol§	37.2%	1.06 (0.86–1.31)	0.58	29.0%	0.93 (0.72–1.20)	0.57
4	Elevated triglycerides‖	34.8%	1.09 (0.92–1.28)	0.30	18.8%	1.16 (0.88–1.52)	0.29
5	Elevated HbA_{1c}¶	24.9%	1.38 (1.10–1.73)	0.01	12.0%	1.62 (1.25–2.09)	<0.001
	MS (Japan, >3 of 1a to 5 components)#	25.7%	1.39 (1.17–1.66)	<0.001	18.9%	1.30 (1.01–1.67)	0.039
	MS (U.S., >3 of 1b to 5 components)#	25.7%	1.39 (1.17–1.66)	<0.001	12.2%	1.48 (1.13–1.93)	<0.01

Baseline CVD history includes coronary heart disease and stroke. HRs were adjusted for age, gender, smoking status, alcohol consumption, and total cholesterol.

* Age-adjusted rate using the world population as a standard across the 2 countries.

† Obesity was defined per the American Heart Association definition (BMI >30 kg/m^2) for the United States population and per the Japan Society for the Study of Obesity (BMI >25 kg/m^2) for the Japanese population.

‡ Defined as self-report of physician diagnosis of hypertension, systolic BP >130 mm Hg or diastolic BP >85 mmHg, or medication use.

§ Defined as HDL cholesterol <40 mg/dl (<1.0 mmol/L) for male participants and <50 mg/dl (<1.3 mmol/L) for female participants.

‖ Defined as nonfasting TG >200 mg/dl (>2.3 mmol/L) in Japan and as fasting TG >150 mg/dl (>1.7 mmol/L) in the United States.

¶ Defined as HbA_{1c} >5.7% or self-report of physician diagnosis of diabetes. We did not use glucose level, because fasting blood samples were not available for most participants in the Japanese data.

Defined as having >3 of the 5 factors (obesity, high BP, low HDL cholesterol, elevated TG, and elevated HbA_{1c}).

used the World Health Organization and the American Heart Association criteria by including 5 factors: (1) Obesity was defined using the World Health Organization criteria of BMI ≥30 kg/m^2. When doing data analysis for Japanese patients only, we also defined obesity using a cut-off point of BMI ≥25 kg/m^2, according to the criteria of the Japan Society for the Study of Obesity.[21] (2) High BP was defined as systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or current use of antihypertensive medication. (3) Decreased high-density lipoprotein (HDL) cholesterol was defined as HDL cholesterol <40 mg/dl (<1.0 mmol/L) for male subjects and HDL cholesterol <50 mg/dl (<1.3 mmol/L) for female subjects.

Table 3
Hazard ratios and 95% confidence intervals for the likelihood of cardiovascular disease mortality between the United States and Japan

Model	Covariates in the Model	United States vs Japan		% of Excess Mortality Accounted For*
		HR (95% CI)	p Value	
In total participants				
M1†	Basic model	2.01 (1.84–2.21)	<0.001	Base model
M2	Adjusted for M1 + obesity (BMI >30 kg/m^2)	1.90 (1.71–2.11)	<0.001	11.26%
M3	Adjusted for M1 + high BP	2.12 (1.93–2.32)	<0.001	10.28%
M4	Adjusted for M1 + low HDL cholesterol	2.00 (1.82–2.19)	<0.001	1.48%
M5	Adjusted for M1 + elevated TG	1.96 (1.79–2.15)	<0.001	5.04%
M6	Adjusted for M1 + elevated HbA_{1c}	1.85 (1.67–2.06)	<0.001	15.81%
M7	Adjusted for M1 + MS‡ (>3 of 5 factors)	1.88 (1.71–2.06)	<0.001	13.34%
M8	Adjusted for M7 + baseline CVD history	1.57 (1.22–2.01)	<0.001	44.17%
In participants without baseline CVD histories				
M1†	Basic model	1.81 (1.62–2.03)	<0.001	Base model
M2	Adjusted for M1 + obesity (BMI >30 kg/m^2)	1.69 (1.49–1.92)	<0.001	15.04%
M3	Adjusted for M1 + high BP	1.92 (1.72–2.15)	<0.001	13.69%
M4	Adjusted for M1 + low HDL cholesterol	1.81 (1.62–2.03)	<0.001	0.25%
M5	Adjusted for M1 + elevated TG	1.79 (1.60–2.00)	<0.001	2.71%
M6	Adjusted for M1 + elevated HbA_{1c}	1.69 (1.48–1.92)	<0.001	15.17%
M7	Adjusted for M1 + MS‡ (>3 of 5 factors)	1.70 (1.52–1.91)	<0.001	13.19%

