(資料8) 各対象地域の死亡率の推移

八尾市・全死亡

死亡年(西暦)		1972-1977	1978-1983	1984-1989	1990-1995	1996-2001	2002-2007
男							
30歳以上総死亡数		3325	3961	6026	5156	5785	6553
死亡年齢	30-39歳	193	159	165	91	91	122
	40-49歳	323	400	483	279	236	197
	50-59歳	413	613	1033	765	797	675
	60-69歳	847	765	1121	1206	1467	1500
	70-79歳	1082	1250	1776	1315	1501	2144
	80-89歳	431	707	1289	1276	1359	1455
	90歳以上	36	67	159	224	334	460
年齢調整死亡率(30歳以上)		1801	1637	2030	1276	1066	994
女							
30歳以上総死亡数		2974	3241	5156	4551	4958	5444
死亡年齢	30-39歳	123	109	107	47	56	70
	40-49歳	221	180	286	185	154	126
	50-59歳	311	330	450	392	363	335
	60-69歳	589	554	788	593	682	646
	70-79歳	945	1054	1545	1169	1148	1141
	80-89歳	680	868	1629	1650	1841	1876
	90歳以上	105	146	351	515	714	1250
年齢調整死亡率(30歳以上)		1281	987	1213	726	585	504

Ⅱ．研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Iso H	Changes in coronary heart disease risk among Japanese.	Circulation	118	2725-2729	2008
Chei CL, Yamagishi K, Tanigawa T, Kitamura A, Imano H, Kiyama M, Sato	Metabolic Syndrome and the Risk of Ischemic Heart Disease and Stroke among Middle-Aged Japanese	Hypertens Res	31	1887-1894	2008
Kato Y, Ikehara S, Maruyama K, Inagawa M, Oshima M, Yokota K, Yamazaki T, Kishi M, Murai S, Umesawa M, Ma E, Yamagishi K, Tanigawa T, Kurokawa M, Sato S, Shimamoto T, Iso H. S, Shimamoto T, Iso H	Trends in dietary intakes of vitamins A, C and E among Japanese men and women from 1974 to 2001	Public Health Nutr	14	1-8	2008
Maruyama K, Sato S, Ohira T, Maeda K, Noda H, Kubota Y, Nishimura S, Kitamura A, Kiyama M, Okada T, Imano H, Nakamura M, Ishikawa Y, Kurokawa M, Sasaki S, Iso H.	The joint impact on being overweight of self reported behaviours of eating quickly and eating until full: cross sectional survey	BMJ	In press		

Chei CL, Iso H, Yamagishi K, Tanigawa T, Cui R, Imano H, Kiyama M, Kitamura A, Sato S, Shimamoto T.	Body fat distribution and the risk of hypertension and diabetes among Japanese men and women	Hypertens Res	31	851-857	2008
Kitamura A, Sato S, Kiyama M, Imano H, Iso H, Okada T, Ohira T, Tanigawa T, Yamagishi K, Nakamura M, Konishi M, Shimamoto T, Iida M, Komachi Y	Trends in the Incidence of Coronary Heart Disease and Stroke and Their Risk Factors in Japan, 1964 to 2003: The Akita-Osaka Study	J Am Coll Cardiol	52	71-79	2008

Ⅲ. 研究成果の刊行物・別刷

1) Iso H. Changes in coronary heart disease risk among Japanese. ***Circulation***. 2008;118:2725-2729.

2) Chei CL, Yamagishi K, Tanigawa T, Kitamura A, Imano H, Kiyama M, Sato S, Iso H. Metabolic syndrome and the risk of ischemic heart disease and stroke among middle-aged Japanese. ***Hypertens Res***. 2008;31:1887-1894

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Changes in Coronary Heart Disease Risk Among Japanese

Hiroyasu Iso, MD

Heart disease is the second most prominent cause of mortality in Japan, and coronary heart disease (CHD) accounts for approximately half of heart disease–related deaths.[1] The CHD mortality rate in Japan has been one-third to one-fifth that in the United States,[1–5] even when validated fatal CHD and sudden cardiac deaths were compared.[3–5] However, there is growing concern about a possible increase in the incidence of and mortality from CHD because of the westernization of lifestyles such as high-fat diets and sedentary work patterns associated with socioeconomic development since the 1960s.[6–11]

The present report reviews original articles on population-based surveys of the mortality, incidence, and risk factors of CHD. It focuses on their trends since the 1960s because Japan has experienced rapid changes in lifestyles and environment accompanying socioeconomic development and maturation.

Methods

To identify the relevant literature, PubMed was searched for articles published from 1963 through June 2007. The following search key words were used: *coronary heart disease* or *coronary artery disease* or *ischemic heart disease* or *myocardial infarction*; *mortality* or *incidence* or *risk factor*; *Japan* or *Japanese*; and *epidemiology*. Bibliographies of key articles were reviewed and experts in the field were consulted to identify all of the major population-based studies.

Trends in Mortality From CHD

Age-adjusted mortality rates from CHD declined 50% for men and 65% for women between 1969 and 1992[8,9] and has continued to decline.[1,2] According to the World Health Organization database, the age-adjusted annual CHD mortality rate in 2000 was 37 per 100 000 for men and 18 per 100 000 for women, which was the lowest among developed countries.[2]

There are, however, sex, age, and regional variations in CHD mortality trends.[9] The age-adjusted CHD mortality rates declined from 57 per 100 000 in 1969 to 1970 to 27 per 100 000 in 1991 to 1992 for men 30 to 69 years of age and from 26 to 9 per 100 000 for women of the same ages.[8] The CHD mortality decline was smaller among men and women residing in the Tokyo and Osaka metropolitan areas than among those in the rest of Japan.[9] Men 30 to 49 years of age in the metropolitan areas showed no substantial change in CHD mortality (≈10 per 100 000), whereas those in the rest of Japan showed a steady decline.[9]

Trends in Incidence of CHD

There also were sex, age, and regional variations in CHD incidence trends reported from long-term population-based studies.[10–14] Those studies used the systematic case ascertainment system, consistent diagnostic criteria, and a panel of physician-epidemiologists for final diagnosis to ensure the validity of CHD surveillance. The age-adjusted incidence of CHD among male employees 40 to 59 years of age in Osaka increased from 0.4 per 1000 person-years in 1963 to 1970 to 1.5 per 1000 person-years in 1979 to 1986 and then plateaued until 1987 to 1994.[10]

More recently, Osaka male residents 40 to 69 years of age have shown a trend for CHD incidence to increase from 0.6 per 1000 person-years in 1980 to 1987 to 1.3 per 1000 person-years in 1996 to 2003.[11] Male residents in Takashima City had an increasing incidence of CHD for all ages from 0.7 per 1000 person-years in 1990 to 1992 to 1.0 per 1000 person-years in 1999 to 2001; the CHD increase was observed primarily for those 65 years of age, and information on risk factor trends was not available.[12]

However, the CHD incidence remained low and did not change materially among female residents in Osaka (≈0.4 per 1000 person-years)[11] and Takashima (≈0.3 per 1000 person-years),[12] nor did the incidence change over time among men and women 40 to 69 years of age in a rural community of Akita Prefecture (≈0.7 per 1000 person-years for men and 0.1 per 1000 person-years for women).[7,11] No significant trends in CHD incidence were observed among the Hiroshima/Nagasaki cohort between 1958 and 1984 (≈2 per 1000 person-years for men and 0.8 per 1000 person-years for women of all ages),[13] for the Hisayama cohort between 1961 and 2000 (≈2 per 1000 person-years in men and 1 per 1000 person-years in women ≥40 years of age),[14] or for residents of Okinawa between 1998 and 1991 (myocardial infarction, ≈1 per 1000 persons-years for men and 0.04 per 1000 person-years for women ≥40 years of age).[15]

Coronary Risk Factors and Their Trends

Major risk factors for CHD from cohort studies and their trends from national studies and population-based studies were reviewed. Trends for the coronary risk factors were examined by use of the same standardized methods and criteria for blood pressure, smoking, overweight, alcohol intake, and diet and by the Centers for Disease Control–National Heart, Lung, and Blood Institute Lipid Standardization Program and the US Cholesterol Reference Laboratory Network for blood lipids.[16]

Smoking and Its Trend

There was a consistent association between smoking and risk of incidence of or mortality from CHD.[13,17–21] The multivariable hazard ratio of CHD incidence or mortality for current smoking compared with never or previous smoking was ≈2 to 3 for either sex, with a dose-response relationship between the number of cigarettes smoked and the risk of CHD.

