HR(95%CI)は境界域代謝性危険因子を持たない者を基準群とするとそれぞれ、1.61(0.74-3.50)，2.02(0.90-4.54)，2.26(0.84-6.10)であり、危険因子数とともに上昇する傾向にあったが、統計的に有意なものではなかった。いずれかの境界域代謝性危険因子が集積する者の循環器疾患死亡 HR(95%CI)は 1.82(0.89-3.73)であった。境界域代謝性危険因子集積による循環器疾患死亡の PAF は 7.3%であった。一方、要医療域の危険因子による循環器疾患死亡の PAF は 52.4%であった。

【結論】やせていない日本人における境界域代謝性危険因子集積者の循環器疾患死亡リスクは上昇傾向にあったが統計的に有意なものではなく、さらに検討する必要がある。要医療域にいたらない境界域の代謝性危険因子を早期にとらえ生活習慣の改善へ導くことには意義があるが、日本人集団においてはその人口寄与危険割合は低い。循環器疾患死亡リスク軽減のためには要医療域にある危険因子の検出と管理にさらなる努力をすることが必要である。

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Atherosclerosis.2011;215:209-213

Atherosclerosis 215 (2011) 209–213

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Relationship of moderate metabolic risk factor clustering to cardiovascular disease mortality in non-lean Japanese: A 15-year follow-up of NIPPON DATA90

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ARTICLE INFO

Article history:
Received 10 December 2009
Received in revised form
21 November 2010
Accepted 25 November 2010
Available online 4 December 2010

Keywords:
Metabolic risk factor
Cardiovascular disease
Mortality
Epidemiology

ABSTRACT

Objective: The individual components of metabolic syndrome are defined as levels ranging from moderate to high level as to require medication. We investigated the impact of moderate metabolic risk factor clustering on cardiovascular disease (CVD) mortality.

Methods: We followed up 6758 non-lean Japanese in randomly selected areas from all over the country who had no history of CVD for 15 years. The multivariate-adjusted hazards ratio (HR) and 95% confidence interval (CI) for CVD mortality according to the number of moderate metabolic risk factors (BMI $\geq$ 25 kg/m^2, 130/85 mmHg $\leq$ systolic/diastolic BP < 140/90 mmHg, 140 mg/dl $\leq$ casual blood glucose < 200 mg/dl, triglycerides $\geq$ 150 mg/dl and/or HDL cholesterol < 40 mg/dl [men], 50 mg/dl [women]) were estimated using the Cox proportional hazards model. The population-attributable risk fraction of moderate metabolic risk factor clustering was also estimated.

Results: During the follow-up, 282 participants died of CVD. CVD mortality tended to increase with the number of moderate metabolic risk factors. However, they were not statistically significant. The multivariate-adjusted HRs were 1.82 (95%CI: 0.89–3.73) for having any moderate metabolic risk factors and 2.87 (95%CI: 1.46–5.64) for having any medication-required metabolic risk factors, compared with participants without any moderate metabolic risk factors. The population-attributable risk fractions were 7.3% and 52.4% for any moderate and medication-required metabolic risk factors, respectively.

Conclusions: We did not find the statistically significant increase of CVD mortality for moderate metabolic risk factor clustering. Its attribution was relatively small in this Japanese population. More efforts would be required to detect and control medication-required risk factors.

1. Introduction

Metabolic syndrome is the concept of metabolic risk factor clustering, which is an appropriate target for therapeutic lifestyle changes [1–4]. Several cohort studies have revealed that metabolic syndrome is associated with an increased risk of cardiovascular disease (CVD) [5–11]. However, the individual component risk factors in the present criteria for metabolic syndrome are not graded by severity but they are defined as levels ranging from moderate to high requiring medication [12–17]. Because individual established risk factors such as hypertension or diabetes strongly and independently increase the risk of CVD [8,18,19], the risk of moderate metabolic risk factor clustering on CVD might escape detection. Individuals with established risk factors often require medication in addition to therapeutic lifestyle changes, whereas moderate risk factors can be controlled with such lifestyle changes [17]. However, the CVD risk for individuals with moderate risk factor clustering has rarely been reported.

Here we investigated the association between clustering of moderate metabolic risk factors and CVD mortality among people with normal weight or more in a 15-year follow-up of a cohort of

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doi:10.1016/j.atherosclerosis.2010.11.033

representative general Japanese, who participated in the National Survey of Circulatory Disorders of Japan in 1990.

2. Methods

2.1. Study population

NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged) is a cohort study of participants in the National Survey on Circulatory Disorders of Japan, which has been conducted by the Ministry of Health, Labor and Welfare of Japan. NIPPON DATA includes two cohort studies of which the baseline data were surveyed in 1980 and in 1990 (NIPPON DATA80 and NIPPON DATA90) and the details of the studies have been described [8,18–20]. Here, we investigated the data from NIPPON DATA90 because some important metabolic risk factors such as HDL cholesterol were not included in the NIPPON DATA80 baseline survey.

A total of 8384 residents (3504 men and 4880 women, aged ≥ 30 years) from 300 randomly selected districts from all over Japan participated in the baseline survey and were followed up until November, 2005. The participation rate in this survey was 76.5%. Of the 8384 participants, 1626 were excluded because of a history of coronary heart disease or stroke (n = 261), information missing at the baseline survey (n = 649), withdrawal due to incomplete residential access information (n = 255) and a low BMI (BMI < 18.5 kg/m^2) (n = 461). We excluded these lean participants because they also have a higher CVD mortality risk in Japan as well as in western studies [21,22]. The remaining 6758 participants (2828 men and 3930 women) were analyzed in this study. The Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000) approved this study.

2.2. Baseline examination

Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Trained observers measured baseline blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants. Non-fasting blood samples were obtained at the baseline survey. Serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to a central laboratory (SRL, Tokyo) for blood measurements. Plasma glucose was measured enzymatically. Serum triglycerides (TG) and total cholesterol were also measured enzymatically and high-density lipoprotein (HDL) cholesterol was measured after heparin–calcium precipitation.

Public health nurses collected the information about smoking, alcohol consumption and medical history. We divided participants into four categories of smokers (never-smoked; ex-smoker; current smoker of <20 or ≥20 cigarettes/day) and six categories of drinking (never-drink; ex-drinker; current drinker of 1–4 and more *gou* of sake/day); 1 *gou* (180 ml) is equivalent to 23 g of alcohol.

2.3. Endpoints

We previously reported that participants who had died in each area were confirmed by computer matching with data from the National Vital Statistics database, using area, gender, date of birth and death as key codes [19,23]. The underlying causes of death in the National Vital Statistics were coded according to the 9th International Classification of Diseases (ICD-9) until 1994 and according to the 10th International Classification of Disease (ICD-10) from 1995. Details of these classifications are described elsewhere [18–20,23]. Deaths coded from 393 to 459 according to ICD-9 and from I00 to I99 according to ICD-10 were defined as CVD deaths in this study.