Percentage of change = (HR_1 HR_2)/(HR_1 1) × 100 (keeping model 1 as HR_1).

* Percentage of the excess CVD and all-cause mortality in the United States that was accounted for by adding the covariates from model 2 to model 8 (in addition to covariates adjusted in model 1).

† Model 1, the basic model, was adjusted for age, gender, smoking, alcohol consumption, and total cholesterol level.

‡ Defined as having >3 of the 5 factors (obesity, high BP, low HDL cholesterol, elevated TG, and elevated HbA_{1c}).

(4) Elevated glucose was defined as serum glycosylated hemoglobin (HbA_{1c}) ≥5.7%. We used HbA_{1c} because it does not require a fasting blood sample. HbA_{1c} level has been shown to be a highly reliable and correlated marker of fasting glucose in several studies when fasting sample is not available.[22 25] Participants with previous diagnoses of diabetes or those using antidiabetic medications (insulin or oral agents) were classified as having elevated glucose.[22] (5) Elevated serum TG was defined as serum TG ≥150 mg/dl (≥1.7 mmol/L) for a fasting sample or TG ≥200 mg/dl (≥2.3 mmol/L) for a nonfasting sample.[3] Subjects with ≥3 of 5 MS components were classified having MS.[6,24]

The 2 countries' CVD deaths were classified using the International Classification of Diseases, 10th Revision as CVD (codes I00 to I99), coronary heart disease (codes I20 to I25), and cerebrovascular disease (codes I60 to I69).

A serial analysis was conducted. First, we described baseline characteristics of participants by gender and country. Analysis of covariance and chi-square tests were used in the descriptive analysis. The age-adjusted prevalence of MS was estimated by the direct method using the World Standard Population.[26,27] Second, we used a Cox proportional-hazards regression model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of individual MS factors and MS for the risk for CVD mortality. To verify the Cox proportional-hazards assumptions, we used plots of the log (log) survival curves and Schoenfeld residuals. Third, we examined the impact of MS on the excess CVD mortality of the United States compared with Japan by conducting 8 multivariate models. Model 1 estimated the HR of the United States versus Japan for CVD mortality and was adjusted for 5 covariates (age, gender, smoking status, alcohol consumption, and total cholesterol). Model 1 served as the base model. Models 2 to 6 adjusted for the same 5 covariates used in model 1 along with each of 5 MS components separately in a step-by-step manner. Model 7 examined the total impact of MS on CVD mortality, and model 8 included adjustment for baseline CVD conditions (coronary heart disease and stroke). The magnitudes of the impact of each MS component and MS on the excess CVD mortality of the United States compared with Japan were expressed using the formula (HR_1 HR_2)/(HR_1 1.0) × 100%, where HR_1 represents then HR derived from model 1, HR_2 represents the HR after adjusting for additional covariates (i.e., models 2 to 8), and 1.0 represents the HR when there was no excess risk.[28,29] Finally, survival functions of participants who had MS for the risk for CVD mortality were estimated and depicted by country and by the number of exposures to MS components. A repeated data analysis was conducted for participants who were free of baseline CVD conditions to examine whether the MS-CVD mortality associations remained observed.