As for an effect of environmental tobacco smoke, age-adjusted CHD mortality was 30% higher for nonsmoking wives with husbands who smoked ≥20 cigarettes per day compared with those with nonsmoking husbands.[22]

The risk of CHD was generally lower for ex-smokers than current smokers,[18–20] which suggests that smoking cessation lowers risk. A recent large cohort study showed that a decline in risk of CHD after smoking cessation occurred within 2 years and reached the level for

From Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Osaka, Japan.

Correspondence to Hiroyasu Iso, MD, Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadagaoka, Suita-shi, Osaka 565-0871, Japan.

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never smokers 10 to 14 years after cessation.[23] In that study, the benefit of smoking cessation was observed similarly among the 40-to-64- and 65-to-79-year age subgroups. The benefit of smoking cessation also was confirmed for patients with a history of myocardial infarction for the prevention of subsequent cardiac events.[24]

In Japan, the prevalence of current smoking has declined from 82% in 1965% to 46% in 2005 for men ≥20 years of age, whereas that for women declined slightly from 16% in 1965% to 12% in 2005.[1,25] However, for women 20 to 29 years old, the prevalence of smoking increased from 7% in 1965 to 21% in 2005.[1,25] Population-based studies have identified similar downward trends in smoking for middle-aged men.[10,11]

High Blood Pressure and Its Trend

High blood pressure has been identified as a risk factor for CHD,[13,26,27] and both systolic and diastolic blood pressure levels were positively associated with CHD risk.[13,26] The multivariable hazard ratio of CHD incidence for high blood pressure (systolic blood pressure ≥135 mm Hg, diastolic blood pressure ≥85 mm Hg, and/or use of antihypertensive medication) was ≈2 for men and 1.5 for women.[28]

According to a national survey, mean systolic blood pressure for persons ≥30 years of age declined from 142 mm Hg in 1961 to 137 mm Hg in 2000 for men and from 141 to 132 mm Hg for women,[29] whereas changes in mean diastolic blood pressure levels were not substantial: from 82 to 83 mm Hg for men and from 81 to 78 mm Hg for women.[29] The prevalence of high blood pressure (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) in 2000 was 52% for men and 40% for women ≥30 years of age.[29]

Similar blood pressure declines were observed between the 1960s and the 1990s in population-based studies of rural men and women and urban women.[11] For urban men, either residents or company employees, systolic blood pressure declined modestly between the 1960s and the 1990s, but diastolic blood pressure started to increase in the 1980s.[10,11] The prevalence of hypertension decreased, along with downward trends in mean systolic blood pressure levels.[10,11] The prevalence of antihypertensive medication use rose substantially between the 1960s and the 1970s but did not change substantially thereafter.[7,10,11]

Blood Lipids and Their Trends

High serum total cholesterol has been a risk factor for CHD.[3,13,19,29,32–34] Serum total cholesterol levels were positively associated with risk of CHD, although mean levels of total cholesterol are lower in Japan than in Western countries.[13,19,32–34] The multivariable hazard ratio of CHD mortality for high (≥220 mg/dL) compared with lower (<180 mg/dL) total cholesterol was 1.6 to 1.8 for both men and women,[19] whereas that for very high (≥260 mg/dL) compared with very low (<160 mg/dL) total cholesterol was ≈3.5 for both men and women.[33,34]

Serum high-density lipoprotein (HDL) cholesterol was inversely associated with risk of CHD.[19] Nonfasting serum triglycerides also were associated with the risk of CHD even after adjustment for HDL cholesterol and other coronary risk factors.[35]

According to a national survey, mean total serum cholesterol levels increased from 186 mg/dL in 1980 to 200 mg/dL in 2000 among men ≥30 years of age and from 191 to 208 mg/dL among women of the same age.[29] The prevalence of high total cholesterol (≥220 mg/dL) increased from 15% to 27% for men and 19% to 35% for women, and that of total cholesterol ≥260 mg/dL increased from 2% to 5% for men and from 3% to 8% for women.[29] The increase in total cholesterol levels and prevalence of high total cholesterol was observed primarily between the 1980s and the 1990s and plateaued thereafter. Mean serum HDL cholesterol levels have been higher for Japanese than for whites[36] and increased from 50 mg/dL in 1990 to 53 mg/dL in 2000 for men and from 53 to 61 mg/dL for women.[29] In addition, mean serum triglyceride levels increased between 1990 and 200 for both men and women.[29]

Similar trends in blood lipids were observed in population-based studies of men and women in rural and urban communities and of male employees in metropolitan areas between the 1960s and the 2000s[7,10,11] and in a large hospital/clinic-based study.[37] The prevalence of the use of lipid-lowering medication increased over time by up to 3% for men and 9% for women, although it was much lower than that of antihypertensive medication.[10,11]

Diabetes Mellitus and Its Trend

Non–insulin-dependent diabetes mellitus may be a risk factor for CHD, although the evidence from community-based cohort studies has been limited. The CHD incidence was twice as high for diabetics as nondiabetics.[38] The multivariable hazard ratio of CHD mortality for diabetics (casual blood glucose ≥200 mg/dL and/or history of diabetes) was ≈1.5 for men and 2.5 for women,[39] and that for diabetics (fasting glucose ≥140 mg/dL, nonfasting glucose ≥200 mg/dL, and/or on treatment) compared with nondiabetics (fasting glucose <100 mg/dL or nonfasting glucose <140 mg/dL) was ≈1.5 for men and 3.5 for women.[19]

No national survey has examined a long-term trend for the prevalence of diabetes mellitus, but the data between 1997 and 2002 showed no change for men and women ≥20 years of age.[40] According to community-based studies, the prevalence of diabetes increased from 2% to 8% in the 1980s to 6% to 13% in the 1990s among middle-aged men and from 1% to 5% in the 1980s to 3% to 9% in the 1990s among middle-aged women.[41,42]

Overweight and Its Trend

Overweight could be a risk factor for CHD, but its independent contribution to CHD risk may be minor.[43,44] Compared with persons with a body mass index (BMI) of 23.0 to 24.9 kg/m^2, the multivariable hazard ratio of CHD mortality for overweight (BMI ≥27.0 kg/m^2) was ≈2 for men and 1.5 for women.[43] As for CHD incidence, high BMI (BMI ≥30 versus 23.0 to 24.9 kg/m^2) was associated with doubling of the risk of CHD for men but not for women.[44] In that study, men who were not overweight at 20 years of age but gained ≥10 kg afterward showed double the risk of CHD compared with those with stable weight.[44]

Mean BMI and the prevalence of overweight have increased consistently among men since the 1980s but did not change among women, according to a national survey.[29,45] Mean BMI increased from 22.5 kg/m^2 in 1980 to 23.4 kg/m^2 in 2000 and the prevalence of overweight (BMI ≥25.0 kg/m^2) increased from 19% to 28% for men ≥30 years of age; the corresponding mean values and prevalence for women were from 22.8 to 22.8 kg/m^2 and 23% to 23%, respectively.[29] Population-based studies showed similar increasing trends among rural and urban men but not women between the 1960s and the 2000s.[9–11]

Alcohol Intake and Its Trend

Light to moderate alcohol intake has been associated with a 30% to 60% reduced risk of CHD compared with no intake.[46–48] Furthermore, the protection by light to moderate alcohol intake against acute myocardial infarction was found for both the presence and absence of alcohol-induced flushing.[48]

No national survey has yielded long-term trends in alcohol intake. However, a population-based study showed that the prevalence of heavy drinkers (46 g ethanol/d) declined while the prevalence of light to moderate drinkers (1 to 45 g ethanol/d) increased between the 1980s and the 1990s among both rural and urban men.[49] The prevalence of any type of drinkers was low and did not change for either rural or urban women.[49]

Fish and Soy Intakes and Their Trends

Dietary intakes of fish and soy were associated with a reduced risk of CHD incidence.[50,51] Compared with men and women with the lowest fish intake (once a week or median intake of 23 g/d) and omega-3 fatty acid intake (median intake of 0.3 g/d), the multivariable hazard ratio of CHD incidence for those with the highest versus lowest fish intake (8 times per week or median intake of 180 g/d and omega-3 fatty acid intake (median intake of 2.1) was ≈0.6 for both fish and omega-3 fatty acid intakes.[50] The multivariable hazard ratio of myocardial infarction incidence for soy intake >5 versus 0 to 2 times per week was ≈0.6; that for the highest versus the lowest quintiles of isoflavone intake was 0.4 for women, but men did not

show such associations. The inverse association between isoflavone intake and risk of myocardial infarction was observed primarily among postmenopausal women.[51]