2.4. Definition of metabolic risk factors

Based on the modified NCEP (National Cholesterol Education Program) metabolic syndrome criteria [12], moderate metabolic risk factors were defined as follows: obesity (BMI ≥ 25 kg/m^2), moderate high blood pressure (130 ≤ systolic blood pressure [SBP] < 140 mmHg and/or 85 ≤ diastolic blood pressure [DBP] < 90 mmHg), dyslipidemia (150 mg/dl ≤ non-fasting triglycerides and/or HDL-cholesterol < 40 mg/dl for men, and <50 mg/dl for women). We also defined moderate high blood glucose (140 mg/dl ≤ non-fasting blood glucose < 200 mg/dl). Because our samples were non-fasting, post load blood glucose of ≥140 mg/dl indicated impaired glucose tolerance [24]. Furthermore, we defined medication-required metabolic risk factors as follows: high blood glucose (non-fasting blood glucose ≥ 200 mg/dl and/or medication), high blood pressure (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or medication) according to the criteria of hypertension stage 1 in JNC7 (The Seventh Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) [25]. We divided the participants into five categories of metabolic risk factor condition (none, moderate metabolic risk factor [1, 2 and ≥3 factors], any medication-required metabolic risk factor). Participants with any one or more of the medication-required metabolic risk factors were categorized as "any medication-required metabolic risk factor" irrespective of the number of moderate metabolic risk factors.

2.5. Statistical analysis

Differences in the baseline characteristics of participants were examined using the analysis of variance for continuous variables and χ^2-test for dichotomized variables according to metabolic risk factors. The multivariate-adjusted hazard ratio (HR) of all CVD mortality for each group was estimated using the Cox proportional hazards model adjusted for age, sex, total cholesterol, smoking and drinking categories. Participants without metabolic risk factors were established as the reference group. Population-attributable risk fraction (PAF) for CVD deaths were estimated using the following equation: proportion of CVD death with moderate metabolic factors among total CVD death × (HR − 1)/HR [26]. All CI values were estimated at the 95% level. A P-value of <0.05 was considered statistically significant. The Statistical Package for the Social Sciences, version 11.0J (SPSS Japan, Inc., Tokyo, Japan) was used for all analysis.

3. Results

Table 1 shows the baseline characteristics of the study participants according to the categories of metabolic risk factors. The mean age of participants was higher and the proportion of women was lower among those with more advanced metabolic risk factors. The proportion of participants with any moderate metabolic risk factors was 33.6%. The total number of person-years was 94,817 and the mean follow-up period was 14.0 years. During the follow-up, 1007 participants died of all causes, 282 of all CVD, 119 of stroke and 63 of coronary heart disease.

Table 2 shows the number of deaths, adjusted HRs and 95%CIs according to metabolic risk factors. Crude HR values for CVD mortality ranged from 2.32 to 5.17 among participants with moderate metabolic risk factors. The trend was statistically significant among the four categories of moderate and the five categories up to medication-required metabolic risk factors (P for trend < 0.001). Multivariate-adjusted HRs among participants with moderate

Table 1
Baseline characteristics of 2828 men and 3930 women aged ≥30 years according to number of moderate or medication-required metabolic risk factors. NIPPON DATA90, 15-year follow-up.

Baseline characteristics	Number of moderate metabolic risk factors[a]				Any medication-required metabolic risk factors[b]
	0	1	2	3 and 4	
Number of participants	1297	1393	683	199	3186
Women (%)	69.1	58.8	56.5	45.7	54.5
Age (years)	44.0 ± 10.5	47.0 ± 11.8	50.0 ± 12.4	50.8 ± 12.8	58.6 ± 12.5
BMI (kg/m²)	21.3 ± 1.7	22.5 ± 2.3	24.5 ± 2.8	26.9 ± 2.6	23.9 ± 3.1
Systolic blood pressure (mmHg)	115.1 ± 8.8	122.4 ± 10.4	127.7 ± 8.2	132.1 ± 4.9	151.7 ± 16.6
Diastolic blood pressure (mmHg)	71.8 ± 7.5	75.6 ± 7.7	78.1±7.4	81.2 ± 6.4	89.1 ± 10.9
Blood glucose (mg/dl)	92.6 ± 13.2	96.3 ± 15.4	100.1 ± 19.6	108.9 ± 25.2	110.3 ± 42.0
HbAlc (%)	4.69 ± 0.34	4.78 ± 0.36	4.89 ± 0.44	5.01 ± 0.52	5.13 ± 0.95
Total cholesterol (mg/dl)	193.7 ± 31.7	195.4 ± 35.8	207.8 ± 38.8	217.1 ± 37.2	210.3 ± 39.5
Triglycerides (mg/dl)	80.0 ± 28.3	123.4 ± 76.7	168.9 ± 93.2	213.9 ± 112.8	150.2 ± 103.2
HDL-cholesterol (mg/dl)	63.6 ± 12.7	52.8 ± 14.2	45.9 ± 12.1	43.2 ± 12.2	52.2 ± 15.3
Drinking					
Never-drink (%)	75.8	69.8	71.6	67.8	63.7
Ex-drinker (%)	1.9	2.2	2.6	1.5	3.7
Current drinker (%)	22.3	28.0	25.8	30.7	32.6
Smoking					
Never-smoked (%)	68.8	61.3	57.8	47.7	57.9
Ex-smoker (%)	9.0	8.4	9.4	10.6	14.0
Current smoker (%)	22.2	30.3	32.8	41.7	28.1
Moderate or medication-required metabolic risk factors (%)					
Obesity	0	12.1	45.1	91.0	33.1
Triglycerides/HDL cholesterol	0	48.8	82.9	97.0	51.4
Blood glucose	0	1.5	5.7	17.1	11.1
Blood pressure	0	37.5	66.3	99.0	97.3

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein.
[a] Moderate metabolic risk factors were defined as follows: moderate high blood glucose (140 mg/dl ≤ non-fasting blood glucose < 200 mg/dl), moderate high blood pressure (130 ≤ SBP < 140 mmHg and/or 85 ≤ DBP < 90 mmHg), moderate dyslipidemia (150 mg/dl ≤ non-fasting triglycerides and/or (HDL-cholesterol < 40 mg/dl in men or HDL-cholesterol < 50 mg/dl in women), obesity (BMI ≥ 25 kg/m²).
[b] Medication-required metabolic risk factors were defined as follows: high blood glucose (non-fasting blood glucose ≥ 200 mg/dl and/or on medication), high blood pressure (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or on medication).

metabolic risk factors ranged from 1.61 to 2.26 with a statistically significant increase. The trend in the multivariate-adjusted model was statistically significant ($P < 0.001$) among the five categories of metabolic risk factors, although it did not reach statistical significance among the four categories of moderate metabolic risk factors. These relationships were similar in gender-specific analyses.

Table 3 shows multivariate adjusted HRs and 95%CIs according to the three categories of metabolic risk factors (none, any moderate metabolic risk factors and any medication-required metabolic risk factors). Crude HR was 2.98 times higher in participants with any moderate metabolic risk factor than in those with none, and multivariate-adjusted HR was 1.82. PAFs calculated by multivariate adjusted HRs were 7.3% and 52.4% for any moderate and medication-required metabolic risk factors, respectively.

4. Discussion

This 15-year follow-up of a representative Japanese cohort did not find the statistically significant increase of CVD mortality for the moderate metabolic risk factor clustering. In addition, PAF was relatively small (7.3%) in people with any moderate factors compared with those with any medication-required factors (52.4%). To the best of our knowledge, this would be the first report to clarify the CVD risk of moderate metabolic risk factor clustering,

Table 2
Multivariate adjusted hazard ratios of cardiovascular deaths according to number of moderate or medication-required metabolic risk factors. NIPPON DATA90, 15-year follow-up.