All data analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). We used sampling weights and accounted for the complex sampling design using "SAS Procedures for Analysis of Sample Survey Data."[26,27] Two-sided p values ≤0.05 were considered as having statistical significance.

Results

Table 1 shows that the United States participants had significantly higher means of BMI, total cholesterol, TG and HbA_{1c} and lower HDL cholesterol than the Japanese

participants. Differences in smoking and other risk factors between male and female participants were also observed in the U.S. and Japan.

The mean follow-up period was 12.7 years (median 13.8) for the NHANES III participants and 13.9 years (median 15) for the Japanese participants. Of 12,561 United States participants, 1,683 died from CVD. Of CVD deaths, 1,058 patients (62.9%) died from coronary heart disease, 315 (18.7%) from cerebrovascular disease, and 310 (18.4%) from other CVD subtypes. Of 7,453 Japanese participants, 369 died from CVD. Of CVD deaths, 81 patients (22.0%) died from coronary heart disease, 160 (43.4%) from cerebrovascular disease, and 128 (34.6%) from other CVD subtypes. Figure 1 shows that the United States had significantly higher CVD mortality than Japan (11.75% vs 3.56%, $p < 0.001$).

Table 2 shows that the United States had significantly higher age-adjusted prevalence rates for individual MS factors, except for having a significantly lower prevalence of high BP than Japan ($p < 0.01$ or $p < 0.05$). The United States had significantly higher prevalence of MS than Japan (26.7% vs 19.3%, $p < 0.01$), when obesity was defined as BMI ≥ 30 kg/m^2 and BMI ≥ 25 kg/m^2 for the United States and Japanese samples, respectively. Obesity, high BP, elevated TG, and elevated HbA_{1c} significantly predicted CVD mortality in the United States population, and high BP and elevated HbA_{1c} predicted CVD mortality in Japan ($p < 0.001$ for all). The HR of MS for CVD mortality was 22.9% higher ([1.43 1.35]/[1.35 1]) in the United States than in Japan ($p < 0.001$) when obesity was defined as BMI ≥ 30 kg/m^2 for the United States and BMI ≥ 25 kg/m^2 for Japan. However, the HR was 23.3% higher in Japan than in the United States ($p < 0.001$) when obesity was classified as BMI ≥ 30 kg/m^2 for the 2 populations. Similar associations were observed for participants without baseline CVD conditions.

Table 3 shows that the HR of the United States versus Japan for CVD mortality was 2.01 (95% CI 1.84 to 2.21; model 1). After additionally adjusting for obesity (model 2), the HR was reduced to 1.90 (955 CI 1.71 to 2.11). However, the HR increased to 2.12 (95% CI 1.93 to 2.32) when adjusting for high BP (model 3). The HR was largely reduced (15.81%) when adjusting for elevated HbA_{1c} (model 6). An overall 13.34% reduction was observed when adjusting for MS (model 7). The HR was further reduced to 44.17% when adjusting for MS plus baseline CVD conditions (model 8). Similar findings were observed in a subsample excluding those who had CVD conditions at baseline. No significant interaction effects of MS and country on CVD mortality were observed in the total study sample (HR 0.99, 95% CI 0.94 to 1.05, p 0.84) and in the subsample (HR 0.98, 95% CI 0.92 to 1.06, p 0.66).

Discussion

The present study, using nationally comparable databases, is the first to document and compare the differences in MS and the impact of MS on CVD mortality between the United States and Japan. The main findings suggest that the United States had a significantly higher prevalence of MS than Japan. An estimated 13% of the excess CVD mortality could be explained by the differences in MS and 44% by MS plus baseline CVD conditions in the United States compared with Japan.