According to the national nutrition survey, mean fish intake for adult men and women was ≈80 g/d in the 1960s and 90 g/d between the 1970s and the 2000s.[52] Mean intake of beans was ≈70 g/d and did not change over time.[52]

Physical Activity and Its Trend

Physical activity was associated with a reduced risk of CHD mortality.[53] The multivariable hazard ratios of CHD mortality for the highest versus the second-lowest category of walking (≥1.0 versus 0.5 h/d) or sports participation (≥5 versus 1 to 2 h/wk) were ≈0.8 and 0.5, respectively.[53]

No robust data are available for long-term trends in physical activity. However, a decline in physical activity is suggested, particularly for men, because of the stable or declined energy intake,[52] the increased BMI,[29,45] the mechanization of the work environment, and motorization.[7]

Discussion

Japan is unique among developed countries in that, since the 1960s, it has had the lowest mortality from CHD, according to vital statistics[1,2] and population-based studies,[3–5] which has been further declining for both men and women.[8,9] Mean systolic blood pressure levels[7,9–11,13,29] and the prevalence of smoking[1,10,11,25] declined, but mean serum total cholesterol and triglyceride[7–11,29,37] levels increased for both men and women. The decline in CHD mortality is attributable to large declines in blood pressure levels and the prevalence of smoking, which may have offset the potentially adverse effects of increased total cholesterol levels during the past decades. High total cholesterol would need a longer incubation period to maximize the effect on CHD risk.[54,55]

Trends in CHD mortality and coronary risk factors have not been uniform and may vary by sex, age, and region. In the 2 largest metropolitan areas, Tokyo and Osaka, where 17% of the total Japanese population resides, the CHD mortality decline was small for men 30 to 49 years of age compared with those residing in the rest of Japan.[9]

The higher sustained cholesterol levels, together with a recent rise in diastolic blood pressure and declines in systolic blood pressure levels and the prevalence of smoking, may explain in part the slowed decline in CHD mortality in middle-aged urban men compared with rural men. Urban men have a higher fat intake than rural men (22% to 26% versus 19% of total energy for men 40 to 59 years of age)[10,11] and lower physical activity (1600 versus 1800 calories consumed per day).[56] According to an autopsy study,[57] the pathology of myocardial infarction among urban men was larger infarction associated with hypercholesterolemia-derived atherosclerosis of coronary arteries as also observed in Western populations, whereas for rural men, the pathology of myocardial infarction was smaller, disseminated infarction associated with hypertension-derived atherosclerosis of coronary arteries.

The annual CHD incidence rate for middle-aged Japanese was ≤2 per 1000 for men and ≤1 per 1000 for women; that for Americans was 5 to 6 per 1000 for men and 2 to 3 per 1000 for women.[58,59] The low CHD incidence for Japanese men and women is explained by more favorable lipid profiles and glucose metabolism, along with lower BMI levels. Lifestyle factors, including low total and saturated fat intakes[7,8,10,55,60] and high fish[50,52] and soy intakes[51,52] for men and women, as well as light to moderate alcohol intake[49,61] for men, may be major contributing factors.

There were sex, age, and area variations in trends in CHD incidence. The CHD incidence tripled among urban male employees 40 to 59 years of age between the 1960s and the 1990s, subsequently doubled for urban male residents 40 to 69 years of age between the 1980 and the 2000s, and increased by ≈50% for rural or semiurban male residents of all ages.[12] The number of CHD incident cases was too small to draw definite inferences from previous trend studies.[10–12] However, the CHD increase was consistent with findings of a Japanese migrant study that the incidence of CHD was higher among Japanese men living in Hawaii and California than among Japanese men living in Japan.[62] The gradient of CHD incidence corresponded to the difference in saturated fat intake and serum total cholesterol levels, supporting environmental effects on CHD risk.[62] For female residents and rural male residents, there was no material change in CHD incidence.[7,11–14]

The decline in CHD mortality, in conjunction with an increase or no change in CHD incidence in Japan, may be accounted for by improvements in medical treatment for CHD and/or decreased severity of CHD during the past decades. In fact, the number of emergency medical centers equipped with an intensive care unit or a cardiac care unit in Japan stood at 17 in 1978, 103 in 1989, and 201 in 2007.[1] In addition, the in-hospital case fatality rates at hospitals with cardiac care units declined by >50% between the early 1980s and the late 1990s, probably because of improvements in treatment, including thrombolytic therapy and percutaneous transluminal coronary angioplasty.[63]

There is no robust evidence on long-term changes in the severity of CHD. A series of autopsy studies showed a decline in the coronary atherosclerosis score for Japanese men and women between the 1960s and the 1980s,[64] suggesting that the severity of CHD may have declined in association with major declines in blood pressure levels and the prevalence of smoking.

The risk of CHD mortality and its incidence for Japanese women are half or lower than for Japanese men. The probable reason for the lower CHD risk among women is the lower coronary risk factors such as blood pressure levels, serum triglycerides, and the prevalence of smoking and diabetes mellitus and the higher levels of serum HDL cholesterol. Serum total cholesterol levels are lower in premenopausal women but higher in postmenopausal women compared with men of the same age group. However, the premenopausal lower total cholesterol levels may have a major impact on the sex difference in CHD because increased cholesterol levels after menopause probably would not be around long enough to lead to the development of CHD in many Japanese women.

The percentages of preventable CHD were 45% in men and 18% in women for control of smoking, 34% in men and 17% in women for control of hypertension, 5% in men and 8% in women for control of hypercholesterolemia (≥260 mg/dL), and 5% in men and 9% in women for control of diabetes mellitus. These percentages were estimated from the population-attributable risk percent[65] using data on hazard ratios (for current

smoking, 2.5 in both men and women; for high blood pressure, 2 in men and 1.5 in women; for hypercholesterolemia, 3.5 in both men and women; and for diabetes, 1.5 in men and 3 in women) and prevalence of risk factors (for current smoking, 54% in men and 15% in women; for high blood pressure, 52% in men and 40% in women; for hypercholesterolemia, 2.0% in men and 3.4% in women; and for diabetes, 10% in men and 5% in women). Therefore, most of the male CHD cases (461 000 patients and 41 970 deaths in 2005)[1,66] and half of the female CHD cases (403 000 patients and 34 533 deaths in 2005)[1,66] in Japan would be preventable if these major coronary risk factors were controlled.

Conclusions

This review presented distinctive trends for the mortality from, incidence of, and risk factors for CHD in Japan. Although it is hard to predict future CHD trends in Japan, middle-aged men, especially in urban areas, may be the victims of an impending epidemic of CHD, as is the case in some developing countries.[67] The potential epidemic, although it should be confirmed by continued surveillance, is an important issue for both public health and clinical practice.

Disclosures

None.

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KEY WORDS: coronary disease ■ mortality ■ risk factors ■ nutrition ■ exercise ■ follow-up studies ■ epidemiology

Original Article

Metabolic Syndrome and the Risk of Ischemic Heart Disease and Stroke among Middle-Aged Japanese

Choy-Lye CHEI[1], Kazumasa YAMAGISHI[1], Takeshi TANIGAWA[1,2], Akihiko KITAMURA[3], Hironori IMANO[3], Masahiko KIYAMA[3], Shinichi SATO[4], and Hiroyasu ISO[5]

Limited information is available regarding risk of cardiovascular disease and trends for the metabolic syndrome in Asia. We examined the impact of the metabolic syndrome and its components on risk of cardiovascular disease among middle-aged Japanese according to four criteria. We followed 2,613 subjects from a rural Japanese community who participated in cardiovascular health examinations between 1990 and 1993. After 27,477 person-years of follow-up through 2003, there were 42 incidents of ischemic heart disease, 73 total strokes (54 ischemic and 18 hemorrhagic), and 115 total cases of cardiovascular disease. The metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), International Diabetes Federation (IDF), and Japanese criteria. The multivariable hazard ratios (95%CI) associated with the metabolic syndrome based on NCEP-ATPIII criteria were 2.1 (1.1–4.0) for ischemic heart disease, 1.7 (1.0–2.7) for total stroke, 2.0 (1.2–3.5) for ischemic stroke, 1.1 (0.4–2.8) for hemorrhagic stroke, 2.0 (1.3–3.1) for ischemic cardiovascular disease, and 1.7 (1.2–2.5) for total cardiovascular disease. The population-attributable fractions of the metabolic syndrome based on NCEP-ATPIII criteria were 26–27% for ischemic heart disease and ischemic stroke and 20% for total cardiovascular disease. The metabolic syndrome based on AHA/NHLBI, IDF and Japanese criteria had weaker associations with risk of cardiovascular disease, and the association with risk of ischemic heart disease was not statistically significant. The metabolic syndrome based on NCEP-ATP III criteria predicted risks of ischemic heart disease, ischemic stroke and total cardiovascular disease, whereas that based on three other criteria predicted them less effectively. (*Hypertens Res* 2008; 31: 1887–1894)

Key Words: **metabolic syndrome, ischemic heart disease, stroke, follow-up study, Japanese**

Introduction

The metabolic syndrome is associated with increased risks of both type 2 diabetes and cardiovascular disease (*1–8*). The criteria of metabolic syndrome defined by the Third Report of the National Cholesterol Educational Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cho-

From the [1]Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences, and Institute of Community Medicine, University of Tsukuba, Tsukuba, Japan; [2]Department of Public Health, Social Medicine and Medical Informatics, Ehime University Graduate School of Medicine, Toon, Japan; [3]Osaka Medical Center for Health Science and Promotion, Osaka, Japan; [4]Chiba Prefectural Institute of Public Health, Chiba, Japan; and [5]Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Japan.