	Number of moderate metabolic risk factors[a]				Any medication-required metabolic risk factors[b]
	0	1	2	3 and 4	
Number of participants	1297	1393	683	199	3186
Person-years	19,082	20,148	9835	2883	42,869
Cardiovascular deaths	9	22	17	7	227
Mortality per 1000 person-years	0.47	1.09	1.73	2.43	5.30
Crude HR (95%CI)	1	2.32 (1.07–5.05)	3.68 (1.64–8.26)	5.17 (1.93–13.88)	11.46 (5.89–22.30)
Age and sex adjusted HR (95%CI)	1	1.58 (0.73–3.43)	1.92 (0.85–4.31)	2.04 (0.76–5.49)	2.70 (1.38–5.30)
Multivariate adjusted HR[c] (95%CI)	1	1.61 (0.74–3.50)	2.02 (0.90–4.54)	2.26 (0.84–6.10)	2.88 (1.47–5.65)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; HR, hazard ratio; CI, confidence interval.
[a] Moderate metabolic factors were defined as follows: moderate high blood glucose (140 mg/dl ≤ non-fasting blood glucose < 200 mg/dl), moderate high blood pressure (130 ≤ SBP < 140 mmHg and/or 85 ≤ DBP < 90 mmHg), moderate dyslipidemia (150 mg/dl ≤ non-fasting triglycerides and/or (HDL-cholesterol < 40 mg/dl in men or HDL-cholesterol < 50 mg/dl in women), obesity (BMI ≥ 25 kg/m²).
[b] Medication-required metabolic factors were defined as follows: high blood glucose (non-fasting blood glucose ≥ 200 mg/dl and/or on medication), high blood pressure (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or on medication).
[c] Multivariate hazard ratios were estimated by Cox proportional hazard model adjusted for sex, age, total cholesterol, smoking habits and drinking habits.

Table 3
Multivariate adjusted hazard ratios of cardiovascular deaths for having any moderate or medication-required metabolic risk factors. NIPPON DATA90, 15-year follow-up.

	None	Any moderate metabolic risk factors[a]	Any medication-required metabolic risk factors[b]	*P* for trend
Number of participants	1297	2275	3186	
Person-years	19,082	32,866	428,69	
Cardiovascular deaths	9	46	227	
Mortality per 1000 person-years	0.47	1.40	5.30	
Crude HR (95%CI)	1	2.98 (1.46–6.09)	11.46 (5.88–22.30)	<0.001
Age and sex adjusted HR (95%CI)	1	1.75 (0.86–3.58)	2.70 (1.38–5.29)	<0.001
Mutivariate adjusted HR[c] (95%CI)	1	1.82 (0.89–3.73)	2.87 (1.46–5.64)	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; HR, hazard ratio; CI, confidence interval.
[a] Moderate metabolic factors were defined as follows: moderate high blood glucose (140 mg/dl < non-fasting blood glucose < 200 mg/dl), moderate high blood pressure (130 ≤ SBP < 140 mmHg and/or 85 ≤ DBP < 90 mmHg), moderate dyslipidemia (150 mg/dl ≤ non-fasting triglycerides and/or (HDL-cholesterol < 40 mg/dl in men or HDL-cholesterol < 50 mg/dl in women), obesity (BMI ≥ 25 kg/m^2).
[b] Medication-required metabolic factors were defined as follows: high blood glucose (non-fasting blood glucose ≥ 200 mg/dl and/or on medication), high blood pressure (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or on medication).
[c] Multivariate hazard ratios were estimated by Cox proportional hazard model adjusted for sex, age, total cholesterol, smoking habits and drinking habits.

especially in Asia, where stroke is the predominant cause of CVD mortality.

The influence of metabolic syndrome on CVD risk has been reported [5–11]. McNeil et al. used NCEP criteria and found that the adjusted HR for coronary heart disease incidence was 1.46 for men and 2.05 for women, and that for ischemic stroke incidence was 1.42 for men and 1.96 for women in the Atherosclerosis Risk in Communities Study [5]. Katzmarzyk et al. investigated the relationship between metabolic syndrome diagnosed by NCEP criteria and CVD mortality among 19,223 men in the USA and found that the adjusted HR was 1.23 [6]. Iso et al. reported in a study using the modified NCEP criteria found that the adjusted HR for the incidence of ischemic heart disease was 2.4 and that of ischemic stroke was 1.8 among 9087 Japanese in five communities [9]. Ninomiya et al. found using modified NCEP criteria that the adjusted HR of CVD incidence among 2452 Japanese in Hisayama Study was 1.86 for men and 1.70 for women [10]. All of these previous studies demonstrate a CVD risk associated with metabolic syndrome irrespective of the severity of the individual component. For example, high blood pressure is defined according to the NCEP criteria as ≥130/85 mmHg, a value that covers a range of blood pressure from high-normal to severe hypertension. However, the CVD risk for individuals with moderate risk factor clustering, which is not usually treated by medication, has rarely been reported.

In the present study, moderate metabolic risk factor clustering tended to increase CVD mortality, however, they were not statistically significant. Several epidemiological studies have revealed that the CVD risk factors included in the criteria for metabolic syndrome are incrementally associated with CVD risk and do not have any threshold [27,28]. Therefore, combined moderate metabolic risk factors might increase the CVD risk. Further studies are required to clarify the relationship of moderate metabolic risk factor clustering and CVD risk.

In the present study, the prevalence of participants with any moderate metabolic risk factor was 33.6% and the PAF of moderate metabolic risk factors on CVD mortality was 7.3%. The impact of moderate metabolic factors on a population should be assessed by estimating population-attributable risk fraction of moderate metabolic factors, which has been seldom reported yet. Vasan et al. investigated the relative contribution of borderline (suboptimal but below current treatment thresholds) and elevated risk factors among US population using five traditional vascular risk factors (blood pressure, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol, glucose tolerance and smoking status) [29]. They found that the prevalence of the isolated borderline risk factors decreased with age and ranged from 19% to 32.6% in men and from 28.6% to 55.2% in women. They also indicated that isolated borderline risk factors without elevated risk factors accounted for only about 10% of hard CHD events. Although different risk factors and different ranges were applied in their study, their results would be comparable to our results. Our smaller PAF in people with moderate metabolic risk factors would be partly due to smaller range of moderate BP elevation (SBP/DBP 130–139/85–89 mmHg) in the criteria of metabolic syndrome.

The present study indicated that HR of CVD deaths was near 3-folds among participants with any medication-required metabolic risk factor and their PAF was over 50%. Previous studies have shown that almost 80% of patients with coronary heart disease had at least one major risk factor [30,31]. Our findings among participants with any medication-required metabolic risk factors were comparable with these results and emphasize the importance of focusing upon individuals with any severe risk factor to prevent CVD. The statement of the American Heart Association and National Heart, Lung and Blood Institute recommends that established risk factors such as elevated blood pressure ≥ 140/90 mmHg and elevated glucose ≥ HbA1c 7% should be medicated in addition to undergoing therapeutic lifestyle changes [17]. However, many people with any medication-required metabolic risk factor are neither yet detected nor controlled. Further efforts are required to identify and control established risk factors.