Of the 5 MS components, obesity significantly predicted CVD mortality in the United States but not in Japan. The reason for the nonsignificant association in Japan is still unknown. Two conditions may partly explain this difference. First, increased BMI as a measure of obesity may be less sensitive than waist circumference. In the present study, we did not use waist circumference as the measure of obesity, because waist circumference was not measured in the Japanese survey. Second, because increased BMI has a stronger association with coronary heart disease than with stroke, the nonsignificant association between obesity and CVD might be due to a significantly different distribution of the subtypes of CVD, in which coronary heart disease is dominant in the United States, while stroke occurs more frequently in Japan.[10] It should be noted that when obesity is defined as BMI ≥ 30 kg/m^2 for the Japanese sample, the HR of MS for CVD mortality was higher in Japan than in the U.S. (1.53 vs 1.43; Table 2). We conducted further sensitivity analyses by comparing the prevalence of MS components in those with MS and with BMIs ≥ 30 kg/m^2 between the United States and Japanese samples. The results showed that the prevalence rates of high BP, decreased HDL cholesterol, and elevated TG were significantly higher in the Japanese compared with Americans (97.5% vs 82.0% for high BP, 82.5% vs 71.7% for decreased HDL cholesterol, and 80.8% vs 74.7% for elevated TG). This difference may partly contribute to a higher HR of MS for CVD mortality in Japan when obesity is defined as BMI ≥ 30 kg/m^2. However, it does not mean that Japanese have a higher risk for CVD, because the Japanese have a much lower prevalence of obesity (BMI ≥ 30 kg/m^2) than Americas (2.4% vs 25.3%, $p < 0.001$). Certainly the magnitudes of individual MS components using different cut-off points on the association between MS and CVD risk in different populations need to be further studied. In the study, we also observed that the HR of high BP for CVD mortality in the Japanese participants was higher than in the American participants. These findings may suggest a different impact of risk factors on CVD mortality across different countries and racial and ethnic populations.

The present study had several strengths. First, its findings are derived from nationally representative population samples. The measurements of exposures and outcomes were conducted using standardized approaches. Therefore, it offers a unique opportunity for the study results to be generalized. Second, the association between MS and CVD mortality was analyzed prospectively, which makes it possible to interpret a potentially temporal association. Third, the findings of the study, by addressing the impacts of individual components of MS on the risk for CVD mortality between countries, are informative for health policy decisions and health practice in controlling CVD mortality.

There were also limitations that should be kept in mind. First, individual MS components that are continuous measures (i.e., BMI, BP, TG, HDL, and HbA_{1c}) were dichotomized on the basis of the current definition of MS. This dichotomization approach would lead a reduction in statistical power and an underestimation of the strengths of

associations between these factors and CVD mortality. Second, all risk factors had single measurements at baseline. Therefore, we are unable to test any time-varying effects of these variables on CVD mortality. Third, because BMI may have less sensitivity for the measure of obesity, new biomarkers should be included in further studies.

Despite these limitations, 2 clear and important conclusions follow from our present study. First, obesity, high BP, elevated TG, and elevated HbA_{1c} in the United States and high BP and elevated HbA_{1c} in Japan were the most significant individual predictors for CVD mortality. Second, MS and MS plus baseline CVD history are among the important risk factors that may significantly contribute to the explanation of excess CVD mortality in the United States versus Japan.

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Disclosures

The authors have no conflicts of interest to disclose.

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7．日本人一般男性における心疾患死亡リスクに対する早期再分極と n-3 不飽和脂肪酸摂取量との交互作用の検討： NIPPON DATA80

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背景： 心電図上の早期再分極（ER）は不整脈による心臓突然死の予測因子であることが近年報告されている。また、多くの観察、介入研究により、n-3 系不飽和脂肪酸（n-3 PUFA）の抗不整脈作用を介した心保護作用も証明されてきている。しかし、ER による心疾患死亡リスクに対する n-3 PUFA の効果について、今までに検討された報告はない。