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Address for Reprints: Hiroyasu Iso, M.D., Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita 565-0871, Japan. E-mail: fvgh5640@mb.infoweb.ne.jp

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lesterol in Adults (Adult Treatment Panel III; NCEP-ATP III) (*9*) have been widely accepted. Recently, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) provided new guidelines for the diagnosis of the metabolic syndrome (*10*). The definition adopted by both NCEP-ATP III and AHA/NHLBI was based on five commonly measured clinical criteria whereas the criteria proposed by the International Diabetes Federation (IDF) (*11*) and the new Japanese definition (*12*) were based on a precondition for the presence of abdominal obesity.

A recent prospective study in Japan has shown that the metabolic syndrome and its components, defined by modified NCEP-ATP III criteria, were associated with an increased risk of ischemic cardiovascular disease (*13*). Another Japanese study of diabetic patients showed an increased risk of cardiovascular disease associated with the metabolic syndrome based on NCEP-ATPIII but not IDF criteria (*14*, *15*). To our knowledge, there are no studies that have examined whether the criteria of the metabolic syndrome can accurately predict the risk of incident cardiovascular disease among the general Japanese population. Limited prospective studies have been undertaken in Asian populations (*13*, *16–18*).

In the present study, we examined the association between the metabolic syndrome and risks of ischemic heart disease and stroke in Japanese men and women according to four different criteria of the metabolic syndrome.

Methods

Study Populations

The subjects were residents of Kyowa, a rural farming community in the Ibaraki Prefecture, mid-eastern Japan (census population in 1990 of ages 40–69: n=6,520), where annual cardiovascular health examinations have been conducted since 1981 (*19*). Residents aged ≥40 years old were invited annually by the municipal government to be assessed for several cardiovascular risk factors as a part of community stroke prevention program. Overall participation rates were approximately 60–70% from 1990 to 2003.

In the present study, we included a total of 2,660 subjects (998 men and 1,662 women) aged 40–69 who participated in cardiovascular health examinations between 1990 and 1993 that included waist circumference measurements. After exclusion of persons with a history of ischemic heart disease (n=15) or stroke (n=32) at baseline, a total of 2,613 subjects were followed-up through 2003 to examine the association between the metabolic syndrome and risks of ischemic heart disease and stroke. There were 17 individuals (0.7%) who moved out of the community during the follow-up period, according to municipal emigration office records. Forty-three (1.6%) people died during the follow-up. These cases were censored at the date of emigration or death, respectively. The median follow-up period was 10.5 years.

The study was approved by the Medical Ethics Committee of the University of Tsukuba.

Endpoint Determination

The follow-up was conducted by annual cardiovascular risk surveys in order to obtain information about ischemic heart disease and stroke incidents from the participants. For non-participants, these endpoints were ascertained by mailed questionnaire and by the use of death certificates. From death certificates, cases with stroke as an underlying cause of death ("International Classification of Diseases," 9th ed., pp. 410–414, 428, 429 and 430–438) were selected. We also used national insurance claims, ambulance records, reports by local physicians and public health nurses for case ascertainment. To confirm the diagnosis, all living patients were telephoned or visited to obtain their medical history and records. For deaths, we obtained information from families and reviewed medical records.

The criteria for ischemic heart disease were modified from those of the WHO Expert Committee (*20*). Definite myocardial infarctions were indicated by typical chest pain, lasting for ≥30 min with the appearance of abnormal and persistent Q or QS waves on the electrocardiogram, changes in cardiac enzyme activity, or both. Probable myocardial infarctions were indicated by typical chest pain for which the findings of electrocardiogram or enzyme activity were not available. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 h of symptom onset, a witnessed cardiac arrest, or abrupt collapse not preceded by more than 1 h of symptoms. Ischemic heart disease included definite or probable myocardial infarction, angina pectoris, and sudden cardiac death.

Stroke was defined as a focal neurological disorder with rapid onset that persisted at least 24 h or until death. The determination of incident stroke was based on clinical criteria (*21*). Stroke events were further subclassified as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke (non-embolic or embolic), primarily based on CT and/or MRI (22). Stroke cases without the imaging studies were subclassified according the clinical criteria (*21*) as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke, or stroke of undetermined type. The proportion of stroke cases confirmed by CT or MRI was 92% for total stroke, 100% for subarachnoid hemorrhage, 86% for intraparenchymal hemorrhage, and 94% for ischemic stroke.

A panel of three or four physician-epidemiologists made the final diagnosis of ischemic heart disease and stroke, blinded to the data of risk factor surveys.

Measurements

Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg) divided

by square of height (m^2). Well-trained observers measured the waist circumference of the subjects at the level of the umbilicus to the nearest 1 cm while subjects were standing and breathing normally. Blood pressure was measured by well-trained technicians using mercury sphygmomanometers on the right arm of seated participants after at least 5 min of rest. Blood was drawn from seated participants into a plain, siliconized glass tube, and serum was separated. Serum glucose was measured by the hexokinase method. Fasting was not required. The distribution of time since the last meal was <2 h (40%), 2 h (35%), 3–7 h (19%) and ≥8 h (6%).

An interview was conducted to ascertain daily alcohol intake, number of cigarettes smoked per day, use of medication for diabetes mellitus and hypertension, and past history of stroke and ischemic heart disease. Persons who smoked at least 1 cigarette/d were defined as current smokers, and those who had not smoked for ≥3 months were defined as former smokers.

Serum total cholesterol and high-density lipoprotein (HDL)-cholesterol after heparin-manganese precipitation were measured by the Liebermann-Burchard direct method using the Autoanalyzer II (Technicon, Tarrytown, USA) at the Osaka Medical Center for Health Science and Promotion. The laboratory has been standardized under the CDC-NHLBI Lipid Standardization Program, Centers for Disease Control and Prevention, Atlanta, and successfully met the criteria for precision and accuracy of triglyceride and total and HDL-cholesterol measurements as an international member of the US National Cholesterol Reference Method Laboratory Network (CRMLN) (*23*).

Definition of the Metabolic Syndrome

According to the modified NCEP-ATPIII definition (*9*), subjects who had three or more of the following criteria were identified as having the metabolic syndrome: 1) triglycerides ≥1.69 mmol/L (≥150 mg/dL), 2) HDL cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women, 3) blood pressure ≥130/85 mmHg, or use of antihypertensives, 4) fasting glucose ≥6.11 mmol/L (≥110 mg/dL) or non-fasting glucose ≥7.77 mmol/L (≥140 mg/dL), or on treatment, or 5) abdominal obesity—modified waist circumference cutoffs (≥90 cm for men and ≥80 cm for women) were used (*24*) instead of the waist circumference cutoffs (>102 cm for men and >88 cm for women) proposed in the existing NCEP-ATPIII criteria.

According to the AHA/NHLBI definition (*10*), the metabolic syndrome was defined as the presence of three or more of the following: 1) elevated triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) reduced HDL-cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women, or on treatment, 3) elevated blood pressure ≥130/85 mmHg, or use of antihypertensive medication, 4) elevated fasting glucose ≥5.56 mmol/L (≥100 mg/dL) or non-fasting glucose ≥7.22 mmol/L (≥130 mg/dL), or on treatment, or 5) abdominal obesity, waist circumference ≥90 cm for men and ≥80 cm for women.