Several limitations should be noted about this study. Firstly, analysis of non-fasting blood samples and no consideration of treatment for dyslipidemia might have resulted in misclassifications of serological abnormalities. Secondly, we used BMI because information about waist circumference was unavailable. Since waist circumference might more precisely enhance the effect of obesity on CVD than BMI, we might have under- or overestimated the effect of obesity. However, BMI is closely related to waist circumference.

In conclusion, we did not find the statistically significant increase of CVD mortality for moderate metabolic risk factor clustering in a representative Japanese population. Further studies are required to clarify the relationship of moderate metabolic risk factor clustering and CVD risk. In addition, its attribution to CVD deaths was relatively small compared with having any medication-required risk factors in this Asian population. People with moderate metabolic risk factors should modify their lifestyle mainly to reduce weight, but more efforts would be required to detect and control medication-required risk factors for CVD prevention.

Conflict of interest

None.

Acknowledgements

This study was supported by the grant-in-aid of the Ministry of Health, Labor and Welfare under the auspices of Japanese Association for Cerebro-cardiovascular Disease Control, the Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare, and the Health and Labor Sciences Research Grant, Japan (Comprehensive Research on Aging and Health [H11-Chouju-046, H14-Chouju-003, H17-Chouju-012, H19-Chouju-Ippan-014] and Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus [H22-Jyunkankitou-Seisyu-Sitei-017]). We appreciate the members of the NIPPON DATA80/90 Research Group which is listed in the Appendix.

Appendix A. The NIPPON DATA80/90 Research Group

Chairperson: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Co-Chairperson: Akira Okayama (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo) for the NIPPON DATA80, Tomonori Okamura (Department of Preventive Medicine and Public Health, Keio University, Tokyo) for the NIPPON DATA90.

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(5) 心不全死、冠疾患死のリスクファクター・NIPPON DATA80, 24 年間追跡

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＜背景＞

心不全予防は国家規模において、また国際的規模においても公衆衛生学上の急務であるが、一般住民を対象とした研究は少ない。

＜方法＞

NIPPON DATA80 研究のデータベースを用いて心不全死、冠疾患死のリスクファクターを検討した。1980 年に無作為抽出した全国 300 ヵ所において 30 才以上の男女を対象として検診を行い、心電図検査と血液生化学検査を行った。追跡開始時にすでに脳梗塞、心筋梗塞の既往のある対象は除外した計 9,300 例（男 44%、平均年齢 51 歳）を 24 年間追跡した。

＜結果＞

24 年追跡期間中に発生した心不全死は 189 例(男 82 例、女 107 例)、冠疾患死は 188 例（男 91 例、女 97 例）であった。Cox 比例ハザード解析を行ってそれぞれの死亡のリスクファクターを抽出した。両疾患死亡に共通なリスクファクターは収縮期血圧が男性心不全死（1 標準偏差毎のハザード比[HR per 1SD]:1.28, P=0.02）と男女の冠疾患死（男 HR per 1SD:1.20, P=0.01；女 HR per 1SD:1.27, P=0.003）；喫煙が男性冠疾患死（HR:1.31, P=0.004）と女性心不全死（HR:1.39, P=0.01）；血糖値が男性心不全死および冠疾患死（心不全死 HR per 1SD:1.21, P=0.009; 冠疾患死 HR per 1SD:1.29, P<0.0001); 心電図 T 波異常が男性心不全死(HR:2.33, P=0.003)と女性冠疾患死(HR:1.84, P=0.001)であった。疾患特異的リスクファクターは BMI 18.5～25.0kg/m^2 と比べて BMI<18.5 kg/m^2 が男女の心不全死（男 HR:1.92, P=0.04;女 HR:1.86, P=0.04）；血清クレアチニン値が男女の心不全死（男 HR per 1SD:1.14,

P<0.0001;女 HR per 1SD:1.09, P=0.01); 血清コレステロール値が男性冠疾患死(HR per 1SD:1.38, P = 0.001)であり、また弁膜症と脳卒中既往が男性心不全死(弁膜症 HR:6.48, P=0.002; 脳卒中既往 HR:2.41,P=0.048)の、また狭心症既往が女性冠疾患死(HR:3.59, P= 0.003)のリスクファクターであった。

＜考案・結論＞

今回同定された心不全死および冠疾患死のリスクファクターの多くはこれまでに提唱されていたものである。肥満は冠疾患他多疾患の誘因となるため BMI<18.5 kg/m^2が男女心不全死のリスクファクターであったことは想定外であった。しかし最近の研究で、心不全存在下の低体重ないし痩身は死亡しやすいこと、また肥満で低下する血清アディポネクチン値低値は心不全症例の予後良好を予測することなどの報告は今回の結果と一致する。

心不全死および冠疾患死を予防するため、今回同定されたリスクファクター是正のための健康施策が必要である。

CVD Prevention and Control (2010) 5, 97–103

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Risk factors for heart failure and coronary heart disease mortality over 24-year follow-up period in Japan: NIPPON DATA80

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Received 24 April 2010; received in revised form 12 June 2010; accepted 20 June 2010
Available online 5 August 2010

KEYWORDS
Heart failure;
Coronary heart disease;
Mortality;
Cohort study;
Body mass index

Summary
Background: Although prevention of heart failure (HF) is an urgent public health need with national and global implications, population-based studies are rare.
Methods and results: We studied risk factors for HF and coronary heart disease (CHD) mortality using the NIPPON DATA80 database with a 24-year follow-up. At the baseline in 1980, data were collected on study participants aged 30 years and over from randomly selected areas in Japan. We followed 9300 participants (44% men, mean age 51). Over the 24-year follow-up, there were 189 deaths from HF (82 men and 107 women) and 188 (91 men and 97 women) from CHD. Cox analyses revealed common and specific risk factors for both mortalities. Common risk factors were: systolic blood pressure for male HF (hazard ratio: 1.28 per 1SD, $P = 0.02$) and for CHD in both (men: 1.20, $P = 0.01$; women: 1.27, $P = 0.003$), smoking for male CHD (1.31, $P = 0.004$) and for female HF (1.39, $P = 0.01$), blood sugar for HF and CHD in men (HF: 1.21 per 1SD, $P = 0.009$; CHD: 1.29, $P < 0.0001$); T wave abnormality in male HF (2.33, $P = 0.003$) and female CHD (1.84, $P = 0.001$). Specific risk factors were: serum creatinine for HF in both (men: 1.14 per 1SD, $P < 0.0001$, women: 1.09, $P = 0.01$); total cholesterol for CHD in men

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1875-4570/$ - see front matter
doi:10.1016/j.cvdpc.2010.06.002

(1.38 per 1SD, $P = 0.001$), history of valvular heart disease (6.48, $P = 0.002$) or stroke (2.41, $P = 0.048$) in male HF, and history of angina in female CHD (3.59, $P = 0.003$).
Conclusion: Common and specific measures need to be undertaken to prevent HF and CHD mortality.