方法： NIPPON DATA80 は 1980 年循環器基礎調査および国民栄養調査対象者のコホート研究である。無作為抽出された日本全国 300 か所から参加した循環器疾患既往のない日本人一般男性 4443 人（平均年齢 49.5 歳）の 24 年間追跡データを分析した。ER は 12 誘導心電図上の 0.1mV 以上の J 点上昇とした。n-3 PUFA 摂取量は 3 日間秤量法を用いて評価された。Cox 比例ハザードモデルにより、n-3 PUFA 摂取量の高摂取群、低摂取群それぞれにおいて ER の心疾患死亡に対する多変量調整ハザード比を算出し、n-3 PUFA 摂取量による交互作用を検討した。

結果： 追跡期間中213人の心疾患死亡が観察された。ERは340人（7.7%）に認められた。n-3 PUFAの食事摂取量の中央値は1.06%kcalであった。低摂取群（1.06%kcal未満）では、ERの心疾患死亡に対する調整後ハザード比は有意に高かった（2.77、95%信頼区間1.60－4.82、P＜0.001）が、高摂取群（1.06%kcal以上）では、有意な上昇を認めなかった（0.85、95%信頼区間0.31－1.97、P=0.711）。また、n-3 PUFAとERとの有意な交互作用も確認された（P=0.032）。2次解析として、魚由来（eicosapentaenoic acid [EPA]、docosahexaenoic acid [DHA]）および植物由来（α-linolenic acid [ALA]）n-3 PUFAについて同様の解析を行ったが、いずれも高摂取群ではERの心疾患死亡に対する調整後ハザード比の有意な上昇を認めなかった。

結語： ERによる心疾患死亡リスク上昇はn-3 PUFAの高摂取により弱められる可能性がある。

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ORIGINAL ARTICLE

Interaction between dietary marine-derived n-3 fatty acids intake and J-point elevation on the risk of cardiac death: a 24-year follow-up of Japanese men

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ABSTRACT

Objective Higher marine-derived n-3 fatty acids (MDn3FAs) intake reduces the risk of sudden cardiac death via antiarrhythmic effects. The article evaluates whether MDn3FAs intake attenuates the increased risk of cardiac death associated with J-point elevation (JPE), characterised by an elevation of QRS-ST junction (J-point) ≥0.1 mV on electrocardiography.

Design A prospective population-based cohort study.

Setting The National Survey on Circulatory Disorders and the National Nutrition Survey of Japan.

Participants A total of 4348 community-dwelling men (mean age 49.3 years), without cardiovascular diseases at baseline, from randomly selected areas across Japan.

Main outcome measures Cardiac death (200 men) during the 24-year follow-up.

Results Dietary MDn3FAs intake was assessed using a dietary method to estimate individual intake of household-based weighed food records for 3 days. Cox models were used to calculate HRs and 95% CIs adjusted for possible confounding factors. JPE was present in 340 participants (7.8%). The median daily intake of MDn3FAs was 0.35%kcal (0.92 g/day). The risk of cardiac death was significantly higher in participants with JPE than in those without JPE in the low intake group (<0.35%kcal; adjusted HR 3.51; 95% CI 1.84 to 6.73; p<0.001), but not in the high intake group (≥0.35%kcal; adjusted HR 1.09; 95% CI 0.56 to 2.16; p=0.795). The interaction between dietary MDn3FAs intake and JPE on the risk of cardiac death was statistically significant (p=0.006).

Conclusions The increased risk of cardiac death associated with JPE may be attenuated by higher dietary MDn3FAs intake.