According to the new IDF definition (*11*) (the IDF consensus worldwide definition of the metabolic syndrome [article online]: available from http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf/), Japanese people were defined as having the metabolic syndrome if the subjects had abdominal obesity (waist circumference cutoffs ≥90 cm for men and ≥80 cm for women) plus two or more of the following risk factors: 1) elevated triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) low HDL cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women or on treatment, 3) high blood pressure ≥130/85 mmHg or use of antihypertensives, or 4) high fasting glucose ≥5.56 mmol/L (≥100 mg/dL) or non-fasting glucose ≥7.22 mmol/L (≥130 mg/dL) or on treatment.

According to the Japanese definition (*12*), the metabolic syndrome was identified if subjects had abdominal obesity (waist circumference ≥85 cm for men and ≥90 cm for women), in addition to two or more of the following criteria: 1) triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) HDL cholesterol <1.03 mmol/L (<40 mg/dL) or on treatment, 3) blood pressure ≥130/85 mmHg or use of antihypertensive medication, or 4) fasting glucose ≥6.11 mmol/L (≥110 mg/dL) or non-fasting glucose ≥7.77 mmol/L (≥140 mg/dL) or on treatment.

Statistical Analysis

Age-adjusted mean values or the prevalence of metabolic syndrome, its components and other cardiovascular risk factors were compared between incident cases of ischemic heart disease and stroke and non-cases using the analysis of covariance or χ^2 tests.

Person-years were calculated as the sum of individual follow-up time until the occurrence of incident ischemic heart disease, stroke, death, emigration, or until the end of 2003. The hazard ratios of ischemic heart disease and stroke and the respective 95% confidence intervals (CI) were calculated with reference to the risk of individuals without the metabolic syndrome using the Cox proportional hazards model. The results were adjusted for age (years), and other potential confounding variables such as smoking status (never, former, and current smokers), alcohol intake category (never, former, and current <46, 46–68 and ≥69 g/d ethanol), time since last meal (<2, 2, 3–7, and ≥8 h), and total serum cholesterol levels (mmol/L). The proportional hazards assumption was tested using an interaction terms of time by metabolic syndrome and was not violated for each analysis. We also calculated the population attributable fraction (PAF) to examine the contribution of the metabolic syndrome to risk of cardiovascular disease using multivariable hazard ratios of statistical significance and the proportions of cases in each categories (*25*). PAF was estimated as $Pd \times (HR - 1)/HR$, where Pd is the proportion of cases falling into the metabolic syndrome category

Table 1. Sex-Specific Baseline Characteristics of Cardiovascular Disease Cases and Non-Cases among Japanese Aged 40–69 Years

	Ischemic heart disease	Total stroke	Ischemic stroke	Hemorrhagic stroke	Ischemic cardiovascular disease	Total cardiovascular disease	Non-cases
Men							
n	28	31	26	5	52	60	908
Age, years	59.5±2*	60.2±2†	60.0±2*	61.6±4	59.6±1*	59.9±1‡	55.6±0.3
Systolic blood pressure, mmHg	138±3	146±3‡	147±3‡	139±7	141±2‡	141±2‡	134±0.5
Diastolic blood pressure, mmHg	82±2	84±2*	84±2	85±5	83±2*	83±1	80±0.3
Use of antihypertensive medication, %	32*	18	19	14	25	23	17
High blood pressure, %	47†	34	34	34	39*	36*	24
Body mass index, kg/m^2	23.5±0.5	23.6±0.5	23.8±0.5	22.6±1.3	23.7±0.4	23.5±0.4	23.7±0.1
Waist circumference, cm	82.9±1.5	84.0±1.4	85.1±1.6	78.3±3.5	84.4±1.1	83.5±1.0	84.0±0.3
Waist circumference (≥85 cm), %	42	50	53	38	49	46	49
Waist circumference (≥90 cm), %	24	41*	41	38	34	32	24
Serum total cholesterol, mmol/L	5.13±0.16	4.87±0.16	4.97±0.17	4.35±0.39	5.06±0.12	5.00±0.11	4.96±0.03
Hypercholesterolemia, %	15	14	17	2	16	16	20
Serum triglycerides, mmol/L	2.13±0.21	1.82±0.20	1.96±0.21	1.13±0.49	2.07±0.15	1.95±0.14	1.79±0.04
Hypertriglyceridemia, %	49	40	47	1	50	43	42
Serum HDL-cholesterol, mmol/L	1.25±0.07	1.36±0.06	1.33±0.07	1.49±0.16	1.29±0.05	1.33±0.05	1.33±0.01
Low HDL-cholesterol, %	10	16	19	1	15	13	19
Serum glucose, mmol/L	8.16±0.45*	8.90±0.41†	9.09±0.44‡	7.79±0.99	8.61±0.33‡	8.46±0.31†	7.02±0.08
Glucose abnormality, % (≥6.11mmol/L)	6	28†	30‡	19	18‡	17†	7
Current smokers, %	59	66	67	62	61	61	53
Ethanol intake, g/d	28.0±4.6	25.4±4.3	26.9±4.7	17.1±10.8	27.8±3.4	27.1±3.1	22.9±0.8
Women							
n	14	42	28	13	40	55	1,590
Age, years	65.6±2‡	62.9±1‡	63.0±2‡	62.2±2†	63.9±1‡	63.6±1‡	54.8±0.2
Systolic blood pressure, mmHg	130±4	136±3*	135±3	139±4*	133±3	134±2	130±0.4
Diastolic blood pressure, mmHg	75±3	79±2	77±2	83±3*	77±2	78±1	77±0.3
Use of antihypertensive medication, %	21	30	35	21	31*	28	19
High blood pressure, %	35	34	39	28	38*	35	24
Body mass index, kg/m^2	24.4±0.8	25.5±0.5‡	25.7±0.6†	25.4±0.9	25.3±0.5†	25.3±0.4‡	23.8±0.1
Waist circumference, cm	84.4±2.5	84.1±1.4*	84.7±1.7*	82.9±2.6	84.6±1.5*	84.0±1.3*	81.0±0.2
Waist circumference (≥90 cm), %	41*	27	29	25	33*	29*	18
Waist circumference (≥80 cm), %	64	56	34	36	65	59	55
Serum total cholesterol, mmol/L	5.41±0.25	5.07±0.15	5.02±0.18	5.15±0.26	5.18±0.15	5.19±0.13	5.26±0.02
Hypercholesterolemia, %	34	22	22	24	27	27	31
Serum triglycerides, mmol/L	1.52±0.23	1.47±0.13	1.49±0.16	1.46±0.24	1.49±0.14	1.48±0.12	1.47±0.02
Hypertriglyceridemia, %	40	43*	46*	40	42	41*	29
Serum HDL-cholesterol, mmol/L	1.32±0.09	1.40±0.05	1.40±0.06	1.40±0.09	1.38±0.05	1.39±0.05	1.46±0.01
Low HDL-cholesterol, %	61*	41	44	36	50*	45*	32
Serum glucose, mmol/L	7.11±0.50	6.96±0.29	7.12±0.36	6.42±0.52	6.90±0.30	6.83±0.26	6.42±0.05
Glucose abnormality, % (≥6.11 mmol/L)	12	15‡	16†	7	13†	13‡	4
Current smokers, %	8	8	8	9	9	8	5
Ethanol intake, g/d	0.4±1.4	2.2±0.8	2.5±1.0	1.8±1.5	1.9±0.9	1.8±0.7	1.1±0.1

Values are mean±SEM, or proportions, adjusted for age. Serum triglycerides and glucose values were also adjusted for time since last meal. Test for significance from non-cases: *$p<0.05$, †$p<0.01$, ‡$p<0.001$. HDL, high-density lipoprotein.