Introduction

Although the incidence and mortality from coronary heart disease (CHD) and stroke have been decreasing in Western industrial countries, the incidence and mortality from heart failure (HF), common pathways from many roots of heart diseases, have been increasing [1,2]. Improved care of acute CHD events and of patients with HF, and aging populations cause these trends [3,4]. Among industrial countries, CHD mortality in Japan has been the lowest and the age-standardized mortality from CHD has been stable for decades [5]. However, crude mortality from CHD and HF has been increasing recently in Japan due to the aging of the population [6,7]. In fact, Japan had the highest proportion of those aged 65 and older in the world in 2005 [8]. In order to prevent HF, the risk factors should be clarified. Most of the knowledge about the risk factors for HF is based on North American and European studies [4,9,11,12]. Since HF is a global burden, studies on the risk factors outside North American and European countries are also needed. For unbiased information on the risk factors for HF, population-based studies are essential; there have been no such studies outside North American and European countries.

In the present study, we examined risk factors for HF and CHD mortality using the NIPPON DATA80 database [9–14] with a 24-year follow-up period.

Methods

Participants

The participants in this cohort were those in the 1980 National Survey on Circulatory Disorders [9]. A total of 10,546 community-based participants aged 30 years and over in 300 randomly selected health districts throughout Japan participated in the survey, which consisted of history-taking, physical examinations, blood tests and a self-administered questionnaire on lifestyle. For the present study, participants were followed up to 2004 (NIPPON DATA80, 1980–2004). The overall population aged 30 years and over in the participating health districts was 13,771. The participation rate was 76.6% (10,546 of 13,771) before exclusion for reasons mentioned below.

We reviewed the residence records of all the study participants for vital status. In fatal cases, the causes were examined. To clarify the cause of death, we used the National Vital Statistics records. The underlying cause of death was coded according to the 9th International Classification of Diseases for the National Vital Statistics until the end of 1994 and according to the 10th International Classification of Diseases from the beginning of 1995. Deaths were confirmed in each district by computer-matching of data from the Vital Statistics records using the district, sex, and dates of birth and death as key codes. Participants were excluded from follow-up because of missing baseline data ($N = 139$), or loss to follow-up ($N = 1105$). The latter group was excluded because of the absence of a permanent address that was needed to link to Vital Statistics records. The final sample comprised 9300 participants (4091 men and 5209 women). There were no significant differences between participants who were lost to follow-up and those who were included in the current study in terms of several risk factors. Therefore, the potential bias regarding the 1105 participants lost to follow-up is thought to be negligible. Permission to use the National Vital Statistics records was obtained from the Management and Coordination Agency, Government of Japan. Ethical approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 12-18, 2000).

Biochemical and baseline examinations

The baseline surveys were conducted at public health centers. Blood pressure was measured by trained research nurses using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest. Height and weight were measured in stocking feet and light clothing. BMI was calculated as weight (kg) divided by the square of height (m^2).

A lifestyle survey was also carried out using a self-administered questionnaire. Participants were asked about their alcohol drinking habit (never, past, occasional, and daily drinkers). Reported information was confirmed by public health nurses through interviews with the study participants regarding smoking, drinking habit, and present and past medical histories.

Casual blood samples were drawn and centrifuged within 60 min of collection and stored at −70 °C until analyses. Serum total cholesterol and creatinine were analyzed in a sequential auto-analyzer (SMA12/60; Technicon, Tarrytown, USA) at a single laboratory (Osaka Medical Center for Health Science and Promotion), a member of the Cholesterol Reference Method Laboratory Network (CRMLN) [10]. Serum concentrations of glucose were measured by the cupric-neocuproline method, and the value was converted so as to better correspond with the more widely used hexokinase method [11].

The ECG findings were independently evaluated by two trained researchers in each of 12 institutions according to the Minnesota Code (mc) as previously described [12]. Major ECG findings were tall R (mc3-1 to 3-4), ST depression (mc4-1 to 4-4) and T abnormality (mc5-1 to 5-5).

Statistical analysis

SAS version 9.1 for Windows (SAS Institute, Cary, NC) was used throughout the analyses. The chi-square test was used to compare dichotomous variables, followed by a *post hoc* application of Bonferroni's method. A one-way analysis of variance was used to compare means among the three groups stratified by outcome, followed by a *post hoc* application of Dunnett's test when the *F* value showed a significant difference at $P < 0.05$. To examine the factors associated with HF and CHD mortality, multivariate-adjusted hazard ratios were calculated using a Cox proportional hazards model. Men and women were analyzed separately. Age, BMI (<18.5 or ⩾25 vs 18.5–25 kg/m^2), systolic BP, cigarette smoking (never and past smokers, current smokers <20 cigarettes/day, current smokers 20–40 cigarettes/day, and current smokers ⩾41 cigarettes/day), alcohol drinking (ex-drinker or current drinker [occasional drinker or daily drinker] vs never-drinker), self-reported history of valvular heart diseases, stroke, angina; serum total cholesterol, blood glucose and serum creatinine concentrations (model 1). The above continuous variables except for age were standardized to have the mean = 0 and standard deviation = 1. For model 2, ECG findings of T wave abnormality, tall R plus ST depression or T abnormality were separately added to model 1. Since there was a temporary sharp decline in mortality from heart diseases in 1995 due to the 10th International Classification of Diseases regarding the description of diagnosis on death certificates, the above analyses were repeated after dividing the follow-up period into the former and the latter halves (–1994, 1995–).

Results

Baseline characteristics according to outcome in men and women

The baseline characteristics in 4091 men according to outcome over the 24 year follow-up are shown in Table 1. There were 84 deaths from HF and 87 from CHD. The mean age, systolic BP and blood glucose concentration were higher in both mortality groups compared to those in the no HF no CHD mortality control group. Current drinkers were less frequent in both mortality groups compared to those in the control group. Those with T abnormality, and those with tall R wave + ST depression or T abnormality were more frequent in both mortality groups compared to those in the control group. The mean diastolic BP and total cholesterol were higher in the CHD mortality group than those in the controls. Those with BMI < 18.5 kg/m^2, a history of valvular heart disease or stroke were more frequent in the HF mortality groups compared to those in the control group.

The baseline characteristics in 5209 women according to outcome over the 24 year follow-up are shown in Table 2. There were 100 deaths from HF and 88 from CHD. The mean age, systolic and diastolic BP, total cholesterol, blood glucose and creatinine concentrations were higher in both mortality groups compared to those in the control group. Those with BMI < 18.5 kg/m^2 were more frequent in the HF mortality group compared to those in the control group. Current drinkers were less frequent in the HF mortality group and current smokers were more frequent in the CHD mortality group than those in the control group. Those with T abnormality, and those with tall R wave + ST depression or T abnormality were more frequent in both mortality groups compared to those in the control group. Those with a history of stroke were more frequent in both mortality groups compared to those in the control group. Those with a history of angina were more frequent in the CHD mortality group than those in the control group.

Factors associated with HF and CHD mortality

The Cox multivariate hazard ratios for HF and CHD mortality in 4091 men are shown in Table 3. Older age, systolic BP, and blood glucose concentration were significantly associated with a higher mortality from HF and CHD. A higher creatinine concentration, history of valvular heart diseases or stroke, and presence of T wave abnormality were associated with a higher HF mortality. Smoking and a higher total cholesterol concentration were associated with a higher CHD mortality.