INTRODUCTION

Overwhelming evidence from epidemiological,[1 2] mechanistic[3] and interventional studies[4 5] indicates that dietary marine-derived n-3 fatty acids (MDn3FAs) reduce the risk of cardiovascular diseases,[2 5–7] particularly sudden cardiac death.[1 4] Experimental data from studies in animals and at the cellular level suggest that the clinical prevention of sudden cardiac death by MDn3FAs is due to their antiarrhythmic properties.[3 8]

Early repolarisation, characterised by an elevation of the QRS-ST junction (J-point) on 12-lead electrocardiography, was recently proposed as an independent predictor of sudden cardiac death from arrhythmia.[9 10] Therefore, identifying measures that could prevent cardiac death associated with J-point elevation (JPE) would be of considerable clinical and public health importance. Based on the results of experimental studies, we hypothesised that a higher dietary intake of MDn3FAs may attenuate the increased risk of cardiac death associated with JPE.

We tested this hypothesis in a 24-year prospective cohort study of a representative general Japanese population—individuals who participated in the National Survey of Circulatory Disorders and the National Nutrition Survey of Japan. The community-based Japanese population tends to have a higher MDn3FAs intake than other populations worldwide[11] and is therefore useful for examining the interaction between dietary MDn3FAs intake and JPE on the risk of cardiac death.

METHODS

Study participants

Cohort studies of the National Survey on Circulatory Disorders and the National Nutrition Survey of Japan are known as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged). We analysed data from NIPPON DATA80 using the baseline survey conducted in 1980. The detailed methods are described elsewhere.[12 13] The present study was approved by the Institutional Review Board of Shiga University of Medical Science (No.12-18, 2000; No.17-21-1, 2010).

Members of an overall population (n=13 771) aged ≥30 years from 300 randomly selected health districts throughout Japan were invited to participate in the study. Among them, 10 546 community-based individuals (76.6% of 13 771) agreed to join the study. The survey consisted of a physical examination, blood test, self-administered questionnaire on lifestyle, dietary assessment and standard 12-lead electrocardiography recording. For the

present study, participants were followed up to 2004 (NIPPON DATA80, 1980–2004).

In all, 364 individuals in the total cohort had JPE, of which the majority (93.7%, n=341) were men. Therefore, we restricted the present analysis to men (n=4639). A total of 291 men were excluded from this analysis for the following reasons: history of cardiovascular diseases (n=131), major conduction defects on electrocardiography (QRS duration ≥ 120 ms) or Brugada-type electrocardiography[14] (n=108), and missing information (electrocardiography or dietary data) at baseline (n=52). Therefore, 4348 men were finally included in the present analyses (mean age, 49.3 years; range, 30–95 years).

End point determination

To determine the cause of death during the 24-year follow-up, the National Vital Statistics database of Japan was used with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death in the National Vital Statistics were coded according to the 9th International Classification of Disease (ICD9) until the end of 1994 and according to the 10th International Classification of Disease (ICD10) from 1995 onwards, as described elsewhere.[12]

The primary end point was cardiac death, and the secondary end point was all-cause death during the follow-up period. The corresponding ICD9 and ICD10 codes on cardiac death were as follows: 393–429 (ICD9) and I01–I09, I11, I13 and I20–I52 (ICD10).

Baseline dietary assessment

A dietary survey in each household was based on weighed food records for three consecutive representative days, avoiding weekends and holidays, by trained dietary interviewers. Dietary data were processed centrally to calculate nutrients. The nutrient intake reported for each household in the National Nutrition Survey of Japan in 1980 was proportionally allocated to each household member according to the mean consumption rate by age and sex. Dietary researchers were blinded to the participants' electrocardiographic and outcome status. For energy-supplying nutrients, the intake was calculated as the percentage of total energy intake (%kcal). Other nutrients were calculated relative to total dietary intake (g/1000 kcal).