Table 2. Hazard Ratios (HR), Population Attributable Fraction (PAF), and 95% Confidence Interval (CI) of Cardiovascular Disease Associated with the Metabolic Syndrome in Japanese Aged 40–69 Years

Metabolic syndrome	NCEP-ATP III criteria		AHA/NHLBI criteria		IDF criteria		Japanese criteria	
	No	Yes	No	Yes	No	Yes	No	Yes
No. at risk	1,808	805	1,750	863	1,919	694	2,174	439
Person-years	18,999	8,478	18,373	9,104	20,142	7,336	22,838	4,639
Ischemic heart disease								
No. of cases	20	22	20	22	25	17	30	12
Age-adjusted HR (95% CI)	1.0	1.9 (1.1–3.6)*	1.0	1.7 (0.9–3.2)	1.0	1.4 (0.8–2.7)	1.0	1.6 (0.8–3.1)
Multivariable HR (95% CI)	1.0	2.1 (1.1–4.0)*	1.0	1.9 (1.0–3.5)	1.0	1.8 (0.9–3.4)	1.0	1.1 (0.5–2.2)
PAF (95% CI), %		27 (−0.5–48)		—		—		—
Total stroke								
No. of cases	38	35	37	36	43	30	50	23
Age-adjusted HR (95% CI)	1.0	1.6 (1.0–2.6)*	1.0	1.5 (1.0–2.4)	1.0	1.5 (0.9–2.4)	1.0	1.9 (1.1–3.1)*
Multivariable HR (95% CI)	1.0	1.7 (1.0–2.7)*	1.0	1.6 (1.0–2.5)	1.0	1.6 (1.0–2.7)	1.0	1.8 (1.1–3.1)*
PAF (95% CI), %		19 (−1–35)		—		—		14.0
Ischemic stroke								
No. of cases	26	28	26	28	29	25	35	19
Age-adjusted HR (95% CI)	1.0	1.9 (1.1–3.3)*	1.0	1.7 (1.0–2.9)	1.0	1.9 (1.1–3.2)*	1.0	2.2 (1.3–3.9)†
Multivariable HR (95% CI)	1.0	2.0 (1.2–3.5)*	1.0	1.8 (1.0–3.1)*	1.0	2.2 (1.2–3.9)†	1.0	2.0 (1.1–3.6)*
PAF (95% CI), %		26 (2–44)		23 (−3–42)		25 (4–42)		18 (−0.6–33)
Hemorrhagic stroke								
No. of cases	11	7	10	8	13	5	14	4
Age-adjusted HR (95% CI)	1.0	1.1 (0.4–2.9)	1.0	1.2 (0.5–3.2)	1.0	0.8 (0.3–2.3)	1.0	1.2 (0.4–3.5)
Multivariable HR (95% CI)	1.0	1.1 (0.4–2.8)	1.0	1.2 (0.5–3.2)	1.0	0.7 (0.3–2.2)	1.0	1.4 (0.5–4.6)
PAF (95% CI), %		—		—		—		—
Ischemic cardiovascular disease								
No. of cases	44	48	44	48	51	41	62	30
Age-adjusted HR (95% CI)	1.0	1.9 (1.3–2.9)†	1.0	1.7 (1.1–2.6)*	1.0	1.7 (1.1–2.6)*	1.0	2.0 (1.3–3.0)†
Multivariable HR (95% CI)	1.0	2.0 (1.3–3.1)†	1.0	1.8 (1.2–2.7)†	1.0	2.0 (1.3–3.2)†	1.0	1.5 (1.0–2.4)
PAF (95% CI), %		26 (8–41)		23 (4–38)		23 (7–36)		—
Total cardiovascular disease								
No. of cases	59	56	58	57	68	47	81	34
Age-adjusted HR (95% CI)	1.0	1.7 (1.2–2.4)†	1.0	1.5 (1.1–2.2)*	1.0	1.5 (1.0–2.1)*	1.0	1.7 (1.1–2.5)*
Multivariable HR (95% CI)	1.0	1.7 (1.2–2.5)†	1.0	1.6 (1.1–2.3)*	1.0	1.6 (1.1–2.4)*	1.0	1.4 (0.9–2.1)
PAF (95% CI), %		20 (4–33)		18 (1–31)		16 (2–28)		—

*$p<0.05$, †$p<0.01$. Multivariable HR adjusted for age, time since last meal, cigarette smoking, alcohol intake and serum total cholesterol.

and HR is hazard ratio in that category. The Greenland formula was used to calculate 95% CI (*26*).

SAS statistical software (version 9.13; SAS Institute Inc., Cary, USA) was used for the analyses, and $p<0.05$ was regarded as statistically significant

Results

After 27,477 person-years of follow-up, we documented 42 incident cases of ischemic heart disease (1.5 per 1,000 person-years), 73 incident cases of total stroke (2.7 per 1,000 person-years), 54 incident cases of ischemic stroke (2.0 per 1,000 person-years), 18 incident cases of hemorrhagic stroke (0.7 per 1,000 person-years), 92 incident cases of ischemic cardiovascular disease (3.4 per 1,000 person-years), and 115 incident cases of total cardiovascular disease (4.2 per 1,000 person-years).

Table 1 compares age-adjusted values and proportions of components of the metabolic syndrome and other cardiovascular risk factors between incident cases and non-cases of cardiovascular disease. Compared with non-cases, cases with ischemic heart disease were older, more hypertensive, smoked more, and had higher mean serum total cholesterol, serum triglycerides, and serum glucose levels, and lower mean HDL-cholesterol levels among both men and women. Compared with non-cases, individuals who suffered from ischemic stroke were older, more hypertensive, smoked more, and had higher mean serum triglycerides and serum glucose

Table 3. Multivariable Hazard Ratios of Ischemic Cardiovascular Disease According to the Number of Components of the Metabolic Syndrome, Stratified by the Presence of Abdominal Obesity

Metabolic syndrome	Abdominal obesity (−)			Abdominal obesity (+)		
	No. of components except abdominal obesity			No. of components except abdominal obesity		
	0	1	2+	0	1	2+
NCEP-ATP III criteria						
No. at risk	415	560	495	126	355	662
Person-years	4,392	5,801	5,145	1,354	3,785	7,001
Ischemic cardiovascular disease						
No. of cases	3	16	24	2	6	41
Multivariable HR (95% CI)	1.0	2.4 (0.7–8.4)	3.3 (1.0–11.2)	2.0 (0.3–11.9)	1.6 (0.4–6.6)	5.1 (1.6–16.9)†
AHA/NHLBI and IDF criteria						
No. at risk	378	552	540	113	336	694
Person-years	3,996	5,719	5,623	1,221	3,583	7,336
Ischemic cardiovascular disease						
No. of cases	2	16	25	1	7	41
Multivariable HR (95% CI)	1.0	3.4 (0.8–14.8)	4.3 (1.0–18.3)*	1.5 (0.1–16.3)	2.8 (0.6–13.7)	6.5 (1.6–27.5)*
Japanese criteria						
No. at risk	567	767	499	67	274	439
Person-years	5,948	8,079	5,255	725	2,830	4,639
Ischemic cardiovascular disease						
No. of cases	5	17	28	2	10	30
Multivariable HR (95% CI)	1.0	1.6 (0.6–4.5)	3.4 (1.3–8.9)*	2.4 (0.5–12.2)	2.2 (0.7–6.6)	3.4 (1.3–9.0)*

*$p<0.05$, †$p<0.01$. Multivariable HR adjusted for age, time since last meal, cigarette smoking, alcohol intake and serum total cholesterol. HR, hazard ratio; CI, confidence interval.

levels among both men and women.

The hazard ratios of the metabolic syndrome and cardiovascular disease are shown in Table 2. The metabolic syndrome based on NCEP-ATP III criteria was significantly associated with risks of ischemic heart disease, total stroke, ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease but was not associated with hemorrhagic stroke. The respective multivariable hazard ratio (95% CI) associated with the metabolic syndrome was 2.1 (1.1–4.0), 1.7 (1.0–2.7), 2.0 (1.2–3.5), 2.0 (1.3–3.1), 1.7 (1.2–2.5) and 1.1 (0.4–2.8). Based on AHA/NHLBI and IDF criteria, we found similar or weaker associations with risks of ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease, and no significant association with total stroke, hemorrhagic stroke or ischemic heart disease. Using the Japanese criteria, the metabolic syndrome was only significantly associated with risks of total and ischemic strokes; the multivariable hazard ratio (95% CI) was 1.8 (1.1–3.1) and 2.0 (1.1–3.6), respectively.

The PAFs of ischemic heart disease, total stroke, ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease were between 19% and 27% for the metabolic syndrome based on NCEP-ATP III criteria. The respective PAFs were between 18% and 23% based on AHA/NHLBI criteria and between 16% and 25% based on IDF criteria. The PAFs of total and ischemic strokes for the metabolic syndrome were between 14% and 18% based on Japanese criteria.

We also analyzed associations of the metabolic syndrome components based on the four criteria and risks of ischemic cardiovascular disease, stratified by the presence of abdominal obesity (Table 3). The multivariate hazard ratio of ischemic cardiovascular disease according to NCEP-ATP III criteria was 3.3 (1.0–11.2) in non-abdominal obese persons with at least two risk factors and 5.1 (1.6–16.9) in abdominal obese persons with at least two risk factors. The respective hazard ratios were 4.3 (1.0–18.3) and 6.5 (1.6–27.5), according to AHA/NHLBI and IDF criteria, and 3.4 (1.3–8.9) and 3.4 (1.3–9.0), according to the Japanese criteria.