The results for 5209 women are shown in Table 4. Among continuous variables, only older age was significantly associated with a higher mortality from HF and CHD. A higher systolic BP and history of angina were associated with a higher CHD mortality, while higher creatinine was associated with a higher HF mortality. Smoking was associated with HF mortality. Both ECG abnormalities were associated with a higher CHD mortality.

Secondary analyses after dividing the follow-up period into the former and latter halves yielded similar results except for reduced statistical significance due to a loss of statistical power.

Discussion

Most of the risk factors for HF mortality found in the present study, such as older age, BP, blood glucose and history of valvular heart disease are compatible with previous studies in the US and Europe [2,4,13–15]. The higher serum creatinine found in the present study has also been reported [13].

In the present study, BMI < 18.5 kg/m^2 was associated with a significant increase in HF mortality in men and women. Although statistically insignificant, BMI ⩾ 25.0 kg/m^2 in men tended to be associated with a lower HF mortality in our study. Obesity has been demonstrated in general populations to predispose people to HF [4,14]. Obesity contributes to atherogenic risk factors through neurohormonal regulation. Obesity also increases preload and afterload, which predispose to HF. However, a number of recent large-scale clinical studies in patients with established heart failure have shown that being underweight or having low BMI was associated with increased mortality, while elevated BMI is associated with a better prognosis [14,15]. Kistorp et al. found lower adiponectin concentrations, that occur in the setting of increased BMI, were associated with improved survival in patients with compensated HF [16]. Furthermore, in other chronic impaired health conditions such as chronic obstructive pulmonary disease, cancer, renal failure, or liver cirrhosis, obese patients show better survival [17]. Possible misdiagnosis of HF in obese people cannot account for all these findings. Because obese people have more adipose tissue, they have more reserves and can survive longer. Another potential explanation is the presence of cardiac cachexia in patients with advanced HF

Table 1 Baseline characteristics according to outcome over a 24 year follow-up in 4091 men — NIPPON DATA80, 1980—2004.

	No HF—CHD	HF death	CHD death	P
N (subtotal 4091)	3918	82	91	
Age (year)	50.2 ± 13.0	67.3 ± 11.0**	61.7 ± 11.0**	<0.0001
BMI (kg/m^2)	22.5 ± 2.9	21.4 ± 2.8**	22.9 ± 3.0	0.0007
BMI < 18.5 kg/m^2 (%)	6.3	15.9**	7.7	0.002
BMI ⩾ 25.0 kg/m^2 (%)	19.2	9.8	20.9	0.09
SBP (mmHg)	138 ± 21	153 ± 24**	150 ± 22**	<0.0001
DBP (mmHg)	84 ± 12	84 ± 11	87 ± 14*	0.04
Smoking (%)	62.9	59.8	62.6	0.84
Drinking (%)	75.0	52.4**	60.4**	<0.0001
Valve HD (%)	0.5	3.7*	1.1	0.0006
Hx of stroke	1.6	7.3**	1.1	0.0004
Hx of angina	1.1	0	2.2	0.39
Hx of AMI	0.5	0	0	0.67
TCH (mg/dl)	186 ± 33	182 ± 29	197 ± 36**	0.004
Blood glucose (mg/dl)	102 ± 31	116 ± 33**	121 ± 60**	<0.0001
Creatinine (mg/dl)	1.05 ± 0.19	1.22 ± 1.06**	1.11 ± 0.24	<0.0001
T abnormality (%)	5.9	23.2**	15.4**	<0.0001
Tall R + (ST depr or T abn) (%)	2.7	11.2*	13.4*	<0.0001

HF = heart failure, CHD = coronary heart disease, No HF—CHD = no HF and no CHD mortality control group, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, valve HD = history of valvular heart disease, TCH = serum total cholesterol concentration, tall R = tall R wave on ECG, ST depr = ST depression, T abn = T abnormality.
* $P < 0.05$: no HF—CHD group vs HF death or CHD death group.
** $P < 0.01$: no HF—CHD group vs HF death or CHD death group.

Table 2 Baseline characteristics according to outcome over 24 year follow-up in 5209 women — NIPPON DATA80, 1980—2004.

	No HF—CHD	HF death	CHD death	P
N (subtotal 5209)	5005	107	97	
Age (year)	50.3 ± 13.0	69.8 ± 9.0**	67.1 ± 9.2**	<0.0001
BMI (kg/m^2)	22.9 ± 3.4	22.5 ± 4.0	22.9 ± 3.7	0.56
BMI < 18.5 kg/m^2 (%)	6.9	15.0**	10.3	0.003
BMI ⩾ 25.0 kg/m^2 (%)	22.9	23.4	23.7	0.97
SBP (mmHg)	133 ± 21	151 ± 25**	151 ± 23**	<0.0001
DBP (mmHg)	79 ± 12	84 ± 13**	85 ± 13**	<0.0001
Smoking (%)	8.7	13.1	15.5*	0.01
Drinking (%)	20.0	7.5**	20.6	0.006
Valve HD (%)	0.6	1.9	1.0	0.27
Hx of stroke	0.6	2.8**	3.1**	0.0007
Hx of angina	1.0	1.9	6.2**	<0.0001
Hx of AMI	0.5	0	0	0.59
TCH (mg/dl)	191 ± 34	202 ± 34**	205 ± 41**	<0.0001
Blood glucose (mg/dl)	100 ± 28	109 ± 39**	114 ± 37**	<0.0001
Creatinine (mg/dl)	0.84 ± 0.15	0.95 ± 0.24**	0.91 ± 0.24**	<0.0001
T abnormality (%)	10.2	26.2**	29.9**	<0.0001
Tall R + (ST depr or T abn) (%)	3.8	9.8**	9.9**	0.0004

HF = heart failure, CHD = coronary heart disease, No HF—CHD = no HF and no CHD mortality control group, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, valve HD = history of valvular heart disease, TCH = serum total cholesterol concentration, tall R = tall R wave on ECG, ST depr = ST depression, T abn = T abnormality.
* $P < 0.05$: no HF—CHD group vs HF death or CHD death group.
** $P < 0.01$: no HF—CHD group vs HF death or CHD death group.

[14]. Basically, the results of our study in a relatively less obese population are consistent with those of previous studies [14,15].

History of stroke in men was one of the risk factors for HF mortality in our study. Although it has not been identified as a risk factor for HF incidence or mortality in previous studies, He et al. showed physical inactivity was an important risk factor for developing HF [18]. As we did not have any quantitative data on physical activity, history of stroke may have reflected physical inactivity.

Table 3 Cox multivariate hazard ratios for heart failure and coronary heart disease mortality in 4091 men — NIPPON DATA80, 1980—2004.