The detailed calculation procedure and validity of the estimation have been described elsewhere[15–17] and in the online supplementary text. Furthermore, energy and macronutrient intake among Japanese individuals estimated using the same dietary assessment as in the present study were highly correlated to the corresponding values with individual-based weighed food records (correlation coefficients 0.90–0.92).[18]

Baseline electrocardiographic measurement

Electrocardiographic measurements are described in more detail elsewhere.[12 13 19] In brief, standard 12-lead electrocardiography was performed at baseline by trained technicians with the participant in the supine position. Electrocardiographic findings were independently evaluated by two trained researchers (blinded to participant dietary and outcome status) in each of 12 institutions in accordance with the Minnesota Code, which was developed to document significant electrocardiographic patterns using objective comparison rules. Codes that showed agreement between the two researchers' assessments were accepted; codes that showed disagreement were adjudicated by a panel of epidemiologists and cardiologists.

JPE was defined as an elevation of the QRS-ST junction (J-point) in at least 1-lead according to Minnesota Code 9.2 as follows: in the inferior (II, III, aVF) and lateral leads (I, aVL, V_6), an elevation of the J-point of ≥0.1 mV from baseline; in the anterior leads (V_1 through V_5), an elevation of the J-point of ≥0.2 mV in leads V_1–V_4 and ≥0.1 mV in lead V_5. Participants with major conduction defects on electrocardiography (QRS duration ≥120 ms) were not included in this definition. Additionally, electrocardiographic findings that we examined were Q wave abnormality (Minnesota Code 1.1–1.3), left ventricular hypertrophy (Minnesota Code 3.1 or 3.3), major ST depression (Minnesota Code 4.1–4.3) and major T abnormality (Minnesota Code 5.1 or 5.2).

Statistical analysis

First, participants were divided into two groups according to median dietary MDn3FAs intake (0.35%kcal: 0.92 g/day) as low (<0.35%kcal) or high (≥0.35%kcal) intake. Baseline characteristics and nutritional intake were presented as means and SDs for continuous variables and as numbers and percentages for categorical variables. Differences in baseline characteristics and nutritional parameters between participants with low or high MDn3FAs intake were evaluated using the unpaired Student t test, Wilcoxon signed-rank test or χ^2 test, as appropriate.

Cox proportional hazards models were used to estimate multivariable adjusted HRs and their 95% CIs for cardiac and all-cause death with the presence of JPE compared with the absence of JPE in both the low and high MDn3FAs intake groups. In model 1, the analysis was adjusted for age. In model 2, the analysis was adjusted for conventional risk factors (age, body mass index, smoking status, drinking habits, medication status, systolic blood pressure, serum total cholesterol, blood glucose and heart rate) and confounding electrocardiographic findings[9 10] (left ventricular hypertrophy classified according to Minnesota Code 3.1 or 3.3, and suspected coronary heart disease classified according to Minnesota Code 1.1–1.3, 5.1–5.2 or 4.1–4.3). In model 3, the analysis was further adjusted for nutritional parameters, including the intake of polyunsaturated fatty acids, saturated fatty acids, sodium and fibre. Tests for an interaction between JPE and dietary MDn3FAs intake were performed by introducing a multiplicative interaction term into the main models.

We further estimated multivariable adjusted HRs and 95% CIs for cardiac death according to four categories cross-classified by MDn3FAs (high or low intake) and JPE (absence or presence): high intake group without JPE (as reference); high intake group with JPE; low intake group without JPE; and low intake group with JPE.

In secondary analyses, we examined the risk of cardiac and all-cause death associated with JPE in participants with low and high intake of eicosapentaenoic acid (EPA) (<0.13 vs ≥0.13% kcal) or docosahexaenoic acid (DHA) (<0.22 vs ≥0.22%kcal).

All analyses were performed with SAS software, V.9.1.3 (SAS Institute, Cary, North Carolina, USA). All p values were two-sided and p values < 0.05 were considered statistically significant.

RESULTS

The baseline characteristics of the two groups of participants according to dietary MDn3FAs are presented in table 1. JPE was present in 6.6% and 8.9% of participants with low and high MDn3FAs intake, respectively (p=0.005). Compared with the low intake group, individuals in the high intake group tended to be older, more commonly alcohol drinkers, had higher blood glucose levels and had higher systolic blood pressure.