Discussion

The metabolic syndrome based on NCEP-ATP III criteria was associated with 2-fold increased risks of ischemic heart disease, ischemic stroke, and total cardiovascular disease, whereas the metabolic syndrome based on AHA/NHLBI, IDF, and Japanese criteria had weaker associations with risk of cardiovascular disease, and the association with risk of ischemic heart disease was not statistically significant. The population attributable fraction of ischemic stroke was lower for the metabolic syndrome based on Japanese criteria than for that based on other criteria. Our results were consistent

with those of other prospective studies that showed that the metabolic syndrome based on NCEP-ATP III criteria was associated with risks of mortality and incidence of cardiovascular disease (*1*, *2*, *4–7*, *13*, *16–18*, *27*, *28*), and that the metabolic syndrome based on IDF criteria was less predictive of cardiovascular disease risk (*29–31*). The metabolic syndrome based on NCEP-ATP III, but not IDF criteria, was associated with cardiovascular disease among male diabetic patients (*14*, *15*).

Based on the Japanese criteria, the excess risk of ischemic cardiovascular disease was similar in non-abdominal obese persons with at least two metabolic risk factors and abdominal obese persons with at least two risk factors. The lack of significant associations of ischemic heart disease and ischemic cardiovascular disease based on the Japanese criteria was due to the inclusion of a high-risk group of persons without abdominal obesity as a reference group. In other words, excess risk of ischemic cardiovascular disease was similar for persons with at least two metabolic risk factors, irrespective of the presence of abdominal obesity. It is controversial whether the abdominal obesity defined by waist circumference should be required for diagnosis of the metabolic syndrome (*27*, *30*). Waist circumference is a valuable component of metabolic syndrome, but the requirement of an increased waist circumference may lead to reduced predictive power for cardiovascular disease (*27*, *29–33*).

The strengths of the present study include the use of standardized measurements of waist circumference, serum lipids, and blood pressure levels. The stroke surveillance was almost complete, and a high percentages of the events were confirmed using imaging studies (92%).

The limitations of the present study were, first, the small number of incident cases, particularly for ischemic heart disease. However, we found a statistically significant association between the metabolic syndrome and risks of ischemic heart disease and ischemic stroke. Second, we collected non-fasting blood samples from 94% of the participants during the 1990–1993 examinations. We used non-fasting data at the baseline examination, in particular, non-fasting serum triglycerides ≥1.69 mmol/L (≥150 mg/dL) as a component of metabolic syndrome. Although the justification of the use for the same cutoff point as fasting status is under debate, the data of non-fasting triglycerides can be used because of their significant predictive power for ischemic heart disease (*34*). We used non-fasting glucose ≥7.77 mmol/L as a component of metabolic syndrome, and we may have misclassified participants with high blood glucose. However, we found no significant difference in the percentage of participants with high blood glucose in non-fasting and fasting blood samples probably because we used the different cutoff points: ≥110 mg/dL for fasting and ≥140 mg/dL for non-fasting. In men, the percentage of high blood glucose was 26% for non-fasting blood samples and 30% for fasting blood samples. In women, the respective percentages were 17% and 14%.

In summary, the metabolic syndrome based on NCEP-ATPIII criteria predicted risks of ischemic heart disease, ischemic stroke and total cardiovascular disease, whereas that based on the other three criteria predicted them to a lesser extent.

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Trends in dietary intakes of vitamins A, C and E among Japanese men and women from 1974 to 2001

Yoshimi Kato[1,†], Satoyo Ikehara[2], Koutatsu Maruyama[2], Mieko Inagawa[3], Miyuki Oshima[3], Kimiko Yokota[2], Taeko Yamazaki[4], Masa Kishi[4], Sachiko Murai[4], Mitsumasa Umesawa[2], Enbo Ma[2], Kazumasa Yamagishi[2], Takeshi Tanigawa[2,‡], Michinori Kurokawa[5], Shinichi Sato[5,§], Takashi Shimamoto[5] and Hiroyasu Iso[2,*]

[1]Department of Public Health Medicine, Graduate School of Comprehensive Human Sciences, Institute of Community Medicine, University of Tsukuba, Tsukuba, Japan: [2]Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan: [3]Chikusei Kyowa Health Center, Chikusei, Japan: [4]Ikawa Municipal Office, Ikawa, Japan: [5]Osaka Medical Center for Health Science and Promotion, Osaka, Japan

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Abstract

Objective: To investigate long-term trends in dietary intakes of vitamins A, C and E in Japanese adults.

Design: Time series by community-based nutrition survey.

Setting: Two rural communities (Ikawa and Kyowa) between 1974 and 2001 in Japan.

Subjects: A total of 3713 men and 3726 women aged 40–69 years.

Methods: Dietary intake data were collected by the 24 h dietary recall.

Results: In Ikawa, mean intake of vitamin A (β-carotene and retinol) increased by 13–40 %; vitamins C and E increased by approximately 23–33 % among men and women from 1974–1977 to 1998–2000. In Kyowa, mean intake of vitamin A, primarily retinol, increased by 13–21 % among men and women; vitamin C from fruits decreased by 16 % among men; and vitamin E increased by 29 % among women from 1982–1986 to 1998–2001. Mean intake of vitamin E in the latest survey period was lower than the Adequate Intake among men and women in both communities. Generally, there were increased intakes of β-carotene and vitamin C from green/yellow and other vegetables; increased retinol intake from fish/shellfish, eggs, milk/dairy products and fats/oils; and increased vitamin E intake from green/yellow and other vegetables, fish/shellfish, eggs, milk/dairy products and fats/oils.

Conclusions: Mean intakes of the antioxidant vitamins A, C and E increased among middle-aged Japanese men and women between the 1970s and the 1990s except for decreased vitamin C among Kyowa men. The lower mean intake of vitamin E than the Adequate Intake should be considered a potential public health issue for the prevention of CVD.

Keywords
Vitamin C
Vitamin E
Vitamin A
Foods
Trends

Vitamins with antioxidant properties may be protective against CVD and cancer[1–3]. Antioxidants can reduce the oxidative modification of LDL to affect blood cholesterol levels[1] and to prevent oxidative damage to cells, thereby reducing the risk of cancer[4–8].

Higher serum levels of carotenoids such as α- and β-carotene have been associated with lower mortality from lung[9,10] and colorectal cancers[11] among Japanese men. Vitamin C was reported to lower blood pressure levels[12] and was inversely associated with the incidence[13] of and mortality[14] from stroke.

Intake of another major antioxidant vitamin, vitamin E, has been associated with reduced risks of CHD and stroke when used in high doses[15–18], although vitamin E supplementation had no effect on mortality from CVD and all causes in clinical trials[19,20]. A clinical trial of approximately 30 000 Chinese adults demonstrated that a diet

† Present affiliation: Nichirei Fresh Inc., Tokyo, Japan.

‡ Present affiliation: Department of Public Health, Social Medicine and Medical Informatics, Ehime University Graduate School of Medicine, Matsuyama, Japan.

§ Present affiliation: Chiba Prefectural Institute of Public Health, Chiba, Japan.

*Corresponding author: Email iso@pbhel.med.osaka-u.ac.jp

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supplemented with β-carotene, vitamin E and Se reduced the risk of cancer by 13%[21]. These findings suggest potential benefits of antioxidant vitamins for the prevention of CVD and cancer.

In 2000, the Ministry of Science and Education revised the Japanese standard food composition table for the first time in 18 years, to reflect the increasing diversification of Japanese dietary habits. Vitamins A, C and E were included in the new table, so that trends for the intake of these vitamins could be evaluated using the existing database of dietary surveys.

In the present study, we investigated long-term trends in dietary intakes of vitamins A, C and E, according to population-based surveys in two Japanese communities between 1974 and 2001.

Methods

The subjects in the present study comprised men and women aged from 40 to 69 years, living in Ikawa town, Akita Prefecture, and Kyowa town (presently a district of Chikusei city), Ibaraki Prefecture. Ikawa is located near the Sea of Japan in the north, where nearly half of the town is forest and rice-crop agriculture is the main industry. Kyowa is on a plain area in the mid-eastern region of Japan; this area is predominantly horticultural with a mix of rice-crop agriculture and light industry.

The nutrition surveys were conducted by 24 h dietary recall in approximately 10% of the participants in the annual cardiovascular risk surveys. Subjects aged over 70 years were excluded from the nutrition survey because the accuracy of recall-based data may decline with ageing. The participants in the cardiovascular risk surveys were recruited for the nutrition surveys, but were not pre-informed of the recruitment.