	HF death	*P*	CHD death	*P*
Model 1				
Age	**1.14 (1.11–1.17)**	**<0.0001**	**1.10 (1.08–1.13)**	**<0.0001**
BMI < 18.5 kg/m^2	**1.92 (1.04–3.55)**	**0.04**	1.25 (0.56–2.76)	0.59
BMI ≥ 25.0 kg/m^2	0.69 (0.33–1.46)	0.71	1.09 (0.63–1.87)	0.76
SBP†	**1.28 (1.04–1.58)**	**0.02**	**1.29 (1.05–1.58)**	**0.01**
Smoking	1.16 (0.92–1.47)	0.21	**1.31 (1.09–1.58)**	**0.004**
Drinking	0.66 (0.40–1.09)	0.11	0.66 (0.41–1.05)	0.08
Valve HD	**6.48 (1.99–21.2)**	**0.002**	1.79 (0.25–13.1)	0.56
Hx of stroke	**2.41 (1.01–5.78)**	**0.048**	0.44 (0.06–3.24)	0.42
Hx of angina	0.00 (0.00–)	0.98	1.23 (0.30–5.06)	0.77
TCH†	0.97 (0.77–1.23)	0.83	**1.38 (1.14–1.67)**	**0.001**
Blood glucose†	**1.21 (1.05–1.39)**	**0.009**	**1.29 (1.17–1.41)**	**<0.0001**
Creatinine†	**1.14 (1.08–1.20)**	**<0.0001**	1.08 (0.96–1.22)	0.20
Model 2 (ECG findings)				
T abnormality	**2.33 (1.33–4.08)**	**0.003**	1.53 (0.84–2.82)	0.16
Tall R + (ST depr or T abn)	1.37 (0.63–2.97)	0.43	1.66 (0.79–3.46)	0.18

Variables with † were standardized to have mean = 0, standard deviation = 1. Model 1 covariates included age, BMI (<18.5 or ≥25 vs 18.5–25 kg/m^2), SBP, smoking (never and past smokers, current smokers <20 cigarettes/day, current smokers 20–40 cigarettes/day, and current smokers ≥41 cigarettes/day), alcohol drinking (ex-drinker or current drinker [occasional drinker or daily drinker] vs never-drinker), self-reported history of valve HD, stroke, angina; serum TCH, blood glucose and serum creatinine concentrations. For model 2, ECG findings of T wave abnormality, or tall R plus ST depression or T abnormality were separately added to model 1. HF = heart failure, CHD = coronary heart disease, no HF–CHD = no HF and no CHD mortality control group, BMI = body mass index, SBP = systolic blood pressure, valve HD = history of valvular heart disease, TCH = serum total cholesterol concentration, tall R = tall R wave on ECG, ST depr = ST depression, T abn = T abnormality.

Table 4 Cox multivariate hazard ratios for heart failure and coronary heart disease mortality in 5209 women — NIPPON DATA80, 1980—2004.

	HF death	*P*	CHD death	*P*
Model 1				
Age	**1.17 (1.15–1.20)**	**<0.0001**	**1.15 (1.12–1.17)**	**<0.0001**
BMI < 18.5 kg/m^2	**1.86 (1.04–3.30)**	**0.04**	1.67 (0.83–3.36)	0.15
BMI ≥ 25.0 kg/m^2	0.98 (0.61–1.56)	0.92	0.95 (0.57–1.58)	0.83
SBP†	1.20 (0.99–1.45)	0.07	**1.27 (1.04–1.56)**	**0.003**
Smoking	**1.39 (1.07–1.81)**	**0.01**	1.35 (0.97–1.89)	0.10
Drinking	**0.44 (0.23–0.98)**	**0.04**	1.49 (0.90–2.46)	0.12
Valve HD	2.14 (0.52–8.74)	0.29	1.09 (0.15–7.88)	0.93
Hx of stroke	1.74 (0.54–5.56)	0.30	1.62 (0.50–5.27)	0.43
Hx of angina	0.91 (0.22–3.73)	0.90	**3.59 (1.53–8.38)**	**0.003**
TCH†	1.01 (0.82–1.24)	0.87	1.09 (0.88–1.35)	0.43
Blood glucose†	1.09 (0.92–1.29)	0.34	**1.15 (1.04–1.37)**	**0.02**
Creatinine†	**1.09 (1.02–1.16)**	**0.01**	1.05 (0.94–1.17)	0.36
Model 2 (ECG findings)				
T abnormality	1.39 (0.89–2.18)	0.14	**1.84 (1.16–2.85)**	**0.01**
Tall R + (ST depr or T abn)	1.65 (0.89–3.07)	0.11	**2.46 (1.34–4.51)**	**0.004**

Variables with † were standardized to have mean = 0, standard deviation = 1. Covariates included in models 1 and 2 were the same as Table 3. HF = heart failure, CHD = coronary heart disease, no HF–CHD = no HF and no CHD mortality control group, BMI = body mass index, SBP = systolic blood pressure, valve HD = history of valvular heart disease, TCH = serum total cholesterol concentration, tall R = tall R wave on ECG, ST depr = ST depression, T abn = T abnormality.

T wave abnormality in men in our study was associated with about a 2.4-fold increase in HF mortality, consistent with previous studies [19,20]. Although the prevalence of current smokers and drinkers in women was lower compared to men, both of them were associated with significant differences in HF mortality, the former with an increase and the latter with a decrease. These results are consistent with previous studies. The reason why these risk factors were not associated with significant changes in HF mortality in men may be due to the fact that there were relatively fewer non-smokers and non-drinkers among the men to serve as references.

Gender specific differences in risk factors for HF or CHD mortality are worth mentioning. Although total cholesterol in men was a significant risk factor for CHD mortality, it was not in women. History of angina in women was a significant risk factor for CHD mortality, it was not in women. In Japan as in rest of the world, CHD mortality is far less in women than in men. Thus, some risk factors, such as a higher total cholesterol might not have been shown as a risk factor due to lack of statistical power. However, history of angina in women was shown as a significant risk factor, while in men there was not even a trace of a trend. It may be related that the syndrome of angina-like chest pain with normal epicardial artery is more common in women than in men [21]. Women with chest pain might have been paid less medical attention than men. The present finding that valvular heart disease in men was a significant risk factor for HF mortality, but not in women, may be related to the fact that valvular aortic stenosis, which has more prognostic significance than the other valvular heart diseases, is more common in men than in women [22].

Strengths and limitations of the study

The strengths of our study include its prospective design and the follow-up of a randomly selected sample from the general population of Japan with a high response rate (76.3%). Since the study included men and women with a broad range of ages, findings are likely to be generalizable to middle-aged and elderly Japanese.

As in any long-term follow-up study, however, there are some weaknesses. We used mortality data as end points, which can lead to misclassification of the cause of death. It has also been reported that most cases of sudden cardiac death tend to be described on Japanese death certificates as "CHD", "HF" or "unknown cause" [21]. Furthermore, mortality statistics for CHD may have been underestimated up to the end of 1994 using ICD9, since deaths from coronary events may have been miscoded as "HF" [23]. However, comparing risk factors for HF and CHD mortality presented in Tables 3 and 4, there were specific risk factors for each of the mortalities, such as history of valvular heart disease in male HF, a higher total cholesterol concentration in male CHD, and history of angina in female CHD mortality. Furthermore, secondary analyses after dividing the follow-up period into the former and latter halves yielded similar results, except for reduced statistical significance due to a loss of statistical power, indicating that our mortality data were reliable despite a few possible misclassifications. Furthermore, recent advances in medical treatment for modifiable risk factors such as hypertension, hypercholesterolemia, or glucose intolerance might have diluted the detrimental effects of risk factors for HF and CHF mortality.

Acknowledgments

The authors thank all members of the Japanese Association of Public Health Center Directors and all staff of the public health centers that cooperated with our study. Investigators and members of the research group are listed in the appendix of Reference [12].