The surveys were conducted from 1974 to 2000 for Ikawa and from 1982 to 2001 for Kyowa. The survey data were collected during autumn in Kyowa and during spring in Ikawa. The nutrition survey term was stratified into seven time periods for Ikawa: 1974–1977, 1978–1981, 1982–1985, 1986–1989, 1990–1993, 1994–1997 and 1998–2000; and into four periods for Kyowa: 1982–1986, 1990–1993, 1994–1997 and 1998–2001. If a participant undertook the nutrition survey more than once during one survey period, we used the data from the earliest year in each survey period. The numbers of subjects by sex and time period in Ikawa and Kyowa are presented in Table 1.

The 24 h dietary recall method involves trained dietitians interviewing the study subjects on what they had eaten during the 24 h prior to examination. The same dietitians were used over the survey periods where possible to avoid fluctuations in interviewing technique over time. New dietitians were carefully trained before interviewing for the survey. In the interviews, actualized food models, pictures of food materials and dishes, and/or real foods and dishes were shown to the participants to enable easy recall of their food intake. The same basic food models and interview forms were used throughout the surveys. Intake of green tea was included in the surveys from 1994. Rice and *miso* soup quantities were estimated by asking the subjects to put the usual amount of their intake into a bowl and this was then measured. We also investigated the intake frequencies of sixteen major foods and food groups per week to confirm that the foods included in the 24 h dietary recall were representative of the subject's usual diet. Survey periods encompassing special events such as a festival or celebration were excluded from the surveys. The interview took approximately 30 min per subject. We did not ask about the use of vitamin supplements because supplement use has been uncommon during the survey periods.

Nutrient intakes were estimated based on fifth revised edition of the *Standard Tables of Food Composition in Japan*[22]. The data were originally coded based on the fourth edition of the food composition tables between 1974 and 1999, and on the fifth edition between 2000 and 2001. Foods appearing for the first time in the fifth and fifth revised editions were rarely eaten by our study participants. The data on vitamins were total vitamin A (μg retinol equivalents (RE)/d), β-carotene (μg/d), vitamin C (mg/d) and α-tocopherol (μg/d) as vitamin E. It is possible that the amounts of vitamins A, C and E contained in the same foods may have changed from the 1970s to the present, but we have no data to support this possibility. Therefore, we used the data in the fifth edition throughout the surveys.

The food composition tables provide nutritional data after cooking only for selected foods. Thus, we evaluated all data in the pre-cooked state to investigate long-term trends, although this may have introduced a systematic overestimation of nutrient intakes.

For primary trend analyses, we did not include dietary intake of green tea because this intake was not surveyed prior to 1994. However, for the secondary analyses, we included vitamins A, C and E from green tea in the latest survey period, to estimate the true proportions of these nutrients in the total intakes. Persons who reported upper and lower 1% of these vitamins were excluded from the analyses (n 528).

Sex-specific age-adjusted mean values and standard errors of vitamin A, C and E intakes were calculated by analysis of covariance for each survey period as described above. We also evaluated intakes of these vitamins by major food group. Differences in mean values from the earliest survey period were determined using Dunnett's multiple comparison method. The SAS statistical software package version 9·13 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. P values less than 0·05 were regarded as statistically significant throughout the surveys.

Results

The number of survey participants in each survey period was between 176 and 370 for men and between 132 and 325 for women in Ikawa, while the respective number in Kyowa was between 355 and 627 and between 433 and 572 (Table 1).

Age-adjusted mean (SE) BMI (kg/m^2) in the latest survey period (1998–2000 in Ikawa, 1998–2001 in Kyowa) was 23·9 (0·2) among men and 24·3 (0·2) among women in Ikawa, and 23·7 (0·1) among men and 23·5 (0·2) among women in Kyowa. The proportion of subjects who drank more than one alcoholic drink per week was 86% among men and 9% among women in Ikawa, and 74% among men and 11% among women in Kyowa.

Table 1 shows trends for sex-specific age-adjusted mean dietary intakes of vitamins A, C and E in the two communities. Mean intake of total vitamin A increased by 13% among men and 40% among women; β-carotene increased by 2% among men and 31% among women; and retinol increased by 56% among men and 105% among women from 1974–1977 to 1998–2000 in Ikawa. Among men and women in Kyowa, mean intake of total vitamin A increased by 13% for men and 21% for women; retinol increased by 16% for men and 29% for women, but β-carotene did not change between 1982–1986 and 1998–2001.

Mean intake of vitamin C increased by 23% among men and 29% among women from 1974–1977 to 1978–1981, and plateaued thereafter in Ikawa. In Kyowa, it decreased by 16% among men, but did not change among women from 1982–1986 to 1990–1993.

Mean intake of vitamin E increased by 34% among men and 33% among women from 1974–1977 to 1982–1985, and plateaued thereafter in Ikawa. In Kyowa, mean intake of vitamin E did not change among men, but increased by 8% among women from 1982–1986 to 1998–2001.

Table 2 shows trends for sex-specific age-adjusted mean dietary intakes of vitamins A, C and E by food group in the two communities. Mean intake of β-carotene from green/yellow vegetables, a primary food source, increased among men from 1974–1977 to 1982–1985, and plateaued thereafter in Ikawa, whereas that from fruits and algae decreased among men and women from 1974–1977 to 1998–2000 in Ikawa. In Kyowa, mean intake of β-carotene from fruits decreased among men, but did not change substantially among women from 1982–1986 to 1990–1993.

Mean intake of retinol from fish/shellfish increased among men and women from 1974–1977 to 1998–2000 in

Table 1 Trends for sex-specific age-adjusted mean dietary intakes of vitamins A, C and E in men and women aged 40–69 years in Ikawa and Kyowa, Japan

Sex/community	Survey years	No. of subjects	Total vitamin A (μg RE/d)		β-Carotene (μg/d)		Retinol (μg/d)		Vitamin C (mg/d)		Vitamin E (mg/d)	
			Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Men												
Ikawa												
	1974–1977	306	506	22·2	4470	198·3	129	14·3	81	3·4	5·9	0·17
	1978–1981	176	515	29·1	4427	259·9	138	18·7	100**	4·5	6·1	0·22
	1982–1985	370	615**	20·0	5503***	179·3	150	12·9	110***	3·1	7·9***	0·15
	1986–1989	308	563	22·0	5375**	197·1	170	14·2	108***	3·4	7·4***	0·16
	1990–1993	262	606*	23·9	5252*	213·7	202**	15·4	98**	3·7	7·3***	0·18
	1994–1997	281	599*	23·2	5591***	207·9	165	15·0	106***	3·6	7·3***	0·17
	1998–2000	224	571	25·8	4559	230·5	201**	16·6	97*	3·9	7·0***	0·19
Kyowa												
	1982–1986	627	436	13·1	3752	119·5	119	7·4	137	3·7	6·4	0·12
	1990–1993	355	426	17·4	3148**	158·4	170***	9·8	116**	4·9	6·4	0·16
	1994–1997	381	448	16·8	3609	153·2	149*	9·4	129	4·8	6·7	0·16
	1998–2001	423	491*	15·9	3682	145·2	138	8·9	115***	4·5	6·6	0·15
Women												
Ikawa												
	1974–1977	253	435	23·9	4106	203·9	83	16·4	90	3·8	5·5	0·16
	1978–1981	132	490	32·9	4346	281·1	123	22·7	116***	5·2	6·1	0·23
	1982–1985	273	578***	22·9	5100**	195·3	145*	15·7	119***	3·6	7·3***	0·16
	1986–1989	266	547**	23·2	5247***	197·9	157**	16·0	114***	3·7	7·0***	0·16
	1990–1993	325	576***	21·0	5437***	179·4	163**	14·5	123***	3·3	7·2***	0·14
	1994–1997	318	626***	21·2	5417***	181·0	185***	14·6	114***	3·4	6·9***	0·14
	1998–2000	242	609***	24·3	5390***	207·5	170**	16·7	121***	3·9	6·7***	0·17
Kyowa												
	1982–1986	572	499	13·7	4525	124·7	119	7·3	154	4·0	6·6	0·12
	1990–1993	433	515	15·7	4230	143·3	157**	8·4	154	4·6	6·7	0·14
	1994–1997	449	518	15·5	4592	140·9	135	8·3	156	4·6	6·6	0·14
	1998–2001	463	603***	15·2	4533	138·5	153**	8·1	150	4·5	7·1*	0·14

RE, retinol equivalents.
Intake of green tea was not taken into account; intakes of nutrients were evaluated in conditions before cooking.
Mean values were significantly different from those of the first survey: *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$.