Funding sources

This study was supported by a grant-in-aid of the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-cardiovascular Disease Control, the Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare and a Health and Labor Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-Chouju-046, H14-Chouju-003, H17-Chouju-012, H19-Chouju-014), and by the Japan Society for the Promotion of Science invitation fellowship programs for research in Japan. Tanvir Chowdhury Turin and Nahid Rumana are supported by the fellowship from the Japan Society for the Promotion of Science (JSPS).

Disclosures

We have no conflicts of interest to disclose.

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(6) 日本人における循環器疾患死亡のST-T異常と左胸部高R波の予後予測能について (NIPPON DATA80の24年化の追跡データより)

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背景　安静時心電図（ECG）はもっとも広く使われている非侵襲的な循環器疾患リスクを疫学あるいは臨床現場で評価するツールである。ST-T異常はECG上でもっとも感度の高い変化であり、左胸部高R波は心電図上でのLVHの兆候であり、ST-T異常と関連がみられる。しかし、心疾患が少なく脳卒中死亡が多いアジアにおけるECGでの左胸部高R波とST-T異常別の将来の循環器疾患（CVD）死亡との関連はあまりよく知られていない。本研究ではNIPPON DATA80を用いて検討した。

方法　NIPPON DATA80の対象者10546名のうちベースライン時の基本情報がありCVD既往と主要な心電図変化（II度、III度AVブロック、完全左脚ブロック、完全右脚ブロック、心房細動など）のない日本人集団8572名を24年間追跡した。

対象者のベースライン時のECG所見別に、左胸部高R波のみ、ST-T異常のみ、左胸部高R及びST-T異常あり及びいずれもなし（正常心電図）の4群に分けた。Cox比例ハザードモデルは正常群と比較してECG異常群のCVD死亡リスクを推定した。

結果　8572名中（男性3806名、平均年齢49.5歳、女性4766名、平均年齢49.4歳）、左胸部高R波のみが1142名、ST-T異常のみが292名、左胸部高R及びST-T異常ありは128名であった。追跡人年181545人年（平均追跡期間21.2年）の間に2244名の死亡を確認し、内循

環器疾患は750名でその中で心疾患は149名であった。左胸部高R波合併のST-T異常のCVD死亡の多変量調整後のハザード比（HR）は男性が1.95(95%信頼区間1.25-3.04)、女性が2.68(1.81-3.97)であった。ST-T異常のみのCVD死亡リスクは男性が1.66倍（1.01-2.71）、女性は1.62倍(1.18-2.24)であった。CVD死亡とECG異常との関連は年齢、BMI、収縮期血圧、コレステロール、血糖値、喫煙及び飲酒、降圧治療歴とは独立に見られた。心疾患（CHD）死亡では左胸部高R波合併のST-T異常の多変量調整後のハザード比（HR）は男性が2.40(0.89-6.44)、女性が2.62(1.02-6.76)であった。ST-T異常のみのCVD死亡リスクは男性が1.80倍（0.61-5.29）、女性は2.39倍(1.25-4.59)であった。

結論　安静時ECGの左胸部高R波の有無にかかわらずST-T異常は日本人の男女においてCVD、CHD死亡の独立した予測因子であった。

Prognostic Value of ST-T Abnormalities and Left High R-waves with Cardiovascular Mortality in Japanese (24-year Follow-up of NIPPON DATA80)

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Abstract

Little is known about the prognostic value of ST segment depression and/or T wave (ST-T abnormalities) with or without left high R-waves on a resting electrocardiogram (ECG) for death from cardiovascular disease (CVD) in Asian populations. Japanese participants without a history of CVD and free of major ECG abnormalities were followed for 24 years. Subjects were divided into four groups based on the baseline ECG findings: isolated left high R-waves, isolated ST-T abnormalities, ST-T abnormalities with left high R-waves, and a normal ECG. A Cox proportional hazard models was used to estimate the risk of CVD mortality in the groups with ECG abnormalities compared with the normal group. Among 8,572 participants (44.4% men, mean age 49.5 years; 55.6% women, mean age 49.4 years), 1,142 had isolated left high R-waves, 292 had isolated ST-T abnormalities, and 128 had ST-T abnormalities with left high R-waves at baseline. The multivariable-adjusted hazard ratio (HR) of ST-T abnormalities with left high R-waves for CVD mortality was 1.95 (95% CI: 1.25 to 3.04) in men and 2.68 (95%CI: 1.81to 3.97) in women. Isolated ST-T abnormalities increased the risk for CVD death by 1.66 (95% CI: 1.01to 2.71) times in men and 1.62 (95%CI: 1.18 to 2.24) times in women. The association of ECG abnormalities with CVD mortality was independent of age, body mass index, systolic blood pressure, serum cholesterol, blood glucose, smoking and drinking and antihypertensive medication. In conclusion, ST-T abnormalities with or without left high R-waves in the resting ECG are an independent predictor of CVD mortality in Japanese men and women.

Keywords: Electrocardiography, epidemiology, mortality, left ventricular hypertrophy, cardiovascular disease

Introduction

The standard resting electrocardiogram (ECG) is the most widely used non-invasive tool for assessing cardiovascular risk in epidemiological studies and clinical practice. ST segment depression and /or an inverse or flat T-wave (ST-T abnormalities) are most sensitive changes on the ECG[1-3]. Additionally, left high R-wave, ECG manifestation of left ventricular hypertrophy (LVH), are often seen in association with ST-T abnormalities[4,5]. Several epidemiological studies have reported that LVH with ST-T abnormalities increase the cardiovascular diseases (CVD) risk [4,6-10] . However, these studies investigating the prognostic value of ST-T abnormalities and left high R-waves were performed predominantly in the Western populations. Information about the prognostic value of ST-T abnormalities in the presence or absence of left high R-waves is meager in the Asian populations that have a higher stroke rate and lower incidence of coronary heart disease (CHD). In a population with a markedly lower coronary mortality, such as Japanese, the benefit of ECG screening may be different from Western populations. The aim of the current study was to assess the independent prognostic value of ST-T abnormalities with or without left high R-waves for mortality due to CVD and its subtypes in a large cohort of participants selected randomly from the overall Japanese population.

Methods

The dataset of the cohort study of the National Survey on Circulatory Disorders comprising the National Integrated Project for Prospective Observation of Non-Communicable Disease And its Trends in the Aged (NIPPON DATA) was used. The present study analyzed data from NIPPON DATA80, in which a baseline survey was performed in 1980. The details of this cohort have been reported elsewhere[11,12]. In brief, 300 areas were selected by stratified random sampling and all the residents aged 30 years or older in these areas were invited to participate. A total of 10,546 residents (4,639 men and 5,907 women) participated in the survey (response rate: 76.6%). The baseline surveys were carried out at local public health centers. The participants were followed for 24 years until November 2004.

In this present study, we excluded participants who had a past history of CHD or stroke at baseline (n = 280), missing information at baseline or were lost to follow-up (n = 913). In addition, participants with baseline ECG abnormalities (n=781) including third degree atrio-ventricular block [The Minnesota Codes (MC), 6-1], second degree atrio-ventricular block [MC, 6-2], Wolf-Parkinson-White syndrome [MC, 6-4], complete left bundle branch block [MC, 7-1], complete right bundle branch block [MC, 7-2], minor ST segment [MC 4-4], non-specific T wave abnormalities [MC 5-4 to 5-5], atrial fibrillation